

Industria y Comercio

SUPERINTENDENCIA

Organización CSA Ltda



Delegatura de Propiedad Industrial

División de Nuevas Creaciones

SOLICITUD

PCT
PATENTE DE INVENCION

NOV 21/07

21. EXPEDIENTE No.

07-123149

54. TÍTULO "MÉTODOS PARA SINTETIZAR DERIVADOS DE 6-ALQUIL-AMINOQUINOLINA"

51. CLASIFICACIÓN INTERNACIONAL

71. SOLICITANTE WYETH

DOMICILIO NUEVA JERSEY, ESTADOS UNIDOS DE AMÉRICA

74. APODERADO ALVARO Correa -Ordoñez T.P. 20.281

22. BOGOTÁ, D. C., NOVIEMBRE 21 de 2007

PETITORIO

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-123149- -00000-0000

Fecha: 2007-11-21 16:08:25 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 206

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FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

25 de 2007

1 SOLICITUD DE : X Patente de Invención X Capítulo I. Patente de Modelo de Utilidad Capítulo II.			
2 SOLICITANTE (71)		Nombre: WYETH Dirección: Five Giralda Farms, Madison, New Jersey 07940, Estados Unidos de América Nacionalidad o Domicilio: Nueva Jersey, Estados Unidos de América Lugar de Constitución: Delaware, Estados Unidos de América Teléfono: Fax: E-Mail IDENTIFICACION C.C. NIT C.E. Otro Cual Número	
3 REPRESENTANTE O APODERADO		Nombre: ALVARO CORREA ORDOÑEZ Dirección: Avenida 82 No.10-62 Piso 6 Teléfono: 634 1500 Fax: 376 2211 E-Mail: office.bogota@bakernet.com IDENTIFICACION C.C. X NIT C.E. Otro Cual Número 79.143.366 de Usaquén TP 20.281	
4 INVENTOR (ES) (72)		Nombre: CHEW, Warren; RABINDRAN, Sridhar Krishna; DISCAFANI-MARRO, Carolyn; MCGINNIS, John Patrick II; WISSNER, Allan y WANG, Youchu Dirección: 751 Querbes Avenue, Outremont, QC H2V 3W8, Canadá; 2 Pamela Drive, Chestnut Ridge, New York 10977, Estados Unidos de América; 8 Brookside Avenue, Cortlandt Manor, New York 10567, Estados Unidos de América; 6 Chaparral Road, Nanuet, New York 10954, Estados Unidos de América; 31 Word Avenue, Ardsley, New York 10502, Estados Unidos de América y 1050 Rue Goulet, #304, St. Laurent, Quebec H4R 2E1, Canadá, respectivamente Nacionalidad o Domicilio: Canadiense, Hindú, Estadounidense, Estadounidense, Estadounidense y Canadiense, respectivamente	
5 PCT (85) Solicitud Internacional No. PCT/US2006/015931 Fecha 26-ABR-06 Publicación Internacional No. WO/2006/127203 Fecha 30-NOV-06			
6 Título (54) MÉTODOS PARA SINTETIZAR DERIVADOS DE 6-ALQUILAMINOQUINOLINA			
7 Clasificación Internacional (51) C07D 215/44, C07C 271/22, C07D 403/12			
8 Prioridad SI X NO		(33) País de Origen US	(32) Fecha 25-MAY-05
(31) Número de Solicitud 60/685,040			
9 Comprobante de pago No. 07-86111 Fecha 19-OCT-07			

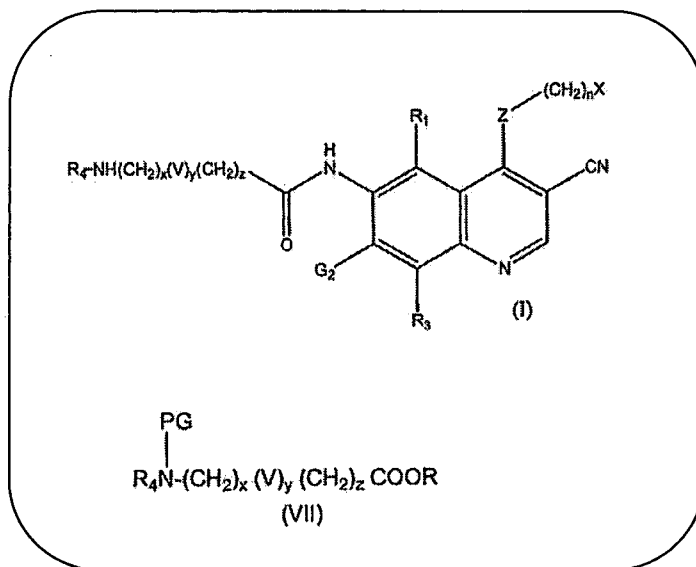
10

ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud
- ☒ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica
- ☒ Poderes, si fuere el caso
- ☒ Documento de cesión del inventor al solicitante o a su causante
- ☐ Declaraciones
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☐ Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen preliminar (IPEA)
- ☐ Traducción del examen preliminar internacional efectuado por la IPEA
- ☐ De ser el caso, copia del contrato de acceso
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas
- ☐ De ser el caso, certificado de depósito del material biológico
- ☐ Arte final 12 x 12
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud
- ☐ De ser el caso, modificaciones efectuadas a la solicitud internacional.
- ☒ Otros: Extractos, Reporte de Búsqueda Internacional y Opinión escrita, notificación de corrección de nombre de inventor y notificación de presentación de documento de prioridad.

11

FIGURA CARATERISTICA



12

Solicito la concesión de la patente,

NOMBRE: ALVARO CORREA ORDOÑEZ

FIRMA:

C.C. 79.143.366 de Usaquén

T.P. 20.281

Instrucciones para la presentación de los anexos, ver reverso de esta página

000003

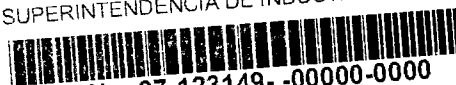
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-123149- -00000-0000

Fecha: 2007-11-21 16:08:25

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Tra. 11 PATENTEIYII

Eve: 378 FASENACIONALI

Act. 411 PRESENTACION

Folios: 206

RECIBO OFICIAL DE CAJA : 07 - 86,111
FECHA : OCTUBRE 19 DE 2007

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
RAISBECK LARA RODRIGUEZ	CONSIGNACION	BANCO POPULAR	050-00110-6	55866787	19/10/2007	50,312,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01	SOLICITUDES	
		1 TRAMITES DE SOL. DE PATENTE DE IN	482,000.00
		TOTAL :	\$ 482,000.00

SON: CUATROCIENTOS OCHENTA Y DOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

Traducción oficial del ingles por Marlén Neira Castro, resolución 2117 del Min-Justicia de Colombia

APOSTILLA EN PODER DE ABOGADO DE WYETH.

En inglés

APOSTILLA

(Convención De La Haya del 5 octubre de 1961)

1. País: Estados Unidos de América
2. Este documento Público ha sido firmado por Michelle L. MC Gowan
3. Quien ejerce funciones de notario público, estado de Nueva Jersey
4. Lleva el sello de Michelle L. MC Gowan, notario público

CERTIFICADO

5. En Trenton, Nueva Jersey
6. El 1 de mayo de 2007.
7. Por Bradley Abelow , tesorero de Nueva Jersey
8. No. A290281
9. Sello del estado de Nueva Jersey
10. Firma legible de Bradley Abelow

PODER DE REPRESENTACION

Bilingüe ingles y español de WYETH, en relación a la solicitud de patente:
"Metodos para sintetizar derivados de 6- alquilaminoquinolina".

Firmado el 25 de abril de 2007 por William H. Calnan el sub-secretario

CERTIFICADO NOTARIAL

Bilingüe ingles y español certificando funciones de William H. Calnan como sub-secretario de WYETH, compañía con sede en Estados Unidos.

Firmado por Michelle L. McGowan. Notario público

Estado de Nueva Jersey.

No. 2108903.

Calificada en el condado Morris

Sus funciones vencen el 9 de febrero de 2011.


MARLEN NEIRA CASTRO
Traductor e Intérprete Oficial
Inglés - Español - Inglés

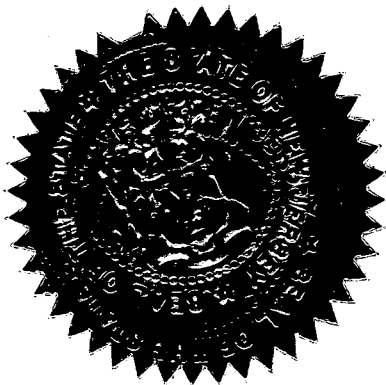
APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA
2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
MICHELLE L MC GOWAN
3. ACTING IN THE CAPACITY OF:
NOTARY PUBLIC OF NEW JERSEY
4. BEARS THE SEAL/STAMP OF:
MICHELLE L MC GOWAN, NOTARY

CERTIFIED

5. AT TRENTON, NEW JERSEY
6. THE 1ST DAY OF MAY 2007
7. BY: Bradley Abelow, NEW JERSEY TREASURER
8. NO. A290281
9. SEAL/STAMP:
10. SIGNATURE

*Bradley Abelow*

Raisbeck, Lara, Rodríguez & Rueda
Av. 82 No. 10 - 62 6th Floor
Bogotá, Colombia

NIT: 860.068.840-3
Tel: +57 1 634 1500
Fax: +57 1 376 2211
www.bakernet.com

POWER OF ATTORNEY

The undersigned.

WYETH

with offices at

Five Giralda Farms, Madison, NJ 07940,
United States of America

declares that it hereby grants to

**ALVARO CORREA-ORDOÑEZ and/or
OLGA GEORGETTE OTERO and/or
RICARDO METKE and/or
JUAN PABLO CONCHA**

all members of the law firm Raisbeck, Lara, Rodriguez & Rueda, with domicile at Av. 82 No. 10 - 62, 6Th floor, of Bogotá D. C., Colombia, and for so long as they remain members of the law firm, a full and sufficient power of attorney with respect to Colombian patent application(s) based on PCT/US2006/015931 and entitled "METHODS OF SYNTHESIZING 6-ALKYLAMINOQUINOLINE DERIVATIVES" and to obtain patent protection thereof, for which purpose I (we) authorize the said attorneys to represent me (us) before any authorities or persons, with or without jurisdiction, specially those administrative, administrative contentious and judicial, as well as before Arbitration Court, in all matters concerning the following: a) Obtainment of a patent(s) based upon said patent application(s), including filing of assignments, change of name or address, voluntary cancellation; and defending oppositions, cancellations, nullity, writ mandamus, and in general the civil, penal, an administrative processes relating to those rights.

I hereby ratify all lawful actions previously taken on behalf of this company by the aforementioned attorneys with respect to the mentioned matters.

Done and subscribed in

On the 25th day of April 2007

Signature of the person issuing the Power

WYETH


William H. Calnan
Assistant Secretary

PODER DE ABOGADO

La abajo firmada,

WYETH

con oficinas en

Five Giralda Farms, Madison, NJ 07940,
Estados Unidos de América

declara por el presente que otorga a

**ALVARO CORREA-ORDOÑEZ y/o
OLGA GEORGETTE OTERO y/o
RICARDO METKE y/o
JUAN PABLO CONCHA**

Todos miembros de la firma de abogados Raisbeck, Lara, Rodríguez & Rueda, con domicilio en la Av. 82 No. 10 - 62 Piso 6 en Bogotá D. C., Colombia, y hasta tanto ellos continúen siendo miembros de la firma, poder especial amplio y suficiente con respecto a la solicitud(es) de patente en Colombia basada(s) en PCT/US2006/015931 y titulada "MÉTODOS PARA SINTETIZAR DERIVADOS DE 6-ALQUILAMINOQUINOLINA"

y para obtener la protección de patente de la misma, a cuyo efecto autorizo (amos) a los dichos apoderados para que me (nos) representen ante cualesquiera autoridades o personas, ejerzan o no jurisdicción, especialmente ante las del orden administrativo, contencioso-administrativo y judicial, así como los tribunales de arbitramento, en todo lo concerniente a los siguientes asuntos: a) Obtención de la(s) patente(s) de invención basada(s) en la mencionada solicitud de patente, incluyendo presentación de traspasos, cambio de nombre o dirección, cancelación voluntaria; y defensa en oposiciones, cancelaciones, nulidades, la tutela, y en general procesos civiles, penales, administrativos relacionados con estos derechos.

Igualmente, ratifico todo lo actuado en derecho hasta el momento en nombre de esta compañía por cualquiera de los mencionados apoderados en los casos mencionados.

Dado y firmado en

A los 25 días del mes de april de 2007

Firma de la persona que firma el Poder

NOTARIAL CERTIFICATION

On this 25th day of April

2007, the undersigned Notary

CERTIFIES

1. That **William H. Calnan**

set his hand on the foregoing document.

2. That the grantor is to me personally known and that he/she has legal capacity to execute the instrument.

3. That the grantor has executed the foregoing document as

Assistant Secretary

of the judicial person **WYETH**

4. That the judicial person **WYETH** having its home office in

Five Giralda Farms, Madison, NJ 07940,
United States of America

is duly organized, has present legal existence and that the purposes for which the power of attorney is granted are within the scope of its corporate purposes.

5. That the grantor has in fact the referred to authority and that his/her representation is legal.

6. That I have based certifications 3, 4 and 5 above on the following authentic documents for such purpose exhibited to me and which I mention specifically, giving their dates and their origin or source:

Minutes of the Board of Directors Meeting held on April 26, 2006.

CERTIFICACION NOTARIAL

A los 25 días del mes de abril

de 2007, el suscrito Notario

- 1 Que **William H. Calnan** ^{DA FE}

suscribió de su puño y letra el documento que antecede.

2. Que conozco al otorgante y que éste tiene capacidad legal para el otorgamiento.

- 3 Que el otorgante ha suscrito el referido documento en su carácter de

Subsecretario

de la persona jurídica **WYETH**

- 4 Que la persona jurídica **WYETH** con sede en

Five Giralda Farms, Madison, NJ 07940,
Estados Unidos de América

está legalmente constituida, que tiene existencia legal actual y que el acto para el cual se otorga el poder está comprendido entre los que constituyen su objeto social.

- 5 Que el otorgante tiene efectivamente la representación que ostenta y que ésta es legítima.

6. Que he basado las certificaciones 3, 4 y 5 anteriores en los siguientes documentos auténticos que al efecto se me exhibieron y que menciono específicamente con expresión de sus fechas y de su origen o procedencia:

Actas de la reunión de Junta Directiva celebrada el 26 de abril de 2006.

Michelle L. McGowan
Notary Public

MICHELLE L. McGOWAN
Notary Public, State of New Jersey
No. 2108903
Qualified in Morris County
Commission Expires Feb. 9, 2011

El Notario Público

TRADUCCIÓN OFICIAL N° 2011072 al español de un documento escrito en inglés, efectuada por Jaime Armando Garavito Burgos, c.c. N° 19.130.702 de Bogotá, Traductor e Intérprete Oficial inglés-español-inglés según Resolución N° 034 de enero 11 de 1983 expedida por el Ministerio de Justicia de la República de Colombia

**DECLARACIÓN JURAMENTADA SOBRE CESIÓN A WYETH
MÉTODOS PARA SISNTETIZAR DERIVADOS DE 6-ALQUILAMINOQUINOLINA.**

APOSTILLA

1. PAÍS: ESTADOS UNIDOS DE AMÉRICA
2. ESTE DOCUMENTO PÚBLICO HA SIDO FIRMADO POR:
BARBARA A. KIELY
3. QUIEN ACTÚA EN CALIDAD DE:
NOTARIO PÚBLICO DE NUEVA JERSEY
4. LLEVA EL SELLO DE:
BARBARA A. KIELY, NOTARIO

CERTIFICADO

Jaime A. Garavito B.
JAIME A. GARAVITO B.
TRADUCTOR E INTERPRETE OFICIAL
Des 034 de Enero 11 de 1983
MINISTERIO DE JUSTICIA

5. EN TRENTON, NUEVA JERSEY
6. EL DÍA 07 DE NOVIEMBRE DE 2007
7. POR: Michellene Davis, TESORERO DE NUEVA JERSEY
8. N° A308261
9. SELLO (APARECE ADHERIDO SELLO DORADO)
10. FIRMA (Firma ilegible)

AM101422L

DECLARACIÓN JURAMENTADA

Yo, Michelle L. McGowan, Asociado de Legalizaciones de Wyeth, por medio del presente certifico que la copia anexa ha sido comparada con la Cesión original (para U.S.S.N. 60/685.040, y cualquier equivalente legal de la

nnnnn

Fechada hoy 29 de octubre de 2007 en Madison, Nueva Jersey, Estados Unidos de América.

PARA SER USADA EN COLOMBIA


JAIME A. GARAVITO B
 TRADUCTOR E INTERPRETE OFICIAL
 Dec 034 de Enero 11 de 1983
 MINISTERIO DE JUSTICIA

Hoy 29 de octubre de 2007, compareció personalmente ante mí Michelle L. McGowan, Asociado de Legalizaciones de Wyeth, a quien conozco como la persona descrita en el anterior instrumento y quien suscribió el mismo y reconoció haberlo suscrito.

[Sello en tinta que dice: "Barbara A. Kiely ID. 33893, Notario Público de Nueva Jersey. Mi comisión vence el 20 de junio de 2009"]

2

TRADUCCIÓN OFICIAL N° 2011072 al español de un documento escrito en inglés, efectuada por Jaime Armando Garavito Burgos, c.c. N° 19.130.702 de Bogotá, Traductor e Intérprete Oficial inglés-español-inglés según Resolución N° 034 de enero 11 de 1983 expedida por el Ministerio de Justicia de la República de Colombia

[De aquí en adelante aparece en el encabezamiento de cada página: "Patente" y en el pie de página: "Cesión de Invención; Solicitud Provisional"]

Cesión de Invención

En consideración del pago por la CESIONARIA a la CEDENTE de una contraprestación válida y suficiente cuyo recibo se acusa por medio del presente, los CEDENTES:

- (1) Nombre Completo del Inventor: Warren CHEW
Residencia: 751 Querves Avenue, Outremont, QC H2V 3W8 Canada
Ciudadanía: Canadá
- (2) Nombre Completo del Inventor: Youchu WANG
Residencia: 1100 rue Goulet, Apt. 101, St. Laurent, QC H4R 2C6 Canada
Ciudadanía: Canadá
- (3) Nombre Completo del Inventor: Sridhar Krishna RABINDRAN
Residencia: 2 Pamela Drive, Chestnut Ridge, NY 10977
Ciudadanía: India
- (4) Nombre Completo del Inventor: Carolyn DISCAFANI-MARRO
Residencia: 8 Brookside Avenue, Cortland Manor, NY 10567
Ciudadanía: Estados Unidos de América
- (5) Nombre Completo del Inventor: John Patrick MCGINNISS II
Residencia: 1191 Washington Green, New Windsor NY 12553
Ciudadanía: Estados Unidos de América
- (6) Nombre Completo del Inventor: Allan WISSNER
Residencia: 31 Wood Avenue, Ardsley, NY 10502
Ciudadanía: Estados Unidos de América

Jaime A. Garavito B.
JAIME A. GARAVITO B.
TRADUCTOR E INTERPRETE OFICIAL
Res. 034 de Enero 11 de 1983
MINISTERIO DE JUSTICIA

por medio del presente venden, ceden y transfieren a la CESIONARIA:

Wyeth
Five Giralda Farms
Madison, New Jersey 07940

y los sucesores, cesionarios y representantes legales de la CESIONARIA, la totalidad del derecho, título e intereses para los Estados Unidos y sus

TRADUCCIÓN OFICIAL N° 2011072 al español de un documento escrito en inglés, efectuada por Jaime Armando Garavito Burgos, c.c. N° 19.130.702 de Bogotá, Traductor e Intérprete Oficial inglés-español-inglés según Resolución N° 034 de enero 11 de 1983 expedida por el Ministerio de Justicia de la República de Colombia

posesiones territoriales y en todos los países extranjeros, incluyendo todos los derechos a reivindicar prioridad con respecto a la invención titulada: **MÉTODOS PARA SISNTETIZAR DERIVADOS DE 6-ALQUILAMINOQUINOLINA.**

e inventada por los CEDENTES y cualesquier inventores adicionales, si los hubiere:

la cual se encuentra en la Solicitud Internacional de Patente N° 60/685.040 presentada el 25 de mayo de 2005

[] Yo/nosotros los CEDENTES que abajo firmamos, por medio del presente autorizamos y solicitamos se inserte arriba el número de la solicitud y la fecha de presentación cuando se conozcan,

[Verificar si también se está(n) cediendo solicitud(es) extranjera(s)]

[X] y cualquier equivalente legal de la misma en un país extranjero]


JAIME A. GARAVITO B
TRADUCTOR E INTÉRPRETE OFICIAL
DEL 034 de Enero 11 de 1983
MINISTERIO DE JUSTICIA

Incluyendo el derecho a invocar prioridad, incluyendo todas y cada una de las mejoras divulgadas en la misma y en todas las patentes que se obtengan para la mencionada invención a través de la anterior solicitud y cualquier solicitud provisional, no provisional, continuación, divisional, renovación o sustitución de la misma presentada posteriormente y en cuanto a la patente, cualquier re-expedición o nuevo examen de la misma.

Los CEDENTES por medio del presente acuerdan que no se ha hecho ni se hará o suscribirá ninguna cesión, venta, acuerdo o gravamen que pueda estar en conflicto con esta cesión.

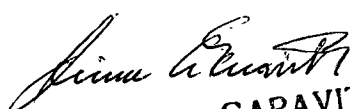
Los CEDENTES autorizan a la CESIONARIA para que haga solicitudes y para que reciban patentes para la mencionada invención en cualquiera de los

TRADUCCIÓN OFICIAL N° 2011072 al español de un documento escrito en inglés, efectuada por Jaime Armando Garavito Burgos, c.c. N° 19.130.702 de Bogotá, Traductor e Intérprete Oficial inglés-español-inglés según Resolución N° 034 de enero 11 de 1983 expedida por el Ministerio de Justicia de la República de Colombia

mencionados países en su propio nombre, o en el nombre de los CEDENTES o a su elección.

Los CEDENTES acuerdan suscribir u obtener cualquier seguridad adicional necesaria del título a dicha invención y cualquier patente que pueda ser expedida para la misma y a entregar en cualquier momento y a solicitud y expensas de la CESIONARIA cualquier testimonio en cualquier derecho preexistente que impida el patentamiento de la invención, litigio o procedimiento relacionado y a suscribir todos los documentos que puedan ser necesarios o convenientes para perfeccionar el título a dicho invento o cualquier patente que pueda ser otorgada para el mismo a la CESIONARIA, sus sucesores, CESIONARIOS u otros representantes legales y a suscribir, en cualquier momento, a solicitud y expensas de la CESIONARIA, cualquier continuación, continuación parcial, divisional, renovación o sustitución de la misma y en cuanto a patentes a re-expedir o re-examinar las mismas, o cualesquier otras solicitudes adicionales de patentes para dicho invento o cualquier parte del mismo, todas las cuales y cualquier patente que se expida se ceden por medio del presente a la CESIONARIA y prestará todos los juramentos legales o declaraciones y hará todos los actos legales requeridos para adquirirlos, sin compensación adicional, pero a expensas de la CESIONARIA, sus sucesores, cesionarios u otros representantes legales.

Los CEDENTES autorizan y solicitan al Comisionado de Patentes expedir todas y cada una de las patentes de los Estados Unidos para la mencionada invención, que resulte de cualquiera de las solicitudes a su CESIONARIA.


JAIME A. GARAVITO B.
TRADUCTOR E INTERPRETE OFICIAL
Res 034 de Enero 11 de 1983
MINISTERIO DE JUSTICIA

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(Firma ilegible)
Warren CHEW

Junio 10, 2005
Fecha

RECONOCIMIENTO

Estado de Canadá)
) Declaración juramentada
Condado de Quebec)

El día 10 de junio de 2005, Warren CHEW, compareció personalmente ante mí, a quien conozco como la persona descrita en el anterior instrumento y quien suscribió el mismo y reconoció haberlo suscrito en forma libre y espontánea para los fines consignados en él.

[Firmado] Line Martin, Notario Público
Mi comisión es vitalicia

(Firma ilegible)
Youchu WANG

Junio 10, 2005
Fecha

RECONOCIMIENTO

Estado de Canadá)
) Declaración juramentada
Condado de Quebec)

El día 10 de junio de 2005, Youchu WANG, compareció personalmente ante mí, a quien conozco como la persona descrita en el anterior instrumento y quien suscribió el mismo y reconoció haberlo suscrito en forma libre y espontánea para los fines consignados en él.

[Firmado] Line Martin, Notario Público
Mi comisión es vitalicia

TRADUCCIÓN OFICIAL N° 2011072 al español de un documento escrito en inglés, efectuada por Jaime Armando Garavito Burgos, c.c. N° 19.130.702 de Bogotá, Traductor e Intérprete Oficial inglés-español-inglés según Resolución N° 034 de enero 11 de 1983 expedida por el Ministerio de Justicia de la República de Colombia

(Firma ilegible)
Sridhar Krishna RABINDRAN

Junio 7, 2005
Fecha

RECONOCIMIENTO

Estado de Nueva York)
) Declaración juramentada
Condado de Rockland)

El día 07 de junio de 2005, Sridhar Krishna RABINDRAN, compareció personalmente ante mí, a quien conozco como la persona descrita en el anterior instrumento y quien suscribió el mismo y reconoció haberlo suscrito en forma libre y espontánea para los fines consignados en él.

[Firmado] Janice A. White, Notario Público

[Sello en tinta que dice: "Janice A. White. Notario Público. Estado de Nueva York. N° 01-WH6052604. Calificado en el Condado de Rockland. Mi comisión vence el 26 de diciembre de 2006"]

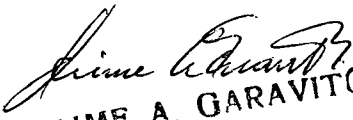
(Firma ilegible)
Carolyn DISCAFANI-MARRO

Junio 16, 2005
Fecha

RECONOCIMIENTO

Estado de Nueva York)
) Declaración juramentada
Condado de Rockland)

El día 16 de junio de 2005, Carolyn DISCAFANI-MARRO, compareció personalmente ante mí, a quien conozco como la persona descrita en el anterior instrumento y quien suscribió el mismo y reconoció haberlo suscrito en forma libre y espontánea para los fines consignados en él.


JAIME A. GARAVITO B
TRADUCTOR E INTERPRETE OFICIAL
RES. 034 de Enero 11 de 1983
MINISTERIO DE JUSTICIA

00015

N° 01-WH6052604. Calificado en el Condado de Rockland. Mi comisión vence el 26 de diciembre de 2006”]

Junio 08, 2005
Fecha

Estado de Nueva York)
)
Condado de Rockland) Declaración juramentada

[Sello en tinta que dice: "ROSEANN D. JASTROW. No. 01JA6085816. Calificado en el Condado de Rockland. Mi comisión vence el 06 de enero de 20__"]

Junio 07, 2005
Fecha

Estado de Nueva York)
)
Condado de Rockland) Declaración juramentada

8

TRADUCCIÓN OFICIAL N° 2011072 al español de un documento escrito en inglés, efectuada por Jaime Armando Garavito Burgos, c.c. N° 19.130.702 de Bogotá, Traductor e Intérprete Oficial inglés-español-inglés según Resolución N° 034 de enero 11 de 1983 expedida por el Ministerio de Justicia de la República de Colombia

El día 07 de junio de 2005, Allan WISSNER, compareció personalmente ante mí, a quien conozco como la persona descrita en el anterior instrumento y quien suscribió el mismo y reconoció haberlo suscrito en forma libre y espontánea para los fines consignados en él.

[Firmado] Rose Ann D. Jastrow

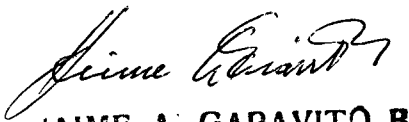
[Sello en tinta que dice: "ROSEANN D. JASTROW. No. 01JA6085816. Calificado en el Condado de Rockland. Mi comisión vence el 06 de enero de 2007"]

La anterior es traducción fiel y completa de la cual se deja copia en esta oficina para su confrontación.



Jaime Armando Garavito Burgos
c.c. N° 19.130.702 de Bogotá
Traductor e Intérprete Oficial según Resolución N° 034 de enero 11 de 1983 expedida por el Ministerio de Justicia

BOGDM5 # 95446


JAIME A. GARAVITO B
TRADUCTOR E INTERPRETE OFICIAL
 RES. 034 de Enero 11 de 1983
 MINISTERIO DE JUSTICIA

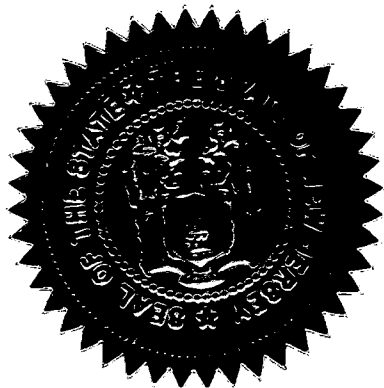
APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA
2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
BARBARA A KIELY
3. ACTING IN THE CAPACITY OF:
NOTARY PUBLIC OF NEW JERSEY
4. BEARS THE SEAL/STAMP OF:
BARBARA A KIELY, NOTARY

CERTIFIED

5. AT TRENTON, NEW JERSEY
6. THE 7TH DAY OF NOVEMBER 2007
7. BY: Michellene Davis, NEW JERSEY TREASURER
8. NO. A308261
9. SEAL/STAMP:
10. SIGNATURE



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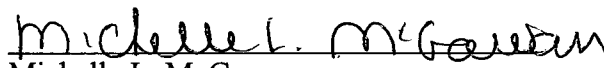
AM101422L

AFFIDAVIT

I, Michelle L. McGowan, Legalization Associate, Wyeth, do hereby certify that the attached copy has been compared with the original Assignment (for U.S.S.N. 60/685,040, and any legal equivalent thereof in a foreign country, for the invention entitled: "METHODS OF SYNTHESIZING 6-ALKYLAMINOQUINOLINE DERIVATIVES") dated June 7, 2005 from Sridhar Krishna Rabindran and Allan Wissner; and dated June 8, 2005 from John Patrick McGinniss II; and dated June 10, 2005 from Warren Chew and Youchu Wang; and dated June 16, 2005 from Carolyn Discafani-Marro to Wyeth and that the said copy is a true copy of the original.

Dated this 29th day of October, 2007, at Madison, New Jersey, United States of America.

Wyeth


Michelle L. McGowan
Legalization Associate

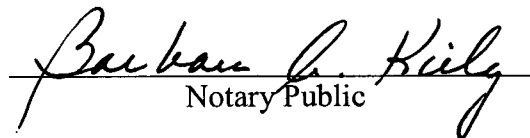
TO BE USED IN COLOMBIA

ACKNOWLEDGMENT

State of New Jersey)
)
County of Morris)

On this 29th day of October, 2007, before me personally appeared Michelle L. McGowan, Legalization Associate of Wyeth, to me known and known to me to be the individual described in and who executed the foregoing instrument, and he acknowledged to me that he executed the same.

Barbara A. Kiely ID. 33893
Notary Public of New Jersey
My Commission Expires June 20, 2009


Notary Public

Assignment of Invention

000019

In consideration of the payment by ASSIGNEE to ASSIGNOR of good and valuable consideration, the receipt of which is hereby acknowledged,
ASSIGNOR:

- (1) Full Name of Inventor: Warren CHEW
Residence: 751 Querbes Avenue, Outremont, QC H2V 3W8 Canada
Citizenship: Canada
-
- (2) Full Name of Inventor: Yochu WANG
Residence: 1100 rue Goulet, Apt. 101, St. Laurent, QC H4R 2C6 Canada
Citizenship: Canada
-
- (3) Full Name of Inventor: Sridhar Krishna RABINDRAN
Residence: 2 Pamela Drive, Chestnut Ridge, NY 10977
Citizenship: India
-
- (4) Full Name of Inventor: Carolyn DISCAFANI-MARRO
Residence: 8 Brookside Avenue, Cortland Manor, NY 10567
Citizenship: United States of America
-
- (5) Full Name of Inventor: John Patrick MCGINNIS II
Residence: ~~6 Chaparral Road, Nanuet, NY 10954~~ 1191 Washington Green, New Windsor
Citizenship: United States of America
NY 12553
-
- (6) Full Name of Inventor: Allan WISSNER
Residence: 31 Wood Avenue, Ardsley, NY 10502
Citizenship: United States of America
-

hereby sells, assigns and transfers to ASSIGNEE:

Wyeth
Five Giralda Farms
Madison, New Jersey 07940

and the successors, assigns and legal representatives of the ASSIGNEE the entire right, title and interest for the United States and its territorial possessions and in all foreign countries, including all rights to claim priority, in and to the invention entitled:

METHODS OF SYNTHESIZING 6-ALKYLAMINOQUINOLINE DERIVATIVES

and invented by ASSIGNOR and the following additional inventors, if any:

and which is found in U.S. Provisional Application No. 60/685,040 filed on: May 25, 2005

☐ I/we the ASSIGNOR signing below, hereby authorize and request insertion above of the application number and filing date, when they become known,

[also check if foreign application(s) is(are) also being assigned]

☒ and any legal equivalent thereof in a foreign country,

including the right to claim priority, including any and all improvements disclosed therein, and in and to all Letters Patent to be obtained for said invention by the above application or any subsequently filed provisional, nonprovisional, continuation, divisional, renewal, or substitute thereof, and as to Letters Patent any reissue or re-examination thereof.

ASSIGNOR hereby covenants that no assignment, sale, agreement or encumbrance has been or will be made or entered into which would conflict with this assignment.

ASSIGNOR authorizes ASSIGNEE to make applications for and to receive Letters patent for said invention in any of said countries in its own name, or in ASSIGNOR's name, at its election.

ASSIGNOR covenants and agrees to execute or procure any further necessary assurance of the title to said invention and any Letters Patent which may issue therefore and to, at any time, upon the request and at the expense of ASSIGNEE deliver any testimony in any interference, litigation or proceeding related thereto and execute all papers that may be necessary or desirable to perfect the title to said invention or any Letters Patent which may be granted therefore in ASSIGNEE, its successors, assigns or other legal representatives, and that to, at any time, upon the request and at the expense of ASSIGNEE execute any continuation, continuation-in-part, divisional, renewal or substitute thereof, and as to Letters Patent and reissue or re-examination thereof, or any other additional applications of Letters Patent for said invention or any part thereof, all of which applications and any Letters Patent issuing thereon are hereby assigned to ASSIGNEE, and will make all rightful oaths or declarations, and do all lawful acts requisite for procuring the same therein, without further compensation, but at the expense of ASSIGNEE, its successors, assigns or other legal representatives.

ASSIGNOR authorizes and requests the Commissioner of Patents to issue any and all Letters Patent of the United States for said invention, resulting from any of the aforesaid applications to its ASSIGNEE.

10-JUNE-2005
Date

State of Canada } ss:
County of Quebec }

On the 10th day of June 2005, Warren CHEW personally appeared before me, known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he/she executed the same, of his/her own free will and for the purposes set forth.

Notary Public
LIVE ^{STARTING} MY COMMISSION IS ^{NOTARY} FOR LIFE


Youchu WANG

Date 10-Jun-2005

State of Canada } ss:
County of Quebec }

On the 10th day of June 2005, Youchu WANG personally appeared before me, known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he/she executed the same, of his/her own free will and for the purposes set forth.

Leech
Notary Public
LINE MARTIN NOTARY
my commission is for 1/2

June 7, 2005
Date

State of New York }
County of Rockland }

JANICE A. WHITE
NOTARY PUBLIC - STATE OF NEW YORK
NO. 01-WH6052604
QUALIFIED IN ROCKLAND COUNTY
MY COMMISSION EXPIRES 12-26-20 06



Notary Public

Carolyn DISCAFANI-MARRO

6/16/05
Date

State of New York }
County of Rockland } ss:

JANICE A. WHITE
NOTARY PUBLIC - STATE OF NEW YORK
NO. 01-WH8052604
QUALIFIED IN ROCKLAND COUNTY
MY COMMISSION EXPIRES 12-26-2016

Janice L. Skita
Notary Public

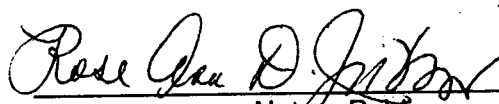
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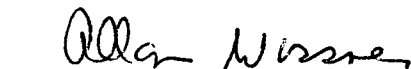

 John Patrick MCGINNIS II

 6/8/05
 Date
ACKNOWLEDGMENT
 State of New York }
 County of Rockland } ss:

On the 8th day of June 2005, John Patrick MCGINNIS II personally appeared before me, known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he/she executed the same, of his/her own free will and for the purposes set forth.

ROSEANN D. JASTROW
 NO. 01JA6086816
 QUALIFIED IN ROCKLAND COUNTY
 MY COMMISSION EXPIRES 01-06-20__

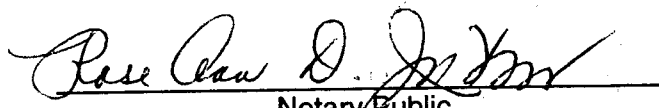

 Notary Public


 Allan WISSNER

 June 7 2005
 Date
ACKNOWLEDGMENT
 State of New York }
 County of Rockland } ss:

On the 7th day of June 2005, Allan WISSNER personally appeared before me, known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he/she executed the same, of his/her own free will and for the purposes set forth.

ROSEANN D. JASTROW
 NO. 01JA6086816
 QUALIFIED IN ROCKLAND COUNTY
 MY COMMISSION EXPIRES 01-06-20 07


 Notary Public

00024

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

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
30 November 2006 (30.11.2006)

PCT

(10) International Publication Number
WO 2006/127203 A3

- (51) International Patent Classification:
C07D 215/44 (2006.01) C07C 271/22 (2006.01)
C07D 403/12 (2006.01)
- (21) International Application Number:
PCT/US2006/015931
- (22) International Filing Date: 26 April 2006 (26.04.2006)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
60/685,040 25 May 2005 (25.05.2005) US
- (71) Applicant (for all designated States except US): **WYETH** [US/US]; Five Giralda Farms, Madison, New Jersey 07940 (US).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): **CHEW, Warren** [CA/CA]; 751 Querbes Avenue, Outremont, QC H2V 3W8 (CA). **RABINDRAN, Sridhar, Krishna** [IN/US]; 2 Pamela Drive, Chestnut Ridge, New York 10977 (US). **DISCAFANI-MARRO, Caroyln** [US/US]; 8 Brookside Avenue, Cortlandt Manor, New York 10567 (US). **MCGINNIS, John, Patrick, III** [US/US]; 6 Chaparral Road, Nanuet, New York 10954 (US). **WISSNER, Allan** [US/US]; 31 Word Avenue, Ardsley, New York 10502 (US). **WANG, Youchu** [CA/CA]; 1050 Rue Goulet, #304, St. Laurent, Quebec H4R 2E1 (CA).

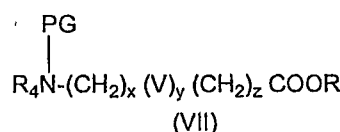
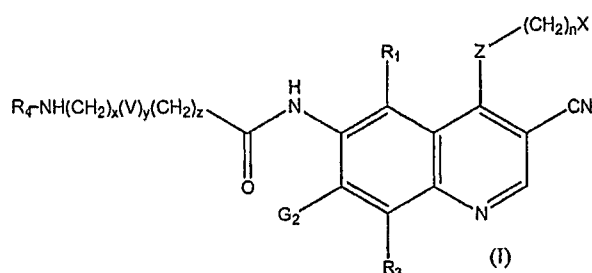
- (74) Agent: **MANDRA, Raymond, R.**; FITZPATRICK, CELLA, HARPER & SCINTO, 30 Rockefeller Plaza, New York, NY 10112-3801 (US).
- (81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— with international search report
— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(88) Date of publication of the international search report:
3 May 2007

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

(54) Title: METHODS OF SYNTHESIZING 6-ALKYLAMINOQUINOLINE DERIVATIVES



(57) Abstract: The present invention is directed to a method of synthesizing compounds of formula (I), wherein X, Z, V, R₁, R₃, R₄, G₂, n, x, y, and z are defined herein. This invention also includes a method of preparing acid compounds of formula (VII), wherein R is H, and R₄, x, y, and z are as defined herein and PG is a protecting group. This invention is also directed to (E) N-[4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl]-4-(methylamino)-2-butenamide, compositions containing it and methods of using the to treat cancer.

WO 2006/127203 A3

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

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
30 November 2006 (30.11.2006)

PCT

(10) International Publication Number
WO 2006/127203 A2

(51) International Patent Classification:
C07D 215/44 (2006.01) C07C 271/22 (2006.01)
C07D 403/12 (2006.01)

(74) Agent: MANDRA, Raymond, R.; FITZPATRICK,
CELLA, HARPER & SCINTO, 30 Rockefeller Plaza,
New York, NY 10112-3801 (US).

(21) International Application Number:
PCT/US2006/015931

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

(22) International Filing Date: 26 April 2006 (26.04.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/685,040 25 May 2005 (25.05.2005) US

(71) Applicant (for all designated States except US): WYETH
[US/US]; Five Giralda Farms, Madison, New Jersey 07940
(US).

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ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,
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RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA,
GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(72) Inventors; and

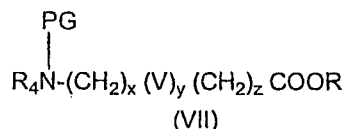
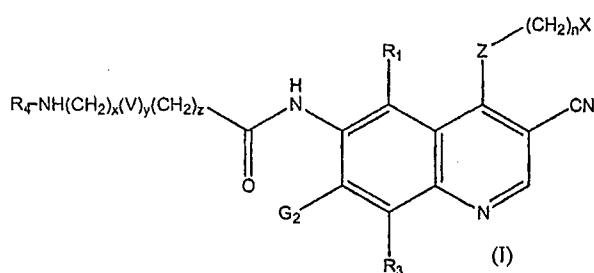
(75) Inventors/Applicants (for US only): CHEW, Warren
[CA/CA]; 751 Querbes Avenue, Outremont, QC H2V
3W8 (CA). RABINDRAN, Sridhar, Krishna [IN/US];
2 Pamela Drive, Chestnut Ridge, New York 10977 (US).
DISCAFANI-MARRO, Caroyln [US/US]; 8 Brook-
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MCGINNIS, John, Patrick, III [US/US]; 6 Chaparral
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[US/US]; 31 Word Avenue, Ardsley, New York 10502
(US). WANG, Youchu [CA/CA]; 1050 Rue Goulet, #304,
St. Laurent, Quebec H4R 2E1 (CA).

Published:

— without international search report and to be republished
upon receipt of that report

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(57) Abstract: The present invention is directed to a method
of synthesizing compounds of formula (I), wherein X, Z, V, R₁,
R₃, R₄, G₂, n, x, y, and z are defined herein. This invention
also includes a method of preparing acid compounds of
formula (VII), wherein R is H, and R₄, x, y, and z are as
defined herein and PG is a protecting group. This invention
is also directed to (E) N-[4-[3-chloro-4-(2-pyridinyl-
methoxy)anilino]-3-cyano-7-ethoxy-6-quinol-
inyl]-4-(methylamino)-2-butenamide, compositions
containing it and methods of using the to treat cancer.

- 1 -

TITLE

**METHODS OF SYNTHESIZING
6-ALKYLAMINOQUINOLINE DERIVATIVES**

BACKGROUND OF THE INVENTION

Field of the Invention

[0001] This invention is directed to a method of synthesizing a series of substituted quinolines, which are metabolites of EGFR and HER2 kinase inhibitors, and have use in the treatment of cancerous tumors.

Related Background Art

[0002] Protein kinases are a class of enzymes that catalyze the transfer of a phosphate group from ATP to a tyrosine, serine, threonine, or histidine residue located on a protein substrate, many of which play a role in normal cell growth. Correspondingly, several growth factor receptor proteins function as protein tyrosine kinases (PTKs) to effect signaling and are known as receptor tyrosine kinases (RTKs).

[0003] The RTKs comprise one of the larger families of PTKs and have diverse biological activity. At present, at least nineteen (19) distinct subfamilies of RTKs have been identified. One such subfamily is the "HER" family of RTKs, which

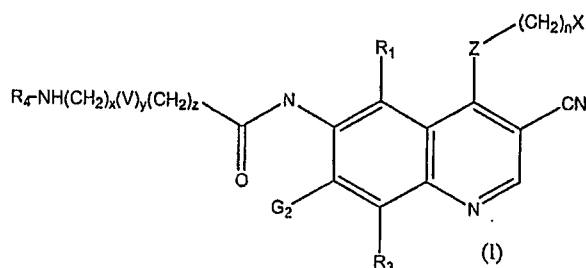
includes EGFR (epithelial growth factor receptor), HER2, HER3 and HER4. It has been shown that under certain conditions, as a result of either mutation or over expression, these RTKs can become deregulated; the result of which is uncontrolled cell proliferation which can lead to tumor growth and cancer [Wilks, A. F., Adv. Cancer Res., 60, 43 (1993) and Parsons, J. T.; Parsons, S. J., Important Advances in Oncology, DeVita, V. T. Ed., J. B. Lippincott Co., Phila., 3 (1993)]. For example, over expression of the receptor kinase product of the erbB-2 oncogene has been associated with human breast and ovarian cancers [Slamon, D. J. et al., Science, 244, 707 (1989) and Science, 235, 177 (1987)]. In addition, deregulation of EGF-R kinase has been associated with epidermoid tumors [Reiss, M., et al., Cancer Res., 51, 6254 (1991)], breast tumors [Macias, A. et al., Anticancer Res., 7, 459 (1987)], and tumors involving other major organs [Gullick, W. J., Brit. Med. Bull., 47, 87 (1991)]. RTK inhibitors, therefore have potential therapeutic value for the treatment of cancer and other diseases characterized by uncontrolled or abnormal cell growth. Accordingly, many recent studies have dealt with the development of specific RTK inhibitors as potential anti-cancer therapeutic agents [some recent reviews: Traxler, P., Exp. Opin. Ther. Patents, 8, 1599 (1998) and Bridges, A. J., Emerging Drugs, 3, 279 (1998)].

[0004] U.S. Patent Nos. 6,002,008, 6,288,082, and 6,297,258, all of Wissner et al., describe such PTK, and particularly, RTK inhibitor compounds. The compounds of the Wissner et al. patents are all substituted 3-cyanoquinolines. The 'des-alkyl' compounds synthesized by the present invention are metabolites of the EGFR kinase inhibitors and the HER2 kinase inhibitors disclosed in Wissner et al.

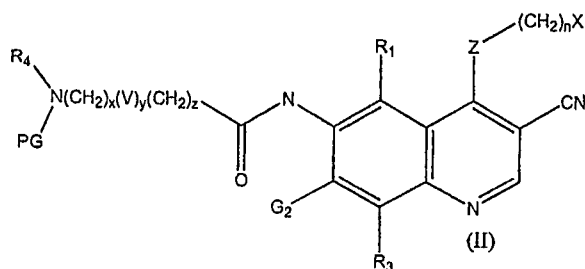
BRIEF SUMMARY OF THE INVENTION

[0005] The present invention is directed to a method of synthesizing compounds of formula (I):

- 3 -

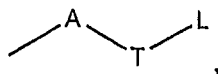


comprising the step of deprotecting a compound of formula (II):

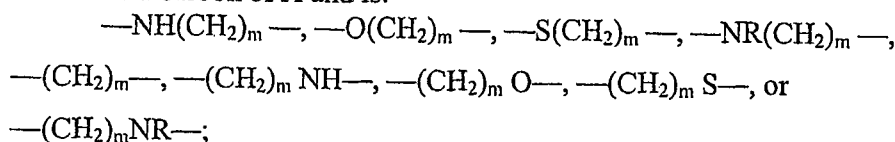


wherein X is cycloalkyl of 3 to 7 carbon atoms, which may be optionally substituted with one or more alkyl of 1 to 6 carbon atom groups; or is a pyridinyl, pyrimidinyl, or phenyl ring; wherein the pyridinyl, pyrimidinyl, or phenyl ring may be optionally mono- di-, or tri-substituted with a substituent selected from the group consisting of halogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, azido, hydroxyalkyl of 1-6 carbon atoms, halomethyl, alkoxymethyl of 2-7 carbon atoms, alkanoyloxymethyl of 2-7 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-6 carbon atoms, hydroxy, trifluoromethyl, cyano, nitro, carboxy, carboalkoxy of 2-7 carbon atoms, carboalkyl of 2-7 carbon atoms, phenoxy, phenyl, thiophenoxy, benzoyl, benzyl, amino, alkylamino of 1-6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, phenylamino, benzylamino, alkanoylamino of 1-6 carbon atoms, alkenoylamino of 3-8 carbon atoms, alkynoylamino of 3-8 carbon atoms, carboxyalkyl of 2-7 carbon atoms, carboalkoxyalkyl of 3-8 carbon atoms, aminoalkyl of 1-5 carbon atoms, N-alkylaminoalkyl of 2-9 carbon atoms, N,N-dialkylaminoalkyl of 3-10 carbon atoms, N-alkylaminoalkoxy of 2-9 carbon atoms, N,N-dialkylaminoalkoxy of 3-10 carbon atoms, mercapto, and benzoylamino; or X is a bicyclic aryl or bicyclic heteroaryl ring system of 8 to 12 atoms where the bicyclic heteroaryl ring contains 1 to 4 heteroatoms selected from N, O, and S with the proviso that the bicyclic heteroaryl ring does not contain O—O, S—S, or S—O bonds and where the bicyclic aryl or bicyclic heteroaryl ring may be optionally mono- di-, tri-, or tetra-substituted with a substituent selected from the group consisting of halogen, oxo, thio, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, azido, hydroxyalkyl of 1-6 carbon atoms, halomethyl, alkoxymethyl of 2-7 carbon atoms, alkanoyloxymethyl of 2-7 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-6 carbon atoms, hydroxy, trifluoromethyl, cyano, nitro, carboxy, carboalkoxy of 2-7 carbon atoms, carboalkyl of 2-7 carbon atoms, phenoxy, phenyl, thiophenoxy, benzoyl, benzyl, amino, alkylamino of 1-6 carbon

atoms, dialkyl amino of 2 to 12 carbon atoms, phenylamino, benzylamino, alkanoylamino of 1-6 carbon atoms, alkenoylamino of 3-8 carbon atoms, alkynoylamino of 3-8 carbon atoms, carboxyalkyl of 2-7 carbon atoms, carboalkoxyalkyl of 3-8 carbon atoms, aminoalkyl of 1-5 carbon atoms, N-alkylaminoalkyl of 2-9 carbon atoms, N,N-dialkylaminoalkyl of 3-10 carbon atoms, N-alkylaminoalkoxy of 2-9 carbon atoms, N,N-dialkylaminoalkoxy of 3-10 carbon atoms, mercapto, and benzoylamino; or X is a radical having the formula:

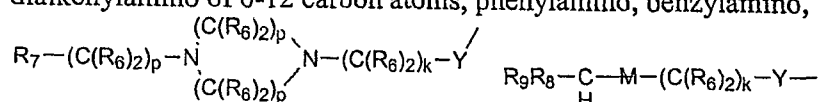


wherein A is a pyridinyl, pyrimidinyl, or phenyl ring; wherein the pyridinyl, pyrimidinyl, or phenyl ring may be optionally mono- or di-substituted with a substituent selected from the group consisting of halogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, azido, hydroxyalkyl of 1-6 carbon atoms, halomethyl, alkoxymethyl of 2-7 carbon atoms, alkanoyloxymethyl of 2-7 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-6 carbon atoms, hydroxy, trifluoromethyl, cyano, nitro, carboxy, carboalkoxy of 2-7 carbon atoms, carboalkyl of 2-7 carbon atoms, phenoxy, phenyl, thiophenoxy, benzoyl, benzyl, amino, alkylamino of 1-6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, phenylamino, benzylamino, alkanoylamino of 1-6 carbon atoms, alkenoylamino of 3-8 carbon atoms, alkynoylamino of 3-8 carbon atoms, carboxyalkyl of 2-7 carbon atoms, carboalkoxyalkyl of 3-8 carbon atoms, aminoalkyl of 1-5 carbon atoms, N-alkylaminoalkyl of 2-9 carbon atoms, N,N-dialkylaminoalkyl of 3-10 carbon atoms, N-alkylaminoalkoxy of 2-9 carbon atoms, N,N-dialkylaminoalkoxy of 3-10 carbon atoms, mercapto, and benzoylamino; T is bonded to a carbon of A and is:

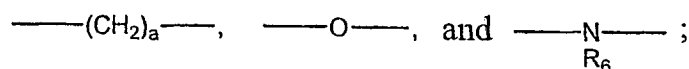


L is an unsubstituted phenyl ring or a phenyl ring mono-, di-, or tri-substituted with a substituent selected from the group consisting of halogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, azido, hydroxyalkyl of 1-6 carbon atoms, halomethyl, alkoxymethyl of 2-7 carbon atoms, alkanoyloxymethyl of 2-7 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-6 carbon atoms, hydroxy, trifluoromethyl, cyano, nitro, carboxy, carboalkoxy of 2-7 carbon atoms, carboalkyl of 2-7 carbon atoms, phenoxy, phenyl, thiophenoxy, benzoyl, benzyl, amino, alkylamino of 1-6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, phenylamino, benzylamino, alkanoylamino of 1-6 carbon atoms, alkenoylamino of 3-8 carbon atoms, alkynoylamino of 3-8 carbon atoms, carboxyalkyl of 2-7 carbon atoms, carboalkoxyalkyl of 3-8 carbon atoms, aminoalkyl of 1-5 carbon atoms, N-alkylaminoalkyl of 2-9 carbon atoms, N,N-dialkylaminoalkyl of 3-10 carbon atoms, N-alkylaminoalkoxy of 2-9 carbon atoms, N,N-dialkylaminoalkoxy of 3-10 carbon atoms, mercapto, and benzoylamino; or L is a 5- or 6-membered heteroaryl ring where the heteroaryl ring contains 1 to 3 heteroatoms selected from N, O, and S, with the proviso that the heteroaryl ring does not contain O—O, S—S, or S—O bonds, and where the heteroaryl ring is

optionally mono- or di-substituted with a substituent selected from the group consisting of halogen, oxo, thio, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, azido, hydroxyalkyl of 1-6 carbon atoms, halomethyl, alkoxyethyl of 2-7 carbon atoms, alkanoyloxyethyl of 2-7 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-6 carbon atoms, hydroxy, trifluoromethyl, cyano, nitro, carboxy, carboalkoxy of 2-7 carbon atoms, carboalkyl of 2-7 carbon atoms, phenoxy, phenyl, thiophenoxy, benzoyl, benzyl, amino, alkylamino of 1-6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, phenylamino, benzylamino, alkanoylamino of 1-6 carbon atoms, alkenoylamino of 3-8 carbon atoms, alkynoylamino of 3-8 carbon atoms, carboxyalkyl of 2-7 carbon atoms, carboalkoxyalkyl of 3-8 carbon atoms, aminoalkyl of 1-5 carbon atoms, N-alkylaminoalkyl of 2-9 carbon atoms, N,N-dialkylaminoalkyl of 3-10 carbon atoms, N-alkylaminoalkoxy of 2-9 carbon atoms, N,N-dialkylaminoalkoxy of 3-10 carbon atoms, mercapto, and benzoylamino; V is ethylene or acetylene; PG is an amine protecting group; R₄ is alkyl of 1 to 6 carbons; Z is NR^z, O or S, wherein R^z is H or C₁-C₆ alkyl; R₁, G₂, and R₃ are each, independently, hydrogen, halogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, alkenyloxy of 2-6 carbon atoms, alkynyloxy of 2-6 carbon atoms, hydroxymethyl, halomethyl, alkanoyloxy of 1-6 carbon atoms, alkenoyloxy of 3-8 carbon atoms, alkynoyloxy of 3-8 carbon atoms, alkanoyloxyethyl of 2-7 carbon atoms, alkenoyloxyethyl of 4-9 carbon atoms, alkynoyloxyethyl of 4-9 carbon atoms, alkoxyethyl of 2-7 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-6 carbon atoms, alkylsulphanyl of 1-6 carbon atoms, alkylsulphonyl of 1-6 carbon atoms, alkylsulfonamido of 1-6 carbon atoms, alkenylsulfonamido of 2-6 carbon atoms, alkynylsulfonamido of 2-6 carbon atoms, hydroxy, trifluoromethyl, trifluoromethoxy, cyano, nitro, carboxy, carboalkoxy of 2-7 carbon atoms, carboalkyl of 2-7 carbon atoms, phenoxy, phthalimide, phenyl, thiophenoxy, benzyl, amino, hydroxyamino, alkoxyamino of 1-4 carbon atoms, alkylamino of 1-6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, N-alkylcarbamoyl, N,N-dialkylcarbamoyl, N-alkyl-N-alkenylamino of 4 to 12 carbon atoms, N,N-dialkenylamino of 6-12 carbon atoms, phenylamino, benzylamino,

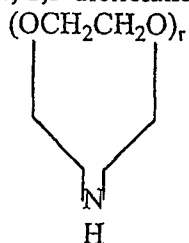


R₇-(C(R₆)₂)_g-Y-, R₇-(C(R₆)₂)_p-M-(C(R₆)₂)_k-Y-, or Het-(C(R₆)₂)_q-W-(C(R₆)₂)₂-Y-; or R₁ and R₃ are as defined above and G₂ is R₂-NH-; or if any of the substituents R₁, G₂ or R₃ are located on contiguous carbon atoms then they may be taken together as the divalent radical -O-C(R₆)₂-O-; Y is a divalent radical selected from the group consisting of

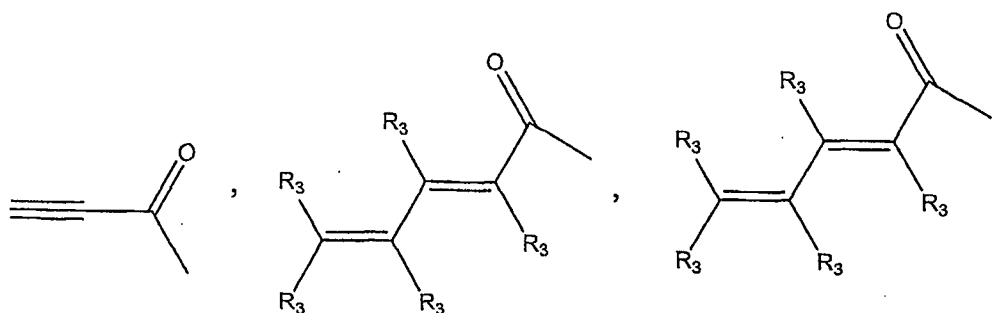


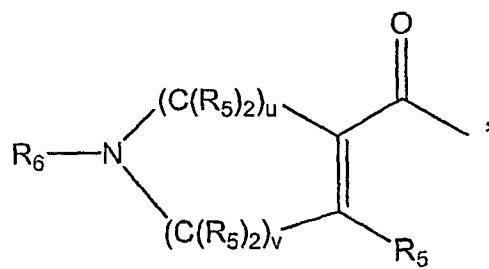
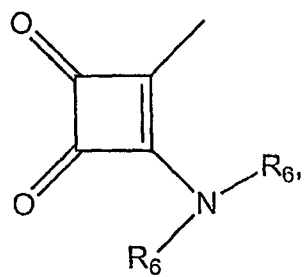
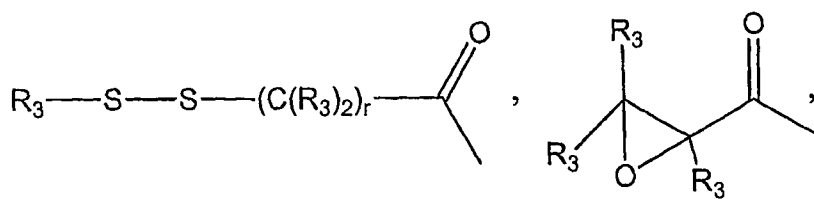
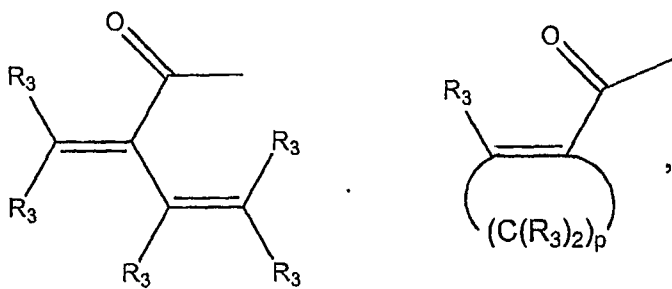
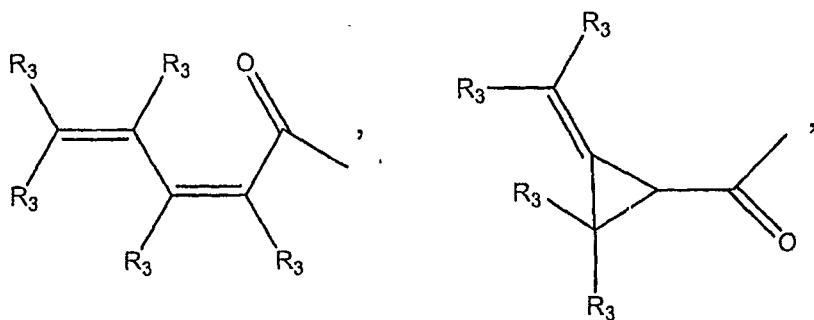
R₇ is -NR₆R₆, -OR₆, -J, -N(R₆)₃+, or -NR₆(OR₆); M is >NR₆, -O-, >N-(C(R₆)₂)_pNR₆R₆, or >N-(C(R₆)₂)_p-OR₆; W is >NR₆, -O- or is a bond; Het is selected from the group consisting of morpholine, thiomorpholine, thiomorpholine S-oxide, thiomorpholine S,S-dioxide, piperidine, pyrrolidine, aziridine, pyridine, imidazole, 1,2,3-triazole, 1,2,4-triazole, thiazole, thiazolidine,

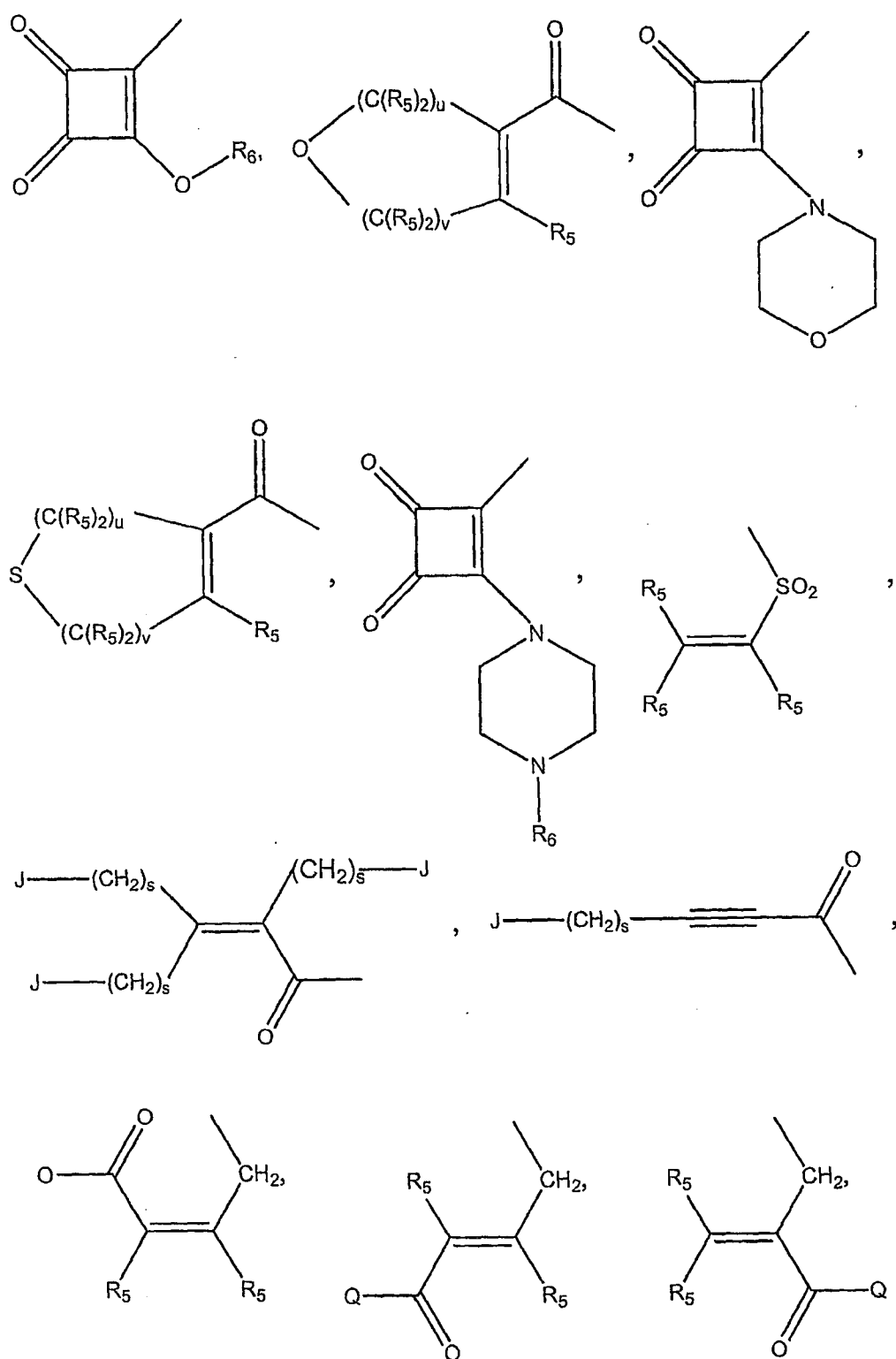
tetrazole, piperazine, furan, thiophene, tetrahydrothiophene, tetrahydrofuran, dioxane, 1,3-dioxolane, tetrahydropyran, and

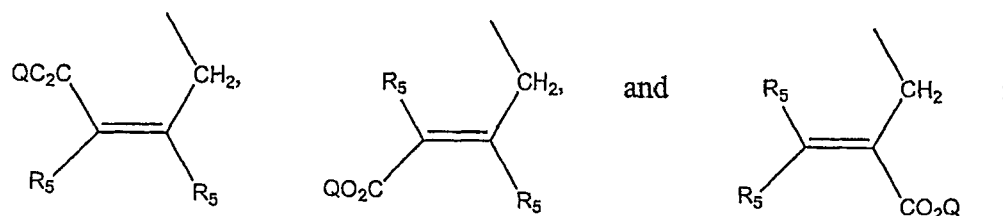


; wherein Het is optionally mono- or di-substituted on carbon or nitrogen with R_6 , optionally mono- or di-substituted on carbon with hydroxy, $\text{---N(R}_6\text{)}_2$, or ---OR_6 , optionally mono or di-substituted on carbon with the mono-valent radicals $\text{---(C(R}_6\text{)}_2\text{)}_s \text{OR}_6$ or $\text{---(C(R}_6\text{)}_2\text{)}_s \text{N(R}_6\text{)}_2$, and optionally mono or di-substituted on a saturated carbon with divalent radicals ---O--- or $\text{---O(C(R}_6\text{)}_2\text{)}_s \text{O---}$; R_6 is hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, cycloalkyl of 1-6 carbon atoms, carboalkyl of 2-7 carbon atoms, carboxyalkyl (2-7 carbon atoms), phenyl, or phenyl optionally substituted with one or more halogen, alkoxy of 1-6 carbon atoms, trifluoromethyl, amino, alkylamino of 1-3 carbon atoms, dialkylamino of 2-6 carbon atoms, nitro, cyano, azido, halomethyl, alkoxymethyl of 2-7 carbon atoms, alkanoyloxymethyl of 2-7 carbon atoms, alkylthio of 1-6 carbon atoms, hydroxy, carboxyl, carboalkoxy of 2-7 carbon atoms, phenoxy, phenyl, thiophenoxy, benzoyl, benzyl, phenylamino, benzylamino, alkanoylamino of 1-6 carbon atoms, or alkyl of 1-6 carbon atoms; with the proviso that the alkenyl or alkynyl moiety is bound to a nitrogen or oxygen atom through a saturated carbon atom; R_2 , is selected from the group consisting of

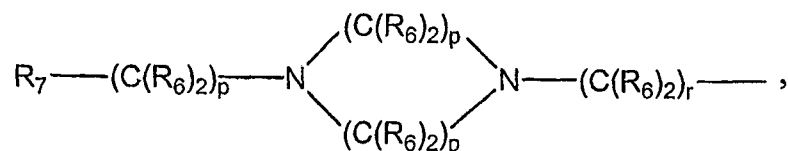




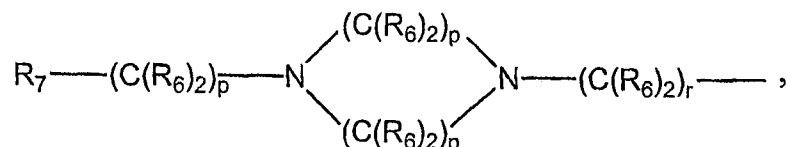




R₃ is independently hydrogen, alkyl of 1-6 carbon atoms, carboxy, carboalkoxy of 1-6 carbon atoms, phenyl, carboalkyl of 2-7 carbon atoms,

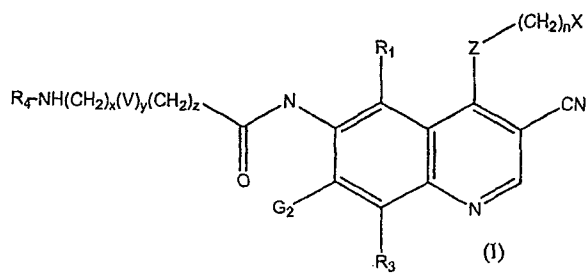


$R_7-(C(R_6)_2)_s-$, $R_7-(C(R_6)_2)_p-M-(C(R_6)_2)_r-$, R_8R_9-CH- , $M-(C(R_6)_2)_r-$, or $Het-(C(R_6)_2)_q-W-(C(R_6)_2)_r-$; R_5 is independently hydrogen, alkyl of 1-6 carbon atoms, carboxy, carboalkoxy of 1-6 carbon atoms, phenyl carboalkyl of 2-7 carbon atoms,

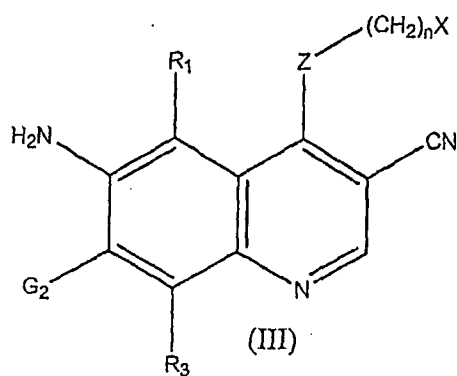


$R_7-(C(R_6)_2)_s-$, $R_7-(C(R_6)_2)_p-M-(C(R_6)_2)_r-$, R_8R_9-CH- , $M-(C(R_6)_2)_r-$,
 or $Het-(C(R_6)_2)_q-W-(C(R_6)_2)_r-$; R_8 , and R_9 are each independently -
 $(C(R_6)_2)_rNR_6R_6$, or $-(C(R_6)_2)_rOR_6$; J is independently hydrogen, chlorine,
 fluorine, or bromine; Q is alkyl of 1-6 carbon atoms or hydrogen; $a=0$ or 1 ; $g=1-6$;
 $k=0-4$; n is $0-1$; m is $0-3$; $p=2-4$; $q=0-4$; $r=1-4$; $s=1-6$; $u=0-4$ and $v=0-4$, wherein
 the sum of $u+v$ is $2-4$; $x=0-3$; $y=0-1$; and $z=0-3$; or a pharmaceutically acceptable
 salt thereof.

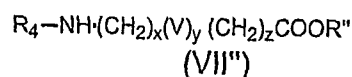
[0006] The present invention is also directed to a method of preparing a compound of formula (I):



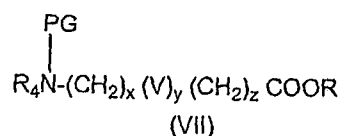
comprising the step of coupling an anilinoquinoline of formula (III):



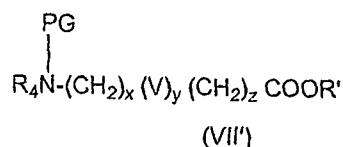
with an acid of formula (VII''):



wherein R'' is H, and R₁, R₃, R₄, Z, G₂, V, n, x, y, and z are as previously defined. [0007] This invention also pertains to a method of preparing acid compounds of formula (VII):



wherein R is H, and R₄, V, x, y, and z are as defined above and PG is an amine protecting group, comprising the step of hydrolyzing a corresponding ester of formula (VII'):



wherein R' is alkyl of 1 to 6 carbon atoms or aryl to form the acid of formula (VII).

[0008] This invention is also directed to (*E*) *N*-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(methylamino)-2-butenamide, or a pharmaceutically acceptable salt thereof. Also contemplated by the present invention are compositions containing the same and methods of using this compound to prevent, treat or inhibit cancers.

DETAILED DESCRIPTION OF THE INVENTION

[0009] The 6-des-alkylaminoquinolines of formula (I) are metabolites of EGFR and HER2 inhibitors, and possess EGFR and HER2 inhibitory activity themselves. A particularly preferred embodiment of the present invention is directed to a method of making these compounds by first arylating a protected 6-anilino-3-cyanoquinoline at the 4-position with a reagent of formula HZ-(CH₂)_nX, which is defined herein. Then the aniline nitrogen is deprotected and the compound is coupled to an acid of formula (R₄)(PG)N-(CH₂)_x(V)_y(CH₂)_zCOOH using standard coupling reagents to form the 6-amidoquinoline of formula (II). The protected secondary amine of this compound can then be deprotected to give the desired product. Alternatively, the 6-des-alkylaminoquinolines of formula (I) can be formed directly by coupling the aniline of formula (III) with unprotected acid of formula (VII'), R₄-NH-(CH₂)_x(V)_y(CH₂)_zCOOH, using standard coupling reagents.

[0010] This method is an improvement over the prior method, which alkylated the 6-anilinoquinoline compound using an acid chloride. The prior method produced poor yields because of the instability of the acid compounds under the reaction conditions. In addition, the prior method also produced a crude product that was extremely difficult to purify. The present method, however, gives reasonable yields and a crude product that can easily be made >97% pure with one flash chromatography.

[0011] For purposes of this invention the term "alkyl", unless stated otherwise, includes both straight and branched alkyl moieties, which can contain as many as 12 carbon atoms. Preferably, the alkyl moiety contains between 1 to 6 carbon atoms, though 1 to 4 carbon atoms is more preferable. The term "alkenyl" refers to a radical aliphatic hydrocarbon containing one double bond and includes both straight and branched alkenyl moieties of 2 to 7 carbon atoms. Such alkenyl moieties may exist in the E or Z configurations; the compounds of this invention include both configurations. The term "alkynyl" includes both straight chain and branched moieties containing 2 to 6 carbon atoms having at least one triple bond. The term "cycloalkyl" refers to alicyclic hydrocarbon groups having 3 to 12 carbon atoms, but is preferably 3 to 7 carbon atoms, and includes but is not

limited to: cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, norbornyl, or adamantyl.

[0012] For purposes of this invention the term "aryl" is defined as an aromatic hydrocarbon moiety, which may be a single ring or a multiple fused ring system in which all the double bonds are in conjugation, and may be substituted or unsubstituted. An aryl group preferably contains 6 to 12 carbon atoms and may be selected from, but not limited to, the group: phenyl, α -naphthyl, β -naphthyl, biphenyl, anthryl, tetrahydronaphthyl, phenanthryl, fluorenyl, indanyl, biphenylenyl, acenaphthenyl, acenaphthylenyl, or phenanthrenyl groups. An aryl group may be optionally mono-, di-, tri- or tetra-substituted with substituents selected from, but not limited to, the group consisting of alkyl, acyl, alkoxy carbonyl, alkoxy, alkoxyalkyl, alkoxyalkoxy, cyano, halogen, hydroxy, nitro, trifluoromethyl, trifluoromethoxy, trifluoropropyl, amino, alkylamino, dialkylamino, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, alkylthio, $-\text{SO}_3\text{H}$, $-\text{SO}_2\text{NH}_2$, $-\text{SO}_2\text{NHalkyl}$, $-\text{SO}_2\text{N(alkyl)}_2$, $-\text{CO}_2\text{H}$, CO_2NH_2 , $\text{CO}_2\text{NHalkyl}$, and $-\text{CO}_2\text{N(alkyl)}_2$. Preferred substituents for aryl include: alkyl, halogen, amino, alkylamino, dialkylamino, trifluoromethyl, trifluoromethoxy, arylalkyl, and alkylaryl.

[0013] For purposes of this invention the term "heteroaryl" is defined as an aromatic heterocyclic ring system (monocyclic or bicyclic) where the heteroaryl moieties are five or six membered rings containing 1 to 4 heteroatoms selected from the group consisting of S, N, and O, and include but is not limited to: (1) furan, thiophene, indole, azaindole, oxazole, thiazole, isoxazole, isothiazole, imidazole, N-methylimidazole, pyridine, pyrimidine, pyrazine, pyrrole, N-methylpyrrole, pyrazole, N-methylpyrazole, 1,3,4-oxadiazole, 1,2,4-triazole, 1-methyl-1,2,4-triazole, 1H-tetrazole, 1-methyltetrazole, benzoxazole, benzothiazole, benzofuran, benzisoxazole, benzimidazole, N-methylbenzimidazole, azabenzimidazole, indazole, quinazoline, quinoline; (2) a bicyclic aromatic heterocycle where a phenyl, pyridine, pyrimidine or pyridazine ring is: (i) fused to a 6-membered aromatic (unsaturated) heterocyclic ring having at least one heteroatom; (ii) fused to a 5-membered aromatic or nonaromatic (unsaturated) heterocyclic ring having at least one heteroatom selected from O, N

or S. Preferably a bicyclic heteroaryl group contains 8 to 12 carbon atoms. Preferred substituents for heteroaryl include: alkyl, halogen, amino, alkylamino, dialkylamino, trifluoromethyl, trifluoromethoxy, arylalkyl, and alkylaryl.

[0014] For the purposes of this invention the term "heterocycloalkyl" refers to a non-aromatic heterocyclic ring system (monocyclic or bicyclic) where the moieties contain 1 to 4 heteroatoms selected from the group consisting of S, N, and O, and include but is not limited to: Pyrrolidine, pyrroline, 1,3-dioxolane, imidazoline, imidazolidine, pyrazoline, pyrazolidine, pyran, piperidine, dioxane, morpholine, dithioxane, thiomorpholine, piperazine, azetidiny, hexahydroazepiny, dihydrobenzimidazolyl, dihydrobenzofuranyl, dihydrobenzothienyl, dihydrobenzoxazolyl, dihydrofuranyl, dihydroimidazolyl, dihydroindolyl, dihydroisooxazolyl, dihydroisothiazolyl, dihydrooxadiazolyl, dihydrooxazolyl, dihydropyrraziny, dihydropyrazolyl, dihydropyridiny, dihydropyrimidiny, dihydropyrroly, dihydroquinoliny, dihydrotetrazolyl, dihydrothiadiazolyl, dihydrothiazolyl, dihydrothienyl, dihydrotriazolyl, dihydroazetidiny, dihydro-1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothienyl, tetrahydroquinoliny, tetrahydroisoquinoliny and indoline. A heterocycloalkyl moiety preferably contains 1-11 carbon atoms. These moieties may be further substituted.

[0015] For the purposes of this invention the term "alkoxy" is defined as C₁-C₆-alkyl-O-; the term "aryloxy" is defined as aryl-O-; the term "heteroaryloxy" is defined as heteroaryl-O-; wherein alkyl, aryl, and heteroaryl are as defined above.

[0016] For purposes of this invention the term "arylalkyl" is defined as aryl-C₁-C₆-alkyl-; arylalkyl moieties include benzyl, 1-phenylethyl, 2-phenylethyl, 3-phenylpropyl, 2-phenylpropyl and the like.

[0017] For purposes of this invention the term "alkanoyloxymethyl" is defined as -CH₂OC(O)R, wherein R is alkyl of 1 to 6 carbon atoms.

[0018] For purposes of this invention the term "alkylthio" is defined as C₁-C₆-alkyl-S.

[0019] For purposes of this invention "alkylthioalkyl," and "alkoxyalkyl," denote an alkyl group as defined above that is further substituted with an alkoxy or alkylthio as defined above.

[0020] The terms "alkylamino" and "dialkylamino" refer to moieties with one or two alkyl groups wherein the alkyl chain is 1 to 6 carbons and the groups may be the same or different. The terms "monoalkylaminoalkyl" and "dialkylaminoalkyl" refer to monoalkylamino and dialkylamino moieties with one or two alkyl groups (the same or different) bonded to the nitrogen atom which is attached to an alkyl group of 1 to 6 carbon atoms. Preferably a dialkylaminoalkyl moiety consist of 3 to 10 carbon atoms and a alkylaminoalkyl moiety consist of from 2 to 9 carbon atoms.

[0021] The terms "alkylaminoalkoxy" and "dialkylaminoalkoxy" refer to alkylamino and dialkylamino moieties with one or two alkyl groups (the same or different) bonded to the nitrogen atom which is attached to an alkoxy group of 1 to 6 carbon atoms. Preferably a dialkylaminoalkoxy moiety consist of 3 to 10 carbon atoms and a alkylaminoalkoxy moiety consist of from 2 to 9 carbon atoms.

[0022] For purposes of this invention the term "benzoylamino" is defined as a Ph-OC(O)NH- moiety.

[0023] For purposes of this invention the term "carboxy" is defined as a -COOH moiety.

[0024] For purposes of this invention the term "alkanoylamino" is defined as a -NH-COOR moiety, wherein R is alkyl of 1 to 6 carbon atoms.

[0025] For purposes of this invention the term "alkenoylamino" and "alkynoylamino" are defined as a -NH-COOR moiety, wherein R is alkenyl or alkynyl of 3 to 8 carbon atoms.

[0026] For purposes of this invention the term "carboalkoxy" is defined as $\text{-CO}_2\text{R}$, wherein R is alkyl of 1 to 6 carbon atoms.

[0027] For purposes of this invention the term "carboalkyl" is defined as -COR , wherein R is alkyl of 1 to 6 carbon atoms.

[0028] For purposes of this invention the term "carboxyalkyl" is defined as a HOOCR- moiety, wherein R is alkyl of 1 to 6 carbon atoms.

[0029] For purposes of this invention the term "carboalkoxyalkyl" is defined as a $\text{-R-CO}_2\text{-R'}$ moiety, wherein R and R' are alkyl and together consist of from 2 to 7 carbon atoms.

[0030] For purposes of this invention the term "aminoalkyl" is defined as H_2N -alkyl, wherein the alkyl group consist of 1 to 5 carbon atoms.

[0031] "Azido" is a radical of the formula $-N_3$.

[0032] "Acy" is a radical of the formula $-(C=O)$ -alkyl or $-(C=O)$ -perfluoroalkyl wherein the alkyl radical or perfluoroalkyl radical is 1 to 6 carbon atoms; preferred examples include but are not limited to, acetyl, propionyl, butyryl, trifluoroacetyl.

[0033] For purposes of this invention the term "alkylsulfinyl" is defined as a $R'SO$ - radical, where R' is an alkyl radical of 1 to 6 carbon atoms. Alkylsulfonyl is a $R'SO_2$ - radical, where R' is an alkyl radical of 1 to 6 carbon atoms.

Alkylsulfonamido, alkenylsulfonamido, alkynylsulfonamido are $R'SO_2NH$ -radicals, where R' is an alkyl radical of 1 to 6 carbon atoms, an alkenyl radical of 2 to 6 carbon atoms, or an alkynyl radical of 2 to 6 carbon atoms, respectively.

[0034] Saturated or partially saturated non-aromatic heteroaryl groups are defined in this invention as heterocyclic rings selected from but not limited to the moieties: azetidiny, 1,4-dioxany, hexahydroazepiny, piperaziny, piperidiny, pyrrolidiny, morpholiny, thiomorpholiny, dihydrobenzimidazolyl, dihydrobenzofurany, dihydrobenzothienyl, dihydrobenzoxazolyl, dihydrofurany, dihydroimidazolyl, dihydroindolyl, dihydroisooxazolyl, dihydroisothiazolyl, dihydrooxadiazolyl, dihydrooxazolyl, dihydropyrraziny, dihydropyrazolyl, dihydropyridiny, dihydropyrimidiny, dihydropyrroly, dihydroquinoliny, dihydrotetrazolyl, dihydrothiadiazolyl, dihydrothiazolyl, dihydrothienyl, dihydrotriazolyl, dihydroazetidiny, dihydro-1,4-dioxany, tetrahydrofurany, tetrahydrothienyl, tetrahydroquinoliny, and tetrahydroisoquinoliny. Preferably such moieties contain 3-10 ring atoms, wherein 1 to 4 are heteroatoms selected from the group consisting of S, N and O.

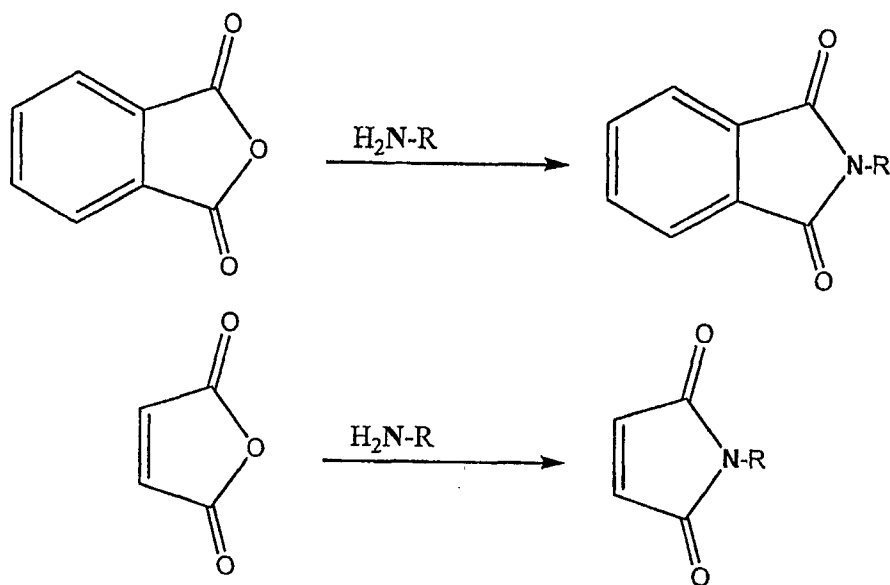
[0035] The term "substituent" is used herein to refer to an atom radical, a functional group radical or a moiety radical that replaces a hydrogen radical on a molecule. Unless expressly stated otherwise, it should be assumed that any of the substituents may be optionally substituted with one or more groups selected from: alkyl, halogen, haloalkyl, hydroxyalkyl, nitro, amino, hydroxy, cyano, alkylamino, dialkylamino, alkoxy, haloalkoxy, alkoxyalkyl, alkoxyalkoxy, oxo,

alkylthio, mercapto, haloalkylthio, aryl, aryloxy, arylthio, heteroaryl, heteroaryloxy, heteroarylthio, acyl, -CO₂-alkyl, -SO₃H, -SO₂NH₂, -SO₂NH-alkyl, -SO₂NH-(alkyl)₂, -CO₂H, -CO₂NH₂, -CO₂NH-alkyl and -CO₂N-(alkyl)₂.

[0036] For the purposes of this invention the term "substituted" refers to where a hydrogen radical on a molecule has been replaced by another atom radical, a functional group radical or a moiety radical; these radicals being generally referred to as "substituents."

[0037] The term "protecting group" refers to a group introduced into a molecule to protect a sensitive functional group or specific position on the molecule from reacting when the molecule is exposed to reagents or conditions to transform or react another part of the molecule. Thereafter the protecting group can be removed. Suitable protecting groups are well known in the art and include acid-labile, base-labile, photoremovable, or removable under neutral conditions. See, e.g., *Green, Protecting Groups in Organic Synthesis*, Wiley 1991, 2nd ed., pp. 309-405, which is incorporated herein by reference. The term "amine protecting group" refers to a moiety capable of protecting an amine functional group from reacting. Exemplary amine protecting groups for the present invention include acyl groups (such as acetyl), t-butoxycarbonyl (t-BOC), benzyloxycarbonyl, trifluoroacetyl, CH₃OC(O)-, EtOC(O)-, Fmoc, Troc, Phenoc, Teoc and PhC(O)-groups, and forming cyclicimides (e.g. phthalimide, maleimide, 2,3-dichloromaleimide, succinimide and dihydrophthalimide) and pyrroles (e.g. dimethyl pyrrole).

[0038] Cyclicimides are useful protecting groups for masking primary amines. They are formed by reacting the primary amine to be masked with a reagent such as phthalic anhydride or maleamic anhydride, thereby incorporating the amine into the cyclicimide, as shown below.



[0039] Thereafter, the cyclicimides can be cleaved under a variety of conditions to give the primary amine in good yield. See *Green* at pp. 358-359. 2,5-Dimethylpyrrole operates similarly.

[0040] The term "cancer" refers to any malignant growth or tumor caused by abnormal and uncontrolled cell division. It may spread to other parts of the body through the lymphatic system or the blood stream. For the purposes of the method of treating cancer described in this application, cancer includes lymphatic cancer, breast cancer, ovarian cancer, epidermoid tumors, colon cancer, prostate cancer, kidney cancer, bladder cancer, larynx cancer, esophagus cancer, stomach cancer, and lung cancer.

[0041] The compounds synthesized by this invention may contain an asymmetric carbon atom and may thus give rise to stereoisomers, such as enantiomers and diastereomers. The stereoisomers of the instant invention are named according to the Cahn-Ingold-Prelog System. While shown without respect to stereochemistry in formula (I), the present invention includes the synthesis of all the individual possible stereoisomers; as well as the racemic mixtures and other mixtures of R and S stereoisomers (scalemic mixtures which are mixtures of unequal amounts of enantiomers). It should be noted that stereoisomers of the invention having the same relative configuration at a chiral center may

nevertheless have different R and S designations depending on the substitution at the indicated chiral center.

[0042] This invention is also directed to pharmaceutical compositions containing a therapeutically effective amount of a compound selected from (*E*) *N*-{4-[3-chloro-4-fluoroanilino]-3-cyano-7-ethoxy-6-quinoliny]-4-(methylamino)-2-butenamide, (*E*) *N*-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinoliny]-4-(methylamino)-2-butenamide, (*E*) *N*-{4-[3-chloro-4-(3-fluorobenzyloxy)anilino]-3-cyano-7-ethoxy-6-quinoliny]-4-(methylamino)-2-butenamide and (*E*) *N*-{4-[3-chloro-4-benzyloxy)anilino]-3-cyano-7-ethoxy-6-quinoliny]-4-(methylamino)-2-butenamide, and a pharmaceutically acceptable carrier. In a preferred embodiment of the composition of the present invention the compound is (*E*) *N*-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinoliny]-4-(methylamino)-2-butenamide.

[0043] The pharmaceutically acceptable carrier contained in the composition of the present invention may be for example a diluent, an aerosol, a topical carrier, an aqueous solution, a nonaqueous solution or a solid carrier. The carrier may be a polymer or a toothpaste. A carrier in this invention encompasses any of the standard pharmaceutically accepted carriers, such as phosphate buffered saline solution, acetate buffered saline solution, water, emulsions such as an oil/water emulsion or a triglyceride emulsion, various types of wetting agents, tablets, coated tablets and capsules. The compositions of the present invention may be formulated with conventional excipients, such as a filler, a disintegrating agent, a binder, a lubricant, a flavoring agent or a color additive.

[0044] When provided orally or topically, such compounds would be provided to a subject by delivery in different carriers. Typically, such carriers contain excipients such as starch, milk, sugar, certain types of clay, gelatin, stearic acid, talc, vegetable fats or oils, gums, or glycols. The specific carrier would need to be selected based upon the desired method of delivery, for example, phosphate buffered saline (PBS) could be used for intravenous or systemic delivery and vegetable fats, creams, salves, ointments or gels may be used for topical delivery.

[0045] The compounds of the present invention may be delivered together with suitable diluents, preservatives, solubilizers, emulsifiers, adjuvants and/or carriers

useful in treatment or prevention of neoplasm. Such compositions are liquids or lyophilized or otherwise dried formulations and include diluents of various buffer content (for example, Tris-HCl, acetate, phosphate), pH and ionic strength, additives such as albumins or gelatin to prevent absorption to surfaces, detergents (for example, TWEEN 20, TWEEN 80, PLURONIC F68, bile acid salts), solubilizing agents (for example, glycerol, polyethylene glycerol), anti-oxidants (for example ascorbic acid, sodium metabisulfate), preservatives (for example, thimerosal, benzyl alcohol, parabens), bulking substances or tonicity modifiers (for example, lactose, mannitol), covalent attachment of polymers such as polyethylene glycol, complexation with metal ions, or incorporation of the compound into or onto particulate preparations of hydrogels or liposomes, micro-emulsions, micelles, unilamellar or multilamellar vesicles, erythrocyte ghosts, or spheroblasts. Such compositions will influence the physical state, solubility, stability, rate of *in vivo* release, and rate of *in vivo* clearance of the compound or composition. The choice of compositions will depend on the physical and chemical properties of the compound capable of treating or preventing a neoplasm.

[0046] The compounds of the present invention may be delivered locally via a capsule that allows a sustained release of the compound over a period of time. Controlled or sustained release compositions include formulation in lipophilic depots (for example, fatty acids, waxes, oils).

[0047] The present invention further provides a method of using the compounds disclosed herein, (*E*) *N*-{4-[3-chloro-4-fluoroanilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(methylamino)-2-butenamide, (*E*) *N*-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(methylamino)-2-butenamide, (*E*) *N*-{4-[3-chloro-4-(3-fluorobenzyloxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(methylamino)-2-butenamide and (*E*) *N*-{4-[3-chloro-4-benzyloxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(methylamino)-2-butenamide, as active therapeutic substances for preventing or inhibiting cancer.

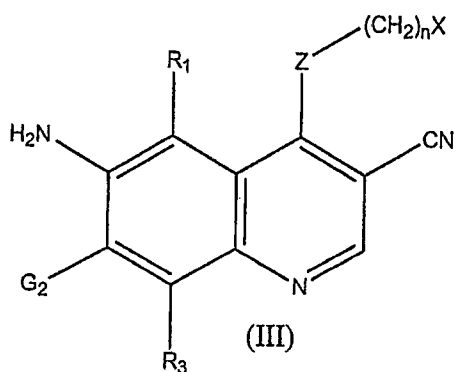
[0048] The present invention further provides a method of treating cancer in humans, which comprises administering to the infected individual an effective amount of a compound or a pharmaceutical composition of the invention. A

“therapeutically effective amount” is an amount sufficient to cure or ameliorate symptoms of a cancer. The effective dosage of active ingredient employed may vary depending on the particular compound employed, the mode of administration and the severity of the condition being treated. In general, satisfactory results are obtained when the compounds of the invention are administered at a daily dosage of from about 0.5 to about 1000 mg/kg of animal body weight, optionally given in divided doses two to four times a day, or in sustained release form. For most large mammals the total daily dosage is from about 1 to 1000 mg, preferably from about 2 to 500 mg. Dosage forms suitable for internal use comprise from about 0.5 to 1000 mg of the active compound in intimate admixture with a solid or liquid pharmaceutically acceptable carrier. This dosage regimen may be adjusted to provide the optimal therapeutic response. For example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation.

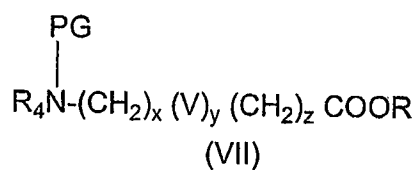
[0049] The compounds of the present invention may be delivered alone or in combination with other compounds used to treat cancer or with radiation therapy. Such compounds include but are not limited to imatinib mesylate (GLEEVEC), hydroxyurea, IFN- α , cytotoxic agents, NSAIDS, gemcitabine, EGFR inhibitors, MEK inhibitors, farnesyltransferase, taxol, vinblastine, cisplatin, cyclophosphamide, 5-fluorouracil, adriamycin, bleomycin, etoposide, camptothecin, tamoxifen or wortmannin.

[0050] In a preferred embodiment of the method of treating cancer disclosed in the present application, the cancer being treated is selected from breast cancer, ovarian cancer, epidermoid tumors, colon cancer, prostate cancer, kidney cancer, bladder cancer, larynx cancer, esophagus cancer, stomach cancer, and lung cancer. In another preferred embodiment the cancer being treated is breast cancer or ovarian cancer.

[0051] In a preferred embodiment of this method of synthesizing the compounds of formula (I) by deprotecting a compound of formula (II), further comprises the step of forming the compound of formula (II) by coupling an anilinoquinoline of formula (III):



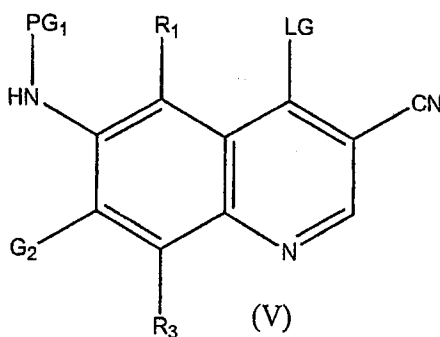
with an acid of formula (VII):



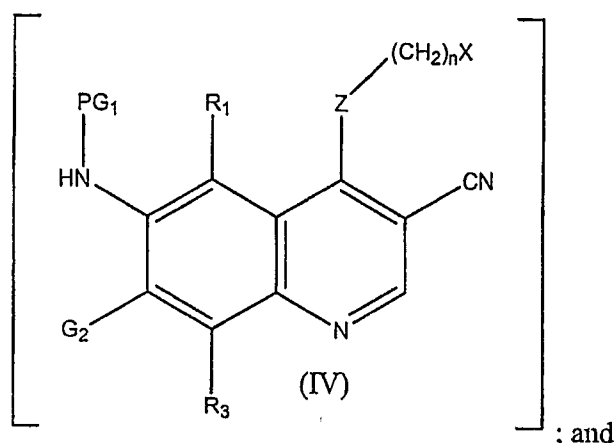
to form a compound of formula (II), wherein R is H, and R_1 , R_3 , R_4 , Z, G_2 , V, PG, n, x, y, and z are as previously defined.

[0052] In yet another preferred embodiment of this method of synthesizing the compounds of formula (I), further comprises the step of forming the anilinoquinoline of formula (III) by:

- a. arylating a compound of formula (V):



with a compound of formula $\text{HZ}-(\text{CH}_2)_n\text{X}$ to form an intermediate of formula (IV):



b. deprotecting the intermediate of formula (IV) to obtain the anilinoquinoline compound of formula (III);

wherein LG is selected from the group of halo, mesylate, tosylate and triflate, PG₁ is an amine protecting group, and wherein R₁, R₃, R₄, Z, G₂, PG, and n are as previously defined.

[0053] Another embodiment of the method of preparing compounds of formula (I) is where the method also involves the step of forming a compound of formula (II) by coupling a compound of formula (III) with an acid of formula (VII), using a coupling reagent selected from DCC, benzotriazolyloxytrispyrrolidino-phosphonium hexafluorophosphate (PyBOP), or N-ethyl-(N'-3-dimethylaminopropyl)-carbodiimide HCl (EDCI) with 1-hydroxybenzotriazole (HOBT), though DCC is the most preferred coupling reagent. It is further preferred that this method also comprise the steps of arylating the 4-position of a compound of formula (V) with a reagent of formula HZ-(CH₂)_nX, preferably using methanesulfonic acid, to form an intermediate of formula (IV), which is subsequently deprotected to yield a compound of formula (III). Wherein LG is a leaving group, such as halo, mesylate, tosylate or triflate, with Cl being the most preferred, and PG₁ is an amine protecting group, with exemplary groups being an acyl group (such as acetyl), t-butoxycarbonyl (t-BOC), CH₃OC(O)-, EtOC(O)-, Fmoc, Troc, Phenoc, Teoc, trifluoroacetyl, benzoxy carbonyl, PhC(O)-, 2,5-dimethylpyrrole, phthalimide, 2,3-dichloromaleimide, succinimide, dihydrophthalimide or maleimide. It is also preferable that PG₁ be removed using an acid. One skilled in the art would also know of other suitable leaving groups,

which could be utilized. The more preferred protecting groups are acetyl, t-BOC, trifluoroacetamide, benzamide, 2,5-dimethylpyrrole, phthalimide and maleimide, with t-BOC and acetyl being the most preferred.

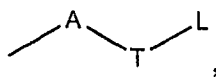
[0054] Another embodiment of the methods of preparing a compound of formula (I) is where the compounds are limited by the following provisos:

- (i) when R_6 is alkenyl of 2-7 carbon atoms or alkynyl of 2-7 carbon atoms, such alkenyl or alkynyl moiety is bound to a nitrogen or oxygen atom through a saturated carbon atom;
- (ii) when Y is $—NR_6—$ and R_7 is $—NR_6R_6$, $—N(R_6)_3$, $N(R_8)_3^+$, or $—NR_6(OR_6)$, then $g=2-6$;
- (iii) when M is $—O—$ and R_7 is $—OR_6$ then $p=1-4$;
- (iv) when Y is $—NR_6—$ then $k=2-4$;
- (v) when Y is $—O—$ and M or W is $—O—$ then $k=1-4$;
- (vi) when W is not a bond with Het bonded through a nitrogen atom then $q=2-4$;

when W is a bond with Het bonded through a nitrogen atom and Y is $—O—$ or $—NR_6—$ then $k=2-4$; and

provided that L can be an unsubstituted phenyl ring only when $m>0$ and T is not $—CH_2NH—$ or $—CH_2O—$.

[0055] Another embodiment of the inventive methods of preparing compounds of formula (I) is wherein X is cycloalkyl, which may be optionally substituted with one or more alkyl groups, or is a pyridinyl, pyrimidinyl, or phenyl ring; wherein the pyridinyl, pyrimidinyl, or phenyl ring may be optionally mono- di-, or tri-substituted as described previously, or X is a radical having the formula:

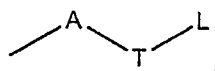


wherein A, T and L are as defined previously, and R_1 , G_2 , and R_3 are each, independently, hydrogen, halogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, alkenyloxy of 2-6 carbon atoms, alkynyloxy of 2-6 carbon atoms, hydroxymethyl, halomethyl, alkanoyloxy of 1-6 carbon atoms, alkenoyloxy of 3-8 carbon atoms, alkynoyloxy of 3-8 carbon atoms, alkanoyloxymethyl of 2-7 carbon atoms, alkenoyloxymethyl of 4-9 carbon atoms, alkynoyloxymethyl of 4-9 carbon atoms, alkoxymethyl of 2-7 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-6 carbon atoms, alkylsulphinyl of 1-6

carbon atoms, alkylsulphonyl of 1-6 carbon atoms, alkylsulfonamido of 1-6 carbon atoms, alkenylsulfonamido of 2-6 carbon atoms, alkynylsulfonamido of 2-6 carbon atoms, hydroxy, trifluoromethyl, trifluoromethoxy, cyano, nitro, carboxy, carboalkoxy of 2-7 carbon atoms, carboalkyl of 2-7 carbon atoms, phenoxy, phthalimide, phenyl, thiophenoxy, benzyl, amino, hydroxyamino, alkoxyamino of 1-4 carbon atoms, alkylamino of 1-6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, N-alkylcarbamoyl, N,N-dialkylcarbamoyl, N-alkyl-N-alkenylamino of 4 to 12 carbon atoms, or N,N-dialkenylamino of 6-12 carbon atoms.

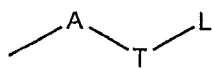
[0056] In another embodiment of the methods of preparing compounds of formula (I) the compounds are defined by X being cycloalkyl, which may be optionally substituted with one or more C₁-C₆-alkyl groups, or is a pyridinyl, pyrimidinyl, or phenyl ring; wherein the pyridinyl, pyrimidinyl, or phenyl ring may be optionally mono- di-, or tri-substituted with the groups described previously. Z is preferably NR^{z'}. When Z is NR^{z'} it is preferable that X be an aromatic moiety, such as pyridinyl, pyrimidinyl, or phenyl ring, with phenyl being the most preferred. These aromatic moieties may be mono-, bi-, or tri-substituted. When Z is NR^{z'} it is also preferable that z and n are 0, y is 1, V is ethylene and R₁, G₂, and R₃ are each, independently, hydrogen, halogen, alkyl of 1-6 carbon atoms, halomethyl, alkoxy of 1-6 carbon atoms, hydroxy, trifluoromethyl, trifluoromethoxy, cyano, nitro, phenoxy, phthalimide, phenyl, thiophenoxy, benzyl, amino, alkylamino of 1-6 carbon atoms, or dialkylamino of 2 to 12 carbon atoms. In this embodiment when X is phenyl and Z is NR^{z'} it is further preferable that R₁, G₂, and R₃ be limited to hydrogen, halogen, alkyl, alkoxy, hydroxy, trifluoromethyl, trifluoromethoxy and that X is only optionally substituted with halo, alkyl, trifluoromethyl and alkoxy. It is also preferable that when X is phenyl and Z is NR^{z'} that R₄ is methyl, ethyl, propyl or isopropyl, R^{z'} is H and that R₁, G₂, and R₃ are further limited to hydrogen, halogen, methoxy, ethoxy, hydroxy, trifluoromethyl, or trifluoromethoxy. A specific embodiment is where the compound prepared is (*E*) *N*-{4-[3-chloro-4-fluoroanilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(methylamino)-2-butenamide.

[0057] Another embodiment of the methods of preparing the compounds of formula (I) is where the compounds are defined by X being a radical having the formula:



where A, T and L are as defined previously. A is most preferably an optionally mono- or di-substituted phenyl ring, and when A is a phenyl ring it is preferable that T is a tether containing an ether or thio linkage, though an ether linkage is most preferred. Z is preferably $\text{NR}^{z'}$ and L is preferably an optionally mono- or di-substituted 5- or 6-membered heteroaryl, such as pyridine, pyrimidine, pyrazine, or pyrazine. The amide moiety at the 6-position of the quinoline ring is preferably limited to where z and n are 0, y is 1 and V is ethylene, while R_1 , G_2 , and R_3 are preferably hydrogen, halogen, alkyl of 1-6 carbon atoms, halomethyl, alkoxy of 1-6 carbon atoms, hydroxy, trifluoromethyl, trifluoromethoxy, cyano, nitro, phenoxy, phthalimide, phenyl, thiophenoxy, benzyl, amino, alkylamino of 1-6 carbon atoms, or dialkylamino of 2 to 12 carbon atoms. When T is an ether linkage it is preferable that m is 1 and that A is optionally mono- or di-substituted with a substituent selected from the group consisting of halogen, alkyl of 1-6 carbon atoms, halomethyl, alkoxy of 1-6 carbon atoms, trifluoromethyl, cyano, amino, alkylamino of 1-6 carbon atoms, and dialkylamino of 2 to 12 carbon atoms. When T is $-\text{OCH}_2-$ it is preferable that R_4 is methyl, ethyl, propyl or isopropyl, $\text{R}^{z'}$ is H, L is pyridine, A and L are optionally mono- or di-substituted with a substituent selected from the group consisting of halogen, methyl, ethyl, methoxy, ethoxy, and trifluoromethyl, and that R_1 , G_2 , and R_3 are further limited to hydrogen, halogen, methoxy, ethoxy, hydroxy, trifluoromethyl, or trifluoromethoxy. A specific embodiment is where the compound prepared is (E) *N*-{4-[3-Chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(methylamino)-2-butenamide.

[0058] Another embodiment of the methods of preparing the compounds of formula (I) is also where the compounds are defined by X being a radical having the formula:



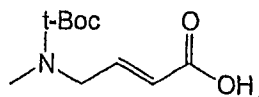
, wherein A and L are phenyl rings, Z is $\text{NR}^{z'}$ and T is a tether containing an ether or thio linkage, though an ether linkage is most preferred. The amide moiety at the 6-position of the quinoline ring is preferably limited to where z and n are 0, y is 1 and V is ethylene, while R_1 , G_2 , and R_3 are preferably hydrogen, halogen, alkyl of 1-6 carbon atoms, halomethyl, alkoxy of 1-6 carbon atoms, hydroxy, trifluoromethyl, trifluoromethoxy, cyano, nitro, phenoxy, phthalimide, phenyl, thiophenoxy, benzyl, amino, alkylamino of 1-6 carbon atoms, or dialkylamino of 2 to 12 carbon atoms. When T is an ether linkage it is preferable that m is 1 and that A is optionally mono- or di-substituted with a substituent selected from the group consisting of halogen, alkyl of 1-6 carbon atoms, halomethyl, alkoxy of 1-6 carbon atoms, trifluoromethyl, cyano, amino, alkylamino of 1-6 carbon atoms, and dialkylamino of 2 to 12 carbon atoms. When T is $-\text{OCH}_2-$ it is preferable that R_4 is methyl, ethyl, propyl or isopropyl, $\text{R}^{z'}$ is H, A is optionally mono- or di-substituted and L is optionally mono-, di- or tri-substituted with a substituent selected from the group consisting of halogen, methyl, ethyl, methoxy, ethoxy, and trifluoromethyl, and that R_1 , G_2 , and R_3 are further limited to hydrogen, halogen, methoxy, ethoxy, hydroxy, trifluoromethyl, or trifluoromethoxy. Specific embodiments are where the compound prepared is (E) *N*-{4-[(3-Chloro-4-benzyloxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-

(methylamino)-2-butenamide or
 (E) *N*-{4-[3-Chloro-4-(3-fluorobenzyloxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(methylamino)-2-butenamide.

[0059] Another embodiment of the method of preparing compounds of formula (I) is where the method also involves the step of coupling a compound of formula (III) with an acid of formula (VII'), using a coupling reagent selected from DCC, benzotriazalyloxytrispyrrolidinophosphonium hexafluorophosphate (PyBoP), or *N*-ethyl-(*N*'-3-dimethylaminopropyl)-carbodiimide HCl (EDCI) with 1-hydroxybenzotriazole (HOBt), though DCC is the most preferred coupling reagent. Alternatively, the acid of formula (VII') can be converted to the corresponding acid halide, for example the acid chloride, and then coupled to the aniline compound of formula (III). The art is replete with methods for converting carboxylic acids into the corresponding acid halides using reagents such as SOCl₂ and oxalyl chloride. The coupling using the coupling reagent is the preferred method. It is further preferred that this method also comprise the steps of arylating the 4-position of a compound of formula (V) with a reagent of formula HZ-(CH₂)_nX, preferably using methylsulfonic acid, to form an intermediate of formula (IV), which is subsequently deprotected to yield a compound of formula (III). Wherein LG is a leaving group, such as halo, mesylate, tosylate or triflate, with Cl being the most preferred, and PG₁ is an amine protecting group, with exemplary groups being an acyl group (such as acetyl), *t*-butoxycarbonyl (*t*-BOC), CH₃OC(O)-, EtOC(O)-, Fmoc, Troc, Phenoc, Teoc, trifluoroacetyl, benzyloxy carbonyl, PhC(O)-, 2,5-dimethylpyrrole, phthalimide, 2,3-dichloromaleimide, succinimide, dihydrophthalimide or maleimide. It is also preferable that PG₁ be removed using an acid. One skilled in the art would also know of other suitable leaving groups, which could be utilized. The more preferred protecting groups are acetyl, *t*-BOC, trifluoroacetamide, benzamide, 2,5-dimethylpyrrole, phthalimide and maleimide, with *t*-BOC and acetyl being the most preferred.

[0060] A embodiment of the method of preparing acid compounds of formula (VII) is wherein the method further comprises the steps of alkylating a compound of formula (VI) with a primary amine of the formula NH₂R₄ to give an aminoester intermediate and subsequently protecting the aminoester intermediate

by alkylating on a protecting group to form an ester compound of formula (VII'). In this embodiment is also preferable that the compounds of formula (VII) be defined by z being 0, y being 1 and V being ethylene. More preferably R₄ is methyl, ethyl, propyl or isopropyl. A specific embodiment is where the acid compound of formula (VII) is



[0061] The preferred compounds synthesized by the present invention include:

(*E*) *N*-{4-[3-chloro-4-fluoroanilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(methylamino)-2-butenamide;

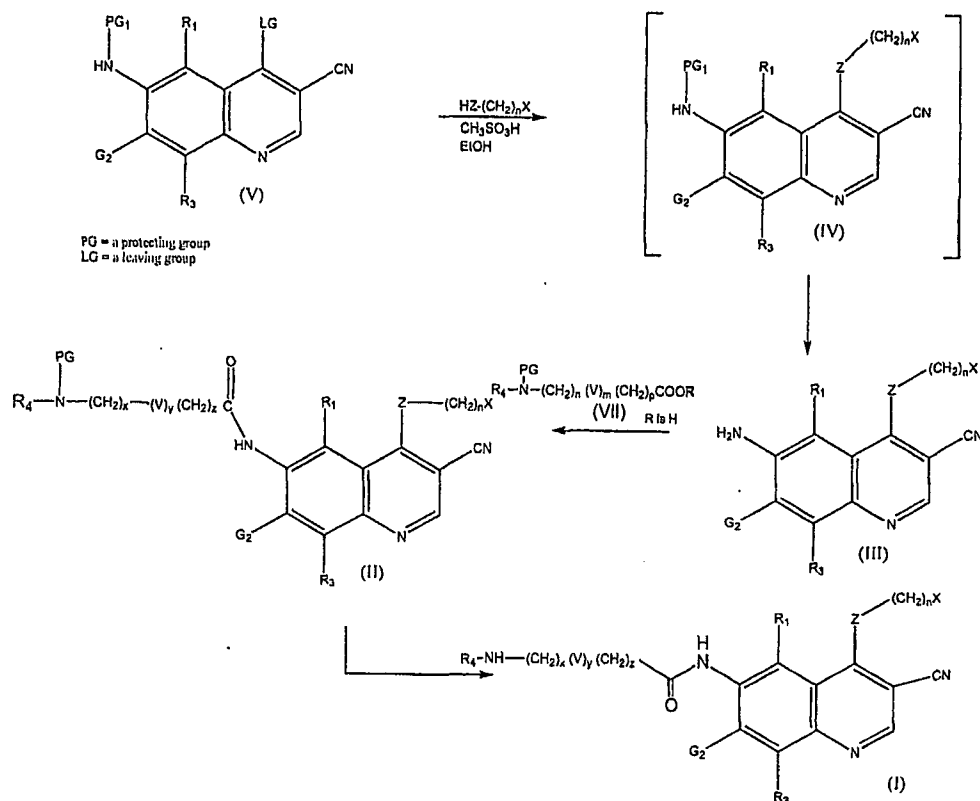
(*E*) *N*-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(methylamino)-2-butenamide;

(*E*) *N*-{4-[3-chloro-4-(3-fluorobenzyloxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(methylamino)-2-butenamide; and

(*E*) *N*-{4-[(3-chloro-4-benzyloxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(methylamino)-2-butenamide.

General Synthesis

Scheme 1

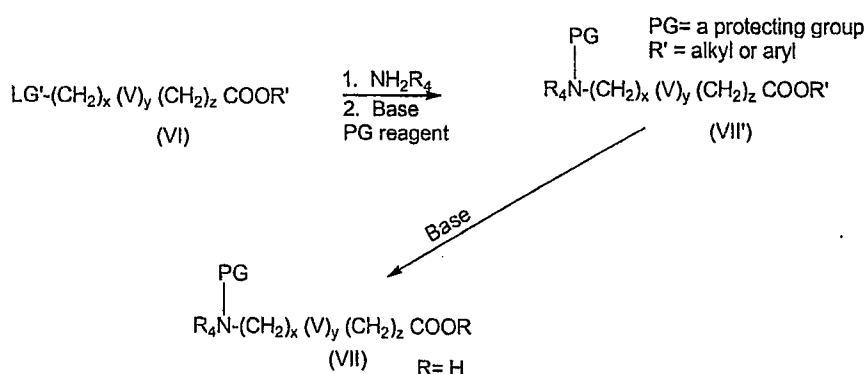


[0062] Scheme 1 illustrates the synthesis of a des-alkylaminoquinoline of formula (I) from the starting protected anilinoquinoline of formula (V), wherein the protecting groups can be any one of those usually employed to protect an amine, such as an acyl group (such as acetyl), t-butoxycarbonyl (t-BOC), benzyloxycarbonyl, $\text{CH}_3\text{OC}(\text{O})-$, $\text{EtOC}(\text{O})-$, Fmoc, Troc, Phenoc, Teoc, $\text{PhC}(\text{O})-$ groups, cyclicimides (e.g. phthalimide, maleimide, 2,3-dichloromaleimide, succinimide and dihydrophthalimide) or a pyrrole (e.g. dimethyl pyrrole). The protected anilinoquinoline is first reacted with methylsulfonic acid and a reagent of formula $\text{HZ}-(\text{CH}_2)_n\text{X}$, wherein Z can be $\text{NR}^{Z'}$, O or S and $\text{R}^{Z'}$ is H or alkyl, n is 0 or 1 and X is as previously defined, to form the intermediate of formula (IV). Reagents such as pyridinium hydrochloride, HCl, sulfuric acid, trifluoroacetic acid, and the like, can be used in place of methylsulfonic acid. The intermediate is then deprotected to provide the anilinoquinoline of formula (III).

[0063] The anilinoquinoline of formula (III) is then coupled with an acid of formula (VII) using a standard coupling reagent such as DCC, benzotriazalyloxytrispyrrolidinophosphonium hexafluorophosphate (PyBoP), or N-ethyl-(N'-3-dimethylaminopropyl)-carbodiimide HCl (EDCI) with 1-hydroxybenzotriazole (HOBt). The technical literature is replete with other coupling reagents and one skilled the art would be aware of such reagents. DCC is preferable. The acid of formula (VII) is defined by V being an ethylene or an acetylene group, x is 0, 1, 2, or 3, y is 0 or 1, z is 0, 1, 2 or 3, R is H, R₄ is an alkyl group of 1 to 6 carbon atoms and PG is an amine protecting group that is stable to basic conditions, such as an acyl group (such as acetyl), t-butoxycarbonyl (t-BOC), benzyloxycarbonyl, CH₃OC(O)-, EtOC(O)-, Fmoc, Troc, Phenoc, Teoc or PhC(O)-. The most preferred is t-BOC. This is not intended to be an exhaustive list and one skilled in the art would be aware of other suitable protecting groups. The synthesis of such acid compounds is shown in Scheme 2 below. This coupling reaction produces compounds of formula (II).

[0064] Amidoquinolines of formula (II) can then be deprotected under acid or neutral conditions to provide the des-alkyl metabolites of formula (I). If PG is a t-BOC group then the acid is preferably HCl, though other acids are also suitable.

Scheme 2

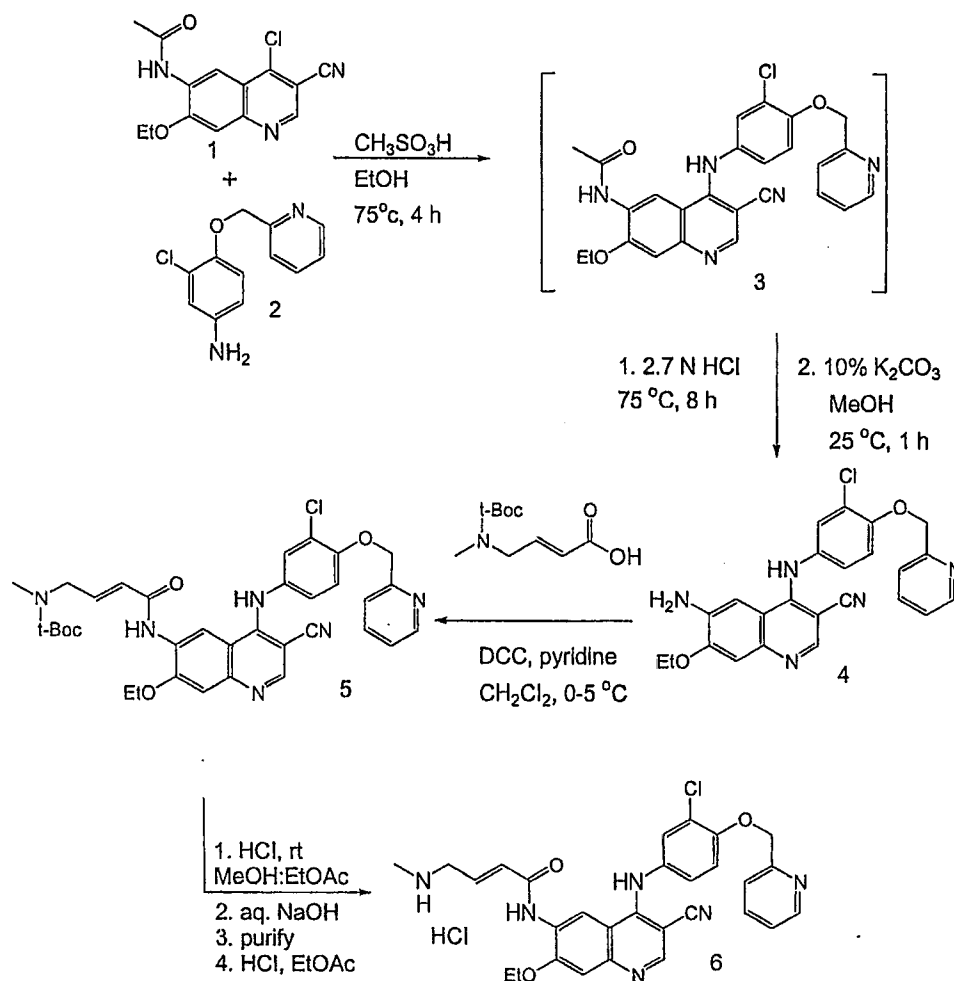


[0065] As illustrated in Scheme 2, esters of formula (VI), wherein LG' is a leaving group, such as halo, mesylate, tosylate or triflate, and R' is alkyl or aryl, are reacted first with primary amines and second with reagent that alkylates a protecting group on the amine nitrogen to give protected alkylamino esters of

formula (VII'). Halogens are the preferred leaving group, especially bromine. The protecting group can be any of the commonly used amine protecting groups that are stable to basic conditions, such as an acyl group (such as acetyl), t-butoxycarbonyl (t-BOC), benzyloxycarbonyl, $\text{CH}_3\text{OC(O)-}$, EtOC(O)- , Fmoc, Troc, Phenoc, Teoc or PhC(O)- . Tert-butoxycarbonyl is the most preferred, and $(\text{BOC})_2\text{O}$ is the most preferred reagent for installing the protecting group. Saponification of the esters provides the corresponding acids of formula (VII), wherein R is H. Coupling of the acids with substituted 4-anilinoquinolines followed by deprotection provides the des-methyl compounds of formula (I) as shown in Scheme 1.

Specific Synthesis

Scheme 3



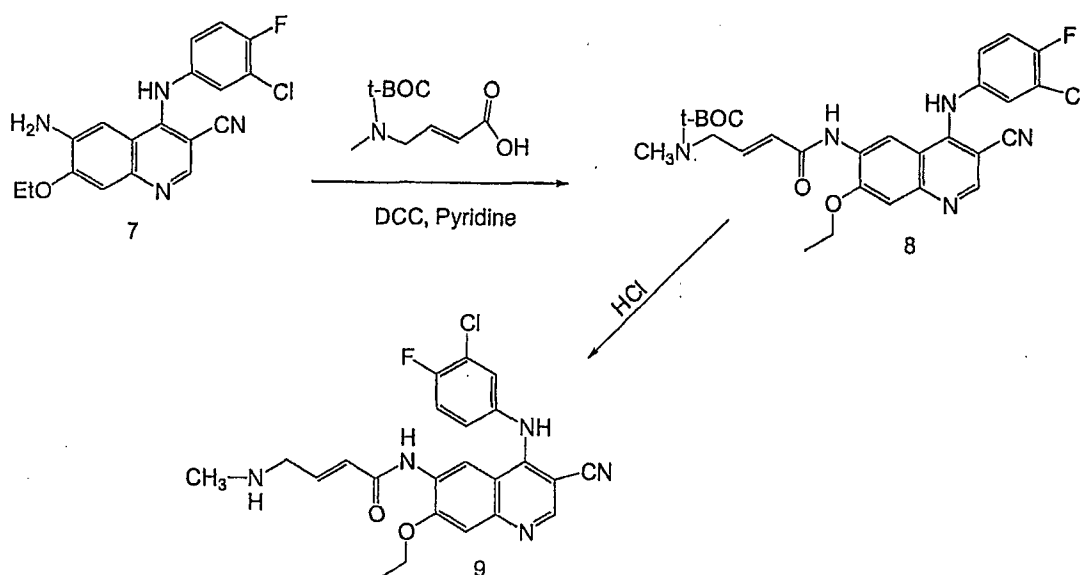
[0066] In Scheme 3 a specific synthesis of 6-(4-alkylamino)-2-butenamidoquinoline 6 is illustrated. Compound 1 is arylated with compound 2 using methanesulfonic acid in ethanol at about 75°C to give intermediate 3. This intermediate is then deprotected under acidic conditions using approximately 2.7 M HCl and heating at 75°C. A basic work up with potassium carbonate then affords 6-aminoquinoline 4.

[0067] Compound 4 is then coupled with t-BOC protected 4-methylaminocrotonic acid using DCC and pyridine at about ice bath temperatures to yield compound 5. Compound 5 is subsequently deprotected using mild HCl

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conditions and a basic work up to provide the free base of 6-(4-alkylamino)-2-butenamido quinoline 6. After purification, the corresponding HCl salt can be formed by exposing the compound to HCl in ethylacetate.

Scheme 4

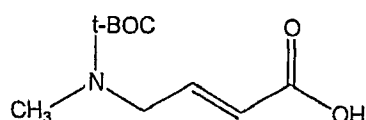


[0068] Scheme 4 shows the synthesis of 6-(4-alkylamino)-2-butenamidoquinoline 9. Compound 7 was formed analogous to compound 4 in Scheme 3, substituting 3-chloro-4-fluoroaniline for 3-chloro-4-(2-pyridinylmethoxy)aniline. Compound 7 is then coupled with t-BOC protected 4-methylaminocrotonic acid using DCC and pyridine to give compound 8, which is subsequently deprotected using HCl to provide 6-(4-alkylamino)-2-butenamidoquinoline 9.

[0069] The following are examples prepared using the methods illustrated in the above schemes. These examples are only some of the compounds envisioned by the present invention and should not be viewed as limiting the present invention in any way.

EXAMPLE 1

4-[N-(t-butyloxycarbonyl)methylamino] crotonic acid



Preparation of methyl 4-methylamino-crotonate HCl.

[0070] A solution of methyl 4-bromocrotonate (66 mL, 0.56 mol) in THF (500 mL) and a solution of 2.0 M methylamine in THF (700 mL, 1.4 mol) were added through additional funnel simultaneously at -20°C over 30 min. The reaction mixture was a light yellow suspension. After addition, the reaction mixture was stirred at -5°C for 2 h, then filtered and washed with THF (2 x 30 mL). The filtrate was concentrated *in vacuo* to give a brown oil. A solution of HCl in IPA (10.5%, 200 mL) was added to the brown oil through an additional funnel at $0-5^{\circ}\text{C}$. The reaction mixture was stirred for 30 min, and then concentrated *in vacuo* to give brown red oil. CH_2Cl_2 (~20 mL) was added and the solution placed in the refrigerator ($\sim 5^{\circ}\text{C}$) to allow for crystallization. The mother liquor gave several batches of crystals. The combined batches were recrystallized from CH_2Cl_2 to obtain 17 g (22% yield) of the desired compound as a colorless solid. ^1H NMR (CDCl_3 , ppm) δ 7.02 (m, 1H), 6.28 (d, 1H), 3.80 (s, 2H), 3.77 (s, 3H), 2.70 (t, 3H); ^{13}C NMR ($\text{DMSO}-d_6$, ppm) δ 165.11, 138.39, 125.43, 51.62, 47.69, 31.81; IR (KBr): ν_{max} 3426, 3285, 3037, 2954, 2805, 2423, 1719, 1667, 1438, 1348, 1272, 1209, 1158, 1027, 1000 cm^{-1} ; Anal. Calc'd for $\text{C}_6\text{H}_{12}\text{ClNO}_2$: C, 43.51; H, 7.30; N, 8.46. Found: C, 43.42; H, 7.36; N, 8.37.

Preparation of methyl 4-[N-(t-butyloxycarbonyl)methylamino] crotonate.

[0071] To a suspension of methyl 4-methylamino-crotonate (14.1 g, 85.3 mmol) in CH_2Cl_2 (150 mL) were added DMAP (10.4 g, 85.3 mmol) and triethylamine (25 mL, 179.2 mmol) while cooling in an ice bath. To this suspension $(\text{Boc})_2\text{O}$ (22.4 g, 102.4 mmol) in CH_2Cl_2 (50 mL) was added slowly. The reaction mixture was stirred at room temperature for 19 h under N_2 , then quenched with H_2O (150 mL). The organic layer was washed with H_2O (2 x 150 mL), 3 N HCl (200 mL), followed by H_2O (100 mL). The organic layer was dried over Na_2SO_4 ,

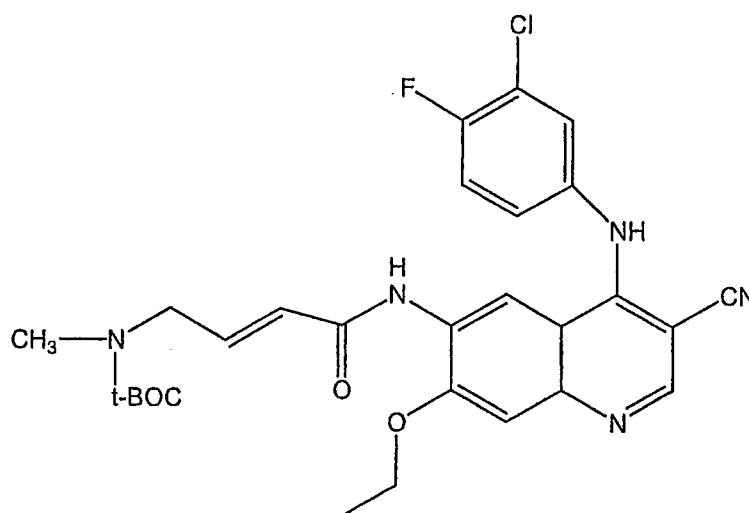
filtered and concentrated *in vacuo* to give 17.3 g (89% yield) of N-Boc Methyl Crotonate as a brown oil. ^1H NMR (CDCl_3 , ppm) δ 6.87 (m, 1H), 5.84 (d, 1H), 3.99 (bs, 2H, NCH_2), 3.75 (s, 3H), 2.85 (bs, 3H), 1.46 (s, 9H); ^{13}C NMR (CDCl_3 , ppm) δ 166.51, 155.38, 143.91, 121.37, 79.98, 51.61, 49.64, 34.36, 28.55; IR (KBr): ν_{max} 3591, 3441, 2976, 2953, 1726, 1699, 1480, 1452, 1392, 1366, 1276, 1228, 1169, 1148, 1039, 947 cm^{-1} ; Anal. Calc'd for $\text{C}_{11}\text{H}_{19}\text{NO}_4$: C, 57.62; H, 8.35; N, 6.11. Found: C, 57.86; H, 8.57; N, 6.30.

Preparation of 4-[N-(t-butyloxycarbonyl)methylamino]-crotonic acid.

[0072] To a solution of methyl 4-[N-(t-butyloxycarbonyl)methylamino]-crotonate (17.5 g, 76.3 mmol) in THF (200 mL) cooled in an ice bath, KOH (17.1 g, 305 mmol) in H_2O (100 mL) was added through an additional funnel. The reaction mixture was stirred in the ice bath for 15 min before removed to stir at room temperature under N_2 . After 16 h, the reaction mixture was concentrated *in vacuo* to give an aqueous layer. The aqueous layer was washed with CH_2Cl_2 (2 x 60 mL) to remove organic impurities, then acidified to $\text{pH} = 1\sim 2$ with 3 N HCl (~130 mL). The aqueous layer was extracted with CH_2Cl_2 (4 x 80 mL). The combined organic layer was dried over Na_2SO_4 , filtered and concentrated *in vacuo* to give 16.0 g (97.5% yield) of the titled compound as a light yellow oil. ^1H NMR (CDCl_3 , ppm) δ 6.98 (m, H), 5.85 (d, 1H), 3.99 (bs, 2H), 2.87 (bs, 3H), 1.46 (s, 9H); ^{13}C -NMR (CDCl_3 , ppm) δ 170.34, 155.72, 145.60, 121.44, 80.18, 49.70, 34.47, 28.23; IR (KBr): ν_{max} 3417, 3144, 2977, 2934, 1699, 1482, 1455, 1394, 1368, 1252, 1152, 948 cm^{-1} ; Anal. Calcd for $\text{C}_{10}\text{H}_{17}\text{NO}_4$: C, 55.80; H, 7.96; N, 6.51. Found: C, 54.46; H, 8.10; N, 6.32.

EXAMPLE 2

(*E*) *N*-{4-[3-chloro-4-fluorophenylamino]-3-cyano-7-ethoxy-6-quinolinyl}-4-[*N*-(*t*-butyloxycarbonyl)methylamino]-2-butenamide



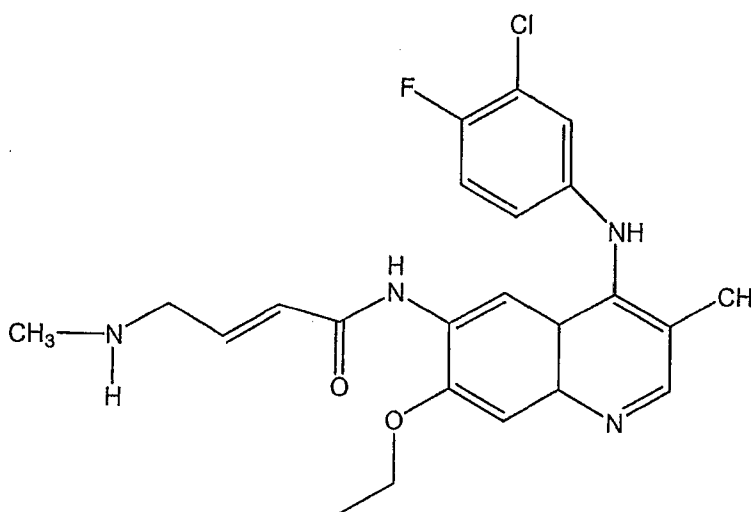
Coupling of *N*-Boc Crotonic Acid with 4-(3-chloro-4-fluorophenylamino)-3-cyano-7-ethoxy-quinoline.

[0073] To a solution of 4-[*N*-(*t*-butyloxy carbonyl) methylamino]-crotonic acid (16.0 g, 74.4 mmol) in CH_2Cl_2 (150 mL), cooled in an ice bath, were added pyridine (60 mL, 744 mmol) and DCC (15.3 g, 74.4 mmol). A suspension of 4-(3-chloro-4-fluorophenylamino)-3-cyano-7-ethoxy-quinoline (13.3 g, 37.2 mmol) in CH_2Cl_2 (100 mL) was added slowly. The reaction flask was covered by alumina foil, stirred at rt under N_2 . After 3 d, the reaction mixture was diluted with CH_2Cl_2 (120 mL), then filtered. The filtrate was washed with H_2O (2 x 60 mL), 2 N HCl (2 x 60 mL), and H_2O (60 mL). The organic layer was dried over Na_2SO_4 , filtered and concentrated *in vacuo* to give crude product as a brown red residue. Purification *via* SiO_2 , eluted with EtOAc to give 7.5 g of 6-(4-[*N*-(*t*-butyloxycarbonyl)-methylamino]-but-2-enyl)-4-(3-chloro-4-fluorophenylamino)-3-cyano-7-ethoxy-quinoline. Recrystallization from ethyl acetate gave 4.9 g (12% yield) of the compound as a light yellow solid. ^1H NMR (CDCl_3 , ppm) δ 9.17 (s, 1H), 8.46 (s, 1H), 7.99 (s, 1H), 7.19-6.96 (m, 3H), 6.83 (m, 1H), 6.05 (d, 1H), 4.25 (q, 2H), 4.02 (bs, 2H), 2.85 (bs, 3H), 1.53 (t, 3H),

1.47 (s, 9H); IR (Nujol): $\nu_{\max}$ 3313, 2951, 2855, 2218, 1707, 1679, 1640, 1531, 1502, 1458, 1377, 1273, 1164, 1146, 1042, 869, 855, 774 cm^{-1} ; m.p.: 106.5-108.0°C; Anal. Calcd for $\text{C}_{28}\text{H}_{29}\text{N}_5\text{O}_4\text{ClF}$: C, 60.76; H, 5.24; N, 12.66. Found: C, 59.70; H, 5.89; N, 10.83.

EXAMPLE 3

(*E*) *N*-{4-[3-chloro-4-fluoroanilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(methylamino)-2-butenamide



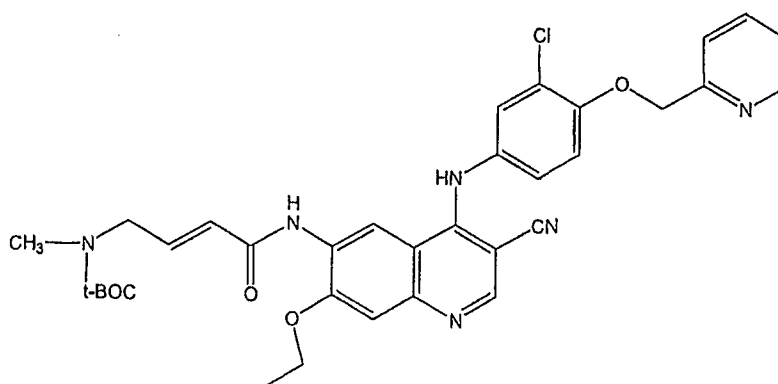
Hydrolysis of t-BOC protecting group.

[0074] To a suspension of the compound of Example 2 (1.86 g, 3.36 mmol) in MeOH (20 mL), was added 1.2 N of HCl in ethyl acetate (74 mL) slowly. The yellow cloudy mixture was stirred at room temperature under N_2 . After 6.5 h, the reaction mixture was concentrated *in vacuo* to give a yellow solid. After purification by crystallization in (60:40) MeOH/IPA, 1.41 g, (80.1 % yield, 96.9 area% by HPLC) of the hydrochloride salt of the titled compound was obtained as a light yellow solid. ^1H NMR (DMSO, ppm) δ 11.1 (bs, 1H), 9.98 (s, 1H), 9.36 (bs, 2H), 9.13 (s, 1H), 9.00 (s, 1H), 7.75 (dd, 1H, $J=3$ Hz, 6Hz), 7.65 (s, 1H), 7.55 (t, 1H, $J=8$ Hz), 7.46-7.48 (m, 1H), 6.75-6.87 (m, 2H), 4.35 (q, 2H, $J=5.1$ Hz), 3.76-3.80 (m, 2H), 2.56 (t, 3H, $J=4.0$ Hz), 1.50 (t, 3H, $J=5.3$ Hz); ^{13}C NMR (DMSO, ppm) δ 163.14, 155.59, 155.36, 153.59, 149.46, 135.77, 135.14, 129.6, 129.0, 128.3, 127.1, 120.3, 120.1, 117.8, 117.6, 116.9, 115.0, 112.9, 87.2, 65.7,

48.6, 32.4, 14.4; IR (Nujol): $\nu_{\max}$ 3580, 3497, 3192, 2900, 2691, 2403, 2224, 1682, 1640, 1584, 1536, 1492, 1460, 1377, 1314, 1264, 1193, 885, 729 cm^{-1} .

EXAMPLE 4

(*E*) *N*-{4-[3-Chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-[*N*-(*t*-butoxycarbonyl)methylamino]-2-butenamide



Preparation of methyl 4-[*N*-(*tert*-butoxycarbonyl)methylamino] crotonate.

[0075] Cool a 4-neck 1-L flask to -15 to -25 °C. Charge an addition funnel with methyl 4-bromocrotonate (25.0 g, 0.118 mole at 85% strength) in THF (125 ml). Charge a second addition funnel with 2.0 M methylamine solution in THF (149 ml, 0.30 mole, 2.5 eq). Add both solutions dropwise and simultaneously over 30 min maintaining the pot temperature at to -15 to -25 °C. Warm the mixture to -10 to -5 °C and hold for 2 h. Add 2.0 M methylamine solution in THF (50 ml, 0.10 mole) if necessary to complete the reaction. When no starting material is detected by TLC (9:1 heptane:EtOAc), cool the reaction mixture to -60 to -65 °C. Add triethylamine (60.0 g, 82.5 ml, 0.59 mole, 5 eq). Add dropwise a solution of di-*t*-butyl dicarbonate (103.75 g, 0.475 mole, 4 eq) in THF (250 ml) over 1h. Hold the mixture overnight while allowing it to warm to room temperature. Check that the reaction is complete by TLC (9:1 heptane:EtOAc). The precipitates are filtered off and the mixture is concentrated to an oil. The oil is re-dissolved in CH_2Cl_2 (250 ml), washed consecutively with water (125 ml), 1 N HCl (125 ml) and water (2 x 125 ml). The organic layer is dried over sodium sulfate (50 g) for 10 mins. The mixture is filtered and concentrated to an oil,

which was passed through a silica gel pad to obtain *N*-*t*-Boc-4-*N*-methylaminocrotonate (19.7 g, 73 %). ¹H NMR (DMSO, ppm) δ 6.79 (dt, 1H, CH₂CH=CH), 5.81 (dt, 1H, CH₂CH=CH), 3.96 (m, 2H, NCH₂), 3.67 (s, 3H, OCH₃), 2.78 (s, 3H, NCH₃), 1.37 (s, 9H, *t*-butyl).

Preparation of methyl 4-[*N*-(tert-butyloxycarbonyl)methylamino] crotonic acid. [0076] Charge a 3-neck 1-L flask with *N*-*t*-Boc-4-*N*-methylaminocrotonate (25.0 g, 0.11 mole) in THF (290 ml) and cool to 0-5 °C. Dissolve a solution of potassium hydroxide (29.0 g, 85%, 0.44 mole, 4.0 eq) in water (145 ml) and add dropwise over 30 min keeping the pot temperature at 0-10 °C. The pH at this stage is 11-12. Stir for 15 min, then warm the mixture to room temperature overnight. After reaction determined to be complete by TLC (8:2 heptane:EtOAc), the reaction mixture is concentrated under vacuo. The aqueous mixture is washed with CH₂Cl₂ (3 x 100 ml), and then acidified to pH 1-2 with 10% HCl (~150 ml). The mixture is extracted with CH₂Cl₂ (3 x 150 ml). The combined organics are dried over Na₂SO₄, filtered and concentrated under *vacuo* to give *N*-*t*-Boc-4-*N*-methylaminocrotonic acid (18.0 g, 75%) as a light yellow oil. ¹H NMR (DMSO, ppm) δ 12.28 (bs, 1H, COOH, D₂O exchangeable), 6.75 (dt, 1H, CH₂CH=CH), 5.75 (dt, 1H, CH₂CH=CH), 3.96 (m, 2H, NCH₂), 2.78 (s, 3H, NCH₃), 1.39 (s, 9H, *t*-butyl).

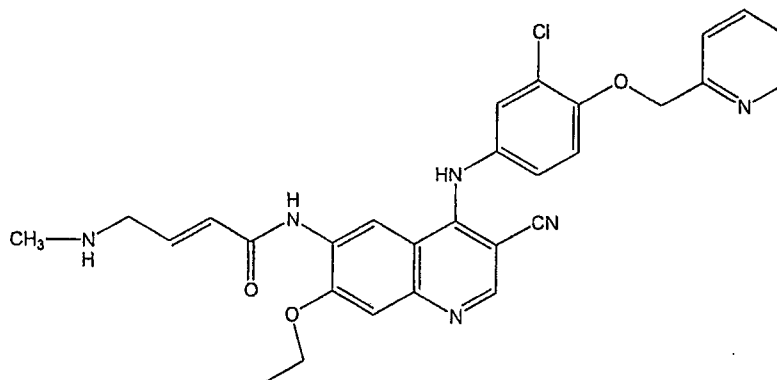
EXAMPLE 5

Preparation of (*E*) *N*-{4-[3-Chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinoliny]-4-[*N*-(*t*-butyloxycarbonyl)methylamino]-2-butenamide. [0077] A solution of *N*-*t*-Boc-4-*N*-methylaminocrotonic acid (18.0 g, 84 mmole, 2.0 eq) in CH₂Cl₂ (171 ml) was cooled to 0-10 °C. Pyridine (68 ml, 840 mmol, 20 eq) and DCC (17.5 g, 84 mmole, 2 eq) were added. A suspension of 6-amino-*N*-4-[3-Chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinoline (19.0 g, 42 mmole) in CH₂Cl₂ (143 ml) was added dropwise and the reaction mixture was held for 5.5 days and monitored by HPLC. The reaction mixture was then diluted with CH₂Cl₂ (120 ml). The mixture was filtered and filtrates were washed with water (2 x 100 ml), 1N HCl (2 x 60 ml) and water (2 x 100

mL), dried over MgSO_4 , filtered and concentrated under *vacuo* to give the crude product as a brown red residue. The crude product was purified by chromatography (CH_2Cl_2 with 0 to 2 % MeOH) to give 15.0 g (56%, ~57% strength by HPLC area) of (*E*) *N*-{4-[3-Chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-[*N*-(*t*-butyloxycarbonyl)methylamino]-2-butenamide. ^1H NMR (DMSO, ppm) δ 9.61 (s, 1H, NH), 9.57 (s, 1H, NH), 8.91 (s, 1H, Ar), 8.60 (m, 1H, Ar), 8.47 (s, 1H, Ar), 7.87 (m, 1H, Ar), 7.58 (m, 1H, Ar), 7.39-7.18 (m, 5H, Ar), 6.74 (dt, 1H, $\text{CH}_2\text{CH}=\text{CH}$), 6.47 (d, 1H, $\text{CH}_2\text{CH}=\text{CH}$), 5.29 (s, 2H, $-\text{OCH}_2\text{Pyr}$), 4.32 (q, 2H, OCH_2CH_3), 3.99 (m, 2H, NCH_2), 3.32 (s, 3H, NCH_3), 1.41 (s, 9H, $(\text{CH}_3)_3\text{C}$).

EXAMPLE 6

(*E*) *N*-{4-[3-Chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(methylamino)-2-butenamide



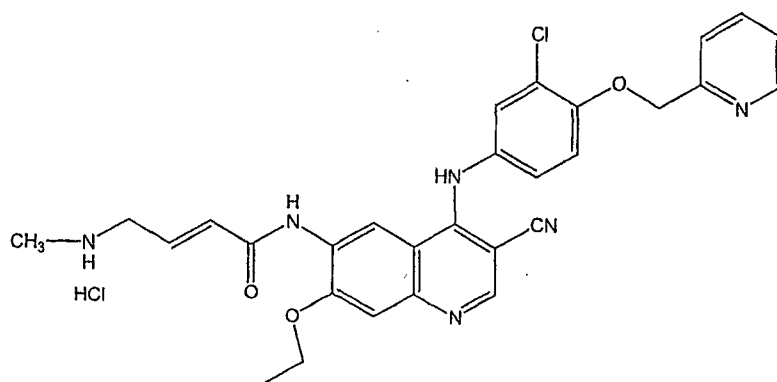
Preparation of (*E*) *N*-{4-[3-Chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(methylamino)-2-butenamide free base.

[0078] To a suspension of (*E*) *N*-{4-[3-Chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-[*N*-(*t*-butyloxycarbonyl)methylamino]-2-butenamide (14.0 g, 21.8 mmole) in methanol (120 ml) was added 1.1 N HCl in ethyl acetate (515 ml) dropwise over 2 h. The resulting yellow suspension mixture was stirred at room temperature for 7.5 h. The reaction mixture was basified by adding 5% aq. NaOH (500 ml) to pH 8. The organic layer was separated, and aq. layer was extracted with EtOAc/MeOH (3 x 200 ml, 9:1),

CH₂Cl₂/MeOH (3 x 200 ml, 9:1). The combined organic layers were dried over MgSO₄ and concentrated. The residue was purified by chromatography to produce 7.8 g, which was slurried in cold MeOH (210 ml) and filtered to obtain 5.23 g of the titled product (44%,) after washing with cold MeOH (65 ml) and vacuum drying at room temperature. ¹H NMR (CDCl₃, ppm) δ 9.17 (s, 1H, NH), 8.59 (m, 1H, NH), 8.41 (s, 1H, Ar), 7.97(s, 1H, Ar), 7.92 (s, 1H, Ar), 7.76 (m, 1H, Ar), 7.64 (d, 1H, Ar), 7.24 (m, 1H, Ar), 7.14 (m, 2H, Ar), 7.09 (m, 1H, Ar), 6.89 (m, 1H, Ar), 6.83 (d, 1H, CH₂CH=CH), 6.14 (dt, 1H, CH₂CH=CH), 5.24 (s, 2H, -OCH₂Pyr), 4.20 (q, 2H, -OCH₂CH₃), 3.38 (m, 2H, NCH₂CH), 2.11 (s, 3H, NCH₃), 1.52 (t, 3H, CH₂CH₃). ¹³C NMR: δ (CDCl₃) 164.6, 156.8, 152.6, 151.2, 150.6, 149.3, 147.4, 145.5, 137.2, 133.0, 128.0, 127.6, 124.8, 123.7, 123.5, 123.0, 121.4, 117.3, 113.7, 113.3, 109.8, 108.8, 88.0, 71.6, 65.2, 52.5, 36.5, 14.8.

EXAMPLE 7

(*E*) *N*-{4-[3-Chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinoliny]-4-(methylamino)-2-butenamide hydrochloride.



[0079] To a solution of (*E*) *N*-{4-[3-Chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinoliny]-4-(methylamino)-2-butenamide free base (4.40 g, 8.12 mmole) dissolved in a mixture of methanol (10 ml) and methylene chloride (50 ml). The solution was added dropwise over 15-20 mins. to a solution of 1.28 N HCl in ethyl acetate (75 ml) and then rinsed with methylene chloride (5 ml). Some fuming occurs and precipitates formed. The mixture is held at room temperature for 20 mins., filtered and washed with ethyl acetate (20 ml). The

yellow solids are dried under pump vacuum for 3 h at room temperature to provide 4.24 g (90% yield) of the titled compound. ¹H NMR (DMSO, ppm) δ 11.43 (bs, 1H, NH), 10.04 (s, 1H, NH), 9.74 (bd, 2H, NH, HC1), 9.18 (s, 1H, Ar), 9.04 (s, 1H, Ar), 8.91 (d, 1H, Ar), 8.50 (dt, 1H, Ar), 8.05 (d, 1H, Ar), 7.93 (t, 1H, Ar), 7.85 (s, 1H, Ar), 7.71 (d, 1H, Ar), 7.49 (dd, 1H, Ar), 7.42 (d, 1H, Ar), 6.97-6.85 (dt, 1H, CH₂CH=CH), 6.81 (d, 1H, CH₂CH=CH), 5.66 (s, 2H, -OCH₂Pyr), 4.33 (q, 2H, -OCH₂CH₃), 3.78 (dd, 2H, NHCH₂CH), 2.54 (t, 3H, NCH₃), 1.51 (t, 3H, CH₂CH₃). ¹³C NMR: δ (DMSO-d₆) 14.7, 32.6, 48.9, 66.2, 68.2, 86.8, 101.6, 112.7, 114.6, 115.3, 117.9, 122.6, 125.5, 126.6, 127.7, 129.2, 129.5, 129.9, 132.5, 135.6, 137.7, 144.4, 145.1, 148.6, 152.4, 153.3, 154.8, 156.4, 163.6.

ANALYSIS

[0080] NMR spectra were recorded on a GE QE 300, a Bruker DPX 301 or a Varian Inova 300 at 300 MHz (¹H) and at 75 or 300 MHz (¹³C) and chemical shifts were identified in ppm relative to TMS internal standard. Analytical and preparative TLCs were performed on Silica Gel 60 F-254 pre-coated plates obtained from EM Science. Compounds were visualized using UV at 254 nm, bromocresol green indicator, or phosphomolybdic acid reagents (20 wt% in EtOH). HPLC analysis was determined on a Waters Alliance 2695 HPLC instrument equipped with a PDA (Model 2996) detector. IR spectra were recorded on a Mattson 5020 FT-IR.

BIOLOGICAL DATA

Kinase assays

[0081] The activity of (*E*) *N*-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(methylamino)-2-butenamide, example 6, was first determined in a HER-2 autophosphorylation assay using the cytoplasmic kinase domain of HER-2. (*E*) *N*-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(methylamino)-2-butenamide reduced receptor autophosphorylation by 50% (IC₅₀) at 3.4 nM (Table 1). This is similar to the IC₅₀ of the dimethylamino compound from which it is metabolized from, (*E*) *N*-

{4-[3-Chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(dimethylamino)-2-butenamide, in this assay (1.1 nM).

TABLE 1. HER-2 AUTOPHOSPHORYLATION ASSAY

COMPOUND	IC ₅₀ (nM) ^a
Dimethylamino	1.1 ± 0.6 (2)
Des-methylamino, (Ex. 6)	3.4 ± 1.6 (2)

Purified recombinant C-terminal fragment of HER-2 was incubated with ATP in the absence or presence of a range of compound concentrations. Autophosphorylation of the receptor was determined using phosphotyrosine antibodies. The concentration of compound that inhibits phosphorylation by 50% is shown.

^a: Mean and SE with the number of independent determinations in parentheses.

[0082] The activity of (*E*) *N*-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(methylamino)-2-butenamide was also tested in a proprietary kinase assay (³³PanQinase[®] assay; ProQinase, Freiburg, Germany) using HER-2 and the related ErbB kinases, EGFR and HER-4, and is shown in Table 2. Here, the ability of the compound to inhibit phosphorylation of a substrate peptide [poly (Glu-Tyr) or poly(Ala-Glu-Lys-Tyr)] was determined. (*E*) *N*-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(methylamino)-2-butenamide inhibited the activity of HER-2 (IC₅₀ = 21 nM), EGFR (IC₅₀ = 7 nM) and HER-4 (IC₅₀ =13 nM). When compared to the dimethylamino derivative, (*E*) *N*-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(methylamino)-2-butenamide showed similar activity against all three kinases in this assay.

TABLE 2. ErbB SUBSTRATE PHOSPHORYLATION ASSAY

COMPOUND	IC ₅₀ (nM)		
	EGFR	HER-2	HER-4
Dimethylamino	12	39	19
Des-methylamino, (Ex. 6)	7	21	13

Purified recombinant C-terminal domain of the ErbB receptors were incubated with [³³P]-ATP and peptide substrate in the absence or presence of a range of compound concentrations. The concentration of compound that inhibits phosphorylation of the peptide by 50% is shown.

Cell proliferation assays

[0083] (*E*) *N*-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(methylamino)-2-butenamide inhibited the proliferation of 3T3/*neu*, a mouse fibroblast cell line transfected with the HER-2 oncogene (IC₅₀

= 40 nM), while having a minimal effect on the isogenic untransfected cells (IC₅₀ = 5460 nM; Table 3). It also inhibited two other breast cancer cell lines that overexpress HER-2, BT474 and SK-Br-3 (IC₅₀ 3, 34 nM, respectively). Consistent with the effect in the EGFR kinase assay, the des-methylamino compound also inhibited the EGFR-dependent cell line, A431 (IC₅₀ = 67 nM). It was substantially less active against SW620 colon carcinoma cells that express neither receptor (IC₅₀ = 1604 nM). When compared with the dimethylamino compound, (E) N-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(methylamino)-2-butenamide was 8-fold less potent against 3T3/*neu* cells, but as potent against other HER-2 and EGFR-expressing cell lines.

TABLE 3. CELL PROLIFERATION ASSAYS

CELL LINE	HER-2	EGFR	IC ₅₀ (nM) ^a	
			Dimethylamino	Des-myhtlamino (Ex. 6)
3T3	-	-	2191 ± 700 (2)	5460 ± 659 (3)
3T3/ <i>neu</i>	+++	-	5 ± 0.2 (2)	40 ± 4 (3)
A431	+	+++	64 ± 3 (2)	67 ± 7 (3)
SK-Br-3	+++	-	36 ± 20 (2)	34 ± 4 (3)
BT474	+++	+	2 ± 0.2 (2)	3 ± 0.5 (3)
SW620	-	-	1215 ± 246 (2)	1604 ± 138 (3)

Cells were incubated with various concentrations of compound for 2 days (6 days for BT474). Cell survival was determined using a protein binding dye assay (SRB). The concentration of compound that reduces cell survival by 50% is shown. Relative expression of EGFR and HER-2 in the cell lines are indicated.

^a Mean and SE are shown with the number of independent determinations in parentheses.

In Vivo Activity

[0084] The *in vivo* activity of (E) N-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(methylamino)-2-butenamide was first studied in xenografts of 3T3/*neu*. Daily oral administration of the compound between 5 and 40 mg/kg/day had no effect on tumor growth, while good antitumor activity was observed for dimethylamino compound at 40 mg/kg/day (74% inhibition, day 18; data not shown). In a second independent test, increasing the dose of the des-methylamino compound to 100 mg/kg/day also had no effect on tumor growth (Table 4), while the dimethylamino

compound showed good antitumor activity between 40 and 80 mg/kg/day (93-100% inhibition, day 14).

[0085] In animals bearing BT474 xenografts, treatment of animals with (E) N-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(methylamino)-2-butenamide had no effect at 10-40 mg/kg/day, as shown in Table 4. In contrast, treatment with the dimethylamino compound at the same doses showed good antitumor activity. Maximum tumor inhibition was observed on day 21 ranging from 64% (10 mg/kg/day) to 97% (40 mg/kg/day).

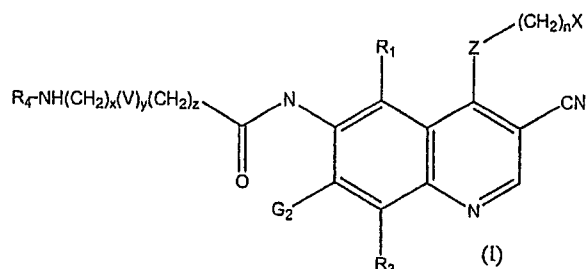
TABLE 4. EFFECT ON TUMOR XENOGRAPHS

Compound	Dose	% T/C (p-value)				
		Day 7/8*	Day 14	Day 21	Day 28	Day 35
3T3/ <i>neu</i> tumors						
Des-methylamino, (Ex. 6)	100	140 (1.00)	113 (0.93)			
Dimethylamino	80	0 (<0.01)	0 (<0.01)			
	40	1 (<0.01)	7 (<0.01)			
BT474 tumors						
Des-methylamino, (Ex. 6)	40	91 (0.49)	75 (0.26)	75 (0.16)	89 (0.26)	89 (0.37)
	10	71 (0.13)	75 (0.30)	85 (0.43)	86 (0.43)	108 (0.74)
Dimethylamino	40	29 (<0.01)	9 (<0.01)	3 (<0.01)	6 (<0.01)	11 (<0.01)
	10	50 (<0.01)	44 (0.01)	36 (<0.01)	47 (0.01)	72 (0.22)

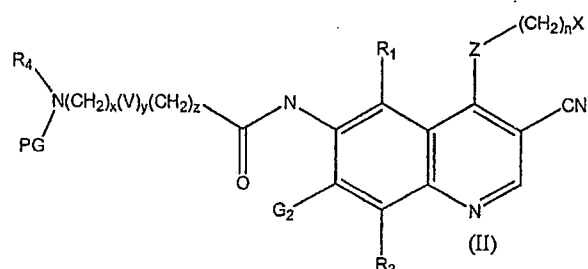
Mice were implanted with 2×10^6 3T3/*neu* cells or a single BT474 tumor fragment (~3 mm³). Animals bearing 3T3/*neu* xenografts were treated with vehicle or compound (10 mice per group) on days 1-10 (PO), beginning the day after implantation. For BT474, tumors were staged when they reached a size of 65-100 mg, animals were assigned to treatment groups (5 mice per group, 10 for vehicle controls), and treated with vehicle or compounds once-daily (PO) on days 1-20. Tumor mass ($[\text{length} \times \text{width}^2]/2$) was determined were once per week. For BT474 xenografts, tumor growth was expressed as Relative Tumor Growth: the ratio of mean tumor mass to the tumor mass on the staging day. %T/C: ratio of tumor burden in treated animals to control animals, expressed as a percentage. Statistical significance was determined using the Students t-test; p<0.05 is considered significant. Doses shown are in mg/kg/day. *, day 8 data for 3T3/*neu* xenografts; day 7 data for BT474 xenografts.

WE CLAIM:

1. A method of preparing a compound of formula (I):



comprising the step of deprotecting a compound of formula (II):



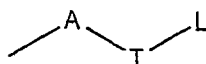
wherein:

X is cycloalkyl of 3 to 7 carbon atoms, which may be optionally substituted with one or more alkyl of 1 to 6 carbon atom groups; or is a pyridinyl, pyrimidinyl, or phenyl ring; wherein the pyridinyl, pyrimidinyl, or phenyl ring may be optionally mono- di-, or tri-substituted with a substituent selected from the group consisting of halogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, azido, hydroxyalkyl of 1-6 carbon atoms, halomethyl, alkoxymethyl of 2-7 carbon atoms, alkanoyloxymethyl of 2-7 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-6 carbon atoms, hydroxy, trifluoromethyl, cyano, nitro, carboxy, carboalkoxy of 2-7 carbon atoms, carboalkyl of 2-7 carbon atoms, phenoxy, phenyl, thiophenoxy, benzoyl, benzyl, amino, alkylamino of 1-6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, phenylamino, benzylamino, alkanoylamino of 1-6 carbon atoms, alkenoylamino of 3-8 carbon atoms, alkynoylamino of 3-8 carbon atoms, carboxyalkyl of 2-7 carbon atoms, carboalkoxyalkyl of 3-8 carbon atoms, aminoalkyl of 1-5 carbon atoms, N-alkylaminoalkyl of 2-9 carbon atoms, N,N-dialkylaminoalkyl of 3-10 carbon

atoms, N-alkylaminoalkoxy of 2-9 carbon atoms, N,N-dialkylaminoalkoxy of 3-10 carbon atoms, mercapto, and benzoylamino; or

X is a bicyclic aryl or bicyclic heteroaryl ring system of 8 to 12 atoms where the bicyclic heteroaryl ring contains 1 to 4 heteroatoms selected from N, O, and S with the proviso that the bicyclic heteroaryl ring does not contain O—O, S—S, or S—O bonds and where the bicyclic aryl or bicyclic heteroaryl ring may be optionally mono- di-, tri, or tetra-substituted with a substituent selected from the group consisting of halogen, oxo, thio, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, azido, hydroxyalkyl of 1-6 carbon atoms, halomethyl, alkoxymethyl of 2-7 carbon atoms, alkanoyloxymethyl of 2-7 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-6 carbon atoms, hydroxy, trifluoromethyl, cyano, nitro, carboxy, carboalkoxy of 2-7 carbon atoms, carboalkyl of 2-7 carbon atoms, phenoxy, phenyl, thiophenoxy, benzoyl, benzyl, amino, alkylamino of 1-6 carbon atoms, dialkyl amino of 2 to 12 carbon atoms, phenylamino, benzylamino, alkanoylamino of 1-6 carbon atoms, alkenoylamino of 3-8 carbon atoms, alkynoylamino of 3-8 carbon atoms, carboxyalkyl of 2-7 carbon atoms, carboalkoxyalkyl of 3-8 carbon atoms, aminoalkyl of 1-5 carbon atoms, N-alkylaminoalkyl of 2-9 carbon atoms, N,N-dialkylaminoalkyl of 3-10 carbon atoms, N-alkylaminoalkoxy of 2-9 carbon atoms, N,N-dialkylaminoalkoxy of 3-10 carbon atoms, mercapto, and benzoylamino; or

X is a radical having the formula:



wherein

A is a pyridinyl, pyrimidinyl, or phenyl ring; wherein the pyridinyl, pyrimidinyl, or phenyl ring may be optionally mono- or di-substituted with a substituent selected from the group consisting of halogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, azido, hydroxyalkyl of 1-6 carbon atoms, halomethyl, alkoxymethyl of 2-7 carbon atoms, alkanoyloxymethyl of 2-7 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-6 carbon atoms, hydroxy, trifluoromethyl, cyano, nitro, carboxy, carboalkoxy of 2-7 carbon atoms, carboalkyl of 2-7 carbon atoms, phenoxy, phenyl, thiophenoxy,

benzoyl, benzyl, amino, alkylamino of 1-6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, phenylamino, benzylamino, alkanoylamino of 1-6 carbon atoms, alkenoylamino of 3-8 carbon atoms, alkynoylamino of 3-8 carbon atoms, carboxyalkyl of 2-7 carbon atoms, carboalkoxyalkyl of 3-8 carbon atoms, aminoalkyl of 1-5 carbon atoms, N-alkylaminoalkyl of 2-9 carbon atoms, N,N-dialkylaminoalkyl of 3-10 carbon atoms, N-alkylaminoalkoxy of 2-9 carbon atoms, N,N-dialkylaminoalkoxy of 3-10 carbon atoms, mercapto, and benzoylamino;

T is bonded to a carbon of A and is:

$\text{—NH(CH}_2\text{)}_m\text{—}$, $\text{—O(CH}_2\text{)}_m\text{—}$, $\text{—S(CH}_2\text{)}_m\text{—}$, $\text{—NR(CH}_2\text{)}_m\text{—}$,
 $\text{—(CH}_2\text{)}_m\text{—}$, $\text{—(CH}_2\text{)}_m\text{NH—}$, $\text{—(CH}_2\text{)}_m\text{O—}$, $\text{—(CH}_2\text{)}_m\text{S—}$, or
 $\text{—(CH}_2\text{)}_m\text{NR—}$;

L is an unsubstituted phenyl ring or a phenyl ring mono-, di-, or tri-substituted with a substituent selected from the group consisting of halogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, azido, hydroxyalkyl of 1-6 carbon atoms, halomethyl, alkoxymethyl of 2-7 carbon atoms, alkanoyloxymethyl of 2-7 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-6 carbon atoms, hydroxy, trifluoromethyl, cyano, nitro, carboxy, carboalkoxy of 2-7 carbon atoms, carboalkyl of 2-7 carbon atoms, phenoxy, phenyl, thiophenoxy, benzoyl, benzyl, amino, alkylamino of 1-6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, phenylamino, benzylamino, alkanoylamino of 1-6 carbon atoms, alkenoylamino of 3-8 carbon atoms, alkynoylamino of 3-8 carbon atoms, carboxyalkyl of 2-7 carbon atoms, carboalkoxyalkyl of 3-8 carbon atoms, aminoalkyl of 1-5 carbon atoms, N-alkylaminoalkyl of 2-9 carbon atoms, N,N-dialkylaminoalkyl of 3-10 carbon atoms, N-alkylaminoalkoxy of 2-9 carbon atoms, N,N-dialkylaminoalkoxy of 3-10 carbon atoms, mercapto, and benzoylamino; or

L is a 5- or 6-membered heteroaryl ring where the heteroaryl ring contains 1 to 3 heteroatoms selected from N, O, and S, with the proviso that the heteroaryl ring does not contain O—O, S—S, or S—O bonds, and where the heteroaryl ring is optionally mono- or di-substituted with a substituent selected from the group consisting of halogen, oxo, thio, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, azido, hydroxyalkyl of 1-6 carbon atoms,

halomethyl, alkoxymethyl of 2-7 carbon atoms, alkanoyloxymethyl of 2-7 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-6 carbon atoms, hydroxy, trifluoromethyl, cyano, nitro, carboxy, carboalkoxy of 2-7 carbon atoms, carboalkyl of 2-7 carbon atoms, phenoxy, phenyl, thiophenoxy, benzoyl, benzyl, amino, alkylamino of 1-6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, phenylamino, benzylamino, alkanoylamino of 1-6 carbon atoms, alkenoylamino of 3-8 carbon atoms, alkynoylamino of 3-8 carbon atoms, carboxyalkyl of 2-7 carbon atoms, carboalkoxyalkyl of 3-8 carbon atoms, aminoalkyl of 1-5 carbon atoms, N-alkylaminoalkyl of 2-9 carbon atoms, N,N-dialkylaminoalkyl of 3-10 carbon atoms, N-alkylaminoalkoxy of 2-9 carbon atoms, N,N-dialkylaminoalkoxy of 3-10 carbon atoms, mercapto, and benzoylamino;

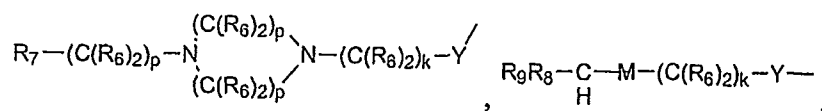
V is ethylene or acetylene;

PG is an amine protecting group;

R₄ is alkyl of 1 to 6 carbons;

Z is NR^{z'}, O or S, wherein R^{z'} is H or C₁-C₆ alkyl;

R₁, G₂, and R₃ are each, independently, hydrogen, halogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, alkenyloxy of 2-6 carbon atoms, alkynyloxy of 2-6 carbon atoms, hydroxymethyl, halomethyl, alkanoyloxy of 1-6 carbon atoms, alkenoyloxy of 3-8 carbon atoms, alkynyloxy of 3-8 carbon atoms, alkanoyloxymethyl of 2-7 carbon atoms, alkenoyloxymethyl of 4-9 carbon atoms, alkynyloxymethyl of 4-9 carbon atoms, alkoxymethyl of 2-7 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-6 carbon atoms, alkylsulphinyl of 1-6 carbon atoms, alkylsulphonyl of 1-6 carbon atoms, alkylsulfonamido of 1-6 carbon atoms, alkenylsulfonamido of 2-6 carbon atoms, alkynylsulfonamido of 2-6 carbon atoms, hydroxy, trifluoromethyl, trifluoromethoxy, cyano, nitro, carboxy, carboalkoxy of 2-7 carbon atoms, carboalkyl of 2-7 carbon atoms, phenoxy, phthalimide, phenyl, thiophenoxy, benzyl, amino, hydroxyamino, alkoxyamino of 1-4 carbon atoms, alkylamino of 1-6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, N-alkylcarbamoyl, N,N-dialkylcarbamoyl, N-alkyl-N-alkenylamino of 4 to 12 carbon atoms, N,N-dialkenylamino of 6-12 carbon atoms, phenylamino, benzylamino,

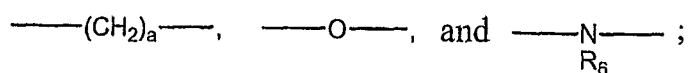


$R_7-(C(R_6)_2)_g-Y-$, $R_7-(C(R_6)_2)_p-M-(C(R_6)_2)_k-Y-$, or $Het-(C(R_6)_2)_q-W-(C(R_6)_2)_2-Y-$;

or R_1 and R_3 are as defined above and G_2 is R_2-NH- ;

or if any of the substituents R_1 , G_2 or R_3 are located on contiguous carbon atoms then they may be taken together as the divalent radical $-O-C(R_6)_2-O-$;

Y is a divalent radical selected from the group consisting of

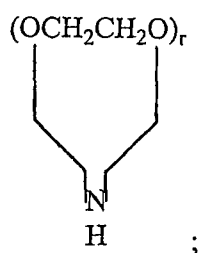


R_7 is $-NR_6R_6$, $-OR_6$, $-J$, $-N(R_6)_3^+$, or $-NR_6(OR_6)$;

M is $>NR_6$, $-O-$, $>N-(C(R_6)_2)_pNR_6R_6$, or $>N-(C(R_6)_2)_p-OR_6$;

W is $>NR_6$, $-O-$ or is a bond;

Het is selected from the group consisting of morpholine, thiomorpholine, thiomorpholine S-oxide, thiomorpholine S,S-dioxide, piperidine, pyrrolidine, aziridine, pyridine, imidazole, 1,2,3-triazole, 1,2,4-triazole, thiazole, thiazolidine, tetrazole, piperazine, furan, thiophene, tetrahydrothiophene, tetrahydrofuran, dioxane, 1,3-dioxolane, tetrahydropyran, and

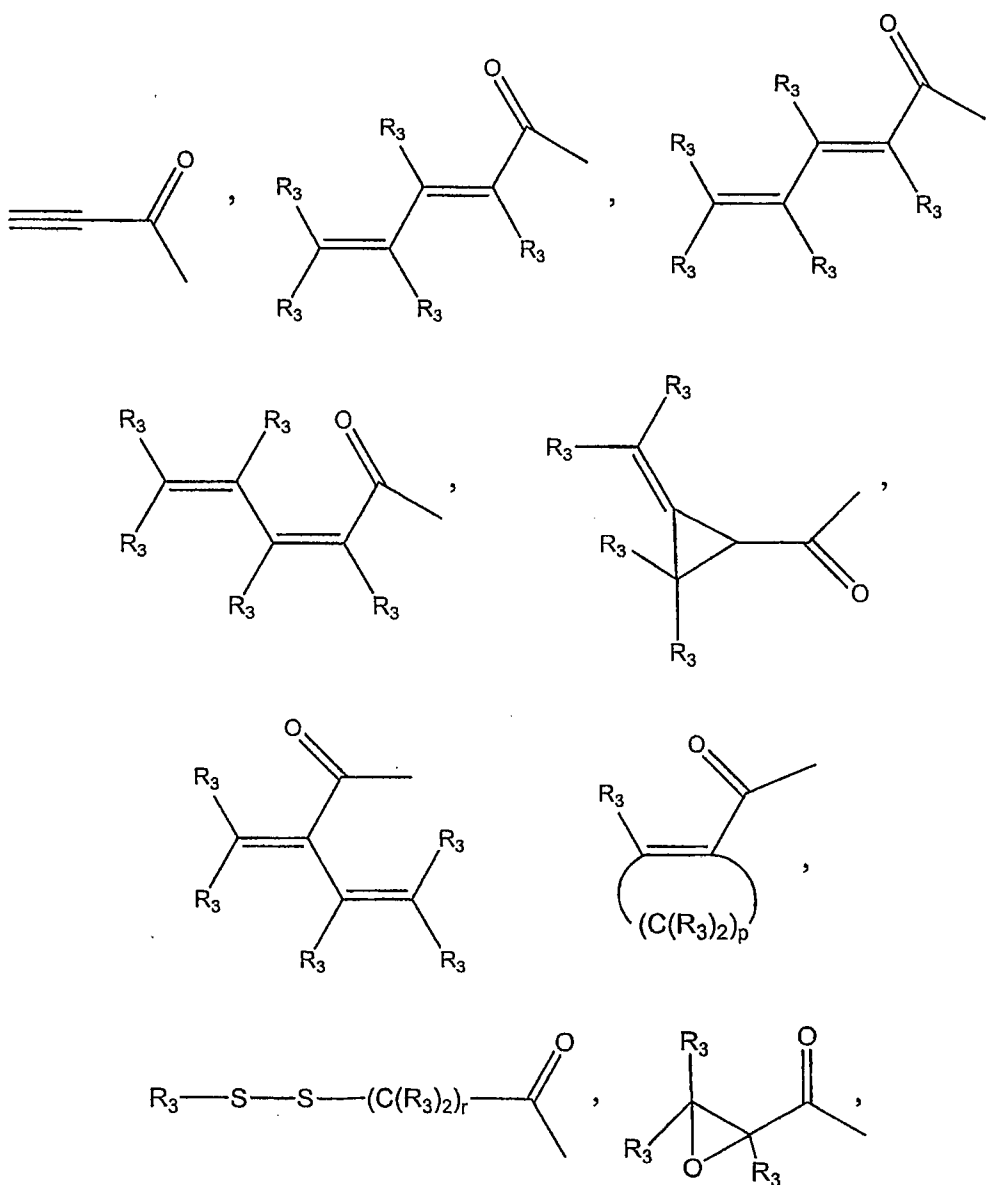


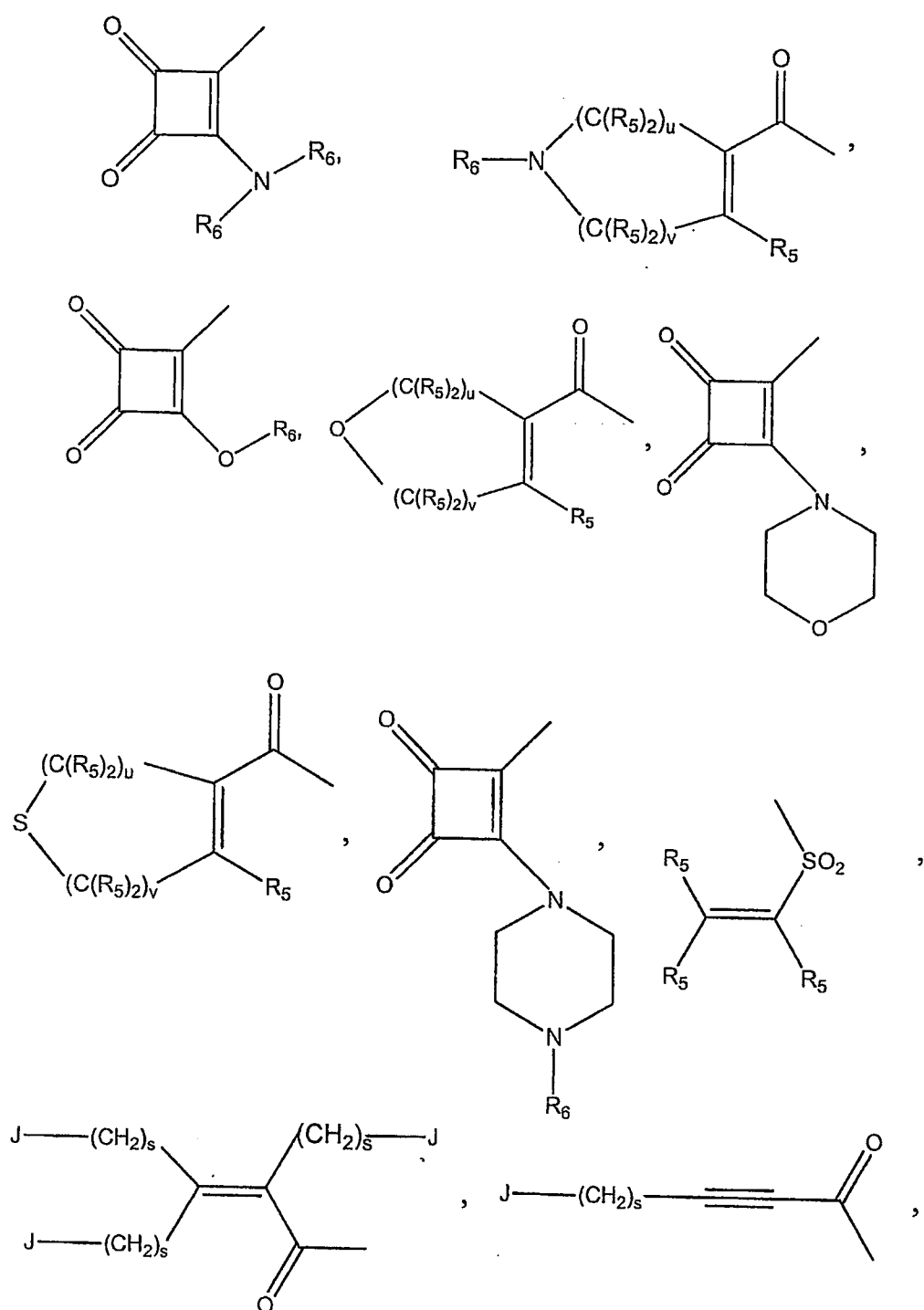
wherein Het is optionally mono- or di-substituted on carbon or nitrogen with R_6 , optionally mono- or di-substituted on carbon with hydroxy, $-N(R_6)_2$, or $-OR_6$, optionally mono or di-substituted on carbon with the mono-valent radicals $-(C(R_6)_2)_sOR_6$ or $-(C(R_6)_2)_sN(R_6)_2$, and optionally mono or di-substituted on a saturated carbon with divalent radicals $-O-$ or $-O(C(R_6)_2)_sO-$;

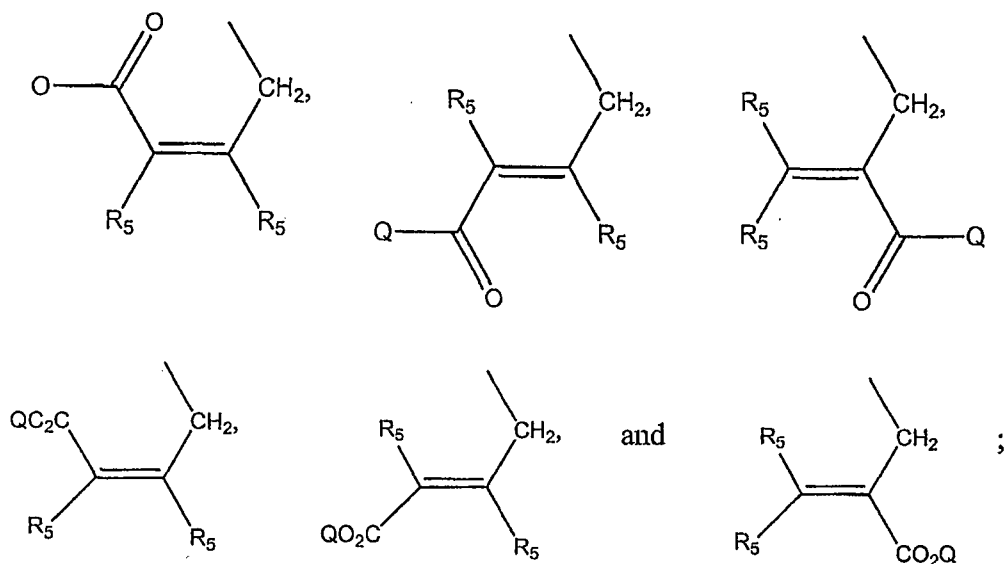
R_6 is hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, cycloalkyl of 1-6 carbon atoms, carboalkyl of 2-7 carbon atoms, carboxyalkyl (2-7 carbon atoms), phenyl, or phenyl optionally substituted with one or more halogen, alkoxy of 1-6 carbon atoms, trifluoromethyl,

amino, alkylamino of 1-3 carbon atoms, dialkylamino of 2-6 carbon atoms, nitro, cyano, azido, halomethyl, alkoxymethyl of 2-7 carbon atoms, alkanoyloxymethyl of 2-7 carbon atoms, alkylthio of 1-6 carbon atoms, hydroxy, carboxyl, carboalkoxy of 2-7 carbon atoms, phenoxy, phenyl, thiophenoxy, benzoyl, benzyl, phenylamino, benzylamino, alkanoylamino of 1-6 carbon atoms, or alkyl of 1-6 carbon atoms; with the proviso that the alkenyl or alkynyl moiety is bound to a nitrogen or oxygen atom through a saturated carbon atom;

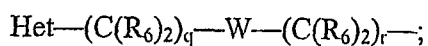
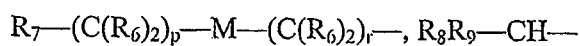
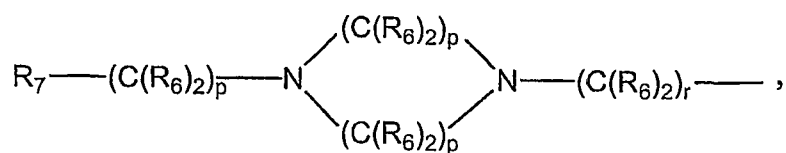
R_2 , is selected from the group consisting of



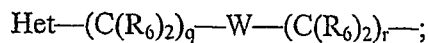
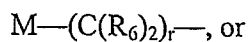
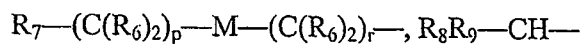
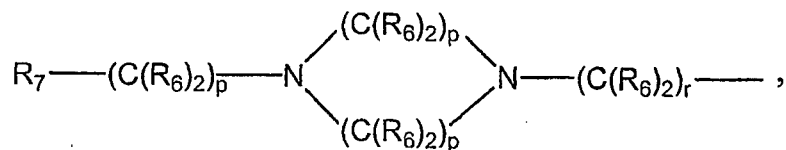




R_3 is independently hydrogen, alkyl of 1-6 carbon atoms, carboxy, carboalkoxy of 1-6 carbon atoms, phenyl, carboalkyl of 2-7 carbon atoms,



R_5 is independently hydrogen, alkyl of 1-6 carbon atoms, carboxy, carboalkoxy of 1-6 carbon atoms, phenyl carboalkyl of 2-7 carbon atoms,



R_8 , and R_9 are each independently $-(C(R_6)_2)_rNR_6R_6$, or $-(C(R_6)_2)_rOR_6$;

J is independently hydrogen, chlorine, fluorine, or bromine;

Q is alkyl of 1-6 carbon atoms or hydrogen;

a=0 or 1;

g=1-6;

k=0-4;

n is 0-1;

m is 0-3;

p=2-4;

q=0-4;

r=1-4;

s=1-6;

u=0-4 and v=0-4, wherein the sum of u+v is 2-4;

x=0-3;

y=0-1; and

z=0-3;

or a pharmaceutically acceptable salt thereof.

2. The method of claim 1, further comprising the following provisos:

when R_6 is alkenyl of 2-7 carbon atoms or alkynyl of 2-7 carbon atoms, such alkenyl or alkynyl moiety is bound to a nitrogen or oxygen atom through a saturated carbon atom;

when Y is $\text{---NR}_6\text{---}$ and R_7 is ---NR_6 , R_6 , $\text{---N(R}_6)_3\text{.N(R}_8)_3^+$, or ---NR_6 (OR_6), then g=2-6;

when M is ---O--- and R_7 is ---OR_6 then p=1-4;

when Y is $\text{---NR}_6\text{---}$ then k=2-4;

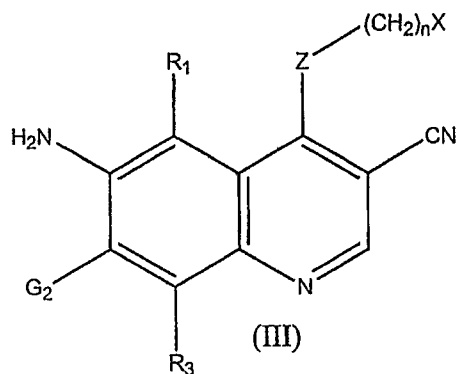
when Y is ---O--- and M or W is ---O--- then k=1-4;

when W is not a bond with Het bonded through a nitrogen atom then q=2-4;

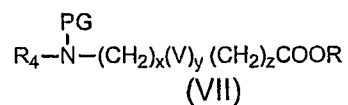
when W is a bond with Het bonded through a nitrogen atom and Y is ---O--- or $\text{---NR}_6\text{---}$ then k=2-4; and

provided that L can be an unsubstituted phenyl ring only when m>0 and T is not $\text{---CH}_2\text{NH---}$ or $\text{---CH}_2\text{O---}$.

3. The method of claim 1, further comprising the step of coupling an anilinoquinoline of formula (III):

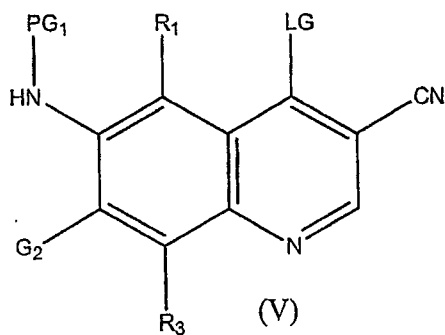


with an acid of formula (VII):

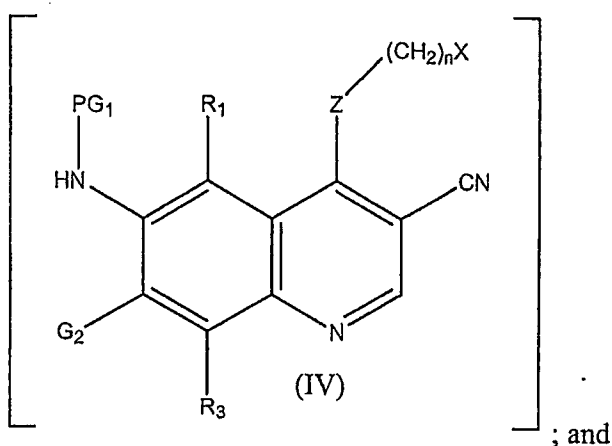


to form a compound of formula (II), wherein R is H, R₁, R₃, R₄, Z, G₂, V, PG, x, y, z, and n are as previously defined.

4. The method of claim 3, further comprising the steps of:
- a. arylating a compound of formula (V):



with a compound of formula HZ-(CH₂)_nX to form an intermediate of formula (IV):

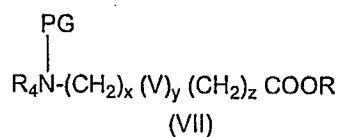


b. deprotecting the intermediate of formula (IV) to obtain the anilinoquinoline compound of formula (III);

wherein LG is selected from the group of halo, mesylate, tosylate and triflylate, PG₁ is an amine protecting group, and wherein R₁, R₃, R₄, Z, G₂, PG and n are as previously defined.

5. The method of claim 1, wherein PG is removed using an acid.

6. A method of preparing an acid of formula (VII):



wherein:

R is H;

R₄ is H or alkyl of 1 to 6 carbon atoms;

V is ethylene or acetylene;

x is 1, 2 or 3;

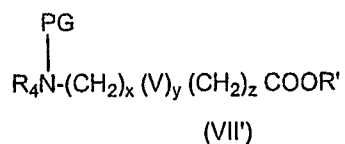
y is 0 or 1;

z is 1, 2 or 3; and

PG is an amine protecting group;

comprising the step of hydrolyzing a corresponding ester of formula (VII'):

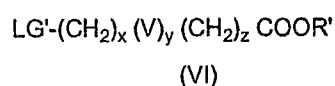
- 56 -



wherein R' is alkyl of 1 to 6 carbon atoms or aryl, to form an acid of formula (VII).

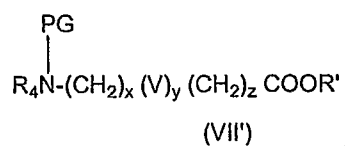
7. The method of claim 6, further comprising the steps of:

a. alkylating a compound of formula (VI):



with a primary amine of the formula NH_2R_4 to give an aminoester intermediate; and

b. subsequently protecting the aminoester intermediate by alkylating on a protecting group to form an ester of formula (VII'):



wherein LG' is selected from halo, mesylate, tosylate and triflate, R' is alkyl or aryl and R₄, V, PG, x, y, and z are as previously defined.

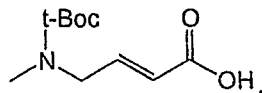
8. The method of claim 7, wherein PG is selected from the group consisting of t-BOC, acetyl, $\text{CH}_3\text{OC}(\text{O})-$, $\text{EtOC}(\text{O})-$, $\text{PhC}(\text{O})-$, $\text{PhCH}_2\text{OC}(\text{O})-$, Fmoc, Troc, Phenoc, and Teoc.

9. The method of claim 8, wherein the PG is t-BOC.

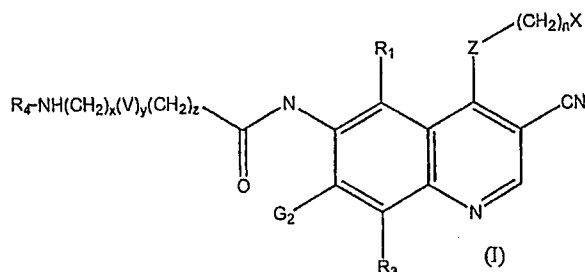
10. The method of claim 7, wherein $(\text{t-BOC})_2\text{O}$ is used in step b. to form the protecting group.

11. The method of claim 7, wherein z is 0, y is 1 and V is ethylene.

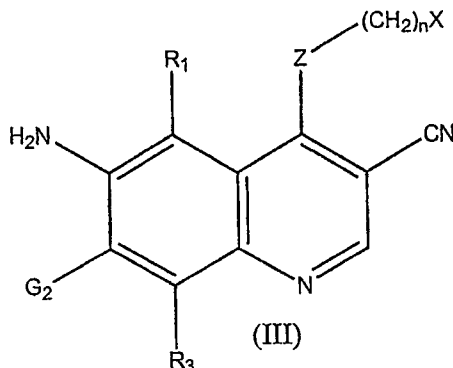
12. The method of claim 7, wherein R_4 is methyl, ethyl, propyl or isopropyl.
13. The method of claim 7, wherein the acid of formula (VII) is:



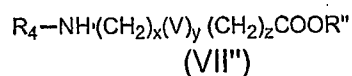
14. A method of preparing a compound of formula (I):



comprising the step of coupling an anilinoquinoline of formula (III):



with an acid of formula (VII''):



wherein:

R'' is H;

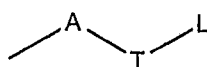
X is cycloalkyl of 3 to 7 carbon atoms, which may be optionally substituted with one or more alkyl of 1 to 6 carbon atom groups; or is a pyridinyl, pyrimidinyl, or phenyl ring; wherein the pyridinyl, pyrimidinyl, or phenyl ring may be optionally mono-, di-, or tri-substituted with a substituent selected from the group

consisting of halogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, azido, hydroxyalkyl of 1-6 carbon atoms, halomethyl, alkoxymethyl of 2-7 carbon atoms, alkanoyloxymethyl of 2-7 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-6 carbon atoms, hydroxy, trifluoromethyl, cyano, nitro, carboxy, carboalkoxy of 2-7 carbon atoms, carboalkyl of 2-7 carbon atoms, phenoxy, phenyl, thiophenoxy, benzoyl, benzyl, amino, alkylamino of 1-6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, phenylamino, benzylamino, alkanoylamino of 1-6 carbon atoms, alkenoylamino of 3-8 carbon atoms, alkynoylamino of 3-8 carbon atoms, carboxyalkyl of 2-7 carbon atoms, carboalkoxyalkyl of 3-8 carbon atoms, aminoalkyl of 1-5 carbon atoms, N-alkylaminoalkyl of 2-9 carbon atoms, N,N-dialkylaminoalkyl of 3-10 carbon atoms, N-alkylaminoalkoxy of 2-9 carbon atoms, N,N-dialkylaminoalkoxy of 3-10 carbon atoms, mercapto, and benzoylamino; or

X is a bicyclic aryl or bicyclic heteroaryl ring system of 8 to 12 atoms where the bicyclic heteroaryl ring contains 1 to 4 heteroatoms selected from N, O, and S with the proviso that the bicyclic heteroaryl ring does not contain O—O, S—S, or S—O bonds and where the bicyclic aryl or bicyclic heteroaryl ring may be optionally mono- di-, tri, or tetra-substituted with a substituent selected from the group consisting of halogen, oxo, thio, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, azido, hydroxyalkyl of 1-6 carbon atoms, halomethyl, alkoxymethyl of 2-7 carbon atoms, alkanoyloxymethyl of 2-7 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-6 carbon atoms, hydroxy, trifluoromethyl, cyano, nitro, carboxy, carboalkoxy of 2-7 carbon atoms, carboalkyl of 2-7 carbon atoms, phenoxy, phenyl, thiophenoxy, benzoyl, benzyl, amino, alkylamino of 1-6 carbon atoms, dialkyl amino of 2 to 12 carbon atoms, phenylamino, benzylamino, alkanoylamino of 1-6 carbon atoms, alkenoylamino of 3-8 carbon atoms, alkynoylamino of 3-8 carbon atoms, carboxyalkyl of 2-7 carbon atoms, carboalkoxyalkyl of 3-8 carbon atoms, aminoalkyl of 1-5 carbon atoms, N-alkylaminoalkyl of 2-9 carbon atoms, N,N-dialkylaminoalkyl of 3-10 carbon atoms, N-alkylaminoalkoxy of 2-9 carbon atoms, N,N-dialkylaminoalkoxy of 3-10 carbon atoms, mercapto, and benzoylamino; or

X is a radical having the formula:

- 59 -



wherein

A is a pyridinyl, pyrimidinyl, or phenyl ring; wherein the pyridinyl, pyrimidinyl, or phenyl ring may be optionally mono- or di-substituted with a substituent selected from the group consisting of halogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, azido, hydroxyalkyl of 1-6 carbon atoms, halomethyl, alkoxymethyl of 2-7 carbon atoms, alkanoyloxymethyl of 2-7 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-6 carbon atoms, hydroxy, trifluoromethyl, cyano, nitro, carboxy, carboalkoxy of 2-7 carbon atoms, carboalkyl of 2-7 carbon atoms, phenoxy, phenyl, thiophenoxy, benzoyl, benzyl, amino, alkylamino of 1-6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, phenylamino, benzylamino, alkanoylamino of 1-6 carbon atoms, alkenoylamino of 3-8 carbon atoms, alkynoylamino of 3-8 carbon atoms, carboxyalkyl of 2-7 carbon atoms, carboalkoxyalkyl of 3-8 carbon atoms, aminoalkyl of 1-5 carbon atoms, N-alkylaminoalkyl of 2-9 carbon atoms, N,N-dialkylaminoalkyl of 3-10 carbon atoms, N-alkylaminoalkoxy of 2-9 carbon atoms, N,N-dialkylaminoalkoxy of 3-10 carbon atoms, mercapto, and benzoylamino;

T is bonded to a carbon of A and is:

$\text{—NH(CH}_2\text{)}_m\text{—}$, $\text{—O(CH}_2\text{)}_m\text{—}$, $\text{—S(CH}_2\text{)}_m\text{—}$, $\text{—NR(CH}_2\text{)}_m\text{—}$,
 $\text{—(CH}_2\text{)}_m\text{—}$, $\text{—(CH}_2\text{)}_m\text{NH—}$, $\text{—(CH}_2\text{)}_m\text{O—}$, $\text{—(CH}_2\text{)}_m\text{S—}$, or
 $\text{—(CH}_2\text{)}_m\text{NR—}$;

L is an unsubstituted phenyl ring or a phenyl ring mono-, di-, or tri-substituted with a substituent selected from the group consisting of halogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, azido, hydroxyalkyl of 1-6 carbon atoms, halomethyl, alkoxymethyl of 2-7 carbon atoms, alkanoyloxymethyl of 2-7 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-6 carbon atoms, hydroxy, trifluoromethyl, cyano, nitro, carboxy, carboalkoxy of 2-7 carbon atoms, carboalkyl of 2-7 carbon atoms, phenoxy, phenyl, thiophenoxy, benzoyl, benzyl, amino, alkylamino of 1-6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, phenylamino, benzylamino, alkanoylamino

of 1-6 carbon atoms, alkenoylamino of 3-8 carbon atoms, alkynoylamino of 3-8 carbon atoms, carboxyalkyl of 2-7 carbon atoms, carboalkoxyalkyl of 3-8 carbon atoms, aminoalkyl of 1-5 carbon atoms, N-alkylaminoalkyl of 2-9 carbon atoms, N,N-dialkylaminoalkyl of 3-10 carbon atoms, N-alkylaminoalkoxy of 2-9 carbon atoms, N,N-dialkylaminoalkoxy of 3-10 carbon atoms, mercapto, and benzoylamino; or

L is a 5- or 6-membered heteroaryl ring where the heteroaryl ring contains 1 to 3 heteroatoms selected from N, O, and S, with the proviso that the heteroaryl ring does not contain O—O, S—S, or S—O bonds, and where the heteroaryl ring is optionally mono- or di-substituted with a substituent selected from the group consisting of halogen, oxo, thio, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, azido, hydroxyalkyl of 1-6 carbon atoms, halomethyl, alkoxymethyl of 2-7 carbon atoms, alkanoyloxymethyl of 2-7 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-6 carbon atoms, hydroxy, trifluoromethyl, cyano, nitro, carboxy, carboalkoxy of 2-7 carbon atoms, carboalkyl of 2-7 carbon atoms, phenoxy, phenyl, thiophenoxy, benzoyl, benzyl, amino, alkylamino of 1-6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, phenylamino, benzylamino, alkanoylamino of 1-6 carbon atoms, alkenoylamino of 3-8 carbon atoms, alkynoylamino of 3-8 carbon atoms, carboxyalkyl of 2-7 carbon atoms, carboalkoxyalkyl of 3-8 carbon atoms, aminoalkyl of 1-5 carbon atoms, N-alkylaminoalkyl of 2-9 carbon atoms, N,N-dialkylaminoalkyl of 3-10 carbon atoms, N-alkylaminoalkoxy of 2-9 carbon atoms, N,N-dialkylaminoalkoxy of 3-10 carbon atoms, mercapto, and benzoylamino;

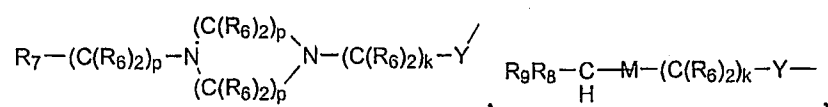
V is ethylene or acetylene;

R₄ is alkyl of 1 to 6 carbons;

Z is NR^{z'}, O or S, wherein R^{z'} is H or C₁-C₆ alkyl;

R₁, G₂, and R₃ are each, independently, hydrogen, halogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, alkenyloxy of 2-6 carbon atoms, alkynyloxy of 2-6 carbon atoms, hydroxymethyl, halomethyl, alkanoyloxy of 1-6 carbon atoms, alkenoyloxy of 3-8 carbon atoms, alkynyloxy of 3-8 carbon atoms, alkanoyloxymethyl of 2-7 carbon atoms, alkenoyloxymethyl of 4-9 carbon atoms, alkynyloxymethyl of 4-9 carbon atoms,

alkoxymethyl of 2-7 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-6 carbon atoms, alkylsulphinyl of 1-6 carbon atoms, alkylsulphonyl of 1-6 carbon atoms, alkylsulfonamido of 1-6 carbon atoms, alkenylsulfonamido of 2-6 carbon atoms, alkynylsulfonamido of 2-6 carbon atoms, hydroxy, trifluoromethyl, trifluoromethoxy, cyano, nitro, carboxy, carboalkoxy of 2-7 carbon atoms, carboalkyl of 2-7 carbon atoms, phenoxy, phthalimide, phenyl, thiophenoxy, benzyl, amino, hydroxyamino, alkoxyamino of 1-4 carbon atoms, alkylamino of 1-6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, N-alkylcarbamoyl, N,N-dialkylcarbamoyl, N-alkyl-N-alkenylamino of 4 to 12 carbon atoms, N,N-dialkenylamino of 6-12 carbon atoms, phenylamino, benzylamino,

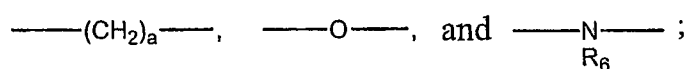


$R_7-(C(R_6)_2)_g-Y-$, $R_7-(C(R_6)_2)_p-M-(C(R_6)_2)_k-Y-$, or $Het-(C(R_6)_2)_qW-(C(R_6)_2)_2-Y-$;

or R_1 and R_3 are as defined above and G_2 is R_2-NH- ;

or if any of the substituents R_1 , G_2 or R_3 are located on contiguous carbon atoms then they may be taken together as the divalent radical $-O-C(R_6)_2-O-$;

Y is a divalent radical selected from the group consisting of

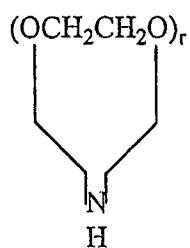


R_7 is $-NR_6R_6$, $-OR_6$, $-J$, $-N(R_6)_3^+$, or $-NR_6(OR_6)$;

M is $>NR_6$, $-O-$, $>N-(C(R_6)_2)_pNR_6R_6$, or $>N-(C(R_6)_2)_p-OR_6$;

W is $>NR_6$, $-O-$ or is a bond;

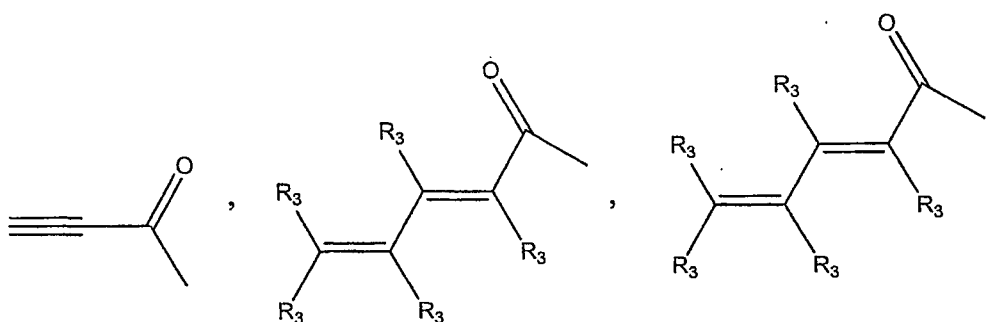
Het is selected from the group consisting of morpholine, thiomorpholine, thiomorpholine S-oxide, thiomorpholine S,S-dioxide, piperidine, pyrrolidine, aziridine, pyridine, imidazole, 1,2,3-triazole, 1,2,4-triazole, thiazole, thiazolidine, tetrazole, piperazine, furan, thiophene, tetrahydrothiophene, tetrahydrofuran, dioxane, 1,3-dioxolane, tetrahydropyran, and

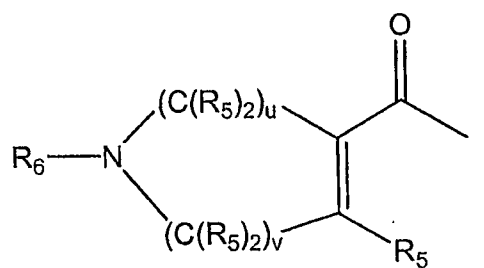
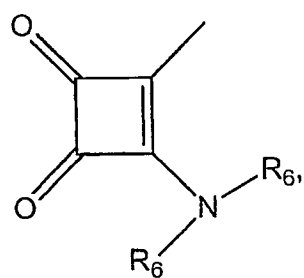
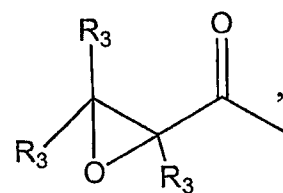
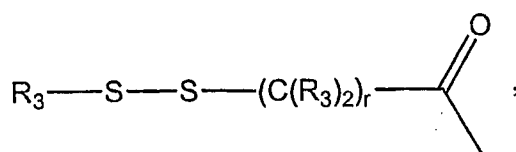
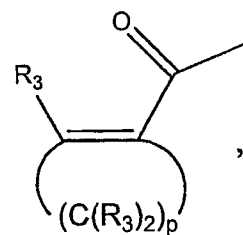
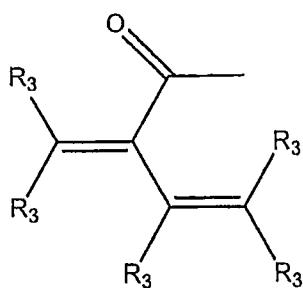
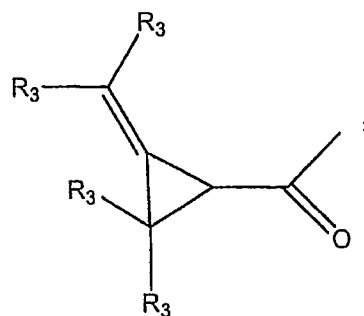
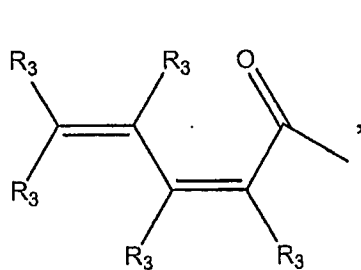


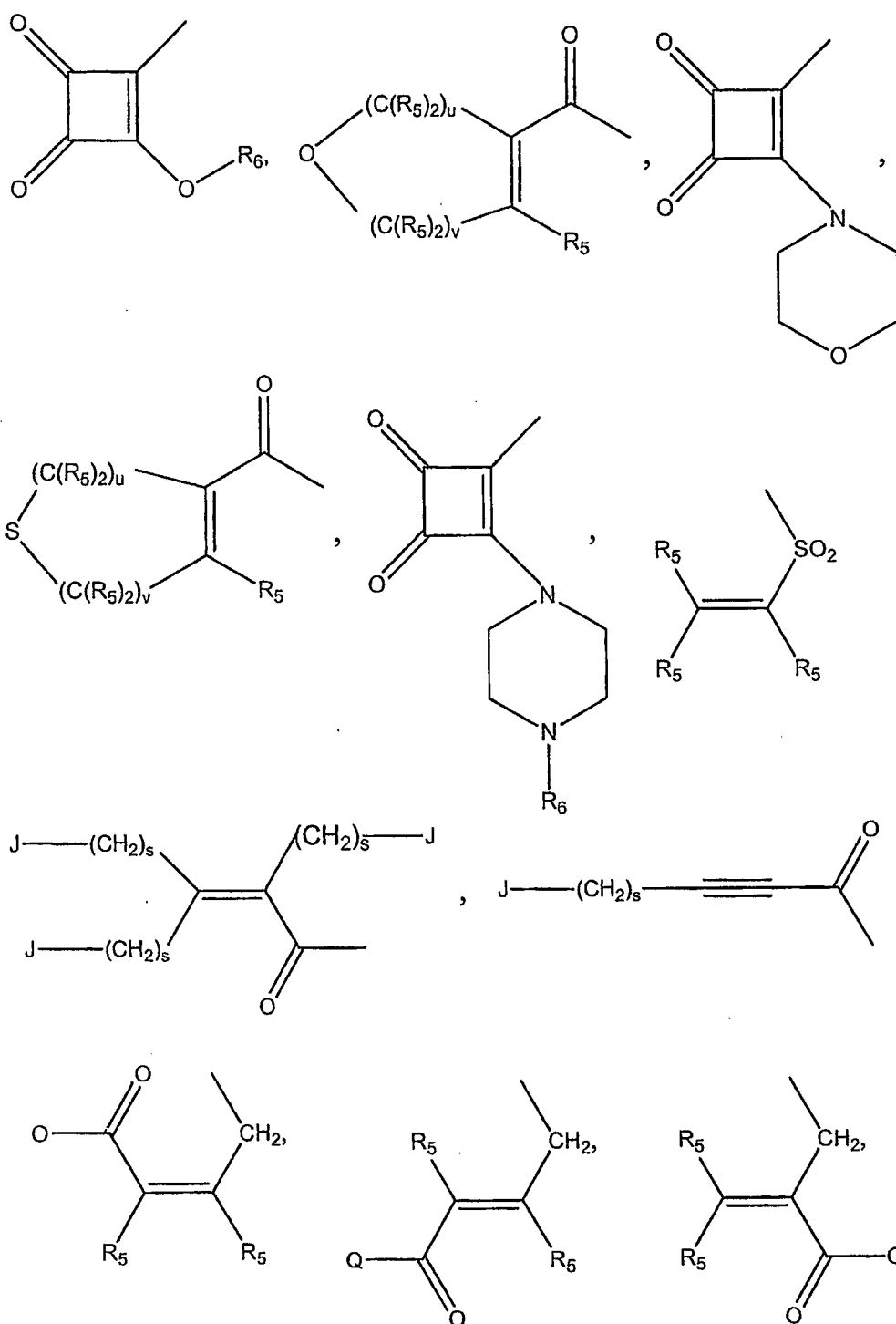
wherein Het is optionally mono- or di-substituted on carbon or nitrogen with R₆, optionally mono- or di-substituted on carbon with hydroxy, —N(R₆)₂, or —OR₆, optionally mono or di-substituted on carbon with the mono-valent radicals —(C(R₆)₂)_s OR₆ or —(C(R₆)₂)_s N(R₆)₂, and optionally mono or di-substituted on a saturated carbon with divalent radicals —O— or —O(C(R₆)₂)_s O—;

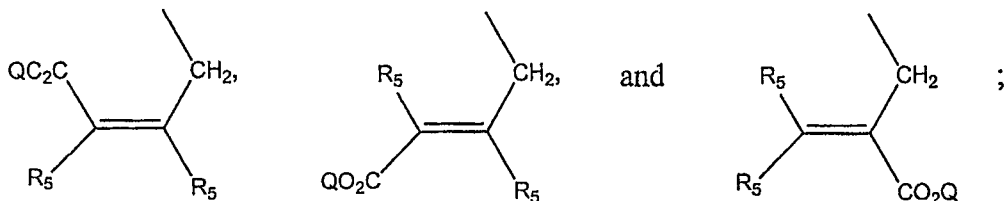
R₆ is hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, cycloalkyl of 1-6 carbon atoms, carboalkyl of 2-7 carbon atoms, carboxyalkyl (2-7 carbon atoms), phenyl, or phenyl optionally substituted with one or more halogen, alkoxy of 1-6 carbon atoms, trifluoromethyl, amino, alkylamino of 1-3 carbon atoms, dialkylamino of 2-6 carbon atoms, nitro, cyano, azido, halomethyl, alkoxymethyl of 2-7 carbon atoms, alkanoyloxymethyl of 2-7 carbon atoms, alkylthio of 1-6 carbon atoms, hydroxy, carboxyl, carboalkoxy of 2-7 carbon atoms, phenoxy, phenyl, thiophenoxy, benzoyl, benzyl, phenylamino, benzylamino, alkanoylamino of 1-6 carbon atoms, or alkyl of 1-6 carbon atoms; with the proviso that the alkenyl or alkynyl moiety is bound to a nitrogen or oxygen atom through a saturated carbon atom;

R₂, is selected from the group consisting of

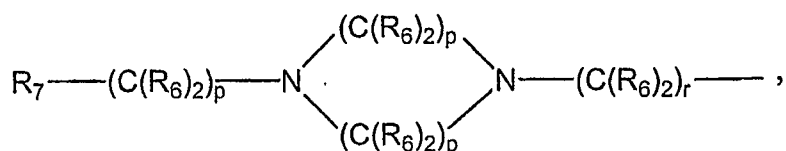








R₃ is independently hydrogen, alkyl of 1-6 carbon atoms, carboxy, carboalkoxy of 1-6 carbon atoms, phenyl, carboalkyl of 2-7 carbon atoms,



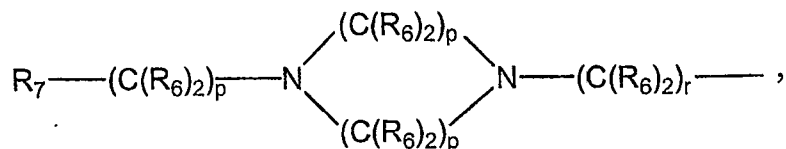
R₇—(C(R₆)₂)_s—,

R₇—(C(R₆)₂)_p—M—(C(R₆)₂)_r—, R₈R₉—CH—

M—(C(R₆)₂)_r—, or

Het—(C(R₆)₂)_q—W—(C(R₆)₂)_r—;

R₅ is independently hydrogen, alkyl of 1-6 carbon atoms, carboxy, carboalkoxy of 1-6 carbon atoms, phenyl carboalkyl of 2-7 carbon atoms,



R₇—(C(R₆)₂)_s—,

R₇—(C(R₆)₂)_p—M—(C(R₆)₂)_r—, R₈R₉—CH—

M—(C(R₆)₂)_r—, or

Het—(C(R₆)₂)_q—W—(C(R₆)₂)_r—;

R₈, and R₉ are each independently —(C(R₆)₂)_rNR₆R₆, or —(C(R₆)₂)_rOR₆;

J is independently hydrogen, chlorine, fluorine, or bromine;

Q is alkyl of 1-6 carbon atoms or hydrogen;

a=0 or 1;

g=1-6;

k=0-4;

n is 0-1;

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m is 0-3;

p=2-4;

q=0-4;

r=1-4;

s=1-6;

u=0-4 and v=0-4, wherein the sum of u+v is 2-4;

x= 0-3;

y= 0-1; and

z= 0-3;

or a pharmaceutically acceptable salt thereof.

15. The method of claim 14, further comprising the following provisos:

when R_6 is alkenyl of 2-7 carbon atoms or alkynyl of 2-7 carbon atoms, such alkenyl or alkynyl moiety is bound to a nitrogen or oxygen atom through a saturated carbon atom;

when Y is $\text{---NR}_6\text{---}$ and R_7 is $\text{---NR}_6\text{R}_6$, $\text{---N(R}_6)_3\text{.N(R}_8)_3^+$, or $\text{---NR}_6\text{.(OR}_6\text{)}$, then $g=2-6$;

when M is ---O--- and R_7 is ---OR_6 then $p=1-4$;

when Y is $\text{---NR}_6\text{---}$ then $k=2-4$;

when Y is ---O--- and M or W is ---O--- then $k=1-4$;

when W is not a bond with Het bonded through a nitrogen atom then $q=2-4$;

when W is a bond with Het bonded through a nitrogen atom and Y is ---O--- or $\text{---NR}_6\text{---}$ then $k=2-4$; and

provided that L can be an unsubstituted phenyl ring only when $m>0$ and T is not $\text{---CH}_2\text{NH---}$ or $\text{---CH}_2\text{O---}$.

MÉTODOS PARA SINTETIZAR DERIVADOS DE 6-ALQUILAMINOQUINOLINA

nnn92

ANTECEDENTES DE LA INVENCION

5 Campo de la Invención

[0001] Esta invención se dirige a un método para sintetizar una serie de quinolinas sustituidas que son metabolitos de inhibidores de cinasa EGFR y HER2, y que tienen uso en el
10 tratamiento de tumores cancerosos.

Antecedentes de la Técnica Relacionada

[0002] Las proteínas cinasas son una clase de enzimas que
15 catalizan la transferencia de un grupo fosfato del ATP a un residuo tirosina, serina, treonina, o histidina ubicado en un sustrato de proteína, mucho de los cuales juegan un papel en el crecimiento celular normal. De forma correspondiente, varias proteínas del receptor del factor de crecimiento funcionan como
20 proteínas tirosina cinasa (PTK) para efectuar la señalización y se conocen como receptores tirosina cinasa (RTK).

[0003] El RTK comprende una de las mayores familias de PTK y tienen diversa actividad biológica. Actualmente, se han
25 identificado por lo menos diecinueve subfamilias distintas de RTK. Una de tales subfamilias es la familia "HER" de RTK, que incluye EGFR (receptor del factor de crecimiento epitelial), HER2, HER3 y HER4. Se ha mostrado que bajo ciertas condiciones, como un resultado de su mutación o sobre expresión, estos RTK se

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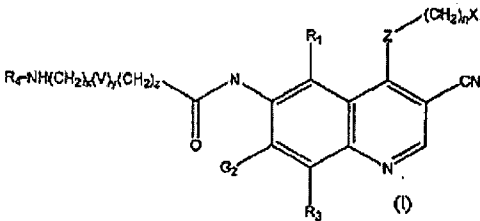
han desregulado; el resultado de lo cual es la proliferación celular no controlada que puede conducir a crecimiento de tumor y cáncer [Wilks, A. F., Adv. Cancer Res., 60, 43 (1993) y Parsons, J. T.; Parsons, S. J., Important Advances en Oncology, DeVita, V. T. Ed., J. B. Lippincort Co., Fila., 3 (1993)]. Por ejemplo, la sobreexpresión del producto cinasa receptor del oncogen erbB-2 se ha asociado con cáncer de ovario y de mama [Slamon, D. J. et al., Science, 244, 707 (1989) y Science, 235, 177 (1987)]. Adicionalmente, la desregulación de la cinasa EGF-R se ha asociado con tumores epidermoides [Reiss, M., et al., Cancer Res., 51, 6254 (1991)], tumores de mama [Macias, A. et al., Anticancer Res., 7, 459 (1987)], y tumores que involucran otros órganos mayores [Gullick, W. J., Brit. Med. Bull., 47, 87 (1991)]. Los inhibidores RTK, por lo tanto, tienen valor terapéutico potencial para el tratamiento de cáncer y otras enfermedades caracterizadas por crecimiento celular anormal no controlado. De acuerdo con esto, muchos estudios recientes han tratado con el desarrollo de inhibidores RTK específicos como agentes terapéuticos anti-cáncer potenciales [some recent reviews: Traxler, P., Exp. Opin. Ther. Patents, 8, 1599 (1998) y Bridges, A. J., Emerging Drugs, 3, 279 (1998)].

[0004] Las Patentes Estadounidenses No. 6,002,008; 6,288,082; y 6,297,258, todas de Wissner et al., describen tal PTK, y particularmente, compuestos inhibidores RTK. Los compuestos de las patentes de Wissner et al. son todos 3-cianoquinolinas sustituidas. Los compuestos sintetizados "des-alquil" de la presente invención son metabolitos de los inhibidores de quinasa

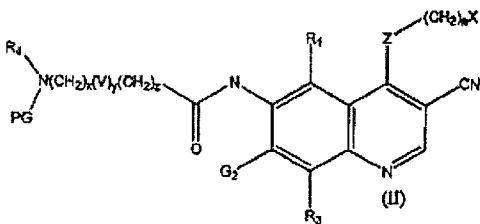
EFGR y los inhibidores de quinasa HER2 descritos en Wissner et al.

BREVE RESUMEN DE LA INVENCION

[0005] La presente invención está dirigida a un método para sintetizar compuestos de la fórmula (I):



que comprende la etapa de un compuesto protector de Fórmula (II):

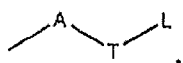


en donde X es cicloalquilo de 3 a 7 átomos de carbono, que pueden
opcionalmente sustituirse con uno o más grupos alquilo de 1 a 6
de átomos de carbono; o es un piridinilo, pirimidinilo, o anillo
fenilo; en donde el piridinilo, pirimidinilo, o anillo fenilo
opcionalmente pueden ser mono- di-, o tri-sustituidos con un
sustituyente seleccionado del grupo que consiste de halógeno,
alquilo de 1-6 átomos de carbono, alqueno de 2-6 átomos de
carbono, alquino de 2-6 átomos de carbono, azido,
hidroxialquilo de 1-6 átomos de carbono, halometilo, alcoximetilo
de 2-7 átomos de carbono, alcaniloximetilo de 2-7 átomos de
carbono, alcoxi de 1-6 átomos de carbono, alquiltio de 1-6 átomos

de carbono, hidroxilo, trifluorometilo, ciano, nitro, carboxi, carboalcoxi de 2-7 átomos de carbono, carboalquilo de 2-7 átomos de carbono, fenoxi, fenilo, tiofenoxi, benzoilo, bencilo, amino, alquilamino de 1-6 átomos de carbono, dialquilamino de 2 a 12
5 átomos de carbono, fenilamino, bencilamino, alcanoilamino de 1-6 átomos de carbono, alquenoilamino de 3-8 átomos de carbono, alquinoilamino de 3-8 átomos de carbono, carboxialquilo de 2-7 átomos de carbono, carboalcoxialquilo de 3-8 átomos de carbono, aminoalquilo de 1-5 átomos de carbono, N- alquilaminoalquilo de
10 2-9 átomos de carbono, N,N-dialquilaminoalquilo de 3-10 átomos de carbono, N-alquilaminoalcoxi de 2-9 átomos de carbono, N,N-dialquilaminoalcoxi de 3-10 átomos de carbono, mercapto, y bencilamino; o X es sistema de anillo arilo bicíclico o heteroarilo bicíclico de 8 a 12 átomos en donde el anillo
15 heteroarilo bicíclico contiene 1 a 4 heteroátomos seleccionados de N, O, y S con la condición que el anillo heteroarilo bicíclico no contiene enlaces O - O, S - S, o S-O y en donde el anillo arilo bicíclico o heteroarilo bicíclico opcionalmente pueden ser mono- di-, tri, o tetra- sustituidos con un sustituyente seleccionado
20 del grupo que consiste de halógeno, oxo, tio, alquilo de 1-6 átomos de carbono, alquenoilo de 2-6 átomos de carbono, alquinoilo de 2-6 átomos de carbono, azido, hidroxialquilo de 1-6 átomos de carbono, halometilo, alcoximetilo de 2-7 átomos de carbono, alcaniloximetilo de 2-7 átomos de carbono, alcoxi de 1-6 átomos
25 de carbono, alquiltio de 1-6 átomos de carbono, hidroxilo, trifluorometilo, ciano, nitro, carboxi, carboalcoxi de 2-7 átomos de carbono, carboalquilo de 2-7 átomos de carbono, fenoxi, fenilo, tiofenoxi, benzoilo, bencilo, amino, alquilamino de 1-6 átomos de carbono, dialquilo amino de 2 a 12 átomos de carbono,

fenilamino, bencilamino, alcanilamino de 1-6 átomos de carbono, alquenilamino de 3-8 átomos de carbono, alquinilamino de 3-8 átomos de carbono, carboxialquilo de 2-7 átomos de carbono, carboalcoxialquilo de 3-8 átomos de carbono, aminoalquilo de 1-5
5 átomos de carbono, N- alquilaminoalquilo de 2-9 átomos de carbono, N,N-dialquilaminoalquilo de 3-10 átomos de carbono, N- alquilaminoalcoxi de 2-9 átomos de carbono, N,N-dialquilaminoalcoxi de 3-10 átomos de carbono, mercapto, y bencilamino; o X es un radical que tiene la fórmula:

10



en donde A es un piridinilo, pirimidinilo, o anillo fenilo; en donde el piridinilo, pirimidinilo, o anillo fenilo opcionalmente
15 pueden ser mono- o di-sustituidos con un sustituyente seleccionado del grupo que consiste de halógeno, alquilo de 1-6 átomos de carbono, alquenilo de 2-6 átomos de carbono, alquinilo de 2-6 átomos de carbono, azido, hidroxialquilo de 1-6 átomos de carbono, halometilo, alcoximetilo de 2-7 átomos de carbono,
20 alcaniloximetilo de 2-7 átomos de carbono, alcoxi de 1-6 átomos de carbono, alquiltio de 1-6 átomos de carbono, hidroxi, trifluorometilo, ciano, nitro, carboxi, carboalcoxi de 2-7 átomos de carbono, carboalquilo de 2-7 átomos de carbono, fenoxi, fenilo, tiofenoxi, benzoilo, bencilo, amino, alquilamino de 1-6
25 átomos de carbono, dialquilamino de 2 a 12 átomos de carbono, fenilamino, bencilamino, alcanilamino de 1-6 átomos de carbono, alquenilamino de 3-8 átomos de carbono, alquinilamino de 3-8 átomos de carbono, carboxialquilo de 2-7 átomos de carbono, carboalcoxialquilo de 3-8 átomos de carbono, aminoalquilo de 1-5

átomos de carbono, N-alquilaminoalquilo de 2-9 átomos de carbono,
 N₃N- dialquilaminoalquilo de 3-10 átomos de carbono, N-
 alquilaminoalcoxi de 2-9 átomos de carbono, N,N-
 dialquilaminoalcoxi de 3-10 átomos de carbono, mercapto, y
 5 bencilamino; T está enlazado con un carbono de A y es:
 $-NH(CH_2)_m-$, $-O(CH_2)_m-$, $-S(CH_2)_m-$, $-NR(CH_2)_m-$,
 $-(CH_2)_m-$, $-(CH_2)_n-$, $NH-$, $-(CH_2)_mO-$, $-(CH_2)_mS-$, o $-(CH_2)_mNR-$;

L es un anillo fenilo no sustituido o un anillo fenilo mono-, di-
 10 , o tri-sustituidos con un sustituyente seleccionado del grupo
 que consiste de halógeno, alquilo de 1-6 átomos de carbono,
 alqueno de 2-6 átomos de carbono, alquino de 2-6 átomos de
 carbono, azido, hidroxialquilo de 1-6 átomos de carbono,
 halometilo, alcoximetilo de 2-7 átomos de carbono,
 15 alcaniloximetilo de 2-7 átomos de carbono, alcoxi de 1-6 átomos
 de carbono, alquiltio de 1-6 átomos de carbono, hidroxilo,
 trifluorometilo, ciano, nitro, carboxi, carboalcoxi de 2-7 átomos
 de carbono, carboalquilo de 2-7 átomos de carbono, fenoxi,
 fenilo, tiofenoxi, benzoilo, bencilo, amino, alquilamino de 1-6
 20 átomos de carbono, dialquilamino de 2 a 12 átomos de carbono,
 fenilamino, bencilamino, alcanilamino de 1-6 átomos de carbono,
 alquencilamino de 3-8 átomos de carbono, alquencilamino de 3-8
 átomos de carbono, carboxialquilo de 2-7 átomos de carbono,
 carboalcoxialquilo de 3-8 átomos de carbono, aminoalquilo de 1-5
 25 átomos de carbono, N-alquilaminoalquilo de 2-9 átomos de carbono,
 N₃N- dialquilaminoalquilo de 3-10 átomos de carbono, N-
 alquilaminoalcoxi de 2-9 átomos de carbono, N,N-
 dialquilaminoalcoxi de 3-10 átomos de carbono, mercapto, y
 bencilamino; o L es un anillo heteroarilo de 5- o 6- miembros en

donde el anillo heteroarilo contiene 1 a 3 heteroátomos seleccionados de N, O, y S, con la condición que el anillo heteroarilo no contiene enlaces O - O, S - S, o S - O, y en donde el anillo heteroarilo es opcionalmente mono- o di-sustituido con

5 un sustituyente seleccionado del grupo que consiste de halógeno, oxo, tio, alquilo de 1-6 átomos de carbono, alquenilo de 2-6 átomos de carbono, alquinilo de 2-6 átomos de carbono, azido, hidroxialquilo de 1-6 átomos de carbono, halometilo, alcoximetilo de 2-7 átomos de carbono, alcaniloximetilo de 2-7 átomos de

10 carbono, alcoxi de 1-6 átomos de carbono, alquiltio de 1-6 átomos de carbono, hidroxí, trifluorometilo, ciano, nitro, carboxi, carboalcoxi de 2-7 átomos de carbono, carboalquilo de 2-7 átomos de carbono, fenoxi, fenilo, tiofenoxi, benzoilo, bencilo, amino, alquilamino de 1-6 átomos de carbono, dialquilamino de 2 a 12

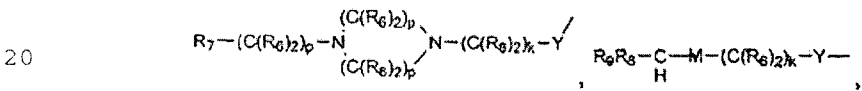
15 átomos de carbono, fenilamino, bencilamino, alcanilaraino de 1-6 átomos de carbono, alquenilamino de 3-8 átomos de carbono, alquinilamino de 3-8 átomos de carbono, carboxialquilo de 2-7 átomos de carbono, carboalcoxialquilo de 3-8 átomos de carbono, aminoalquilo de 1-5 átomos de carbono, N- alquilaminoalquilo de

20 2-9 átomos de carbono, N,N-dialquilaminoalquilo de 3-10 átomos de carbono, N-alquilaminoalcoxi de 2-9 átomos de carbono, N,N-dialquilaminoalcoxi de 3-10 átomos de carbono, mercapto, y bencilamino; V es etileno o acetileno; PG es un grupo protector de amina; R₄ es alquilo de 1 a 6 carbonos; Z es NR², O o S, en

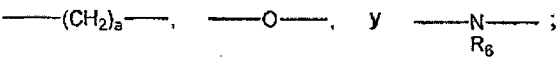
25 donde R² es H o C₁-C₆ alquilo; R₁, G₂, y R₃ son cada uno independientemente, hidrógeno, halógeno, alquilo de 1-6 átomos de carbono, alquenilo de 2-6 átomos de carbono, alquinilo de 2-6 átomos de carbono, alqueniloxi de 2-6 átomos de carbono, alquiniloxi de 2-6 átomos de carbono, hidroximetilo, halometilo,

nnnqg

alcaniloxi de 1-6 átomos de carbono, alqueniloxi de 3-8 átomos de carbono, alquiniloxi de 3-8 átomos de carbono, alcaniloximetilo de 2-7 átomos de carbono, alqueniloximetilo de 4-9 átomos de carbono, alquiniloximetilo de 4-9 átomos de carbono, alcoximetilo de 2-1 átomos de carbono, alcoxi de 1-6 átomos de carbono, alquiltio de 1-6 átomos de carbono, alquilsulfinil de 1-6 átomos de carbono, alquilsulfonil de 1-6 átomos de carbono, alquilsulfonamido de 1-6 átomos de carbono, alquenilosulfonamido de 2-6 átomos de carbono, alquinilsulfonamido de 2-6 átomos de carbono, hidroxí, trifluorometilo, trifluorometoxi, ciano, nitro, carboxi, carboalcoxi de 2-7 átomos de carbono, carboalquilo de 2-7 átomos de carbono, fenoxi, naftalamida, fenilo, tiofenoxi, bencilo, amino, hidroxiamino, alcoxiamino de 1-4 átomos de carbono, alquilamino de 1- 6 átomos de carbono, dialquilamino de 2 a 12 átomos de carbono, N-alquilcarbamoil, N,N-dialquilcarbamoil, N-alquil-N-alquenilamino de 4 a 12 átomos de carbono, N,N-dialquilamino de 6-12 átomos de carbono, fenilamina bencilamino,

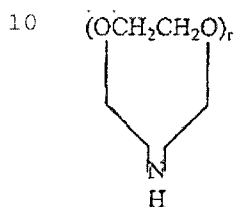


$R_7-(C(R_6)_2)_g-Y-$, $R_7-(C(R_6)_2)_p-M-(C(R_6)_2)_k-Y-$, or $Het-(C(R_6)_2)_qW-(C(R_6)_2)_2-Y-$; o R_1 y R_3 son como se definió anteriormente y G_2 es R_2-NH- ; o si cualquiera de los sustituyentes G_2 o R_3 se localizan en átomos de carbono contiguos luego ellos pueden tomarse juntos como un radical divalente $-O-C(R_6)_2-O-$; Y es un radical divalente seleccionado del grupo que consiste de



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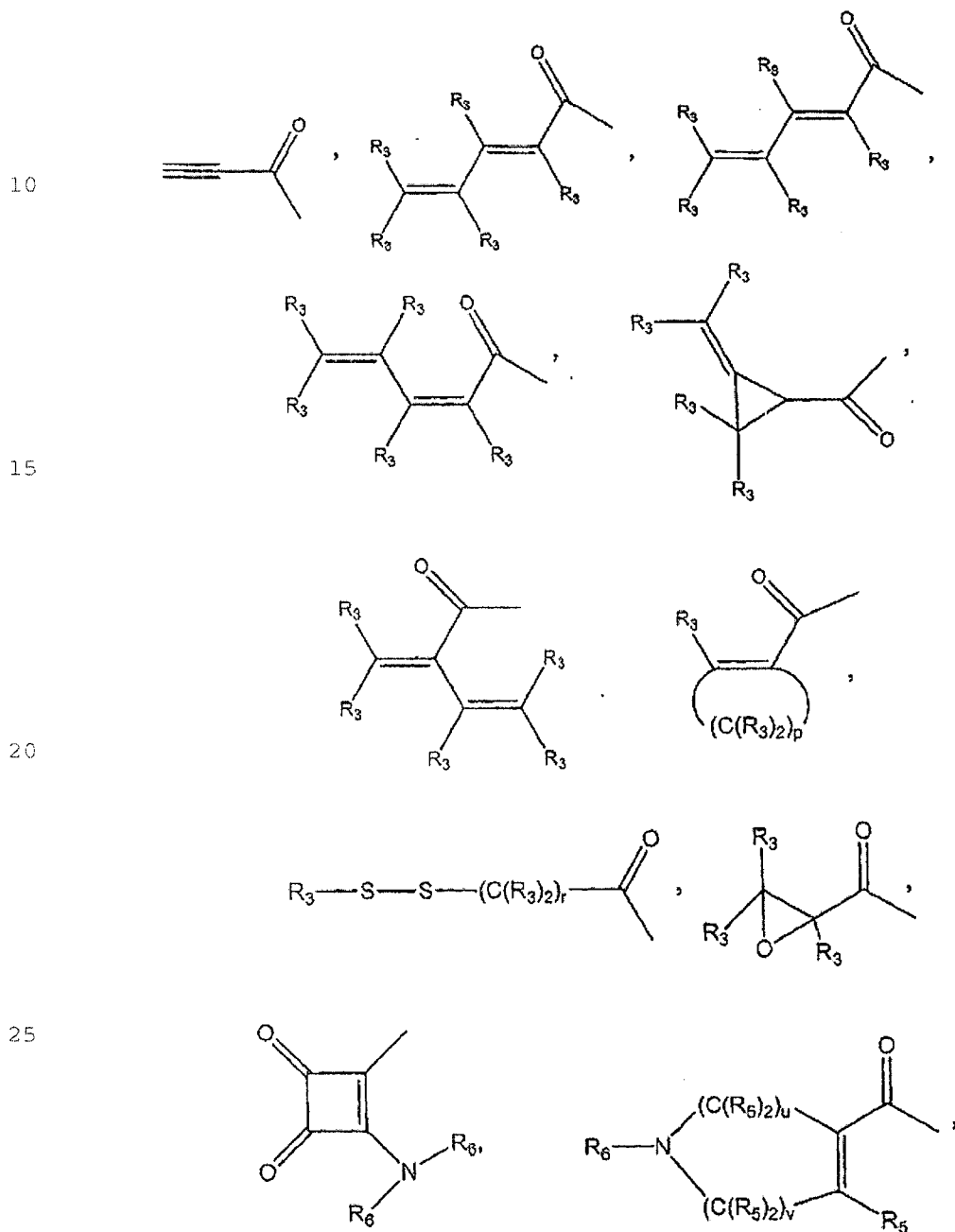
R_7 es $-NR_6R_6$, $-OR_6$, $-J$, $-N(R_6)_3+$, o $-NR_6(OR_6)$; M es $>NR_6$, $-O-$,
 $>N-(C(R_6)_2)_pNRR_6$, o $>N-(C(R_6)_2)_p-OR_6$; W es $>NR_6$, $-O-$ o es un
 enlace; Het es seleccionado del grupo que consiste de morfolina,
 5 tiomorfolina, tiomorfolina S-óxido, tiomorfolina S,S-dióxido,
 piperidina, pirrolidina, aziridina, piridina, imidazol, 1,2,3-
 triazol, 1,2,4-triazol, tiazol, tiazolidina, tetrazol,
 piperazina, furan, tiofeno, tetrahidrotiofeno, tetrahidrofurano,
 dioxáno, 1,3-dioxolano, tetrahidropiran, y



; en donde Het es opcionalmente mono- o di-sustituidos
 en carbono o nitrógeno con R_6 , opcionalmente mono- o di-
 15 sustituidos en carbono con hidroxil, $-N(R_6)_2$, o $-ORG$,
 opcionalmente mono o di-sustituidos en carbono con el radical
 mono-valente $-(C(R_6)_2)_sOR_6$ o $-(C(R_6)_2)_sN(R_6)_2$, y opcionalmente
 mono o di-sustituidos un carbono saturado con radicales
 divalentes $-O-$ o $-O(C(R_6)_2)_sO-$; R_6 es hidrógeno, alquilo de
 20 1-6 átomos de carbono, alquénilo de 2-6 átomos de carbono,
 alquínilo de 2-6 átomos de carbono, cicloalquilo de 1-6 átomos de
 carbono, carboalquilo de 2-7 átomos de carbono, carboxialquilo
 (2-7 átomos de carbono), fenilo, o fenilo opcionalmente
 sustituido con uno o más de halógeno, alcoxi de 1-6 átomos de
 25 carbono, trifluorometilo, amino, alquilamino de 1-3 átomos de
 carbono, dialquilamino de 2-6 átomos de carbono, nitro, ciano,
 azido, halometilo, alcóximetilo de 2-7 átomos de carbono,
 alcaniloximetilo de 2-7 átomos de carbono, alquiltio de 1-6
 átomos de carbono, hidroxil, carboxilo, carboalcoxi de 2-7 átomos

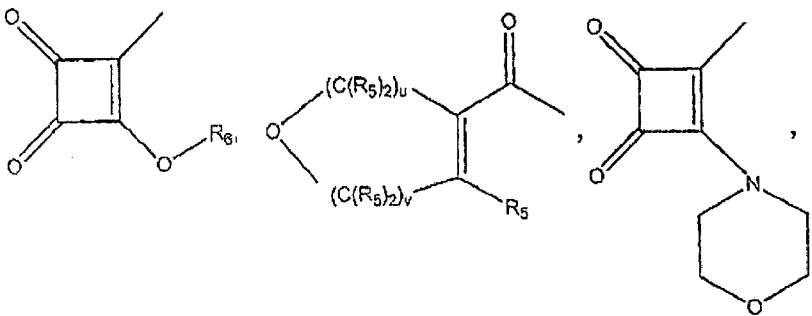
de carbono, fenoxi, fenilo, tiofenoxi, benzoilo, bencilo, fenilamino, bencilamino, alcanilamino de 1-6 átomos de carbono, o alquilo de 1-6 átomos de carbono; con la condición que la cantidad de alquenilo o alquinilo se enlaza con un átomo de

5 oxígeno o nitrógeno a través de un átomo de carbono saturado; R_2 , es seleccionado del grupo que consiste de

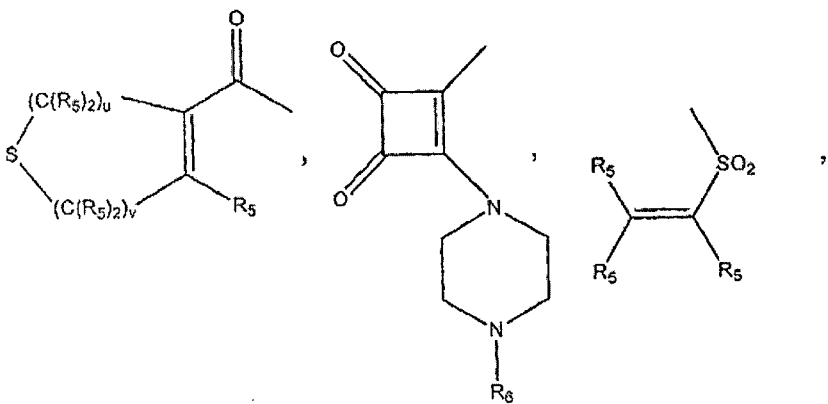


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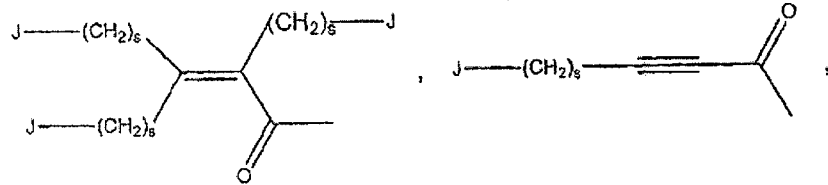
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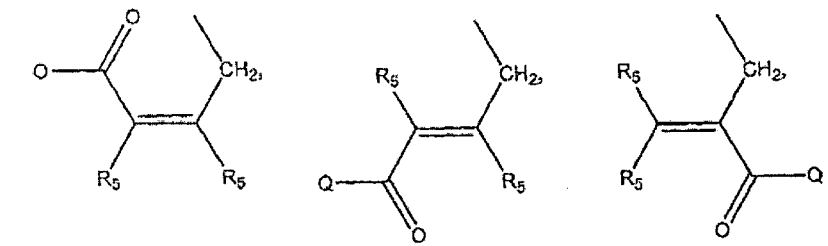
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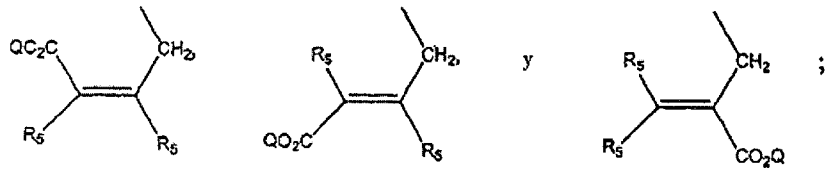
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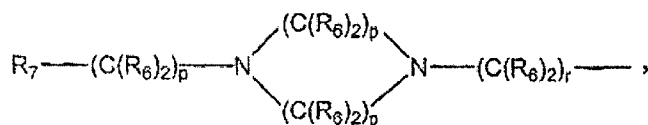
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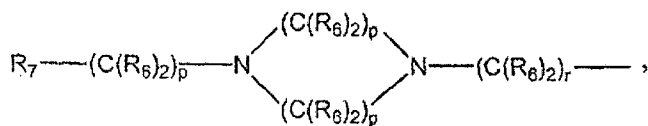


R₃ es independientemente hidrógeno, alquilo de 1-6 átomos de carbono, carboxi, carboalcoxi de 1-6 átomos de carbono, fenilo, carboalquilo de 2-7 átomos de carbono,



5 $R_7-(C(R_6)_2)_s-$, $R_7-(C(R_6)_2)_p-M-(C(R_6)_2)_1-$, R_8R_9-CH- , $M-(C(R_6)_2)_r-$, o $Het-(C(R_6)_2)_{c1}-W-(C(R_6)_2)_r-$; R_5 es independientemente hidrógeno, alquilo de 1-6 átomos de carbono, carboxi, carboalcoxi de 1-6 átomos de carbono, fenilo carboalquilo de 2-7 átomos de carbono,

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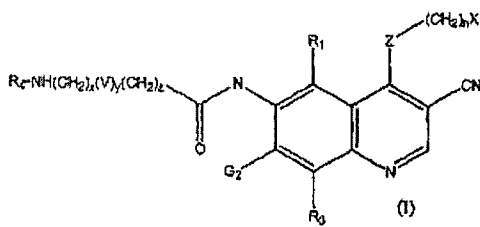


$R_7-(C(R_6)_2)_s-$, $R_7-(C(R_6)_2)_p-M-(C(R_6)_2)_r-$, $R_8R_9-CH-M-(C(R_6)_2)-$, o $Het-(C(R_6)_2)_q-W-(C(R_6)_2)_r-$; R_8 , y R_9 son cada uno independientemente $-(C(R_6)_2)_1-NR_6R_6$, o $-(C(R_6)_2)_r-OR_6$; J es independientemente hidrógeno, cloro, fluor, o bromo; Q es alquilo de 1-6 átomos de carbono o hidrógeno; $a=0$ o 1 ; $g=1-6$; $k=0-4$; n es $0-1$; m es $0-3$; $?=2-4$; $q=0-4$; $r=1-4$; $s=1-6$; $u=0-4$ y $v=0-4$, en donde la suma de $u+v$ es $2-4$; $x=0-3$; $y=0-1$; y $z=0-3$; o a una sal farmacéuticamente aceptable de estos.

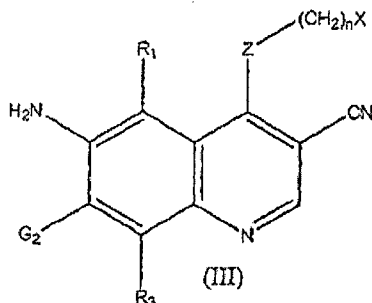
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[0006] La presente invención está también dirigida a un método para preparar un compuesto de Fórmula (I):

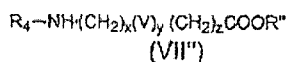
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que comprende la etapa de acoplar una anilinoquinolina de Fórmula (III):

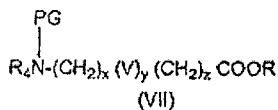


con un ácido de Fórmula (VII''):

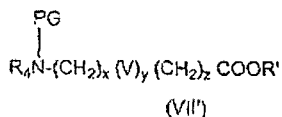


en donde R'' es H, y R₁, R₃, R₄, Z, G₂, V, n, x, y, y z son como se definió anteriormente.

[0007] Esta invención también pertenece a un método para preparar compuestos de ácido de Fórmula (VII):



en donde R es H, y R₄, V, x, y, y z son como se definió anteriormente y PG es un grupo protector de amina, que comprende la etapa de hidrolizado para un éster correspondiente de Fórmula (VII'):



00105

en donde R' es alquilo de 1 a 6 átomos de carbono o unpara
formará del ácido arilo de Fórmula (VII).

[0008] Esta invención está también dirigida a (E) N-{4-[3-cloro-
5 4-(2-piridinilmetoxi)anilino]-3-ciano-7-etoxi-6-quinolinil}-4-
(metilamino)-2- butenamida, o a una sal farmacéuticamente
aceptable de estos. También se contempla mediante la presente
invención composiciones que contienen los mismos y métodos para
utilizar este compuesto para prevenir, tratar o inhibir cánceres.

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DESCRIPCIÓN DETALLADA DE LA INVENCION

[0009] Las 6-des-alquilaminoquinolinas de fórmula (I) son
metabolitos de inhibidores de EGFR y HER2, y poseen actividad
15 inhibitoria EGFR y HER2 ellas mismas. Una modalidad
particularmente preferida de la presente invención se dirige a un
método para elaborar estos compuestos al arilar primero una 6-
anilino-3-cianoquinolina protegida en la posición 4 con un
reactivo de fórmula $HZ-(CH_2)_nX$, que se definió aquí. Luego el
20 nitrógeno de la anilina se les protege el compuesto se acopla a
un ácido de fórmula $(R_4)(PG)N-(CH_2)_x(V)_y(CH_2)_zCOOH$, utilizando los
reactivos de acoplamiento estándar para formar las 6-
amidoquinolina de fórmula (II). La amina secundaria protegida de
este compuesto se puede entonces desproteger para dar el producto
25 deseado. Alternativamente, las 6-des-alquilaminoquinolinas de
fórmula (I) se pueden formar directamente al acoplar la anilina
de fórmula (III) con un ácido no protegido de fórmula (VII'),
 $R_4-NH-(CH_2)_x(V)_y(CH_2)_zCOOH$, utilizando reactivos de acoplamiento
estándar.

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[0010] Este método es una mejora sobre el método anterior, que alquilataba el compuesto 6-anilinoquinolina utilizando un cloruro ácido. El método anterior producía por los rendimientos en razón
5 de la inestabilidad de los compuestos ácidos bajo las condiciones de reacción. Además, el método anterior también producida un producto crudo que era extremadamente difícil de purificar. El presente método, sin embargo, da rendimiento razonables y un producto crudo que puede ser fácilmente hecho >97% puro con
10 cromatografía flash.

[0011] Para los propósitos de esta invención el término "alquilo" a menos que se establezca otra cosa, incluye tanto porciones alquilo rectas como ramificadas, que pueden contener tanto como
15 12 átomos de carbono. Preferiblemente, la porción alquilo contiene entre 1 a 6 átomos de carbono, aunque 1 a 4 átomos de carbono es mas preferible. El término "alquenilo" se refiere a un radical de hidrocarburo alifático que contiene un doble enlace que incluye tanto porciones alquenilo rectas como ramificadas de
20 2 a 7 átomos de carbono. Tales porciones alquenilo pueden existir en las configuraciones E o Z; los compuestos de esta invención incluyen ambas configuraciones. El término "alquinilo" incluye tanto porciones de cadena rectas como ramificada que contienen 2 a 6 átomos de carbono que tiene por lo menos un triple enlace. El
25 término "cicloalquilo" se refiere a los grupos hidrocarburos alicíclicos que tienen 3 a 12 átomos de carbono, pero es preferiblemente de 3 a 7 átomos de carbono, e incluye pero no está limitado a: ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, norbornilo, y adamantilo.

[0012] Para los propósitos de esta invención el término "arilo" se define como una porción de hidrocarburo aromático, que puede ser un anillo simple o un sistema de anillo fusionado múltiple en el cual todos los enlaces dobles están en conjugación, y pueden ser sustituidos o no sustituidos. Un grupo arilo preferiblemente contiene 6 a 12 átomos de carbono y se puede seleccionar de, pero no está limitado a, el grupo: fenilo, α -naftilo, β -naftilo, bifenilo, anitrilo, tetrahidronaftilo, fenantrilo, fluórenilo, indanilo, bifenilenilo, acenaftenilo, acenaftilenilo, o los grupos fenantrenilo. Un grupo arilo puede ser opcionalmente mono, di, tri o tetra sustituido con sustituyentes seleccionados de, pero no limitados a, el grupo que consiste de alquilo, acilo, alcoxicarbonilo, alcoxi, alcoxialquilo, alcoxialcoxi, ciano, halógeno, hidroxilo, nitro, trifluorometilo, trifluorometoxi, trifluoropropilo, amino, alquilamino, dialquilamino, dialquilaminoalquilo, hidroxialquilo, alcoxialquilo, alquiltio, -SO₃H, -SO₂NH₂, -SO₂NHalquilo, -SO₂N(alquilo)₂, -CO₂H, CO₂NH₂, CO₂NHalquilo, y CO₂N(alquilo)₂. Los sustituyentes preferidos para arilo incluyen: alquilo, halógeno, amino, alquilamino, dialquilamino, trifluorometilo, trifluorometoxi, arilalquilo, y alquilarilo.

[0013] Para los propósitos de esta invención el término "heteroarilo" se define como un sistema de anillo heterocíclico aromático (monocíclico o bicíclico) donde las porciones heteroarilo tienen anillos de cinco o seis miembros que contiene 1 a 4 heteroátomos seleccionados del grupo que consiste de S, N y O, e incluyen pero no están limitados a: (1) furano, tiofeno,

indol, azaindol, oxazol, tiazol, isoxazol, isotiazol, imidazol, N-metilimidazol, piridina, pirimidina, pirazina, pirrol, N-metilpirrol, pirazol, N-metilpirazol, 1,3,4-oxadiazol, 1,2,4-triazol, 1-metil-1,2,4-triazol, 1H-tetrazol, 1-metiltetrazol, 5 benzoxazol, benzotiazol, benzofurano, benzisocazol, benzimidazol, N-metilbenzimidazol, azabenzimidazol, indazol, quinazolina, quinolina; (2)un heterociclo aromático bicíclico en donde el anillos de fenilo, piridina, pirimidina o piridizina es: (i) fusionado a un anillo heterocíclico aromático de 6 miembros 10 (insaturado) que tiene por lo menos un heteroátomo; (ii) fusionado a un anillo heterocíclico aromático o no aromático de 5 miembros (insaturado) que tiene por lo menos un heteroátomo seleccionado de O, N o S. preferiblemente un grupo heteroarilo bicíclico contiene 8 a 12 átomos de carbono.

15

Los sustituyentes preferidos para el heteroarilo incluyen: alquilo, halógeno, amino, alquilamino, dialquilamino, trifluorometilo, trifluorometoxi, arilalquilo y alquilarilo.

20 [0014] Para los propósitos de esta invención el término "heterocicloalquilo" se refiere a un sistema de anillo heterocíclico no aromático (monocíclico o bicíclico) donde las porciones contienen 1 a 4 heteroátomos seleccionados del grupo que consiste de S, N, O, e incluye pero no está limitado a: 25 pirrolidina, pirrolina, 1,3-dioxolano, imidazolina, imidazolidina, pirazolina, pirazolidina, piran, piperidina, dioxano, morfolino, dioxano, tiomorfolino, piperazina, azetidino, hexahidroazepino, dihidrobenzimidazolilo, dihidrobenzofuranilo, dihidrobenzotienilo, dihidrobenzoxazolilo,

dihidrofuranilo, dihidroimidazolilo, dihidroindolilo,
dihidroisooxazolilo, dihidroisotriazolilo, dihidrooxadiazolilo,
dihidrooxazolilo, dihidropirrazinil, dihidropirazolilo,
dihidropiridinilo, dihidropirimidinilo, dihidropirrolilo,
5 dihidroquinolinilo, dihidrotetrazolilo, dihidrotiadiazolilo,
dihidrotiazolilo, dihidrotriazolilo, dihidroazetidinilo, dihidro-
1,4-dioxanilo, tetrahidrofuranilo, tetrahidrotienilo,
tetrahidroquinolinilo, tetrahidroisoquinolinilo e indolino. Una
porción heterocicloalquilo contiene preferiblemente 1-11 átomos
10 de carbono. Estas porciones pueden ser además sustituidas.

[0015] Para el propósito de esta invención el término "alcoxi" se
define como C₁-C₆-alquilo-O; el término "ariloxi" se definió como
un aril-O-; el término "heteroariloxi" se definió como un
15 heteroaril-O-; en donde alquilo, arilo y heteroarilo son como se
definió anteriormente.

[0016] Para los propósitos de esta invención el término
"arilalquilo" se definió como aril-alquilo C₁-C₆-; las porciones
20 arilalquilo incluyen benzilo, 1-feniletilo, 2-feniletilo, 3-
fenilpropilo, 2-fenilpropilo y similares.

[0017] Para los propósitos de esta invención el término
"alcanoyloximetilo" se define como -CH₂OC(O)R, donde R es alquilo
25 de 1 a 6 átomos de carbono.

[0018] Para los propósitos de esta invención el término
"alquiltio" se definió como un alquil-S C₁-C₆.

[0019] Para los propósitos de esta invención "alquiltioalquilo", y "alcoxialquilo", denota un grupo alquilo como se definió anteriormente que es además sustituido con un alcoxi o alquiltio como se definió anteriormente.

5

[0020] Los términos "alquilamina" y "dialquilamina" se refieren a porciones con uno o dos grupos alquilo en donde la cadena de alquilo es de 1 a 6 átomos de carbono y los grupos pueden ser iguales o diferentes. Los términos "monoalquilaminoalquilo" y
10 "dialquilaminoalquilo" se refieren a porciones monoalquilamino y dialquilamino con uno o dos grupos alquilo (los mismos o diferentes) unidos al átomo de nitrógeno que esta unidos a un grupo alquilo de 1 a 6 átomos de carbono. Preferiblemente una porción de dialquilaminoalquilo consiste de 3 a 10 átomos de
15 carbono y una porción alquilaminoalquilo consiste de 2 a 9 átomos de carbono.

[0021] Los términos "alquilaminoalcoxi" y "dialquilaminoalcoxi" se refieren a las porciones alquilamino y dialquilamino con uno o
20 dos grupos alquilo (iguales o diferentes) unidos al átomo de nitrógeno que está unido a un grupo alcoxi de 1 a 6 átomos de carbono. Preferiblemente hubo una porción dialquilaminoalcoxi consiste de 3 a 10 átomos de carbono y una porción alquilaminoalcoxi consiste de 2 a 9 átomos de carbono.

25

[0022] Para los propósitos de esta invención el término "benzoilamino" se definió como una porción Ph-OC(O)NH- .

[0023] Para los propósitos de esta invención el término "carboxi"
se definió como una porción $-\text{COOH}$.

[0024] para los propósitos de esta invención el término
5 "alcanoilamino" se definió como una porción $-\text{NH}-\text{COOR}$, en donde R
es alquilo de 1 a 6 átomos de carbono.

[0025] Para los propósitos de esta invención el término
"alquenoilamino" y "alquinoilamino" se definió como una porción -
10 $\text{NH}-\text{COOR}$, en donde R es alquenilo o alquinilo de 3 a 8 átomos de
carbono.

[0026] Para los propósitos de esta invención el término
"carboalcoxi" se definió como $-\text{CO}_2\text{R}$, en donde R es alquilo de 1 a
15 6 átomos de carbono.

[0027] Para los propósitos de esta invención el término
"carboalquilo" se definió como $-\text{COR}$, en donde R es alquilo de 1 a
6 átomos de carbono.

20

[0028] Para los propósitos de esta invención el término
"carboxialquilo" se definió como una porción $\text{HOOCR}-$, donde R es
alquilo de 1 a 6 átomos de carbono.

25 [0029] Para los propósitos de esta invención el término
"carboalcoxialquilo" se definió como una porción $-\text{R}-\text{CO}_2-\text{R}'$, en
donde R y R' son alquilo y juntos consisten de 2 a 7 átomos de
carbono.

[0030] Para los propósitos de esta invención el término "aminoalquilo" se definió como H_2N -alquilo, en donde el grupo alquilo consiste de 1 a 5 átomos de carbono.

5 [0031] "Azido" es un radical de fórmula $-N_3$.

[0032] "Acilo" es un radical de fórmula $-(C=O)$ -alquilo o $-(C=O)$ -perfluoroalquilo en donde el radical alquilo o el radical perfluoroalquilo es de 1 a 6 átomos de carbono;

10 Ejemplos preferidos incluyen pero no están limitados a, acetilo, propionilo, butirilo, trifluoroacetilo.

[0033] Para los propósitos de esta invención el término "alquilsulfinilo" se definió como un radical $R^{\cdot}SO-$, donde $R^{\cdot}$ es
15 un radical alquilo de 1 a 6 átomos de carbono. Alquilsulfonilo es un radical $R^{\cdot}SO_2$, en donde $R^{\cdot}$ es un radical alquilo de 1 a 6 átomos de carbono. Alquilsulfonamido, alquenilsulfonamido, alquinilsulfonamido son radicales $R^{\cdot}SO_2NH$, donde $R^{\cdot}$ es un radical alquilo de 1 a 6 átomos de carbono, un radical alquenilo de 2 a 6
20 átomos de carbono, o un radical alquinilo de 2 a 6 átomos de carbono, respectivamente.

[0034] Los grupos heteroarilo no aromáticos saturados o parcialmente saturados se definen en esta invención como anillos
25 heterocíclicos seleccionados de pero no limitados a las porciones: azetidínilo, 1,4-dioxanilo, hexahidroazepínilo, piperazínilo, piperidínilo, pirrolidínilo, morfolínilo, tiomorfolínilo, dihidrobenzimidazolilo, dihidrobenzofuranilo, dihidrobenzotienilo, dihidrobenzoxazolilo, dihidrofuranilo,

dihidroimidazolilo, dihidroindolilo, dihidroisooxazolilo,
dihidroisotiazolilo, dihidrooxadiazolilo, dihidrooxazolilo,
dihidropirrazinilo, dihidropirazolilo, dihidropiridinilo,
dihidropirimidinilo, dihidropirrolilo, dihidroquinolinilo,
5 dihidrotetrazolilo, dihidrotiazolilo, dihidrotiazolilo,
dihidrotienilo, dihidrotriazolilo, dihidroazetidínilo, dihidro-
1,4-dioxanil, tetrahidrofuranilo, tetrahidrotienilo,
tetrahidroquinolinilo, y tetrahidroisoquinolinilo.
Preferiblemente tales porciones contiene 3 a 10 átomos por
10 anillo, en donde 1 a 4 es un heteroátomo seleccionado del grupo
que consiste de S, N y O.

[0035] El término "sustituyente" se utiliza aquí para referirse
aun átomo radical, un radical del grupo funcional o un radical
15 porción que reemplaza el radical hidrogeno en una molécula. A
menos de que se establezca expresamente otra cosa se debe asumir
que cualquiera de los sustituyentes puede ser opcionalmente
sustituidos con uno o mas grupos seleccionados de: alquilo,
halógeno, haloalquilo, hidroxialquilo, nitro, amino, hidroxí,
20 ciano, alquilamino, dialquilamino, alcoxi, haloalcoxi,
alcoxialquilo, alcoxialcoxi, oxo,
alquiltio, mercapto, haloalquiltio, arilo, ariloxi, ariltio,
heteroarilo, heteroariloxi, heteroariltio, acilo, -CO₂-alquilo, -
SO₃H, -SO₂NH₂, -SO₂NH-alquilo, -SO₂NH-(alquilo)₂, -CO₂H, -CO₂NH₂, -
25 CO₂NH-alquilo y -CO₂N-(alquilo)₂.

[0036] Para los propósitos de esta invención es término
"sustituido" se refiere a donde un radical hidrógeno sobre una
molécula ha sido reemplazado por otro átomo radical, un grupo

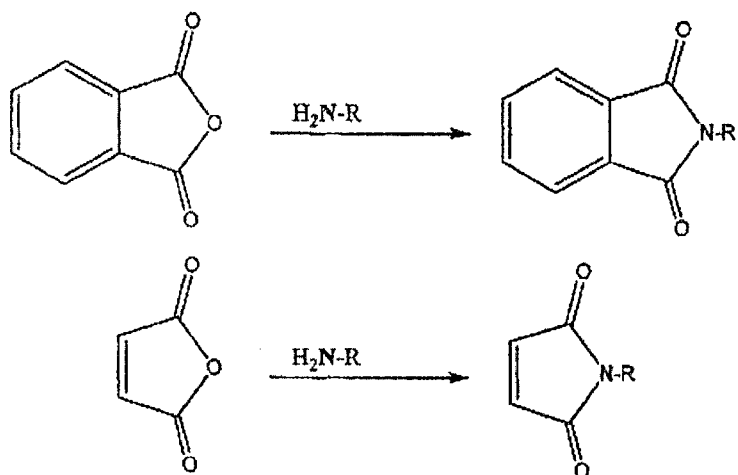
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funcional radical o una porción radical; estos radicales son generalmente denominados como "sustituyentes".

[0037] El término "grupo protector" se refiere a un grupo
5 introducido en una molécula para proteger un grupo funcional sensible o una posición específica sobre la molécula de reaccionar cuando la molécula se expone a reactivos o condiciones para transformar o reaccionar otra parte de la molécula. Posteriormente el grupo protector se puede remover. Los grupos
10 protectores adecuados son bien conocidos en la técnica e incluyen lábil ácido, lábil base, fotoremovible, o removible bajo condiciones neutras. Ver, por ejemplo, Green, Protecting Groups in Organic Synthesis, Wiley 1991, 2^{da} ed., pp. 309-405, que se incorpora aquí como referencia. el término "grupo protector
15 amina" se refiere a una porción capaz de proteger un grupo funcional amina de reaccionar. Los grupos protectores amina de ejemplo para la presente invención incluyen los grupos acilo (tal como acetilo), t-butoxicarbonilo (t-BOC), benciloxicarbonilo, trifluoroacetilo, grupos $\text{CH}_3\text{OC}(\text{O})-$, $\text{EtOC}(\text{O})-$, Fmoc, Troc, Fenoc,
20 Teoc y los grupos $\text{PhC}(\text{O})-$, y formar ciclicimidas (por ejemplo, ftalamida, maleimida, 2,3-dicloromaleimida, succinimida y dihidroftalamida) y pirroles (por ejemplo, dimetil pirrol).

[0038] Las ciclicimidas son grupos protectores útiles para
25 enmascarar aminas primarias. Ellas se forman al reaccionar la amina primaria a ser enmascarada con un reactivo tal como anhídrido ftálico o anhídrido maleámico, incorporando así la amina en la ciclicimida, como se muestra adelante.

5



10 [0039] Posteriormente, las ciclicimidas se pueden clivar bajo una variedad de condiciones para dar la amina primaria en buen rendimiento. Ver *Green* en pp. 358-359. El 2,5-Dimetilpirrolo opera similarmente.

15 [0040] El término "cáncer" se refiere a cualquier crecimiento maligno o tumor causado por la división celular anormal o no controlada. Ésta se puede esparcir a otras partes del cuerpo a través del sistema linfático o el torrente sanguíneo para los propósitos del método de tratar cáncer descrito en esta
20 solicitud, el cáncer incluye cáncer linfático, cáncer de mama, cáncer de ovario, tumores epidermoide, cáncer de colon, cáncer de próstata, cáncer de riñón, cáncer de vejiga, cáncer de laringe, cáncer de esófago, cáncer de estómago, y cáncer de pulmón.

25 [0041] Los compuestos sintetizados por esta invención pueden contener un átomo de carbono asimétrico y pueden así dar origen a estereoisómeros, tales como enantiómeros y diastereómeros. Los estereoisómeros de la presente invención se nombran de acuerdo al Sistema Cahn-Ingold-Prelog. Aunque mostrados sin respecto a la

estereoquímica en la fórmula (I), la presente invención incluye la síntesis de todos los posibles estereoisómeros individuales; así como también las mezclas racémicas y otras mezclas de los estereoisómeros R y S (mezclas escalémicas que son mezclas de 5 cantidades desiguales de enantiómeros). Se debe notar que los estereoisómeros de la invención que tienen la misma configuración relativa en un centro quiral puede sin embargo tener diferentes designaciones R y S dependiendo de la sustitución en el centro quiral indicado.

10

[0042] Esta invención también se dirige a composiciones farmacéuticas que contienen una cantidad terapéuticamente efectiva de un compuesto seleccionado de (E)N-{4-[3-cloro-4-fluoroanilino]-3-ciano-7-etoxi-6-quinolinil}-4-(metilamino)-2-
15 butenamida, (E)N-{4-[3-cloro-4-(2-pridinilmetoxi)anilino]-3-ciano-7-etoxi-6-quinolinil}-4-(metilamino)-2-butenamida, (E)N-{4-[3-cloro-4-(3-fluorobenciloxi)anilino]-3-ciano-7-etoxi-6-quinolinil}-4-(metilamino)-2-butenamida y (E)N-{4-[3-cloro-4-benciloxi)anilino]-3-ciano-7-etoxi-6-quinolinil}-4-(metilamino)-
20 2-butenamida, y un portador farmacéuticamente aceptable. En una modalidad preferida de la composición de la presente invención el compuesto es (E)N-{4-[3-cloro-4-(2-pridinilmetoxi)anilino]-3-ciano-7-etoxi-6-quinolinil}-4-(metilamino)-2-butenamida.

25 [0043] El portador farmacéuticamente aceptable contenido en la composición de la presente invención puede ser por ejemplo un diluyente, un aerosol, un portador tópico, una solución acuosa, una solución no acuosa o un portador sólido. El portador puede ser un polímero o una pasta dental. Un portador en esta invención

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comprende cualquiera de los portadores farmacéuticamente aceptados estándar, tal como solución salina amortiguada de fosfato, solución salina amortiguada de acetato, agua, emulsiones tales como emulsión de aceite/agua o una emulsión de triglicérido, varios tipos de agentes humectantes, tabletas, 5 tabletas recubiertas y cápsulas. Las composiciones de la presente invención se pueden formular con excipientes convencionales, tales como un llenador, un agente desintegrante, un ligador, un lubricante, un agente saborizante o un aditivo de color.

10

[0044] Cuando se suministra oralmente o tópicamente, tales compuestos se suministrarían a un sujeto por suministro en diferentes portadores. Típicamente, tales portadores contienen excipientes tales como almidón, leche, azúcar, ciertos tipos de 15 arcilla, gelatina, ácido esteárico, talco, grasas vegetales o aceites, gomas, o glicoles. El portador específico necesitaría ser seleccionado con base en el método deseado de suministro, por ejemplo, solución salina amortiguada de fosfato (PBS) se podría utilizar para suministro intravenoso o sistémico y grasas 20 vegetales, cremas, emplastos, ungüentos o geles se pueden utilizar para el suministro tópico.

[0045] Los compuestos de la presente invención se pueden suministrar junto con diluyentes adecuados, preservativos, 25 solubilizantes, emulsificadores, adyuvantes y/o portadores, útiles en el tratamiento o prevención de neoplasma. Tales composiciones son líquidos o liofilizados o formulaciones secadas de otra manera e incluyen diluyentes de contenido de amortiguador vario (por ejemplo, Tric-HCl, acetato, fosfato), pH y fuerza

iónica, aditivos tales como albúminas o gelatina para evitar la absorción a las superficies, detergentes (por ejemplo, TWEEN 20, TWEEN 80, PLURONIC F68, sales de ácido biliar), agentes solubilizantes (por ejemplo, glicerol, polietileno glicerol),
5 antioxidantes (por ejemplo, ácido ascórbico, metabisulfato de sodio), preservativos (por ejemplo, timerosal, bencil alcohol, parabenos), sustancias en masa o modificadores de tonicidad (por ejemplo, lactosa, manitol), unión covalente de polímeros tales como polietilen glicol, complejación con iones de metal, o
10 incorporación del compuesto en o sobre preparaciones de partículas de hidrogeles o liposomas, micro-emulsiones, micelas, vesículas unilamelares o multilamelares, espectros de eritrocito o esferoblastos. Tales composiciones influenciarán el estado físico, la solubilidad, la estabilidad, la proporción de
15 liberación *in vivo*, y la proporción de limpieza *in vivo* del compuesto o composición. La elección de las composiciones dependerá de las propiedades físicas y químicas del compuesto capaz de tratar o evitar un neoplasma.

20 [0046] Los compuestos de la presente invención se pueden suministrar localmente por vía de una cápsula que permita una liberación sostenida del compuesto durante un período de tiempo. Las composiciones de liberación controlada o sostenida incluyen formulación en depósitos lipófilos (por ejemplo, ácidos grasos,
25 ceras, aceites).

[0047] La presente invención suministra además un método para utilizar los compuestos descritos aquí, (E)N-{4-[3-cloro-4-fluoroanilino]-3-ciano-7-etoxi-6-quinolinil}-4-(metilamino)-2-

butenamida, (E)N-{4-[3-cloro-4-(2-pridinilmetoxi)anilino]-3-ciano-7-etoxi-6-quinolinil}-4-(metilamino)-2-butenamida, (E)N-{4-[3-cloro-4-(3-fluorobenciloxi)anilino]-3-ciano-7-etoxi-6-quinolinil}-4-(metilamino)-2-butenamida y (E)N-{4-[3-cloro-4-benciloxi)anilino]-3-ciano-7-etoxi-6-quinolinil}-4-(metilamino)-2-butenamida, como sustancias terapéuticas activas para evitar o inhibir el cáncer.

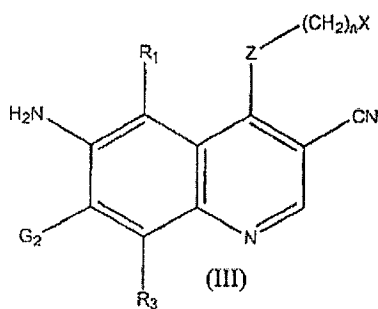
[0048] La presente invención suministra además un método para tratar cáncer en humanos, que comprende administrar al individuo infectado una cantidad efectiva de un compuesto o una composición farmacéutica de la invención. Una "cantidad terapéuticamente efectiva" es una cantidad suficiente para curar o mejorar los síntomas de un cáncer. La dosis efectiva de un ingrediente activo empleado puede variar dependiendo del compuesto particular empleado, el modo de administración y la severidad de la condición a ser tratada. En general, se obtienen resultados satisfactorios cuando los compuestos de la invención se administra en una dosis diaria de desde aproximadamente 0.5 a aproximadamente 1000 mg/kg de peso de cuerpo de animal, opcionalmente dada en dosis divididas dos a cuatro veces al día, o en forma de liberación sostenida. Para la mayoría de los mamíferos grandes la dosis diaria total es de aproximadamente 1 a 1000 mg, preferiblemente de aproximadamente 2 a 500 mg. Las formas de dosis adecuadas para uso interno comprenden desde aproximadamente 0.5 a 1000 mg del compuesto activo en mezcla íntima con un portador farmacéuticamente aceptable sólido o líquido. Este régimen de dosis se puede ajustar para suministrar la respuesta terapéutica óptima. Por ejemplo, se pueden

administrar varias dosis divididas diariamente o la dosis se puede reducir proporcionalmente como se indica por las exigencias de la situación terapéutica.

5 [0049] Los compuestos de la presente invención se pueden suministrar solos o en combinación con otros compuestos utilizados para tratar cáncer o con terapia de radiación. Tales compuestos incluyen pero no están limitados a imatinib mesilato (GLEEVEC), hidroxiúrea, IFN-a, agentes citotóxicos, NSAIDS, 10 gemcitabina, inhibidores EGFR, inhibidores MEK, farnesiltransferasa, taxol, vinblastina, cisplatina, ciclofosamida-5-fluorouracilo, adriamicina, bleomicina, etopósido, campptotecina, tamoxifeno o wortmanina.

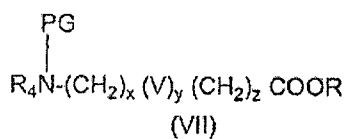
15 [0050] En una modalidad preferida del método de tratar cáncer descrito en la presente solicitud, el cáncer a ser tratado se selecciona de cáncer de mama, cáncer de ovario, tumores epidermoides, cáncer de colon, cáncer de próstata, cáncer de riñón, cáncer de vejiga, cáncer de laringe, cáncer de esófago, 20 cáncer de estómago y cáncer de pulmón. En otra modalidad preferida el cáncer a ser tratado es cáncer de mama o cáncer de ovario.

[0051] En una modalidad preferida de este método de sintetizar 25 los compuestos de fórmula (I) al desproteger un compuesto de fórmula (II), comprende además la etapa de formar el compuesto de fórmula (II) al acoplar una anilinoquinolina de fórmula (III):



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con un ácido de Fórmula (VII):



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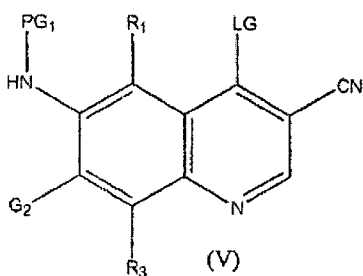
para formar un compuesto de Fórmula (II), en donde R es H, y R₁, R₃, R₄, Z, G₂, V, PG, n, x, y, y z son como se definió anteriormente.

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[0052] En todavía otra modalidad preferida de este método para sintetizar los compuestos de Fórmula (I), adicionalmente comprende la etapa de formar la anilinoquinolina de Fórmula (III) mediante:

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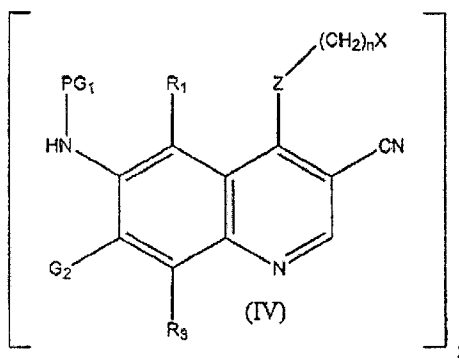
a. arilatar un compuesto de Fórmula (V):



25

con un compuesto de Fórmula $HZ-(CH_2)_nX$ para formar un intermedio de Fórmula (IV):

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b. desprotección del intermedio de Fórmula (IV) para obtener el compuesto de aniloquinolina de Fórmula (III);

en donde LG se selecciona del grupo de halo, mesilato, tosilato y trifilato, PG_1 es un grupo protector de amina, y en donde R_1 , R_3 , R_4 , Z , G_2 , PG , y n son como se definió anteriormente.

[0053] Otra modalidad del método para preparar compuestos de Fórmula (I) es en donde el método también involucra la etapa de formar un compuesto de Fórmula (II) al acoplar un compuesto de Fórmula (III) con un ácido de Fórmula (VII), utilizando un reactivo de acoplamiento seleccionado de DCC, benzotriazoliloxitrispirrolidino-fosfonio hexafluorofosfato (PyBOP), o N-etil-(N'-3-dimetilaminopropil)-carbodiimida 'HCl (EDCI) con 1-hidroxibenzotriazol (HOBt), aunque DCC es el reactivo acoplante más preferido. Es adicionalmente preferido que este método también comprende la etapas de arilatar la posición 4 de un compuesto de Fórmula (V) con un reactivo de Fórmula HZ-

25

(CH₂)_nX, preferiblemente utilizando ácido metilosulfónico, para formar un intermedio de Fórmula (IV), que es subsecuentemente desprotegido para producir un compuesto de Fórmula (III). En donde LG es un grupo saliente, tal como halo, mesilato, tosilato o triflato, en donde Cl es el más preferido, y PG₁ es un grupo protector de amina, con grupos de ejemplo siendo un grupo acilo (tal como acetilo), t-butoxicarbonilo (t-BOC), CH₃OC(O)-, EtOC(O)-, Fmoc, Troc, Fenoc, Teoc, trifluoroacetilo, benzoxi carbonilo, FC(O)-, 2,5- dimetilopirrol, naftalamida, 2,3-
10 dicloromaleimida, succinimida, dihidronaftalamida o maleimida. Es también preferible que el PG₁ se remueva utilizando un ácido. Un experto en la técnica podría también conocer otros grupos salientes adecuados, que se pueden utilizar. Los grupos protectores más preferidos son acetilo, t-BOC,
15 trifluoroacetamida, benzamida, 2,5-dimetilopirrol, naftalamida y maleimida, con t-BOC y acetilo que es el más preferido.

[0054] Otra modalidad del método para preparar un compuesto de Fórmula (I) es en donde los compuestos se limitan mediante las
20 siguientes cláusulas:

(i) cuando R₆ es alquenilo de 2-7 átomos de carbono o alquinilo de 2-7 átomos de carbono, tal cantidad de alquenilo o alquinilo se enlaza con un átomo de oxígeno o nitrógeno a través
25 de un átomo de carbono saturado;

(ii) cuando Y es -NR₆ - y R₇ es -NR₆ R₆, - N(R₆)₃.N(Rs)₃⁺, o - NR₆ (OR₆), luego g=2-6;

(iii) cuando M es - O - y R₇ es - OR₆ luego p=1-4;

(iv) cuando Y es -NR₆ - luego k=2-4;

(v) cuando Y es - O - y M o W es - O - luego k=1-4 ;

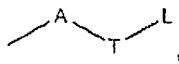
(vi) cuando W no es un enlace con Enlace Het a través del átomo de nitrógeno luego q=2-4;

5 cuando W es un enlace con Enlace Het a través del átomo de nitrógeno y Y es - O - o - NR₆, - luego k=2-4; y

con tal de que L sea un anillo fenilo no sustituido solo cuando m>0 y T no es -CH₂NH- o -CH₂O-.

10

[0055] Otra modalidad del método inventivo para preparar compuestos de Fórmula (I) es en donde X es cicloalquilo, que puede opcionalmente sustituirse con uno o más grupos alquilo, o es un piridinilo, pirimidinilo, o anillo fenilo; en donde el
15 piridinilo, pirimidinilo, o anillo fenilo opcionalmente pueden ser mono- di-, o tri-sustituidos como se describió anteriormente, o X es un radical que tiene la Fórmula:

20 , en donde A, T y L son como se definió anteriormente, y R₁, G₂, y R₃ son cada uno independientemente, hidrógeno, halógeno, alquilo de 1-6 átomos de carbono, alquenilo de 2-6 átomos de carbono, alquinilo de 2-6 átomos de carbono, alqueniloxi de 2-6 átomos de carbono, alquiniloxi de 2-6 átomos
25 de carbono, hidroximetilo, halometilo, alcaniloxi de 1-6 átomos de carbono, alqueniloxi de 3-8 átomos de carbono, alquiniloxi de 3-8 átomos de carbono, alcaniloximetilo de 2-7 átomos de carbono, alqueniloximetilo de 4-9 átomos de carbono, alquiniloximetilo de 4-9 átomos de carbono, alcoximetilo de 2-7 átomos de carbono,

alcoxi de 1-6 átomos de carbono, alquiltio de 1-6 átomos de carbono, alquilsulfinil de 1-6 átomos de carbono, alquilsulfonil de 1-6 átomos de carbono, alquilsulfonamido de 1-6 átomos de carbono, alquenosulfonamido de 2-6 átomos de carbono, alquinsulfonamido de 2-6 átomos de carbono, hidroxil, trifluorometilo, trifluorometoxi, ciano, nitro, carboxi, carboalcoxi de 2-7 átomos de carbono, carboalquilo de 2-7 átomos de carbono, fenoxi, naftalamida, fenilo, tiofenoxi, bencilo, amino, hidroxiamino, alcoxi-amino de 1-4 átomos de carbono, alquil-amino de 1-6 átomos de carbono, dialquil-amino de 2 a 12 átomos de carbono, N-alquilcarbamoilo, N,N-dialquilcarbamoilo, N-alquil-N-alquenosilamino de 4 a 12 átomos de carbono, o N,N-dialquenosilamino de 6-12 átomos de carbono.

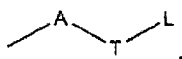
[0056] En otra modalidad del método para preparar compuestos de Fórmula (I) los compuestos se definen mediante X que es cicloalquilo, que pueden opcionalmente sustituirse con uno o más grupos alquilo C₁-C₆, o es un piridinilo, pirimidinilo, o anillo fenilo; en donde el piridinilo, pirimidinilo, o anillo fenilo opcionalmente pueden ser mono-, di-, o tri-sustituidos con los grupos descritos anteriormente. Z es preferiblemente NR². Cuando Z es NR^{2'} este es preferiblemente X sea un grupo aromático, tal como piridinilo, pirimidinilo, o anillo fenilo, con fenilo que es el más preferido. These aromatic moieties may be mono-, bi-, o tri-sustituidos. Cuando Z es NR^{2'} es también preferible que z y n son 0, y es 1, V es etileno y R₁, R₂, y R₃ son cada uno independientemente, hidrógeno, halógeno, alquilo de 1-6 átomos de carbono, halometilo, alcoxi de 1-6 átomos de carbono, hidroxil, trifluorometilo, trifluorometoxi, ciano, nitro, fenoxi,

naftalamida, fenilo, tiofenoxi, bencilo, amino, alquilamino de 1
-6 átomos de carbono, o dialquilamino de 2 a 12 átomos de
carbono. En esta modalidad cuando X es fenilo y Z es $NR^{Z'}$ es
adicionalmente preferible que R_1 , G_2 , y R_3 se limiten a hidrógeno,
5 halógeno, alquilo, alcoxi, hidroxilo, trifluorometilo,
trifluorometoxi y que X es solo opcionalmente sustituido con
halo, alquilo, trifluorometilo y alcoxi. Es también preferible
que cuando X es fenilo y Z es NR^Z que R_4 sea metilo, etilo,
propilo o isopropilo, R^Z es H y que R_1 , G_2 , y R_3 este
10 adicionalmente limitados por hidrógeno, halógeno, metoxi, etoxi,
hidroxilo, trifluorometilo, o trifluorometoxi. Una modalidad
específica es en donde el compuesto preparado es (E) N-{4-[3-
cloro-4-fluoroanilino]-3-ciano-7-etoxi-6-quinolinil}-4-
(metilamino)-2-butenamida.

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[0057] Otra modalidad del método para preparar los compuestos de
Fórmula (I) es en donde los compuestos se definen mediante X que
es un radical que tiene la fórmula:

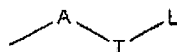
20



en donde A, T y L son como se definió anteriormente. A es más
preferiblemente un anillo fenilo opcionalmente mono- o di-
sustituido, y cuando A es un anillo fenilo este es
25 preferiblemente T es un éter que contiene un ligador tio o éter,
aunque un ligador éter es el más preferido. Z es preferiblemente
 $NR^{Z'}$ y L es preferiblemente un heteroarilo de 5 o 6 miembros
opcionalmente mono- o di- sustituido, tal como piridina,
pirimidina, piriazina, o pirazina. La cantidad amida en la

posición 6 del anillo quinolina está preferiblemente limitado en donde z y n son 0, y es 1 y V es etileno, mientras R , G_2 , y R_3 son preferiblemente hidrógeno, halógeno, alquilo de 1-6 átomos de carbono, halometilo, alcoxi de 1- 6 átomos de carbono, hidroxilo, trifluorometilo, trifluorometoxi, ciano, nitro, fenoxi, naftalamida, fenilo, tiofenoxi, bencilo, amino, alquilamino de 1-6 átomos de carbono, o dialquilamino de 2 a 12 átomos de carbono. Cuando T es un ligador éter este es preferiblemente m es 1 y que A es opcionalmente mono- o di-sustituido con un sustituyente seleccionado del grupo que consiste de halógeno, alquilo de 1-6 átomos de carbono, halometilo, alcoxi de 1-6 átomos de carbono, trifluorometilo, ciano, amino, alquilamino de 1-6 átomos de carbono, y dialquilamino de 2 a 12 átomos de carbono. Cuando T es -OCH₂- este es preferiblemente R_4 es metilo, etil, propilo o isopropilo, $R^{7'}$ es H, L es piridina, A y L son opcionalmente mono- o di-sustituidos con un sustituyente seleccionado del grupo que consiste de halógeno, metilo, etilo, metoxi, etoxi, y trifluorometilo, y que R_1 , G_2 , y R_3 esten adicionalmente limitados por hidrógeno, halógeno, metoxi, etoxi, hidroxilo, trifluorometilo, o trifluorometoxi. Una modalidad específica es en donde el compuesto preparado es (E) N-{4-[3-Cloro-4-(2-piridinilmetoxi)anilino]-3-ciano-7-etoxi-6-quinolinil)-4-(metilamino)-2-butenamida.

[0058] Otra modalidad del método para preparar los compuestos de Fórmula (I) es también en donde los compuestos se definen mediante X que es un radical que tiene la fórmula:



en donde A y L son anillos fenilo, Z es NR^z y T es un éter que
contiene un ligador tio o éter, aunque un ligador éter es el más
preferido. La cantidad amida en la posición 6 del anillo
quinolina está preferiblemente limitado en donde z y n son 0, y
5 es 1 y V es etileno, mientras R_1 , G_2 , y R_3 son preferiblemente
hidrógeno, halógeno, alquilo de 1-6 átomos de carbono,
halometilo, alcoxi de 1-6 átomos de carbono, hidroxí,
trifluorometilo, trifluorometoxi, ciano, nitro, fenoxi,
naftalamida, fenilo, tiofenoxi, bencilo, amino, alquilamino de 1-
10 6 átomos de carbono, o dialquilamino de 2 a 12 átomos de carbono.
Cuando T es un ligador éter este preferiblemente es m es 1 y que
A es opcionalmente mono- o di-sustituidos con un sustituyente
seleccionado del grupo que consiste de halógeno, alquilo de 1-6
átomos de carbono, halometilo, alcoxi de 1-6 átomos de carbono,
15 trifluorometilo, ciano, amino, alquilamino de 1-6 átomos de
carbono, y dialquilamino de 2 a 12 átomos de carbono. Cuando T es
-OCH₂- este es preferiblemente R_4 es metilo, etil, propilo o
isopropilo, R^z es H, A es opcionalmente mono- o di-sustituidos y
L es opcionalmente mono-, di- o tri- sustituidos con un
20 sustituyente seleccionado del grupo que consiste de halógeno,
metilo, etil, metoxi, etoxi, y trifluorometilo, y que R_1 , G_2 , y R_3
están adicionalmente limitados por hidrógeno, halógeno, metoxi,
etoxi, hidroxí, trifluorometilo, o trifluorometoxi. Las
modalidades específicas son en donde el compuesto preparado es
25 (E) N-{4-[(3-Cloro-4-benziloxi)anilino]-3-ciano-7-etoxi-6-
quinolinil} -4-(metilamino)-2-butenamida o (E) N-{4-[3-Cloro-4-
(3-fluorobenziloxi)anilino]-3-ciano-7-etoxi-6-quinolil}-4-
(metilamino)-2-butenamida.

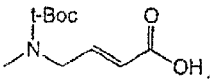
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[0059] Otra modalidad del método para preparar compuestos de Fórmula (I) es en donde el método también involucra la etapa de acoplar un compuesto de Fórmula (III) con un ácido de Fórmula (VII'), utilizando un reactivo de acoplamiento seleccionado de DCC, benzotriazoliloxitrispirrolidinofosfonio hexafluorofosfato (PyBoP), o N-etil-(N'-3-dimetilaminopropil)-carbodiimida HCl (EDCI) con 1-hidroxibenzotriazol (HOBt), aunque DCC es el reactivo acoplante más preferido. Alternativamente, el ácido de Fórmula (VII") se puede convertir al haluro ácido correspondiente, por ejemplo ácido clorhídrico, y luego acoplarse al compuesto de anilina de Fórmula (III). La técnica está repleta con métodos para convertir ácidos carboxílicos en los haluros de ácido correspondientes utilizando reactivos tales como SOCl_2 y oxalilo clorhídrico. El acoplar utilizando el reactivo de acoplamiento es el método preferido. Es adicionalmente preferido que este método también comprenda la etapas de arilatar la posición 4 de un compuesto de Fórmula (V) con un reactivo de Fórmula $\text{HZ}-(\text{CH}_2)_n\text{X}$, preferiblemente utilizando ácido metilosulfónico, para formar un intermedio de Fórmula (IV), que es subsecuentemente desprotegido para producir un compuesto de Fórmula (III). En donde LG es un grupo saliente, tal como halo, mesilato, tosilato o triflato, con Cl que es el más preferido, y PG_1 es un grupo protector de amina, con grupos de ejemplo siendo un grupo acilo (tal como acetilo), t-butoxicarbonilo (t-BOC), $\text{CH}_3\text{OC(O)-}$, EtOC(O)- , Fmoc, Troc, Fenoc, Teoc, trifluoroacetilo, benzoxi carbonilo, FC(O)- , 2,5-dimetilpirrol, naftalamida, 2,3-dicloromaleimida, succinimida, dihidronaftalamida o maleimida. Es también preferible que PG_1 se remueva utilizando un ácido. Un experto en la técnica también conoce otros grupos salientes

adecuados, que se pueden utilizar. Los grupos protectores más preferidos son acetilo, t-BOC, trifluoroacetamida, benzamida, 2,5-dimetilopirrol, naftalamida y maleimida, con t-BOC y acetilo que es el más preferido.

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[0060] Una modalidad del método para preparar compuestos de ácido de Fórmula (VII) es en donde el método adicionalmente comprende la etapas de alquilatar un compuesto de Fórmula (VI) con una amina primaria de la Fórmula NH_2R_4 para dar un intermedio aminoéster y subsecuentemente proteger el intermedio aminoéster mediante alquilatar en un grupo protector para formar un compuesto éster de Fórmula (VII'). En esta modalidad es también preferible que los compuestos de Fórmula (VII) se definan mediante z que es 0, y que es 1 y V que es etileno. Más preferiblemente R_4 es metilo, etilo, propilo o isopropilo. Una modalidad específica es en donde el compuesto ácido de Fórmula (VII) es



20 [0061] Los compuestos preferidos sintetizados mediante la presente invención incluyen:

(E) N-{4-[3-cloro-4-fluoroanilino]-3-ciano-7-etoxi-6-quinolinil}-4-(metilamino)-2-butenamida;

25 (E) N-{4-[3-cloro-4-(2-piridinilmetoxi)anilino]-3-ciano-7-etoxi-6-quinolinil}-4-(metilamino)-2-butenamida;

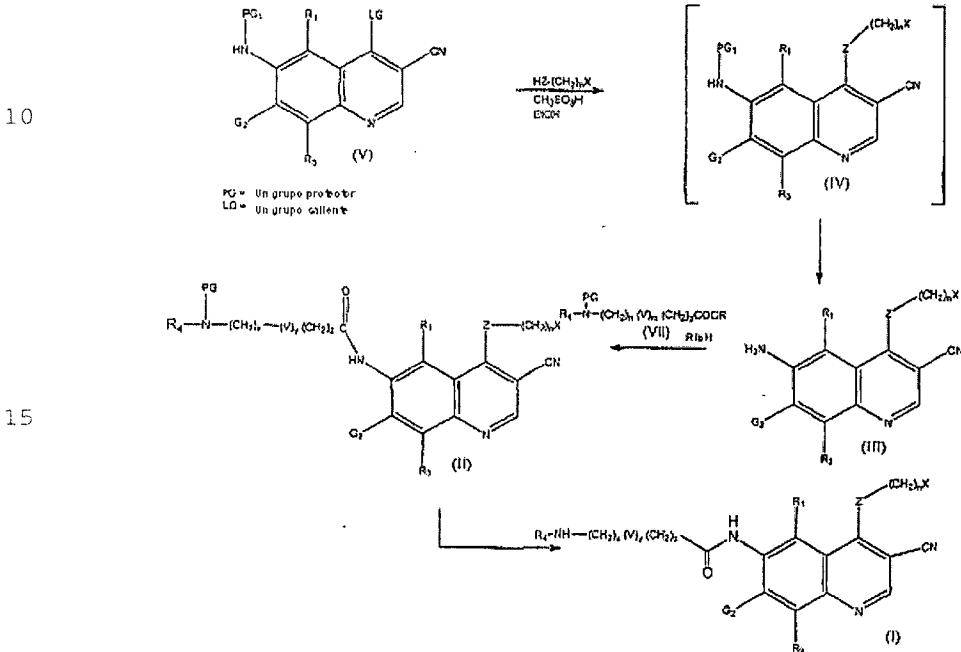
(E) N-{4-[3-cloro-4-(3-fluorobenziloxi)anilino]-3-ciano-7-etoxi-6-quinolinil}-4-(metilamino)-2-butenamida; y

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(E) N-{4-[(3-cloro-4-benziloxi)anilino]-3-ciano-7-etoxi-6-quinolinil}-4-(metilamino)-2-butenamida.

Síntesis general

Esquema 1



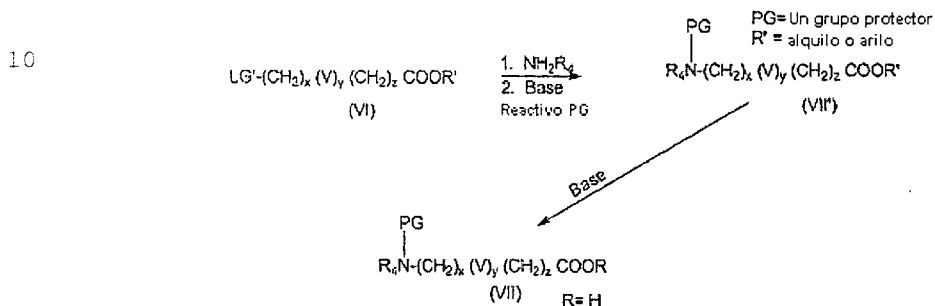
20 [0062] El Esquema 1 ilustra la síntesis de una des-
alquilaminoquinolina de Fórmula (I) del protector de partida
anilinoquinolina de Fórmula (V), en donde los grupos protectores
uno cualquiera de aquellos pueden usualmente emplear una amina
protectora, tal como un grupo acilo (tal como acetilo), t-
25 butoxicarbonilo (t-BOC), benziloxicarbonilo, los grupos CH₃OC(O)-
, EtOC(O)-, Fmoc, Troc, Fenoc, Teoc, FC(O)-, ciclicimides (por
ejemplo, naftalamida, maleimida, 2,3-dicloromaleimida,
succinimida y dihidronaftalamida) o un pirrol (por ejemplo,
dimetilo pirrol). La anilinoquinolina protectora primero

reacciona con ácido metilosulfónico y un reactivo de Fórmula HZ-
(CH₂)_nX, en donde Z puede ser NR^{z'}, O o S y R^{z'} es H o alquilo, n
es 0 o 1 y X es como se definió anteriormente, para formar un
intermedio de Fórmula (IV). Los Reactivos tal como piridinio
5 hidrociorhídrico, HCl, ácido sulfúrico, ácido trifluoroacético, y
similares, pueden ser utilizados en lugar de ácido
metilosulfónico. El Intermedio es luego desprotegido para
suministrar la anilinoquinolina de Fórmula (III).

10 [0063] La anilinoquinolina de fórmula (III) es luego acoplada con
un ácido de Fórmula (VII) utilizando un reactivo de acoplamiento
estándar tal como DCC, benzotriazaliloxitrispinolidinofosfonio
hexafluorofosfato (PyBoP), o N-etil-(N'-3-dimetilaminopropil)-
carbodiimida "HCl (EDCI) con 1- hidroxibenzotriazol (HOBt). La
15 técnica de la literatura está repleta con otros reactivos de
acoplamiento y un experto en la técnica estaría enterado de tales
reactivos. DCC es preferible. El ácido de Fórmula (VII) se define
mediante V siendo etileno o un grupo acetileno, x es 0, 1, 2, o
3, y es 0 o 1, z es 0, 1, 2 o 3, R es H, R₄ es un grupo alquilo
20 de 1 a 6 átomos de carbono y PG es un grupo protector de amina
que es estable en condiciones básicas, tal como un grupo acilo
(tal como acetilo), t- butoxycarbonilo (t-BOC),
benziloxycarbonilo, CH₃OC(O)-, EtOC(O)-, Fmoc, Troc, Fenoc, Teoc
o FC(O)-. El más preferido es t-BOC. Este no está destinado a ser
25 una lista exhaustiva y un experto en la técnica estará enterado
de otros grupos protectores adecuados. La síntesis de tales
compuestos de ácido se muestra en el Esquema 2 adelante. Este
reacción de acoplamiento produce compuestos de Fórmula (II).

[0064] Las Amidoquinolinas de Fórmula (II) pueden luego ser desprotegidas bajo condiciones de ácido o neutro para suministrar los metabolitos des-alquilo de Fórmula (I). IfPG es un grupo t-BOC luego el ácido es preferiblemente HCl, aunque otros ácidos son también adecuados.

Esquema 2



15 [0065] Como se ilustra en el Esquema 2, ésteres de Fórmula (VI), en donde LG' es un grupo saliente, tal como halo, mesilato, tosilato o triflato, y R' es alquilo o arilo, reaccionan primero con aminas primarias y secundarias con reactivo que alquilate un grupo protector en la amina de nitrógeno para dar alquilamino

20 ésteres protegidos de Fórmula (VII'). Los Halógenos son el grupo saliente preferido, especialmente bromo. El grupo protector puede ser cualquiera de los grupos amina comúnmente utilizados que son estables bajo condiciones básicas, tal como un grupo acilo (tal como acetilo), t- butoxicarbonilo (t-BOC), benziloxicarbonilo,

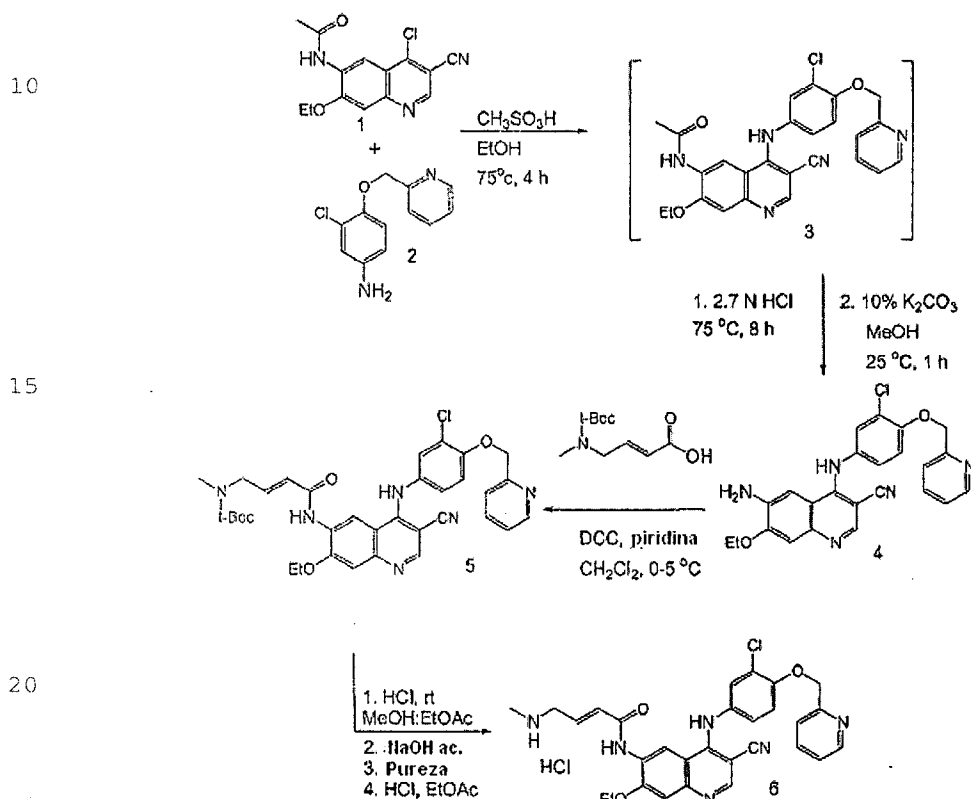
25 CH₃OC(O)-, EtOC(O)-, Fmoc, Troc, Fenoc, Teoc o FC(O)-. Tert-butoxicarbonilo es el más preferido, y (BOC)₂O es el reactivo más preferido para instalar el grupo protector. La Saponificación de los ésteres suministra los ácidos correspondientes de Fórmula (VII), en donde R es H. Acoplar los ácidos con sustituidos 4-

001.34

anilinoquinolinas seguidos por la desprotección suministra los compuestos des-metilo de Fórmula (I) como se muestra en el Esquema 1.

5 Síntesis específica

Esquema 3



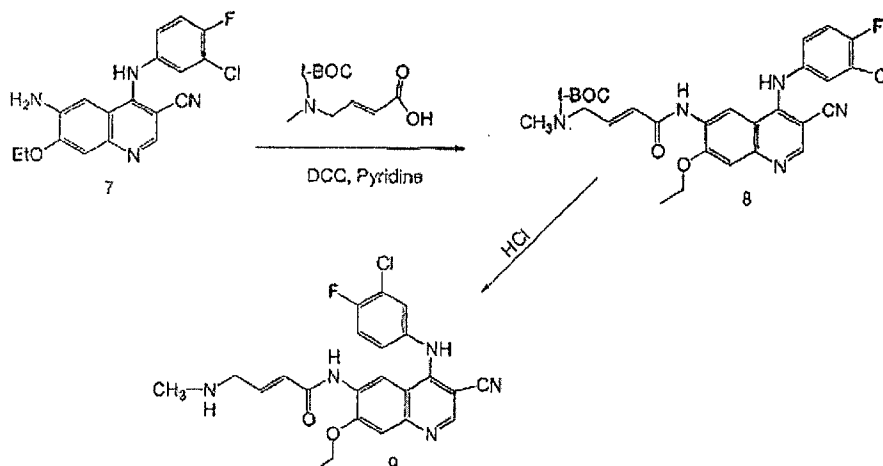
[0066] En el Esquema 3 se ilustra una síntesis específica de 6-(4-alkilamino)-2-butenamido quinolina 6. El Compuesto 1 es arilado con el compuesto 2 utilizando ácido metilosulfónico en etanol a aproximadamente 75°C para dar un intermedio 3. Este intermedio es luego desprotegido bajo condiciones acídicas utilizando aproximadamente 2.7 M de HCl y calentando a 75°C. Un

trabajo básico con carbonato de potasio luego proporciona 6-anilinoquinolina 4.

[0067] El Compuesto 4 es luego acoplado con ácido 4-metilaminocrotónico protegido t-BOC utilizando DCC y piridina en un baño de hielo para producir el compuesto 5. El compuesto 5 es subsecuentemente desprotegido utilizando condiciones HCl templadas y un trabajo básico para suministrar la base libre de 6-(4-alkilamino)-2-butenamido quinolina 6. Después de la purificación, la sal correspondiente HCl puede ser formada mediante exponer el compuesto a HCl en etilacetato.

Esquema 4

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[0068] El Esquema 4 muestra la síntesis de 6-(4-alkilamino)-2-butenamidoquinolina 9. El compuesto 7 se forma análogo a un compuesto 4 en el Esquema 3, sustituyendo 3-cloro-4-fluoroanilina para 3-cloro-4-(2-piridmilmetoxi)anilina. El compuesto 7 es luego acoplada con t-BOC protector ácido A- metilaminocrotónico utilizando DCC y piridina para dar el compuesto 8, que es

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00136

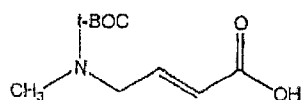
subsecuentemente desprotegido utilizando HCl para suministrar 6-(4-alquilamino)-2-butenamidoquinolina 9.

[0069] Los siguientes son ejemplos preparados utilizando los métodos ilustrados en los esquemas anteriores. Estos ejemplos son solo algunos de los compuestos mencionados por la presente invención y no deben limitar la presente invención en ninguna forma.

10 EJEMPLO 1

Ácido 4-[N-(t-butiloxycarbonil)metilamino] crotonico

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Preparación de metil HCl 4-metilamino-crotonato.

[00701 Una solución de metilo 4-bromocrotonato (66 mL, 0.56 mol) en THF (500 mL) y una solución de 2.0 M metilamina en THF (700 mL, 1.4 mol) se agregaron a través de un embudo adicional simultáneamente a -20°C durante 30 min. La mezcla de reacción se suspende en un amarillo suave. Luego de la adición, la mezcla de reacción se agita a -5°C durante 2h, luego se filtra y se lava con THF (2 x 30 mL). El filtrado se concentra in vacío para dar un aceite marrón. Una solución de HCl en EPA (10.5%, 200 mL) se agrega al aceite marrón a través de un embudo adicional a 0-5°C. La mezcla de reacción se agita durante 30 min, y luego se concentra in vacío para dar un aceite rojo marrón. Se agrega

CH₂Cl₂ (-20 mL) y la solución se coloca en el refrigerador (-5°C) para permitir su cristalización. Al licor madre se le da varios baños de cristales. Los baños combinados se recrystalizan de CH₂Cl₂ para obtener 17 g (rendimiento 22%) del compuesto deseado
5 as como un sólido incoloro. ¹H RMN (CDCl₃, ppm) d 7.02 (m, 1H), 6.28 (d, 1H), 3.80 (s, 2H), 3.77 (s, 3H), 2.70 (t, 3H); ¹³C RMN (DMSO-d₆, ppm) d 165.11, 138.39, 125.43, 51.62, 47.69, 31.81; IR (KBr): ν_{max} 3426, 3285, 3037, 2954, 2805, 2423, 1719, 1667, 1438, 1348, 1272, 1209, 1158, 1027, 1000 cm⁻¹; Anal. calculado para C₆H₁₂ClNO₂: C, 43.51; H, 7.30; N, 8.46. Encontrado: C, 43.42; H, 7.36; N, 8.37.

Preparación de metil 4-[N-(t-butiloxicarbonil)metilamino]crotonato.

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[0071] a una suspensión de metilo 4-metilamino-crotonato (14.1 g, 85.3 mmol) en CH₂Cl₂ (150 mL) se agregaron DMAP (10.4 g, 85.3 mmol) y trietilamina (25 mL, 179.2 mmol) mientras se enfría en un baño de hielo. A esta suspensión (Boc)₂O (22.4 g, 102.4 mmol) se
20 agrega lentamente CH₂Cl₂ (50 mL). La mezcla de reacción se agita a temperatura ambiente durante 19 h bajo N₂, luego se satisface con H₂O (150 mL). La capa orgánica se lava con H₂O (2 x 150 mL), 3 N HCl (200 mL), seguido por H₂O (100 mL). La capa orgánica se seca durante Na₂SO₄, se filtra y se concentra in vacuo para dar
25 17.3 g (rendimiento 89%) de N-Boc Metilo Crotonato como un aceite marrón. ¹H RMN (CDCl₃, ppm) d 6.87 (m, 1H), 5.84 (d, 1H), 3.99 (bs, 2H, NCH₂), 3.75 (s, 3H), 2.85 (bs, 3H), 1.46 (s, 9H); ¹³C RMN (CDCl₃, ppm) d 166.51, 155.38, 143.91, 121.37, 79.98, 51.61, 49.64, 34.36, 28.55; IR (KBr): ν_{max} 3591, 3441, 2976, 2953, 1726,

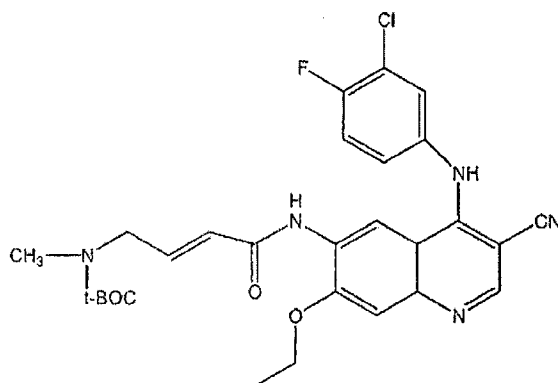
1699, 1480, 1452, 1392, 1366, 1276, 1228, 1169, 1148, 1039, 947
cm⁻¹; Anal. calculado para C₁₀H₁₇NO₄: C, 57.62; H, 8.35; N, 6.11.
Encontrado: C, 57.86; H, 8.57; N, 6.30.

Preparación de ácido.4-[N-(t-butiloxicarbonil)metilamino]-
5 cotónico.

[0072] Una solución de metilo 4-[N-(t-butiloxicarbonil)metilamino]-crotonato (17.5 g, 76.3 mmol) en THF (200 mL) se enfría en un baño de hielo, KOH (17.1 g, 305 mmol) en
10 H₂O (100 mL) se agrega a través de un embudo adicional. La mezcla de reacción se agita en el baño de hielo durante 15 min antes de remover el agitador a temperatura ambiente bajo N₂. Después de 16 h, la mezcla de reacción se concentra in vacuo para dar una capa acuosa. La capa acuosa se lava con CH₂Cl₂ (2 x 60
15 mL) para remover las impurezas orgánicas, luego se acidifica a pH = 1-2 con 3 N HCl (~130 mL). La capa acuosa se extrae con CH₂Cl₂ (4 x 80 mL). La capa orgánica combinada se seca durante Na₂SO₄, se filtra y se concentra in vacuo para dar 16.0 g (97.5% rendimiento) de del compuesto del título como un aceite amarillo
20 claro. ¹H RMN (CDCl₃, ppm) δ 6.98 (m, H), 5.85 (d, 1H), 3.99 (bs, 2H), 2.87 (bs, 3H), 1.46 (s, 9H); ¹³C-RMN (CDCl₃, ppm) δ 170.34, 155.72, 145.60, 121.44, 80.18, 49.70, 34.47, 28.23; IR (KBr): ν_{max} 3417, 3144, 2977, 2934, 1699, 1482, 1455, 1394, 1368, 1252, 1152, 948 cm⁻¹; Anal. calculado para C₁₀H₁₇NO₄: C, 55.80; H, 7.96; N, 6.51. Encontrado: C, 54.46; H, 8.10; N, 6.32.
25

EJEMPLO 2

(E) N-{4-[3-cloro-4-fluoroanilino]-3-ciano-7-etoxi-6-quinolinil}-
4-[N-(t-butiloxicarbonil)metilamino]-2-butenamida



Acoplamiento de Ácido N-Boc Cotónico con 4-(3-cloro-4-fluoro-
fenilamino)-3- ciano-7-etoxi-quinolina.

[0073] a una solución de ácido 4-[N-(t-butiloxi carbonil)
15 metilamino-cotónico (16.0 g, 74.4 mmol) en CH_2Cl_2 (150 mL), se
enfriada en un baño de hielo, se agrega piridina (60 mL, 744
mmol) y DCC (15.3 g, 74.4 mmol). Una suspensión de 4- (3-cloro-4-
fluoro-fenilamino)-3-ciano-7-etoxi-quinolina (13.3 g, 37.2 mmol)
en CH_2Cl_2 (100 mL) se agrega lentamente. El frasco de reacción se
20 cubre con hojuela de alúmina, se agita a rt bajo N_2 . Después de 3
d, la mezcla de reacción se diluye con CH_2Cl_2 (120 mL), luego se
filtra. El filtrado se lava con H_2O (2 x 60 mL), 2 N HCl (2 x 60
mL), y H_2O (60 mL). La capa orgánica se seca durante Na_2SO_4 , se
filtra y se concentra in vacío para dar el producto crudo como un
25 residuo rojo marrón. La purificación vía SiO_2 , se eluye con EtOAc
para dar 7.5 g de 6-(4-[N-(t-butiloxicarbonil)-metilamino]-but-
2-enil)-4-(3-cloro-4-fluoro-fenilamino)-3-ciano-7-etoxi-
quinolina. La Recristalización del acetato de etilo da 4.9 g (12%
de rendimiento) del compuesto como un sólido amarillo claro. ^1H

00140

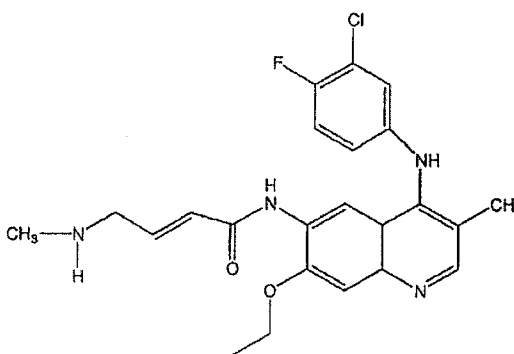
RMN (CDCl_3 , ppm) d 9.17 (s, 1H), 8.46 (s, 1H), 7.99 (s, 1H), 7.19-6.96 (m, 3H), 6.83 (m, 1H), 6.05 (d, 1H), 4.25 (q, 2H), 4.02 (bs, 2H), 2.85 (bs, 3H), 1.53 (t, 3H), 1.47 (s, 9H); IR (Nujol): ν_{max} 3313, 2951, 2855, 2218, 1707, 1679, 1640, 1531, 1502, 1458, 1377, 1273, 1164, 1146, 1042, 869, 855, 774 cm^{-1} ; nLp.: 106.5-108.0°C; Anal. calculado para $\text{C}_{28}\text{H}_{29}\text{N}_5\text{O}_4\text{ClF}$: C, 60.76; H, 5.24; N, 12.66. Encontrado: C, 59.70; H, 5.89; N, 10.83.

EJEMPLO 3

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(E) N-{4-[3-cloro-4-fluoroanilino]-3-ciano-7-etoxi-6-quinolinil}-4-(metilamino)-2-butenamida

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Hidrólisis del grupo protector t-BOC.

[0074] a una suspensión del compuesto del Ejemplo 2 (1.86 g, 3.36 mmol) en MeOH (20 mL), se agrega lentamente 1.2 N de HCl en acetato de etilo (74 mL). La mezcla nubosa amarilla se agita a temperatura ambiente bajo N_2 . Después de 6.5 h, la mezcla de reacción se concentra in vacuo para dar un sólido amarillo. Después de la purificación por cristalización en (60:40) MeOH/IPA, 1.41 g, (80.1 % rendimiento, 96.9 %de área mediante

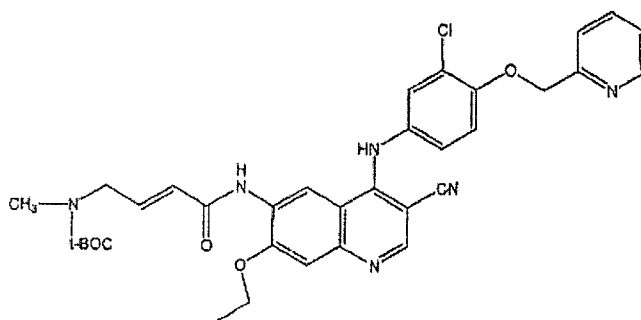
HPLC) de la sal de clorhidrato del compuesto del título se
obtiene como un sólido amarillo claro. ^1H RMN (DMSO, ppm) d 11.1
(bs, 1H), 9.98 (s, 1H), 9.36 (bs, 2H), 9.13 (s, 1H), 9.00 (s, 1H,
7.75 (dd, 1H, $J=3$ Hz, 6Hz), 7.65 (s, 1H), 7.55 (t, 1H, $J=8$ Hz),
5 7.46-7.48 (m, 1H), 6.75-6.87 (m, 2H), 4.35 (q, 2H, $J=5.1$ Hz),
3.76-3.80 (m, 2H), 2.56 (t, 3H, $J=4.0$ Hz), 1.50 (t, 3H, $J=5.3$
Hz); ^{13}C RMN (DMSO, ppm) d 163.14, 155.59, 155.36, 153.59,
149.46, 135.77, 135.14, 129.6, 129.0, 128.3, 127.1, 120.3, 120.1,
117.8, 117.6, 116.9, 115.0, 112.9, 87.2, 65.7,
10 48.6, 32.4, 14.4; IR (Nujol): ν_{max} 3580, 3497, 3192, 2900, 2691,
2403, 2224, 1682, 1640, 1584, 1536, 1492, 1460, 1377, 1314, 1264,
1193, 885, 729 cm^{-1} .

EJEMPLO4

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(E) N-{4-[3-Cloro-4-(2-piridinilmetoxi)anilino]-3-ciano-7-etoxi-
6-quinolinil}-4-[N-(t-butiloxicarbonil)metilamino]-2-butenamida

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25 Preparación de metilo 4-[N-(terc-butiloxicarbonil)metilamino]
crotonato.

[0075] Se enfría en un frasco de cuatro cuellos de -15 a -25 °C.
Se carga del embudo de adición con metilo 4-bromocrotonato (25.0

g, 0.118 mol a 85% de fuerza) en THF (125 ml). Se carga con un segundo embudo de adición con 2.0 M solución de metilamina en THF (149 ml, 0.30 mol, 2.5 eq). Se agregan ambas soluciones en gotas y simultáneamente durante 30 min se mantiene la temperatura a -15 a -25 °C. La mezcla se calienta a -10 a -5 °C y se mantiene durante 2h. Se agrega solución de metilamina 2.0 M en THF (50 ml, 0.10 mol) si es necesario para completar la reacción. Cuando no se detecta el material de partida mediante TLC (9:1 heptano:EtOAc), se enfría la mezcla de reacción a -60 a -65 °C. Se agrega trietilamina (60.0 g, 82.5 ml, 0.59 mol, 5 ec). Se agrega en gotas una solución de di-t-butyl dicarbonato (103.75 g, 0.475 mol, 4 ec) en THF (250 ml) durante 1h. Se mantiene la mezcla durante la noche mientras se le permite calnetarse a temperatura ambiente. Se revisa que la reacción se complete mediante TLC (9:1 heptano:EtOAc). Los precipitados se filtran y la mezcla se concentra en un aceite. El aceite se re-redisuelve en CH₂Cl₂ (250 ml), se lava consecutivamente con agua (125 ml), 1 N HCl (125 ml) y agua (2 x 125 ml). La capa orgánica se seca mediante sulfato de sodio (50 g) durante 10 mins. La mezcla se filtra y se concentra en un aceite, que se pasa a través de almohadilla de gel de sílice para obtener N-t-Boc-4-N-metillaminocrotonato (19.7 g, 73 %). ¹HRMN (DMSO, ppm) d 6.79 (dt, 1H, CH₂CH=CH), 5.81 (dt, 1H, CH₂CH=CH), 3.96 (m, 2H, NCH₂), 3.67 (s, 3H, OCH₃), 2.78 (s, 3H, NCH₃), 1.37 (s, 9H, t-butyl).

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Preparación de metilo ácido 4-[N-(terc-butiloxycarbonil)metilamino] cotónico.

[0076] Se carga un frasco con 3 cuellos con N-Boc-4-N-metilaminocrotonato (25.0 g, 0.11 mol) en THF (290 ml) y se enfría a 0-5 °C. Se disuelve una solución de hidróxido de potasio (29.0 g, 85%, 0.44 mol, 4.0 ac) en agua (145 ml) y se agrega en 5 gotas durante 30 min se mantiene a temperatura ambiente a 0-10 °C. El pH en esta etapa es 11-12. Se agita durante 15 min, luego la mezcla se calienta a temperatura ambiente durante la noche. Después de la reacción se determina al ser completada en TLC (8:2 heptano: EtOAc), la mezcla de reacción se concentra in vacío. La 10 mezcla acuosa se lava con CH₂Cl₂ (3 x 100 ml), y luego se acidifica a 11-12 con 10% HCl (-150 ml). La mezcla se extrae con CH₂Cl₂ (3 x 150 ml). Los orgánicos combinados se secan durante Na₂SO₄, se filtran y se concentran bajo vacío para dar ácido N-Boc-4-N-metilaminocotónico (18.0 g, 75%) como un aceite amarillo 15 claro. ¹H RMN (DMSO, ppm) d 12.28 (bs, 1 H, COOH, D₂O exchangeable), 6.75 (dt, 1H, CH₂CH=CH), 5.75 (dt, 1H, CH₂CH=CH), 3.96 (m, 2H, NCH₂), 2.78 (s, 3H, NCH₃), 1.39 (s, 9H, t-butyl).

EJEMPLO 5

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Preparación de (E) N-{4-[3-Cloro-4-(2-piridinilmetoxi)anilino]-3-ciano-7-etoxi-6-quinolinil}-4-[N-(t-butiloxicarbonil)metilamino]-2-butenamida.

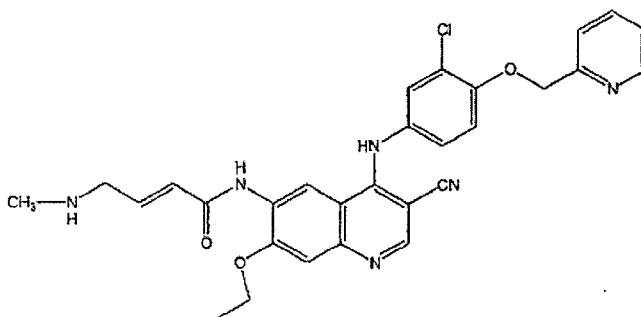
25 [0077] Una solución de ácido N-t-Boc-4-N-metilaminocotónico (18.0 g, 84 mmol, 2.0 ac) en CH₂Cl₂ (171 ml) se enfría a 0-10 °C. Se agregaron Piridina (68 ml, 840 mmol, 20 ac) y DCC (17.5 g, 84 mmol, 2 ac). Una suspensión de 6-amino- N-4-[3-Cloro-4-(2-piridinilmetoxi)anilino]-3-ciano-7-etoxi-6-quinolina (19.0 g, 42

00124

mmol) en CH_2Cl_2 (143 ml) se agrega en gotas y la mezcla de reacción se mantiene durante 5.5 días y se monitorea mediante HPLC. La mezcla de reacción luego se diluye con CH_2Cl_2 (120 ml). La mezcla se filtra y los filtrados se lavan con agua (2 x 100 ml), en HCl (2 x 60 ml) y agua (2 x 100 mL), se seca sobre MgSO_4 , se filtra y se concentra bajo vacío para dar el producto crudo como un residuo rojo marrón. El producto crudo se purifica mediante cromatografía (CH_2Cl_2 con 0 a 2 % MeOH) para dar 15.0 g (56%, -57% de fuerza por área HPLC) de (E) N-{4-[3-Cloro-4-(2-piridinilmetoxi)anilino]-3-ciano-7-etoxi-6-quinolil}-4-[N-(t-butiloxicarbonil)metilamino]-2-butenamida. ^1H MMR (DMSO, ppm) d 9.61 (s, 1H, NH), 9.57 (s, 1H, NH), 8.91 (s, 1H, Ar), 8.60 (m, 1H, Ar), 8.47 (s, 1H, Ar), 7.87 (m, 1H, Ar), 7.58 (m, 1H, Ar), 7.39-7.18 (m, 5H, Ar), 6.74 (dt, 1H, $\text{CH}_2\text{CH}=\text{CH}$), 6.47 (d, 1H, $\text{CH}_2\text{CH}=\text{CH}$), 5.29 (s, 2H, $-\text{OCH}_2\text{Pyr}$), 4.32 (q, 2H, OCH_2CH_3), 3.99 (m, 2H, NCH_2), 3.32 (s, 3H, NCH_3), 1.41 (s, 9H, $(\text{CH}_3)_3\text{C}$).

EJEMPLO 6

(E) N-{4-[3-Cloro-4-(2-piridinilmetoxi)anilino]-3-ciano-7-etoxi-6-quinolil}-4-(metilamino)-2-butenamida



00145

Preparación de (E) N-{4-[3-Cloro-4-(2-piridinilmetoxi)anilino]-3-ciano-7-etoxi-6-quinolinil}-4-(metilamino)-2-butenamida de base libre.

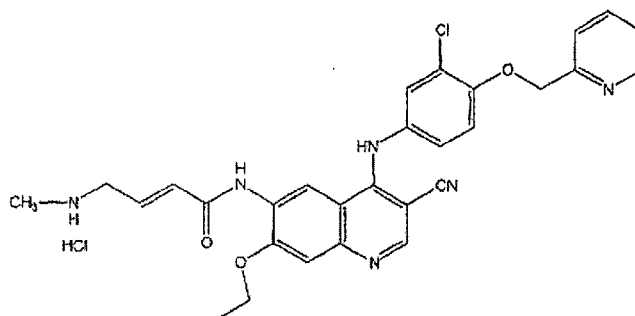
5 [0078] a una suspensión de (E) N-{4-[3-Cloro-4-(2-piridinilmetoxi)anilino]-3-ciano-7-etoxi-6-quinolinil}-4-[N-(t-butiloxicarbonil)metilamino]-2-butenamida (14.0 g, 21.8 mmol) en metanol (120 ml) se agrega 1.1 N HCl en acetato de etilo (515 ml) en gotas durante 2 h. La mezcla de suspensión amarilla resultante
10 se agita a temperatura ambiente durante 7.5 h. La mezcla de reacción se basifica al agregar 5% NaOH ac. (500 ml) a t 8. La capa orgánica se separa, y la capa ac. Se extrae con EtOAc/MeOH (3 x 200 ml, 9:1), CH₂CVMeOH (3 x 200 ml, 9:1). Las capas orgánicas combinadas se secan sobre MgSO₄, y se concentran. El
15 residuo se purifica mediante cromatografía para producir 7.8 g, que se suspende en frío MeOH (210 ml) y se filtra para obtener 5.23 g el producto del título (44%,) después de lavado con frío MeOH (65 ml) y secado al vacío a temperatura ambiente. ¹H RMN (CDCl₃, ppm) d 9.17 (s, 1H, NH), 8.59 (m, 1H, NH), 8.41 (s, 1H, Ar), 7.97(s, 1H, Ar), 7.92 (s, 1H, Ar), 7.76 (m, 1H, Ar), 7.64
20 (d, 1H, Ar), 7.24 (m, 1H, Ar), 7.14 (m, 2H, Ar), 7.09 (m, 1H, Ar), 6.89 (m, 1H, Ar), 6.83 (d, 1H, CH₂CH=CH), 6.14 (dt, 1H, CH₂CH=CH), 5.24 (s, 2H, -OCH₂Pir), 4.20 (q, 2H, -OCH₂CH₃), 3.38 (m, 2H₃ NCH₂CH), 2.11 (s, 3H, NCH₃), 1.52 (t, 3H, CH₂CH₃). ¹³C RMN: d (CDCl₃) 164.6, 156.8, 152.6, 151.2, 150.6, 149.3, 147.4, 145.5, 137.2, 133.0, 128.0, 127.6, 124.8, 123.7, 123.5, 123.0, 121.4, 117.3, 113.7, 113.3, 109.8, 108.8, 88.0, 71.6, 65.2, 52.5, 36.5, 14.8.

EJEMPLO 7

(E) N-{4-[3-Cloro-4-(2-piridinilmetoxi)anilino]-3-ciano-7-etoxi-6-quinolinil}-4-(metilamino)-2-butenamida hidrocclorhídrico.

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[0079] a una solución de (E) N-{4-[3-Cloro-4-(2-piridinilmetoxi)anilino]-3-ciano-7-etoxi-6-quinolinil}-4-(metilamino)-2-butenamida de base libre (4.40 g, 8.12 mmol) se disuelve en una mezcla de metanol (10 ml) y metileno clorhídrico (50 ml). La solución se agrega en gotas durante 15-20 mins. A una solución de 1.28 N HCl en acetato de etilo (75 ml) y luego se enjuaga con metileno clorhídrico (5 ml). Aparece algo de humo y se forman los precipitados. La mezcla se mantiene a temperatura ambiente durante 20 mins., se filtra y se lava con acetato de etilo (20 ml). Los sólidos amarillos se secan bajo bomba de vacío durante 3 h a temperatura ambiente para suministrar 4.24 g (90% rendimiento) de del compuesto del título. ¹H RMN (DMSO, ppm) d 11.43 (bs, 1H, NH), 10.04 (s, 1H, NH), 9.74 (bd, 2H, NH, HCl), 9.18 (s, 1H, Ar), 9.04 (s, 1H, Ar), 8.91 (d, 1H, Ar), 8.50 (dt, 1H, Ar), 8.05 (d, 1H, Ar), 7.93 (t, 1H, Ar), 7.85 (s, 1H, Ar), 7.71 (d, 1H, Ar), 7.49 (dd, 1H, Ar), 7.42 (d, 1H, Ar), 6.97-6.85 (dt, 1H, CH₂CH=CH), 6.81 (d, 1H, CH₂CH=CH), 5.66 (s, 2H, -OCH₂Pir), 4.33 (q, 2H, -OCH₂CH₃), 3.78 (dd, 2H, NHCH₂CH), 2.54 (t,

3H₅ NCH₃), 1.51 (t, 3H, CH₂CH₃). ¹³C RMN: d (DMSO-d₆) 14.7, 32.6, 48.9, 66.2, 68.2, 86.8, 101.6, 112.7, 114.6, 115.3, 117.9, 122.6, 125.5, 126.6, 127.7, 129.2, 129.5, 129.9, 132.5, 135.6, 137.7, 144.4, 145.1, 148.6, 152.4, 153.3, 154.8, 156.4, 163.6.

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ANÁLISIS

[0080] Se registra el espectro de RMN en un GE QE 300, un Bruker DPX 301 o un Varian Inova 300 a 300 MHz (¹H) y en 75 o 300 MHz
10 (¹³C) y se identifican los cambios químicos en ppm con relación al estándar interno TMS. Se desarrolla TLC analítico y preparativo en placas pre-cubiertas con gel de sílice 60 F-254 pre-coated plates obtenida de EM Science. Los Compuestos visualizados utilizando UV en 254 nm, indicador verde
15 bromocresol, o reactivos de ácido fosfomolibdico (20 % en peso en EtOH). Se determina análisis HPLC en un instrumento Waters Alliance 2695 HPLC equipado con un detector PDA (Modelo 2996). Se registra el espectro IR en un Mattson 5020 FT-IR.

20 DATOS BIOLÓGICOS

Ensayos de cinasa

[0081] La actividad del (E) N-{4-[3-cloro-4-(2-
25 piridinilmetoxi)anilino]-3-ciano-7-etoxi-6-quinolinil}-4-(metilamino)-2-butenamida, ejemplo 6, se determina primero en un ensayo de auto fosforilación HER-2 utilizando el dominio de cinasa citoplásmico de HER-2. (E) N-{4-[3-cloro-4-(2-piridinilmetoxi)anilino]-3-ciano-7-etoxi-6-quinolinil}-4-

00128

(metilamino)-2-butenamida reduce la auto fosforilación del recetor al 50% (IC₅₀) en 3.4 nM (Tabla 1). Esto es similar al IC₅₀ del compuesto dimetilamino del cual este se metaboliza, (E) N-{4-[3-Cloro-4-(2-piridinilmetoxi)anilino]-3-ciano-7-etoxi-6-quinolinil}-4-(dimetilamino)-2-butenamida, en este ensayo (1.1 nM).

TABLA 1. ENSAYO DE AUTOFOFORILACIÓN HER-2

10	COMPUESTO	IC ₅₀ (nM) ^a
	Dimetilamino Des-metilamino, (Ex. 6)	
	Fragmento C-terminal recombinante purificado de HER-2 se incubó con ATP en la ausencia o presencia de un rango de concentraciones de compuesto. La auto-fosforilación del receptor se determinó utilizando anticuerpos de fosfotirosina. La concentración del compuesto que inhibe la fosforilación en un 50% se muestra. ^a : Media y SE con el número de determinaciones independientes en paréntesis.	
15		

[0082] La actividad de paréntesis (E)N-{4-[3-cloro-4-(2-pridinilmetoxi)anilino]-3-ciano-7-etoxi-6-quinolinil}-4-(metilamino)-2-butenamida también se probó en un ensayo 20 propietario de quinasa (ensayo ³³PanQinase[®]; Propinaza, Freiburg, Alemania) utilizando HER-2 y las quinasas ErbB relacionadas, EGFR y HER-4, y se muestran en la Tabla 2. Aquí, la capacidad del compuesto para inhibir la fosforilación de un sustrato péptido [poli (Glu-Tyr) o poli(Ala-Glu-Lys-Tyr)] se determinó. E)N-{4-[3- 25 cloro-4-(2-pridinilmetoxi)anilino]-3-ciano-7-etoxi-6-quinolinil}-4-(metilamino)-2-butenamida inhibió la actividad del HER-2 (IC₅₀ = 21 nM), EGFR (IC₅₀ = 7 nM) y HER-4 (IC₅₀ = 13 nM). Cuando se comparó con el derivado dimetilamino, E)N-{4-[3-cloro-4-(2-pridinilmetoxi)anilino]-3-ciano-7-etoxi-6-quinolinil}-4-

(metilamino)-2-butenamida mostró actividad similar contra todas las tres quinasas en este ensayo.

TABLA 2. ENSAYO DE FOSFORILACIÓN DE SUSTRATO ErbB

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COMPUESTO	IC ₅₀ (nM)		
	EGFR	HER-2	HER-4
Dimetilamino	12	39	19
Des-metilamino, (Ex6)	7	21	13
El dominio C-terminal recombinante purificado de los receptores ErbB se incubó con [³² P]-ATP y el sustrato de péptido en la ausencia o presencia de un rango de concentraciones de compuesto. La concentración del compuesto que inhibe la fosforilación del péptido en un 50% se muestra.			

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Ensayos de proliferación de célula

[0083] (E)N-{4-[3-cloro-4-(2-pridinilmetoxi)anilino]-3-ciano-7-etoxi-6-quinolinil}-4-(metilamino)-2-butenamida inhibió la proliferación de 3T3/*neu*, una línea celular de fibroblasto de ratón transfectada con el encogen HER-2 (IC₅₀ = 40 nM), aunque teniendo un efecto mínimo sobre las células no transfectadas isogénicas (IC₅₀ = 5460 nM; Tabla 3). También se inhibió otras dos líneas celulares de cáncer de mama que sobre expresaron HER-2, BT474 y SK-Br-3 (IC₅₀ 3,34 nM, respectivamente). Consistente con el efecto en el ensayo de EGFR quinasa, el compuesto des-metilamino también inhibió la línea celular dependiente de EGFR, A431 (IC₅₀ = 67 nM). Éste fue sustancialmente menos activo contra células de carcinoma de colon SW620 que no expresan ningún receptor (IC₅₀ = 1604 nM). Cuando se compara con el compuesto de dimetilamino, (E)N-{4-[3-cloro-4-(2-pridinilmetoxi)anilino]-3-ciano-7-etoxi-6-quinolinil}-4-(metilamino)-2-butenamida fue 8

nn150

veces menos potente contra las células 3T3/neu, pero tan potente contra otras líneas celulares que expresan HER-2 y EGFR.

TABLA 3. ENSAYOS DE PROLIFERACIÓN DE CÉLULA

5

10

15

LÍNEA CELULAR	HER-2	EGFR	IC ₅₀ (nM) ^a	
			Dimetilamino	Des- metilamino (Ex. 6)
3T3	-	-	2191 ± 700 (2)	5460 ± 659 (3)
3T3/neu	+++	-	5 ± 0.2 (2)	40 ± 4 (3)
A431	+	+++	64 ± 3 (2)	67 ± 7 (3)
SK-Br-3	+++	-	36 ± 20 (2)	34 ± 4 (3)
BT474	+++	+	2 ± 0.2 (2)	3 ± 0.5 (3)
SW620	-	-	1215 ± 246 (2)	1604 ± 138 (3)

Las células se incubaron con varias concentraciones de compuesto durante 2 días (6 días para BT474). La supervivencia de la célula se determinó utilizando un ensayo de tinte de unión de proteína (SRB). La concentración del compuesto que reduce la supervivencia de la célula en un 50% se muestra. La expresión relativa del EGFR y el HER-2 en las líneas celulares se indica.

^a: Media y Se muestran con el número de determinaciones dependientes en paréntesis.

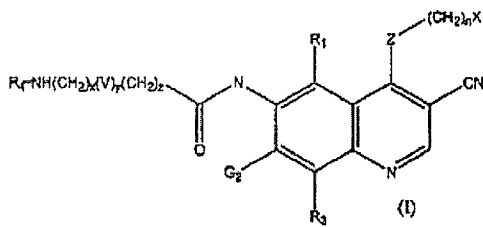
Actividad *In Vivo*

[0084] La actividad *in vivo* de (E)N-{4-[3-cloro-4-(2-
pridinilmetoxi)anilino]-3-ciano-7-etoxi-6-quinolinil}-4-
(metilamino)-2-butenamida se estudió primero en xenoinjertos de
3T3/neu. La administración oral diaria del compuesto entre 5 y 40
mg/kg/día no tuvo efecto sobre el crecimiento tumoral, aunque la
actividad antitumoral buena se observó para el compuesto
dimetilamino a 40 mg/kg/día (74% de inhibición, día 18; datos no
mostrados). En una segunda prueba independiente, incrementar la
dosis del compuesto des-metilamino a 100 mg/kg/día tampoco tuvo
un efecto sobre el crecimiento del tumor (Tabla 4), aunque el
compuesto dimetilamino mostró buena actividad antitumoral entre
40 y 80 mg/kh/día (93-100% de inhibición, día 14).

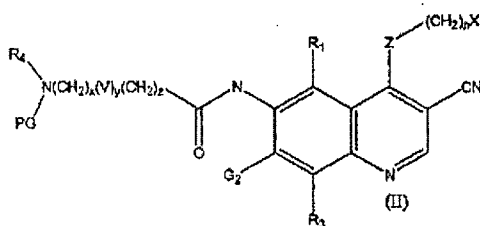
REIVINDICACIONES

Reivindicamos:

- 5 1. Un método para preparar un compuesto de Fórmula (I):



que comprende la etapa de un compuesto protector de Fórmula (II):



en donde:

X es cicloalquilo de 3 a 7 átomos de carbono, que pueden
20 opcionalmente sustituirse con uno o más alquilo de 1 a 6 grupos
de átomos de carbono; o es un piridinilo, pirimidinilo, o anillo
fenilo; en donde el piridinilo, pirimidinilo, o anillo fenilo
opcionalmente pueden ser mono- di-, o tri-sustituidos con un
sustituyente seleccionado del grupo que consiste de halógeno,
25 alquilo de 1-6 átomos de carbono, alquenilo de 2-6 átomos de
carbono, alquinilo de 2-6 átomos de carbono, azido,
hidroxialquilo de 1-6 átomos de carbono, halometilo, alcoximetilo
de 2-7 átomos de carbono, alcaniloximetilo de 2-7 átomos de
carbono, alcoxi de 1-6 átomos de carbono, alquiltio de 1-6 átomos

00153

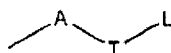
de carbono, hidroxilo, trifluorometilo, ciano, nitro, carboxi, carboalcoxi de 2-7 átomos de carbono, carboalquilo de 2-7 átomos de carbono, fenoxi, fenilo, tiofenoxi, benzoilo, bencilo, amino, alquilamino de 1-6 átomos de carbono, dialquilamino de 2 a 12
5 átomos de carbono, fenilamino, bencilamino, alcanilamino de 1-6 átomos de carbono, alquenilamino de 3-8 átomos de carbono, alquinilamino de 3-8 átomos de carbono, carboxialquilo de 2-7 átomos de carbono, carboalcoxialquilo de 3-8 átomos de carbono, aminoalquilo de 1-5 átomos de carbono, N- alquilaminoalquilo de
10 2-9 átomos de carbono, N,N-dialquilaminoalquilo de 3-10 carbon átomos, N-alquilaminoalcoxi de 2-9 átomos de carbono, N,N-dialquilaminoalcoxi de 3-10 átomos de carbono, mercapto, y bencilamino; o

15 X es un sistema de anillo arilo bicíclico o heteroarilo bicíclico de 8 a 12 átomos en donde el anillo heteroarilo bicíclico contiene 1 a 4 heteroátomos seleccionados de N, O, y S con la condición que el anillo heteroarilo bicíclico no contiene O - O, S - S, o S - O enlaces y en donde el anillo arilo bicíclico
20 o heteroarilo bicíclico opcionalmente pueden ser mono- di-, tri, o tetra-sustituídos con un sustituyente seleccionado del grupo que consiste de halógeno, oxo, tio, alquilo de 1-6 átomos de carbono, alquenilo de 2-6 átomos de carbono, alquinilo de 2-6 átomos de carbono, azido, hidroxialquilo de 1-6 átomos de
25 carbono, halometilo, alcoximetilo de 2-7 átomos de carbono, alcaniloximetilo de 2-7 átomos de carbono, alcoxi de 1-6 átomos de carbono, alquiltio de 1-6 átomos de carbono, hidroxilo, trifluorometilo, ciano, nitro, carboxi, carboalcoxi de 2-7 átomos de carbono, carboalquilo de 2-7 átomos de carbono, fenoxi,

fenilo, tiofenoxi, benzoilo, bencilo, amino, alquilamino de 1-6
átomos de carbono, di alquilo amino de 2 a 12 átomos de carbono,
fenilamino, bencilamino, alcanilamino de 1 -6 átomos de carbono,
alquenilamino de 3-8 átomos de carbono, alquinilamino de 3-8
5 átomos de carbono, carboxialquilo de 2-7 átomos de carbono,
carboalcoxialquilo de 3-8 átomos de carbono, aminoalquilo de 1-5
átomos de carbono, N- alquilaminoalquilo de 2-9 átomos de
carbono, N,N-dialquilaminoalquilo de 3-10 átomos de carbono, N-
alquilaminoalcoxi de 2-9 átomos de carbono, N,N-
10 dialquilaminoalcoxi de 3-10 átomos de carbono, mercapto, y
bencilamino; o

X es un radical que tiene la fórmula:

15



en donde

A es un piridinilo, pirimidinilo, o anillo fenilo; en donde
20 el piridinilo, pirimidinilo, o anillo fenilo opcionalmente pueden
ser mono- o di-sustituídos con un sustituyente seleccionado del
grupo que consiste de halógeno, alquilo de 1-6 átomos de carbono,
alquenilo de 2-6 átomos de carbono, alquinilo de 2-6 átomos de
carbono, azido, hidroxialquilo de 1-6 átomos de carbono,
25 halometilo, alcoximetilo de 2-7 átomos de carbono,
alcaniloximetilo de 2-7 átomos de carbono, alcoxi de 1-6 átomos
de carbono, alquiltio de 1-6 átomos de carbono, hidroxí,
trifluorometilo, ciano, nitro, carboxi, carboalcoxi de 2-7 átomos
de carbono, carboalquilo de 2-7 átomos de carbono, fenoxi,

00155

fenilo, tiofenoxi, benzoilo, bencilo, amino, alquilamino de 1-6
 átomos de carbono, dialquilamino de 2 a 12 átomos de carbono,
 fenilamino, bencilamino, alcanilamino de 1-6 átomos de carbono,
 alquenilamino de 3-8 átomos de carbono, alquinilamino de 3-8
 5 átomos de carbono, carboxialquilo de 2-7 átomos de carbono,
 carboalcoxialquilo de 3-8 átomos de carbono, aminoalquilo de 1-5
 átomos de carbono, N-alquilaminoalquilo de 2-9 átomos de carbono,
 N₃N- dialquilaminoalquilo de 3-10 átomos de carbono, N-
 alquilaminoalcoxi de 2-9 átomos de carbono, N,N-
 10 dialquilaminoalcoxi de 3-10 átomos de carbono, mercapto, y
 bencilamino;

T está enlazado con un carbono de A y es:

15 - NH(CH₂)_m - - O(CH₂)_m - - S(CH₂)_m - - NR(CH₂)_m - - (CH₂)_n, - - (CH₂)_m
 NH-, - (CH₂)_m O- - (CH₂)_m S-, o - (CH₂)_mNR- ;

L es un anillo fenilo no sustituido o un anillo fenilo mono-
 , di-, o tri- sustituidos con un sustituyente seleccionado del
 20 grupo que consiste de halógeno, alquilo de 1-6 átomos de carbono,
 alquenilo de 2-6 átomos de carbono, alquinilo de 2-6 átomos de
 carbono, azido, hidroxialquilo de 1-6 átomos de carbono,
 halometilo, alcoximetilo de 2-7 átomos de carbono,
 alcaniloximetilo de 2-7 átomos de carbono, alcoxi de 1-6 átomos
 25 de carbono, alquiltio de 1-6 átomos de carbono, hidroxí,
 trifluorometilo, ciano, nitro, carboxi, carboalcoxi de 2-7 átomos
 de carbono, carboalquilo de 2-7 átomos de carbono, fenoxi,
 fenilo, tiofenoxi, benzoilo, bencilo, amino, alquilamino de 1-6
 átomos de carbono, dialquilamino de 2 a 12 átomos de carbono,

fenilamino, bencilamino, alcanilamino de 1-6 átomos de carbono, alquenilamino de 3-8 átomos de carbono, alquinilamino de 3-8 átomos de carbono, carboxialquilo de 2-7 átomos de carbono, carboalcoxialquilo de 3-8 átomos de carbono, aminoalquilo de 1-5
5 átomos de carbono, N-alquilaminoalquilo de 2-9 átomos de carbono, N,N-dialquilaminoalquilo de 3-10 átomos de carbono, N-alquilaminoalcoxi de 2-9 átomos de carbono, N,N-dialquilaminoalcoxi de 3-10 átomos de carbono, mercapto, y bencilamino; o

10

L es un anillo heteroarilo de 5- o 6- miembros en donde el anillo heteroarilo contiene 1 a 3 heteroátomos seleccionados de N, O, y S, con la condición que el anillo heteroarilo no contiene O - O, S - S, o S - O enlaces, y en donde el anillo heteroarilo
15 es opcionalmente mono- o di-sustituidos con un sustituyente seleccionado del grupo que consiste de halógeno, oxo, tio, alquilo de 1-6 átomos de carbono, alqueno de 2-6 átomos de carbono, alquino de 2-6 átomos de carbono, azido, hidroxialquilo de 1-6 átomos de carbono, halometilo, alcoximetilo
20 de 2-7 átomos de carbono, alcaniloximetilo de 2-7 átomos de carbono, alcoxi de 1-6 átomos de carbono, alquiltio de 1-6 átomos de carbono, hidroxilo, trifluorometilo, ciano, nitro, carboxi, carboalcoxi de 2-7 átomos de carbono, carboalquilo de 2-7 átomos de carbono, fenoxi, fenilo, tiofenoxi, benzoilo, bencilo, amino,
25 alquilamino de 1-6 átomos de carbono, dialquilamino de 2 a 12 átomos de carbono, fenilamino, bencilamino, alcanilamino de 1-6 átomos de carbono, alquenilamino de 3-8 átomos de carbono, alquinilamino de 3-8 átomos de carbono, carboxialquilo de 2-7 átomos de carbono, carboalcoxialquilo de 3-8 átomos de carbono,

aminoalquilo de 1-5 átomos de carbono, N- alquilaminoalquilo de
2-9 átomos de carbono, N,N-dialquilaminoalquilo de 3-10 átomos de
carbono, N-alquilaminoalcoxi de 2-9 átomos de carbono, N,N-
dialquilaminoalcoxi de 3-10 átomos de carbono, mercapto, y
5 bencilamino;

V es etileno o acetileno;

PG es un grupo protector de amina;

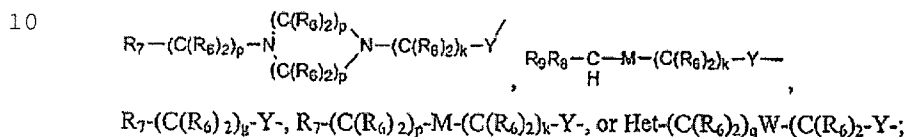
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R₄ es alquilo de 1 a 6 carbonos;

Z es NR^{Z'}, O o S, en donde R^{Z'} es H o C₁-C₆ alquil;

15 R₁, G₂, y R₃ son cada uno independientemente, hidrógeno,
halógeno, alquilo de 1-6 átomos de carbono, alquenilo de 2-6
átomos de carbono, alquinilo de 2-6 átomos de carbono,
alqueniloxi de 2-6 átomos de carbono, alquiniloxi de 2-6 átomos
de carbono, hidroximetilo, lialometilo, alcaniloxi de 1-6 átomos
20 de carbono, alqueniloxi de 3-8 átomos de carbono, alquiniloxi de
3-8 átomos de carbono, alcaniloximetilo de 2-7 átomos de carbono,
alqueniloximetilo de 4-9 átomos de carbono, alquiniloximetilo de
4-9 átomos de carbono, alcoximetilo de 2-7 átomos de carbono,
alcoxi de 1-6 átomos de carbono, alquiltio de 1-6 átomos de
25 carbono, alquilsulfinil de 1-6 átomos de carbono, alquilsulfonil
de 1-6 átomos de carbono, alquilsulfonamido de 1-6 átomos de
carbono, alquenilosulfonamido de 2-6 átomos de carbono,
alquinilsulfonamido de 2-6 átomos de carbono, hidroxí,
trifluorometilo, trifluorometoxi, ciano, nitro, carboxi,

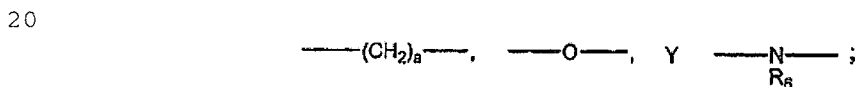
carboalcoxi de 2-7 átomos de carbono, carboalquilo de 2-7 átomos de carbono, fenoxi, naftalamida, fenilo, tiofenoxi, bencilo, amino, hidroxiamino, alcoxi-amino de 1-4 átomos de carbono, alquilamino de 1- 6 átomos de carbono, dialquilamino de 2 a 12 átomos de carbono, N-alquilcarbamoil, N,N- dialquilcarbamoil, N-alquil-N-alquenilamino de 4 a 12 átomos de carbono, N,N-dialquenilamino de 6-12 átomos de carbono, fenilamino, bencilamino,



o R_1 y R_3 son como se definió anteriormente y G_2 es R_2-NH- ;

o si cualquiera de los sustituyentes R_1 , G_2 o R_3 se localizan en átomos de carbono contiguos luego ellos pueden tomarse juntos como un radical divalente $-O-C(R_6)_2-O-$;

Y es un radical divalente seleccionado del grupo que consiste de (



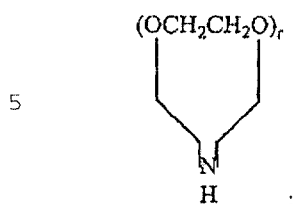
R_7 es $-NR_6R_6$, $-OR_6$, $-J$, $-N(R_6)_3^+$, o $-NR_6(OR_6)$;

M es $>NR_6$, $-O->N-(C(R_6)_p)NR_6R_6$, o $>N-(C(R_6)_p)OR_6$;

W es $>NR_6$, $-O-$ o es un enlace;

Het es seleccionado del grupo que consiste de morfolina, tiomorfolina, tiomorfolina S-óxido, tiomorfolina S,S-dióxido, piperidina, pirrolidina, aziridina, piridina, imidazol, 1,2,3-triazol, 1,2,4-triazol, tiazol, tiazolidina, tetrazol,

piperazina, furano tiofeno, tetrahidrotiofeno, tetrahidrofurano, dioxáno, 1,3-dioxolano, tetrahidropiran, y

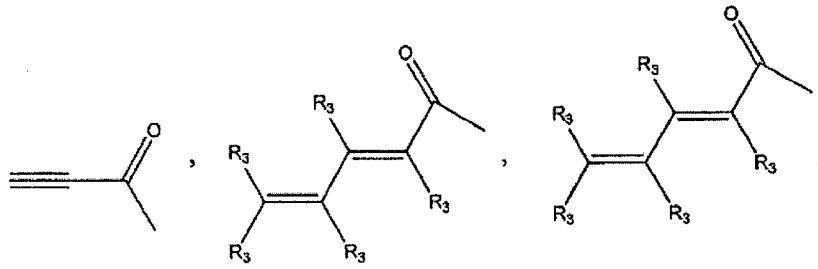


en donde Het es opcionalmente mono- o di-sustituidos en carbono o nitrógeno con R₆, opcionalmente mono- o di-sustituidos en carbono con hidroxil, - N(R₆)₂, o - OR₆, opcionalmente mono o di-sustituidos en carbono con el radical mono-valente - (C(R₆)₂)_s OR₆ o - (C(R₆)₂)_s N(RO)₂, y opcionalmente mono o di-sustituidos un carbono saturado con radicales divalentes - O - o - O(C(R₆)₂)_s O-;

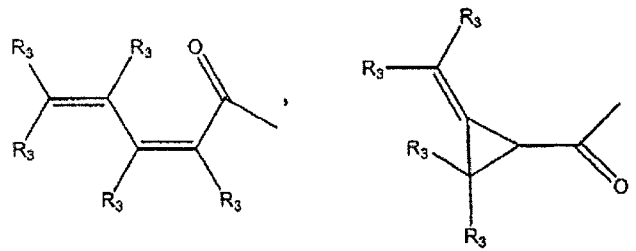
15 R₆ es hidrógeno, alquilo de 1-6 átomos de carbono, alquenilo de 2-6 átomos de carbono, alquinilo de 2-6 átomos de carbono, cicloalquilo de 1-6 átomos de carbono, carboalquilo de 2-7 átomos de carbono, carboxialquilo (2-7 átomos de carbono), fenilo, o fenilo opcionalmente sustituido con uno o más halógeno, alcoxi de 20 1-6 átomos de carbono, trifluorometilo, amino, alquilamino de 1-3 átomos de carbono, dialquilamino de 2-6 átomos de carbono, nitro, ciano, azido, halometilo, alcoximetilo de 2-7 átomos de carbono, alcaniloximetilo de 2-7 átomos de carbono, alquiltio de 1-6 átomos de carbono, hidroxil, carboxilo, carboalcoxi de 2-7 átomos de carbono, fenoxil, fenilo, tiofenoxil, benzoilo, bencilo, 25 fenilamino, bencilamino, alcanilamino de 1-6 átomos de carbono, o alquilo de 1-6 átomos de carbono; con la condición que la cantidad de alquenilo o alquinilo se enlaza con un átomo de

oxígeno o nitrógeno a través de un átomo de carbono saturado; R_2 , es seleccionado del grupo que consiste de

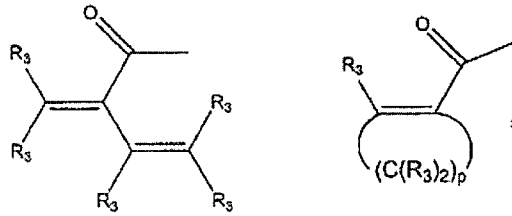
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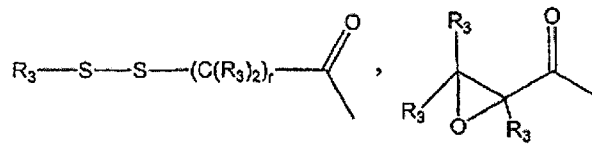
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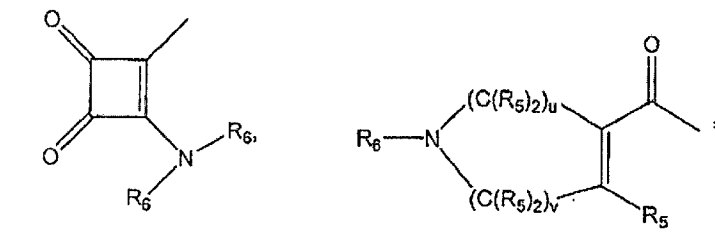
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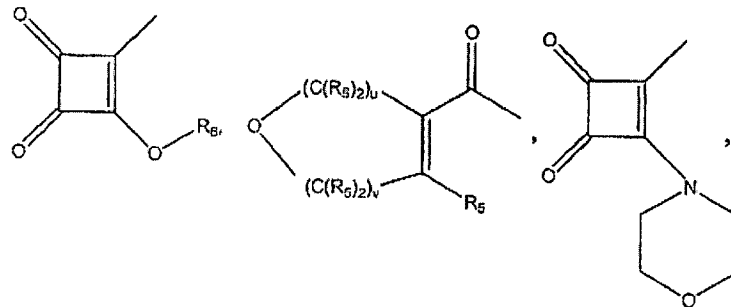
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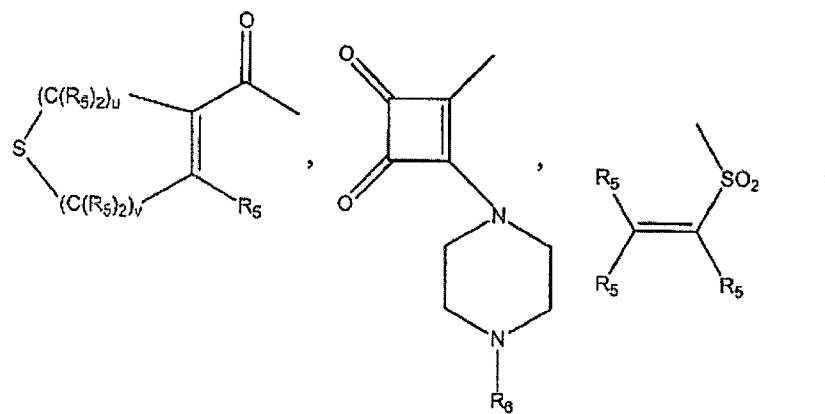
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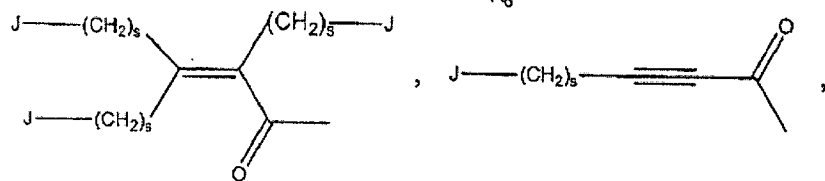
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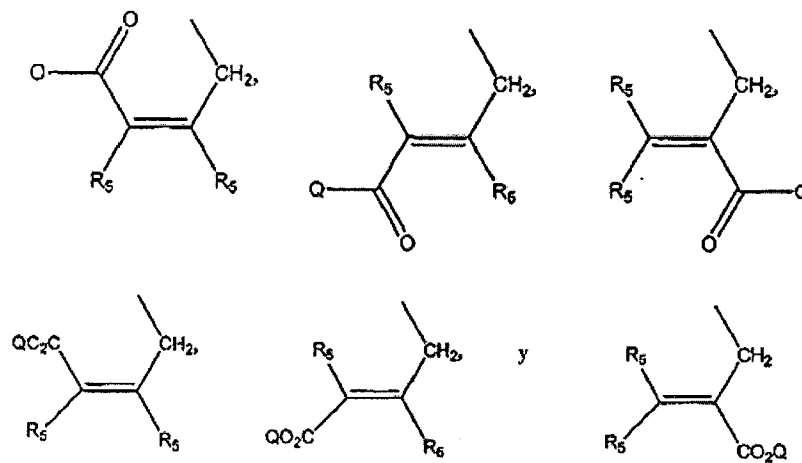
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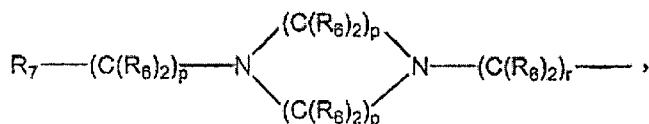
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R₃ es independientemente hidrógeno, alquilo de 1-6 átomos de carbono, carboxi, carboalcoxi de 1-6 átomos de carbono, fenilo, carboalquilo de 2-7 átomos de carbono,

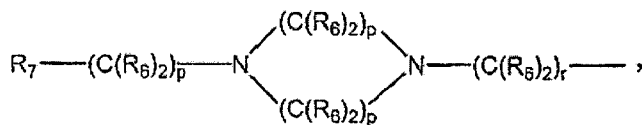
5



R₇- (C(R₆)₂)_s-

10 R₇- (C(R₆)₂)_p- M- (C(R_fO₂))₋ , R₈R₉- CH- Het- (C(R₆J₂)CT- W- (C(RO)₂))₋ ;

R₅ es independientemente hidrógeno, alquilo de 1-6 átomos de carbono, carboxi, carboalcoxi de 1-6 átomos de carbono, fenilo
15 carboalquilo de 2-7 átomos de carbono,



20

R₇- (C(R₆)₂)_s- ,

R₇- (C(RO)₂)_p- M- (C(R₆))₋ , R₈R₉- CH- M- (C(Re)₂)₋ , o Het- (C(R₆)₂)_q- W- (C(R₆))₋ ;

25 R₈, y R₉ son cada uno independientemente - (C(R₆)₂)_rNR₆R₆, o - (C(Re)₂)₋ OR₆;

J es independientemente hidrógeno, cloro, fluor, o bromo;

Q es alquilo de 1-6 átomos de carbono o hidrógeno;

a=0 o 1;
g=1-6;
k=0-4;
n es 0-1;
5 m es 0-3;
p=2-4;
q=0-4;
s=1 -6;
u=0-4 y v=0-4, en donde la suma de u+v es 2-4;
10 x= 0-3;
y= 0-1; y
z= 0-3;
o una sal farmacéuticamente aceptable de estos.

15 2. El método de la reivindicación 1, que comprende adicionalmente las siguientes condiciones:

Cuando R_6 es alquenilo de 2-1 átomos de carbono o alquinilo de 2-7 átomos de carbono, tal cantidad de alquenilo o alquinilo
20 se enlaza con un átomo de oxígeno o nitrógeno a través de un átomo de carbono saturado;

Cuando Y es $-NR_6-$ y R_7 es $-NR_6$, R_6 , $-N(R_6)_3$, $N(R_s)_3^+$, o $-NR_6$
(OR_6), luego g=2-6;

25

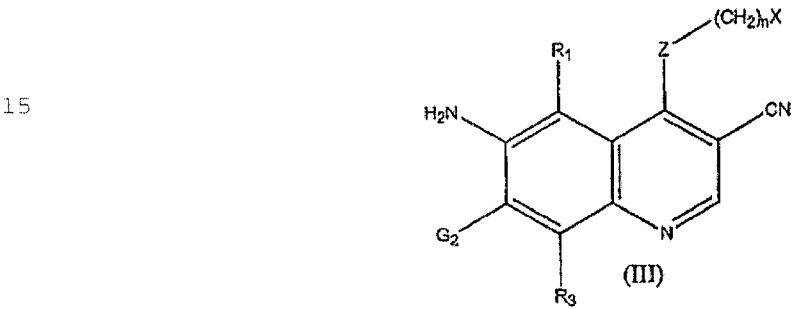
Cuando M es $-O-$ y R_7 es $-OR_6$ luego p=1-4; cuando Y es $-NR_6-$ luego k=2-4;

Cuando Y es $-O-$ y M o W es $-O-$ luego k=1-4;

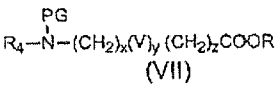
Cuando W no es un enlace con Enlace Het a través del átomo de nitrógeno luego q=2-4;

5 cuando W es un enlace con Enlace Het a través del átomo de nitrógeno y Y es - O - o - NR₆ - luego k=2-4; y con tal de que L sea un anillo fenilo no sustituido solo cuando m>0 y T no es - CH₂NH- o -CH₂O-.

10 3. El método de la reivindicación 1, que comprende adicionalmente la etapa de acoplar una anilinoquinolina de Fórmula (III):



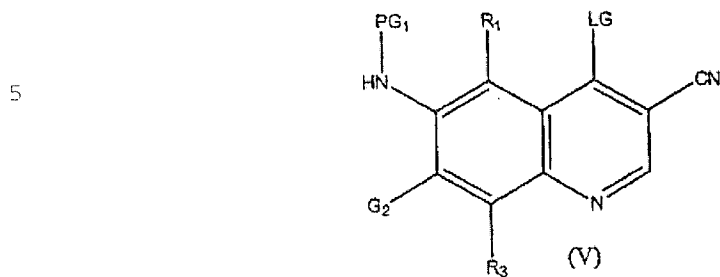
20 con un ácido de Fórmula (VII):



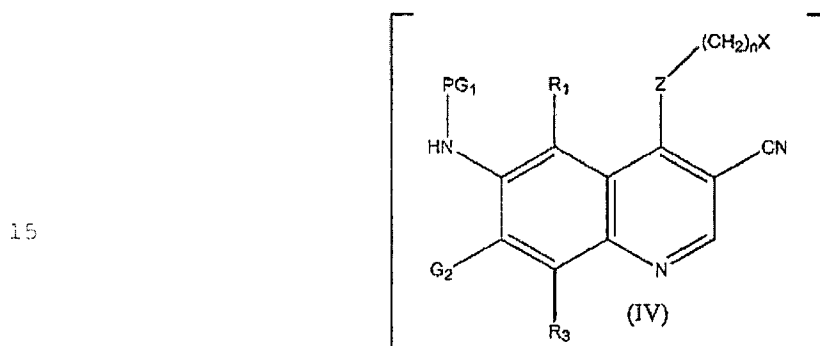
para formar un compuesto de Fórmula (II), en donde R es H, 25 R₁, R₃, R₄, Z, G₂, V, PG, x, y, z, y n son como se definió anteriormente.

4. El método de la reivindicación 3, que comprende adicionalmente las etapas de:

a. arilatar un compuesto de Fórmula (V):



con un compuesto de Fórmula $HZ-(CH_2)_nX$ para formar un intermedio
10 de Fórmula (IV):



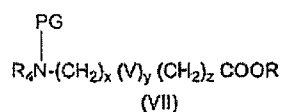
y

b. desprotección del intermedio de Fórmula (IV) para obtener
20 el compuesto de aniloquinolina de Fórmula (III); en donde LG se
selecciona del grupo de halo, mesilato, tosilato y trifilato, PG₁
es un grupo protector de amina, y en donde R₁, R₃, R₄, Z, G₂, PG y
n son como se definió anteriormente.

25 5. El método de la reivindicación 1, en donde PG se remueve
utilizando un ácido.

6. Un método para preparar un ácido de Fórmula (VII):

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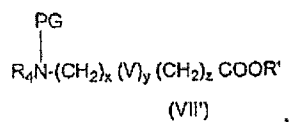
en donde:

5 R es H;

R₄ es H o alquilo de 1 a 6 átomos de carbono;

V es etileno o acetileno; x es 1, 2 o 3; y es 0 o 1; z es 1, 2 o 3; y

PG es un grupo protector de amina; que comprende la etapa de
10 hidrolizado para un éster correspondiente de Fórmula

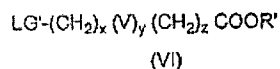


15 en donde R' es alquilo de 1 a 6 átomos de carbono o arilo,
para formar un ácido de Fórmula (VII).

7. El método de la reivindicación 6, que comprende
adicionalmente las etapas de:

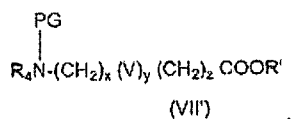
20

a. alquilatar un compuesto de Fórmula (VI):



con una amina primaria de la Fórmula NH₂R₄ para dar un intermedio
25 aminoéster; y

b. subsecuentemente proteger el aminoéster intermedio
mediante alquilatar en un grupo protector para formar un éster de
Fórmula (VII'):



en donde LG' es seleccionados de halo, mesilato, tosilato y
 5 triflato, R' es alquilo o arilo y R₄, V, PG, x, y, y z son como
 se definió anteriormente.

8. El método de la reivindicación 7, en donde PG es
 seleccionado del grupo que consiste de t-BOC, acetilo, CH₃OC(O)-,
 10 EtOC(O)-, FC(O)-, FCH₂OC(O)-, Fmoc, Troc, Fenoc, y Teoc.

9. El método de la reivindicación 8, en donde el PG es t-BOC.

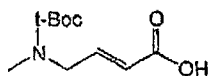
10. El método de la reivindicación 7, en donde (t-BOC)₂O es
 15 utilizado en la etapa b. para formar el grupo protector.

11. El método de la reivindicación 7, en donde z es 0, y es 1 y
 V es etileno.

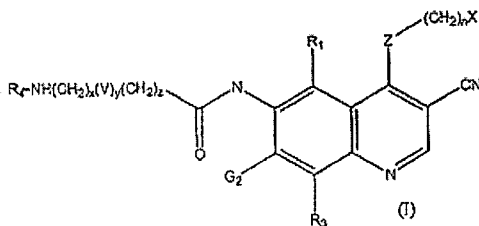
20 12. El método de la reivindicación 7, en donde R₄ es metilo,
 etil, propilo o isopropilo.

13. El método de la reivindicación 7, en donde el ácido de
 Fórmula (VII) es:

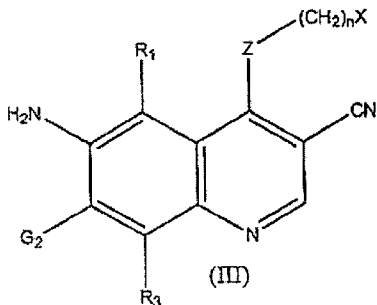
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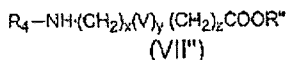
14. Un método para preparar un compuesto de Fórmula (I):



que comprende la etapa de acoplar una anilinoquinolina de Fórmula (III):



con un ácido de Fórmula (VII''):



en donde:

R'' es H;

X es cicloalquilo de 3 a 7 átomos de carbono, que pueden opcionalmente sustituirse con uno o más alquilo de 1 a 6 grupos de átomos de carbono; o es a piridinilo, pirimidinilo, o anillo fenilo; en donde el piridinilo, pirimidinilo, o anillo fenilo opcionalmente pueden ser mono- di-, o tri-sustituidos con un sustituyente seleccionados del grupo que consiste de de halógeno, alquilo de 1-6 átomos de carbono, alquenilo de 2-6 átomos de carbono, alquinilo de 2-6 átomos de carbono, azido,

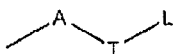
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hidroxialquilo de 1-6 átomos de carbono, lialometilo, alcoximetilo de 2-7 átomos de carbono, alcaniloximetilo de 2-7 átomos de carbono, alcoxi de 1-6 átomos de carbono, alquiltio de 1-6 átomos de carbono, hidroxi, trifluorometilo, ciano, nitro, carboxi, carboalcoxi de 2-7 átomos de carbono, carboalquilo de 2-7 átomos de carbono, fenoxi, fenilo, tiofenoxi, benzoilo, bencilo, amino, alquilamino de 1-6 átomos de carbono, dialquilamino de 2 a 12 átomos de carbono, fenilamino, bencilamino, alcanilamino de 1-6 átomos de carbono, alquenilamino de 3-8 átomos de carbono, alquinilamino de 3-8 átomos de carbono, carboxialquilo de 2-7 átomos de carbono, carboalcoxialquilo de 3-8 átomos de carbono, aminoalquilo de 1-5 átomos de carbono, N-alquilaminoalquilo de 2-9 átomos de carbono, N,N-dialquilaminoalquilo de 3-10 átomos de carbono, N-alquilaminoalcoxi de 2-9 átomos de carbono, N,N-dialquilaminoalcoxi de 3-10 átomos de carbono, mercapto, y bencilamino; o

X es un sistema de anillo arilo bicíclico o heteroarilo bicíclico de 8 a 12 átomos en donde el anillo heteroarilo bicíclico contiene 1 a 4 heteroátomos seleccionados de N, O, y S con la condición que el anillo heteroarilo bicíclico no contiene O - O, S - S, o S - O enlaces y en donde el anillo arilo bicíclico o heteroarilo bicíclico opcionalmente pueden ser mono- di-, tri, o tetra-sustituidos con un sustituyente seleccionado del grupo que consiste de halógeno, oxo, tio, alquilo de 1-6 átomos de carbono, alquenilo de 2-6 átomos de carbono, alquinilo de 2-6 átomos de carbono, azido, hidroxialquilo de 1-6 átomos de carbono, halometilo, alcoximetilo de 2-7 átomos de carbono,

alcaniloximetilo de 2-7 átomos de carbono, alcoxi de 1-6 átomos
de carbono, alquiltio de 1-6 átomos de carbono, hidroxí,
trifluorometilo, ciano, nitro, carboxi, carboalcoxi de 2-7 átomos
de carbono, carboalquilo de 2-7 átomos de carbono, fenoxi,
5 fenilo, tiofenoxi, benzoilo, bencilo, amino, alquilamino de 1-6
átomos de carbono, dialquilo amino de 2 a 12 átomos de carbono,
fenilamino, bencilamino, alcanilamino de 1-6 átomos de carbono,
alquenilamino de 3-8 átomos de carbono, alquinilamino de 3-8
átomos de carbono, carboxialquilo de 2-7 átomos de carbono,
10 carboalcoxialquilo de 3-8 átomos de carbono, aminoalquilo de 1-5
átomos de carbono, N- alquilaminoalquilo de 2-9 átomos de
carbono, N,N-dialquilaminoalquilo de 3-10 átomos de carbono, N-
alquilaminoalcoxi de 2-9 átomos de carbono, N,N-
dialquilaminoalcoxi de 3-10 átomos de carbono, mercapto, y
15 bencilamino; o

X es un radical que tiene la fórmula:



20

en donde

A es un piridinilo, pirimidinilo, o anillo fenilo; en donde
el piridinilo, pirimidinilo, o anillo fenilo opcionalmente pueden
ser mono- o di-sustituidos con un sustituyente seleccionado del
25 grupo que consiste de halógeno, alquilo de 1-6 átomos de carbono,
alquenilo de 2-6 átomos de carbono, alquinilo de 2-6 átomos de
carbono, azido, hidroxialquilo de 1-6 átomos de carbono,
halometilo, alcoximetilo de 2-7 átomos de carbono,
alcaniloximetilo de 2-7 átomos de carbono, alcoxi de 1-6 átomos

de carbono, alquiltio de 1-6 átomos de carbono, hidroxí,
 trifluorometilo, ciano, nitro, carboxi, carboalcoxi de 2-7 átomos
 de carbono, carboalquilo de 2-7 átomos de carbono, fenoxi,
 fenilo, tiofenoxi, benzoilo, bencilo, amino, alquilamino de 1-6
 5 átomos de carbono, dialquilamino de 2 a 12 átomos de carbono,
 fenilamino, bencilamino, alcanilamino de 1-6 átomos de carbono,
 alquenilamino de 3-8 átomos de carbono, alquinilamino de 3-8
 átomos de carbono, carboxialquilo de 2-7 átomos de carbono,
 carboalcoxialquilo de 3-8 átomos de carbono, aminoalquilo de 1-5
 10 átomos de carbono, N-alquilaminoalquilo de 2-9 átomos de carbono,
 N,N-dialquilaminoalquilo de 3-10 átomos de carbono, N-
 alquilarninoalcoxi de 2-9 átomos de carbono, N,N-
 dialquilaminoalcoxi de 3-10 átomos de carbono, mercapto, y
 bencilamino;

15

T está enlazado con un carbono de A y es:

-- NH(CH₂)_m -- , --O(CH₂)_m -- , -- S(CH₂)_m -- , -- NR(CH₂)_m -- -(CH₂)_m -- ,
 (CH₂)_m NH-, -- (CH₂)_m O- , -- (CH₂)_m S-, o -- (CH₂)_mNR- ;

20

L es un anillo fenilo no sustituido o un anillo fenilo mono-
 , di-, o tri- sustituidos con un sustituyente seleccionado del
 grupo que consiste de halógeno, alquilo de 1-6 átomos de carbono,
 alquenilo de 2-6 átomos de carbono, alquinilo de 2-6 átomos de
 25 carbono, azido, hidroxialquilo de 1-6 átomos de carbono,
 halometilo, alcoximetilo de 2-7 átomos de carbono,
 alcaniloximetilo de 2-7 átomos de carbono, alcoxi de 1-6 átomos
 de carbono, alquiltio de 1-6 átomos de carbono, hidroxí,
 trifluorometilo, ciano, nitro, carboxi, carboalcoxi de 2-7 átomos

de carbono, carboalquilo de 2-7 átomos de carbono, fenoxi, fenilo, tiofenoxi, benzoilo, bencilo, amino, alquilamino de 1-6 átomos de carbono, dialquilamino de 2 a 12 átomos de carbono, fenilamino, bencilamino, alcanilamino de 1-6 átomos de carbono, 5 alquenilamino de 3-8 átomos de carbono, alquinilamino de 3-8 átomos de carbono, carboxialquilo de 2-7 átomos de carbono, carboalcoxialquilo de 3-8 átomos de carbono, aminoalquilo de 1-5 átomos de carbono, N-alquilaminoalquilo de 2-9 átomos de carbono, N,N-dialquilaminoalquilo de 3-10 átomos de carbono, N- 10 alquilaminoalcoxi de 2-9 átomos de carbono, N,N-dialquilaminoalcoxi de 3-10 átomos de carbono, mercapto, y bencilamino; o

L es un anillo heteroarilo de 5 a 6 miembros en donde el 15 anillo heteroarilo contiene 1 a 3 heteroátomos seleccionados de N, O, y S, con la condición que el anillo heteroarilo no contiene O - O, S - S, o S - O enlaces, y en donde el anillo heteroarilo es opcionalmente mono- o di-sustituidos con un sustituyente seleccionado del grupo que consiste de halógeno, oxo, tio, 20 alquilo de 1-6 átomos de carbono, alquenido de 2-6 átomos de carbono, alquinilo de 2-6 átomos de carbono, azido, hidroxialquilo de 1-6 átomos de carbono, halometilo, alcoximetilo de 2-7 átomos de carbono, alcaniloximetilo de 2-7 átomos de carbono, alcoxi de 1-6 átomos de carbono, alquiltio de 1-6 átomos 25 de carbono, hidroxí, trifluorometilo, ciano, nitro, carboxi, carboalcoxi de 2-7 átomos de carbono, carboalquilo de 2-7 átomos de carbono, fenoxi, fenilo, tiofenoxi, benzoilo, bencilo, amino, alquilamino de 1-6 átomos de carbono, dialquilamino de 2 a 12 átomos de carbono, fenilamino, bencilamino, alcanilamino de 1-6

átomos de carbono, alquenilamino de 3-8 átomos de carbono,
alquinilamino de 3-8 átomos de carbono, carboxialquilo de 2-7
átomos de carbono, carboalcoxialquilo de 3-8 átomos de carbono,
aminoalquilo de 1-5 átomos de carbono, N- alquilaminoalquilo de
5 2-9 átomos de carbono, N,N-dialquilaminoalquilo de 3-10 átomos de
carbono, N-alquilaminoalcoxi de 2-9 átomos de carbono, N,N-
dialquilaminoalcoxi de 3-10 átomos de carbono, mercapto, y
bencilamino;

10 V es etileno o acetileno;

R₄ es alquilo de 1 a 6 carbonos;

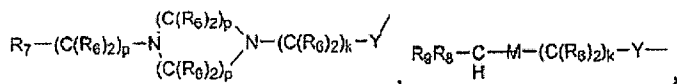
Z es NR^{Z'}, O o S, en donde R^{Z'} es H o C₁-C₆ alquilo;

15

R₁, G₂, y R₃ son cada uno independientemente, hidrógeno,
halógeno, alquilo de 1-6 átomos de carbono, alqueno de 2-6
átomos de carbono, alquino de 2-6 átomos de carbono,
alquenilo de 2-6 átomos de carbono, alquinoxido de 2-6 átomos
20 de carbono, hidroximetilo, halometilo, alcaniloxido de 1-6 átomos
de carbono, alquenilo de 3-8 átomos de carbono, alquinoxido de
3-8 átomos de carbono, alcaniloximetilo de 2-7 átomos de carbono,
alquinoximetilo de 4-9 átomos de carbono, alquinoximetilo de
4-9 átomos de carbono, alcoximetilo de 2-7 átomos de carbono,
25 alcoxido de 1-6 átomos de carbono, alquiltio de 1-6 átomos de
carbono, alquilsulfinilo de 1-6 átomos de carbono, alquilsulfonilo
de 1-6 átomos de carbono, alquilsulfonamido de 1-6 átomos de
carbono, alquenosulfonamido de 2-6 átomos de carbono,
alquinsulfonamido de 2-6 átomos de carbono, hidroxido,

trifluorometilo, trifluorometoxi, ciano, nitro, carboxi, carboalcoxi de 2-7 átomos de carbono, carboalquilo de 2-7 átomos de carbono, fenoxi, naftalamida, fenilo, tiofenoxi, bencilo, amino, hidroxiamino, alcoxiamino de 1-4 átomos de carbono, 5 alquilamino de 1- 6 átomos de carbono, dialquilamino de 2 a 12 átomos de carbono, N-alquilcarbamoil, N,N- dialquilcarbamoil, N-alquil-N-alquenilamino de 4 a 12 átomos de carbono, N ,N-dialquenilamino de 6-12 átomos de carbono, fenilamino, bencilamino,

10

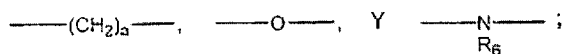


$R_7-(C(R_6)_2)_k-Y$, $R_7-(C(R_6)_2)_p-M-(C(R_6)_2)_k-Y$, or $Het-(C(R_6)_2)_q-W-(C(R_6)_2)_2-Y$;

o R_1 y R_3 son como se definió anteriormente y G_2 es R_2-NH- ; o si cualquiera de los sustituyentes $R-$, G_2 o R_3 se localizan en 15 átomos de carbono contiguos luego ellos pueden tomarse juntos como un radical divalente $-O-C(R_6)_2-O-$;

Y es un radical divalente seleccionado del grupo que consiste de $(CH_2)_a$, o, y N ;

20



R_7 es $-NR_6R_6$, $-OR_6$, $-J$, $-N(R_6)_3^+$, o $-NR_6(OR_6)$;

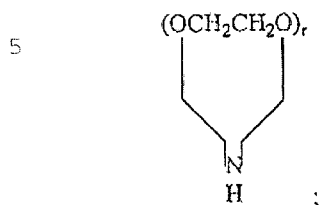
M es $>NR_6O-O->N-(C(R_6)_2)_pNR_6R_6$, o $>N-(C(R_6)_2)_p-OR_6$;

W es $>NR_6$, $-O-o$ es un enlace;

25

Het es seleccionado del grupo que consiste de morfolina, tiomorfolina, tiomorfolina S-óxido, tiomorfolina S,S-dióxido, piperidina, pirrolidina, aziridina, piridina, imidazol, 1,2,3-

triazol, 1,2,4-triazol, tiazol, tiazolidina, tetrazol,
piperazina, furan, tiofeno, tetrahidrotiofeno, tetrahidrofuran,
dioxáno, 1,3-dioxolano, tetrahidropiran, y



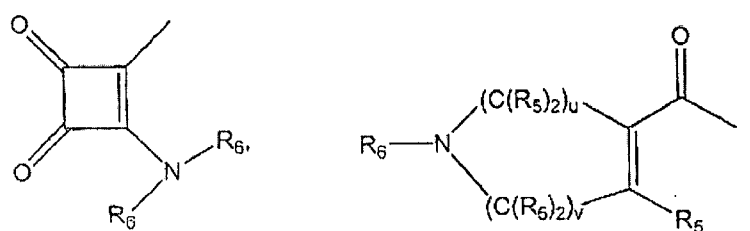
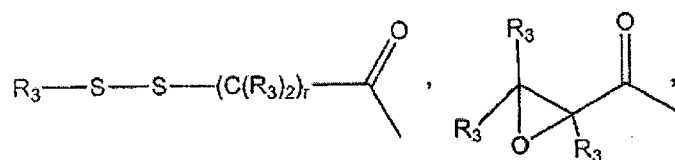
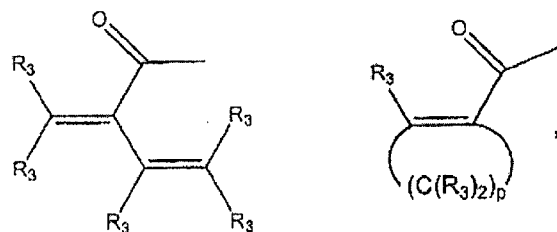
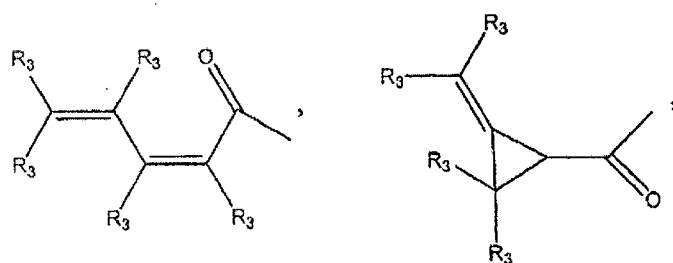
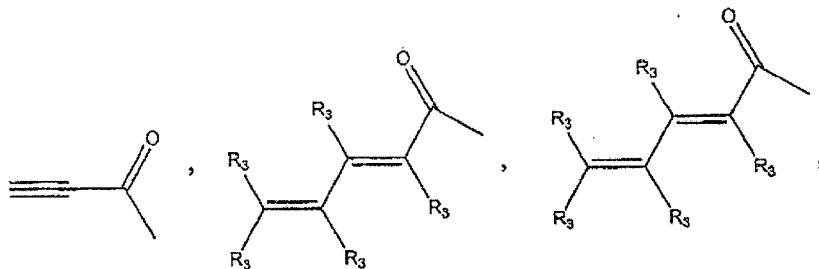
en donde Het es opcionalmente mono- o di-sustituidos en carbono o
10 nitrógeno con R_6 , opcionalmente mono- o di-sustituidos en carbono
con hidroxil, $-N(R_6)_2$, o $-OR_6$, opcionalmente mono o di-
sustituidos en carbono con el radical mono-valente OR_6 o $-$
 $(C(R_n)_2)_s N(R_g)_2$, y opcionalmente mono o di-sustituidos un carbono
saturado con radicales divalentes $-O-O-O-(C(R_6)_2)_s O-$;

15

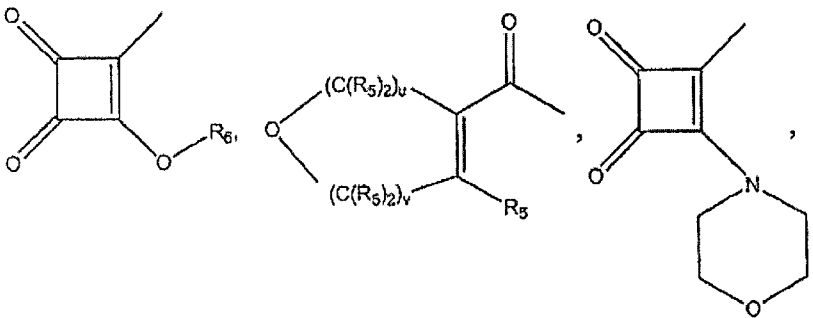
R_6 es hidrógeno, alquilo de 1-6 átomos de carbono, alquenilo
de 2-6 átomos de carbono, alquinilo de 2-6 átomos de carbono,
cicloalquilo de 1-6 átomos de carbono, carboalquilo de 2-7 átomos
de carbono, carboxialquilo (2-7 átomos de carbono), fenilo, o
20 fenilo opcionalmente sustituidos con uno o más halógeno, alcoxi
de 1-6 átomos de carbono, trifluorometilo, amino, alquilamino de
1-3 átomos de carbono, dialquilamino de 2-6 átomos de carbono,
nitro, ciano, azido, halometilo, alcoximetilo de 2-7 átomos de
carbono, alcaniloximetilo de 2-7 átomos de carbono, alquiltio de
25 1-6 átomos de carbono, hidroxil, carboxilo, carboalcoxi de 2-7
átomos de carbono, fenoxil, fenilo, tiofenoxil, benzoilo, bencilo,
fenilamino, bencilamino, alcanilamino de 1-6 átomos de carbono, o
alquilo de 1-6 átomos de carbono; con la condición que la

cantidad de alquenilo o alquinilo se enlaza con un átomo de oxígeno o nitrógeno a través de un átomo de carbono saturado;

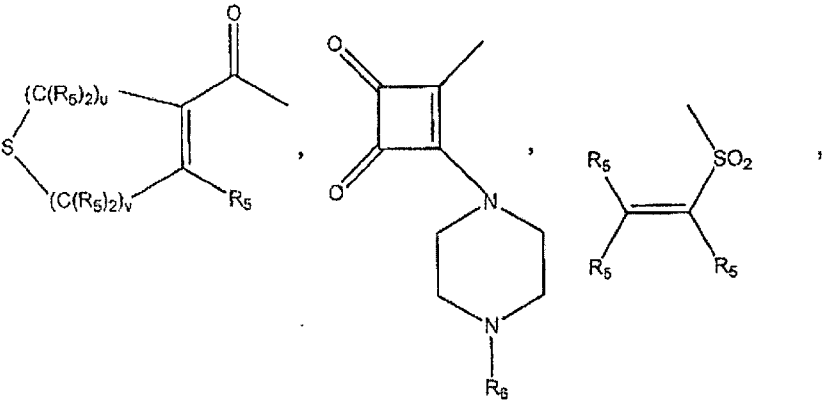
R_2 , es seleccionado del grupo que consiste de



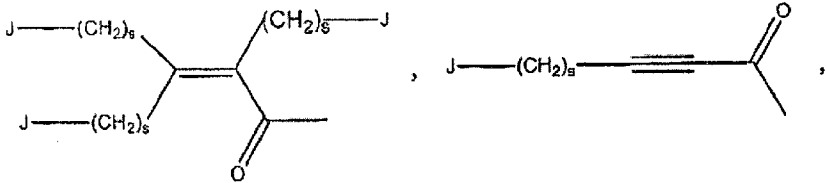
5



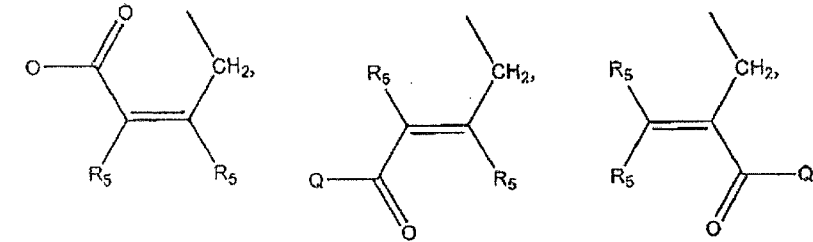
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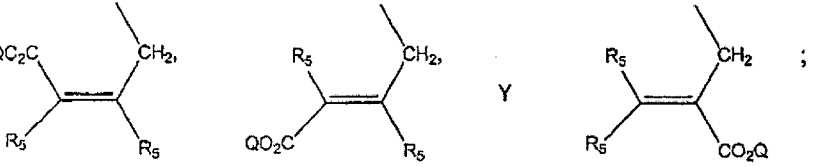
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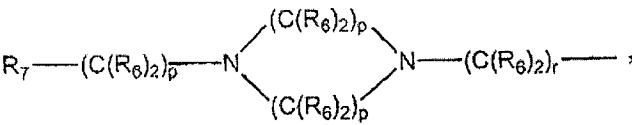


25



R₃ es independientemente hidrógeno, alquilo de 1-6 átomos de carbono, carboxi, carboalcoxi de 1-6 átomos de carbono, fenilo, carboalquilo de 2-7 átomos de carbono,

5



R₇- (C(R₆)₂) - ,

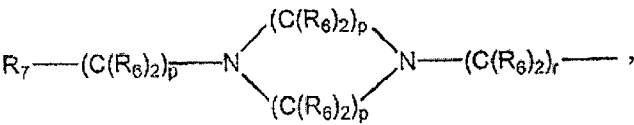
10 R₇-(C(R₆)₂)_p- M-(C(R₆)₂) - , R₈R₉-CH-

M- (C(R_s)₂) , - , o

Het- (C(R₆)₂)_q-W- (C(R₆)₂) - ;

15 R₅ es independientemente hidrógeno, alquilo de 1-6 átomos de carbono, carboxi, carboalcoxi de 1-6 átomos de carbono, fenilo carboalquilo de 2-7 átomos de carbono,

20



R₇-(C(R₆)₂)_s- ,

R₇-(C(R₆)₂)_p-M-(C(R₆)₂)_r- R₈R₉-CH-

M- (C(R_a)₂) - , o

Het- (C(R₆)₂)_q- W- (C(R₆)₂)_r - ;

25

R₈, y R₉ son cada uno independientemente - (C(R₆)₂)_rNR₆R₆ o - (C(R₆)₂)_r OR₆;

J es independientemente hidrógeno, cloro, fluor, o bromo;

Q es alquilo de 1-6 átomos de carbono o hidrógeno; a=0 o 1;
g=1-6; k=0-4; n es 0-1 ;

5 m es 0-3; p=2-4; q=0-4; r=1-4; s=1 -6; u=0-4 y v=0-4, en
donde la suma de u+v es 2-4; x= 0-3; y= 0-1; y z= 0-3; o a una
sal farmacéuticamente aceptable de estos.

15. El método de la reivindicación 14, que comprende
10 adicionalmente las siguientes cláusulas:

cuando R_6 es alquenilo de 2-7 átomos de carbono o alquinilo
de 2-7 átomos de carbono, tal cantidad de alquenilo o alquinilo
se enlaza con un átomo de oxígeno o nitrógeno a través de un
15 átomo de carbono saturado;

cuando Y es $-NR_6 -$ y R_7 es $-NR_6$, R_6 , $-N(R_o)_3-N(R_g)_3^+$, o $-NR_6$
(OR_6), luego g=2-6;

20 cuando M es $-O -$ y R_7 es $-OR_6$ luego p=1-4;

cuando Y es $-NR_6 -$ luego k=2-4; cuando Y es $-O -$ y M o W es
 $-O -$ luego k=1-4;

25 cuando W no es un enlace con Enlace Het a través de un átomo
de nitrógeno luego q=2-4;

cuando W es un enlace con Enlace Het unido a través de un
átomo de nitrógeno y Y es $-O -$ o $-NR_6 -$ luego k=2-4; y

nn180

siempre y cuando L sea un anillo fenilo no sustituido solo
cuando $m > 0$ y T no es $-\text{CH}_2\text{NH}-$ o $-\text{CH}_2\text{O}-$.

MÉTODOS PARA SINTETIZAR DERIVADOS DE 6-ALQUILAMINOQUINOLINA

00181

<http://www.wipo.int/ipdl/IPDL-IMAGES/PCT->[IMAGES/03052007/US2006015931_03052007_pf_fp.x4-b.jpg](http://www.wipo.int/ipdl/IPDL-IMAGES/PCT-IMAGES/03052007/US2006015931_03052007_pf_fp.x4-b.jpg)**RESUMEN**

5

La presente invención está dirigida a un método para sintetizar compuestos de Fórmula (I), en donde X, Z, V, R₁, R₃, R₄, G₂, n, x, y, y z son como se define aquí. Esta invención también incluye un método para preparar compuestos de ácido de Fórmula (VII), en
10 donde R es H, y R₄, x, y, y z son como se define aquí y PG es un grupo protector. Esta invención está también dirigida a (E) N-{4-[3-cloro-4-(2-piridinilmetoxi)anilino]-3-ciano-7-etoxi-6-quinolinil}-4-(metilamino)-2-butenamida, composiciones que contienen estos métodos para utilizar en el tratamiento del
15 cáncer.

PATENT COOPERATION TREATY

AM101422

From the INTERNATIONAL SEARCHING AUTHORITY

RECEIVED

PCT

To:

FITZPATRICK CELLA HARPER & SCINTO
Attn. Mandra, Raymond R.
30 Rockefeller Plaza
New York, NY 10112-3801
ETATS-UNIS D'AMERIQUE

2007 MAR 28

FITZPATRICK, CELLA HARPER & SCINTO

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

FILE NO. 01997 032400. PC

ATTORNEY SV

DUE DATE 5/20/07

DOCKETED YMG 3/28/07

(PCT Rule 44.1)

Date of mailing
(day/month/year)

20/03/2007

Applicant's or agent's file reference

01997.032400

FOR FURTHER ACTION

See paragraphs 1 and 4 below

International application No.

PCT/US2006/015931

International filing date
(day/month/year)

26/04/2006

Applicant

WYETH

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the international Application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the International Search Report.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes
1211 Geneva 20, Switzerland. Facsimile No.: (41-22) 338.82.70

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.
3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:
- ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
- ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Reminders

Shortly after the expiration of 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within 19 months from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later); otherwise, the applicant must, within 20 months from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of 30 months (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the PCT Applicant's Guide, Volume II, National Chapters and the WIPO Internet site.

RECEIVED

Name and mailing address of the International Searching Authority

European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Jaap Hurenkamp

APR 30 2007

SHEILA MORRIS

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see *PCT Applicant's Guide*, Volume I/A, Annexes B1 and B2).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, Volume I/A, paragraph 296).

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

00124

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

If a demand for international preliminary examination is made, the written opinion of the International Searching Authority will, except in certain cases where the International Preliminary Examining Authority did not act as International Searching Authority and where it has notified the International Bureau under Rule 66.1 b/s(b), be considered to be a written opinion of the International Preliminary Examining Authority. If a demand is made, the applicant may submit to the International Preliminary Examining Authority a reply to the written opinion together, where appropriate, with amendments before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later (Rule 43bis.1(c)).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices. Instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see the *PCT Applicant's Guide*, Volume II.

00125

04/27/2007 16:27 FAX 1 212 218 4551

FITZPATRICK NY

007

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1)Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)Applicant's or agent's file reference
see form PCT/ISA/220FOR FURTHER ACTION
See paragraph 2 belowInternational application No.
PCT/US2006/015931International filing date (day/month/year)
26.04.2006Priority date (day/month/year)
25.05.2005International Patent Classification (IPC) or both national classification and IPC
INV. C07D215/44 C07D403/12 C07C271/22Applicant
WYETH

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

FILE NO. 01997 032400 PC

ATTORNEY SV

DUE DATE 6/20/07

DOCKETED MS 3/28/07

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office - P.B. 5818 Patentlaan
NL-2280 HV Rijswijk - Pays Bas
Tel. +31 70 340 - 2040 Tx: 31 651 epo nl
Fax: +31 70 340 - 3016

Date of completion of
this opinionsee form
PCT/ISA/210

Authorized Officer

Diederer, Jeroen

Telephone No. +31 70 340-1097



**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**International application No.
PCT/US2006/015931

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ on paper
 - ☐ in electronic form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in electronic form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

00187

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**International application No.
PCT/US2006/015931**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 6-13

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international search (*specify*):

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):

☒ no international search report has been established for the whole application or for said claims Nos. 6-13

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13ter.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-bis of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.

☐ See Supplemental Box for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

 International application No.
PCT/US2006/015931

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has, within the applicable time limit:
- ☐ paid additional fees
 - ☐ paid additional fees under protest and, where applicable, the protest fee
 - ☐ paid additional fees under protest but the applicable protest fee was not paid
 - ☒ not paid additional fees
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
- ☐ complied with
 - ☒ not complied with for the following reasons:
see separate sheet
4. Consequently, this report has been established in respect of the following parts of the international application:
- ☐ all parts.
 - ☒ the parts relating to claims Nos. 1-5, 14, 15

Box No. V Reasoned statement under Rule 43b/s.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
1. Statement

Novelty (N)	Yes: Claims	<u>1-5, 14, 15</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>3-5, 14, 15</u>
	No: Claims	<u>1, 2</u>
Industrial applicability (IA)	Yes: Claims	<u>1-5, 14, 15</u>
	No: Claims	

2. Citations and explanations
see separate sheet

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2006/015931

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/US2006/015931**Re Item III.**

Claims 6-13 were not searched and therefore no examination can be carried out on these claims.

Re Item IV.

The separate inventions/groups of inventions are:

1-5,14,15

Methods for the preparation of compounds of Formula (I)

6-13

An alternative method for the preparation of compounds of Formula (VII)

They are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons:

The present application deals with two different processes for the preparation of compounds of Formula (I). The said compounds are novel over the prior art. Claim 6 deals with a process for the preparation of compounds of Formula (VII). The latter compounds are used to prepare compounds of Formula (I). The only technical feature which is shared by both compounds is the structure of Formula (VII).

Document D1 (J. Med. Chem. (2002) 45, 753-757 and document D2 (J. Med. Chem. (1999) 42, 4669-4679) disclose processes for the preparation of compounds of Formula (VII) by hydrolysis of the ester group with LiOH (see in D1 the conversion of 15a to 16a and in D2 the conversion of 6i to 7i). As the compounds of Formula (VII) and its process according to claim 6 is not novel, the said feature cannot act as the special technical feature as referred to in Rule 13.2 PCT. As there are no other common technical features which can act as the special technical feature, there is a lack of Unity of Invention.

The problems underlying the present application are therefore:

- 1) The provision of a method for the preparation of compounds of Formula (I)
- 2) The provision of an alternative process for the preparation of compounds of Formula

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/US2006/015931

(VII)

The first problem is solved by the applicant by deprotecting a compound of Formula (II) (claim 1) or by coupling an aminoquinoline of Formula (III) with an acid of Formula (VII'). The second problem is solved by the applicant by hydrolising a corresponding ester of Formula (VII').

Re Item V.

1 Reference is made to the following documents:

D3 : WISSNER A ET AL: "Synthesis and Structure-Activity Relationships of 6,7-Disubstituted 4-Aminoquinoline-3-carbonitriles. The Design of an Orally Active, Irreversible Inhibitor of the Tyrosine Kinase Activity of the Epidermal Growth Factor Receptor (EGFR) and the Human Epidermal Growth Factor Receptor-2 (HER-2)" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, US, vol. 46, 12 February 2002 (2002-02-12), pages 49-63, XP002310736 ISSN: 0022-2623

D4 : EP 1 263 503 A (AMERICAN CYANAMID COMPANY; WYETH HOLDINGS CORPORATION) 11 December 2002 (2002-12-11)

Document D3 discloses in Scheme 4, the preparation of 6-alkylamino-3-cyanoquinolines starting from acid chlorides and the aminoquinoline. The yields reported have a maximum of 50 %. Document D4 discloses in example 145 a similar reaction (yield around 21%).

The difference of the disclosure of the present application and the subject-matter of claim 1 is that in the prior art, acid chlorides are used to couple the aminoquinoline with the aminoalkyl group, whereas in the present application protected amine-alkylacids are used (Formula VII). The technical effect of this difference is that better yields are obtained due to instability of the acid compounds in the prior art.

The problem to be solved by the applicant was to provide an improved process for the preparation of compounds of Formula (I). The applicant solves this by coupling an aminoquinoline with an acid of Formula (VII). A skilled person would not have expected

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/US2006/015931

that by coupling a protected amine-alkylacid of Formula (VII) with an aminoquinoline, the yields would be so much better than the prior art, where acidchlorides are used. The combination of claim 3 and 1 is therefore considered inventive over the prior art. Claim 3 contains the essential feature underlying the solution to the problem of the present application. It is therefore considered that claim 3-5 is inventive over the prior art. Claims 1,2 are not considered inventive over the prior art. Claims 14 and 15 are considered inventive because claim 14 contains all the essential features underlying the invention.

Re Item VIII.

Claim 1 is not clear with respect to Article 6 PCT. The wording amine protecting group is vague and leaves the reader in doubt as to what it exactly means. It is written as a result to be achieved, which is not allowable. Furthermore is claim 1 not clear, as there is no definition for the radical "R2".

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 01997.032400	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/US2006/015931	International filing date (day/month/year) 26/04/2006	(Earliest) Priority Date (day/month/year) 25/05/2005
Applicant WYETH		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 6 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the language, the international search was carried out on the basis of:

- ☒ the international application in the language in which it was filed
☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

b. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2. ☐ Certain claims were found unsearchable (See Box No. II)

3. ☒ Unity of invention is lacking (see Box No. III)

4. With regard to the title,

- ☒ the text is approved as submitted by the applicant
☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

- ☒ the text is approved as submitted by the applicant
☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the drawings,

- a. the figure of the drawings to be published with the abstract is Figure No. _____
☐ as suggested by the applicant
☐ as selected by this Authority, because the applicant failed to suggest a figure
☐ as selected by this Authority, because this figure better characterizes the invention
b. ☐ none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US2006/015931

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D215/44 C07D403/12 C07C271/22

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MANFRED JUNG ET AL: "Amide Analogues of Trichostatin A as Inhibitors of Histone Deacetylase and Inducers of Terminal Cell Differentiation" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, US, vol. 42, no. 22, 4 November 1999 (1999-11-04), pages 4669-4679, XP002144226 ISSN: 0022-2623 conversion 6i -> 7i ----- -/--	6

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the International filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

7 September 2006

Date of mailing of the International search report

20.03.2007

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 851 epo nl
Fax: (+31-70) 340-3016

Authorized officer

Diederer, Jeroen

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2006/015931

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	REMISZEWSKI S W ET AL: "Inhibitors of Human Histone Deacetylase: Synthesis and Enzyme and Cellular Activity of Straight Chain Hydroxamates" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, US, vol. 45, no. 4, 14 February 2002 (2002-02-14), pages 753-757, XP002303393 ISSN: 0022-2623 15a step (b), Scheme 3	6
A	WISSNER A ET AL: "Synthesis and Structure-Activity Relationships of 6,7-Disubstituted 4-Anilinoquinoline-3-carbonitriles. The Design of an Orally Active, Irreversible Inhibitor of the Tyrosine Kinase Activity of the Epidermal Growth Factor Receptor (EGFR) and the Human Epidermal Growth Factor Receptor-2 (HER-2)" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, US, vol. 46, 12 February 2002 (2002-02-12), pages 49-63, XP002310736 ISSN: 0022-2623 Scheme 5	1,14
A	EP 1 263 503 A (AMERICAN CYANAMID COMPANY; WYETH HOLDINGS CORPORATION) 11 December 2002 (2002-12-11) example 145	1,14
A	US 6 002 008 A (WISSNER ET AL) 14 December 1999 (1999-12-14) example 101	1,14

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2006/015931

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 1263503	A	11-12-2002	
		AT 308364 T	15-11-2005
		AU 4545201 A	24-09-2001
		BR 0109165 A	22-04-2003
		CA 2402742 A1	20-09-2001
		CN 1429126 A	09-07-2003
		DE 60114580 D1	08-12-2005
		DE 60114580 T2	27-07-2006
		DK 1263503 T3	13-02-2006
		ES 2248302 T3	16-03-2006
		HK 1048775 A1	20-01-2006
		HU 0300547 A2	28-07-2003
		JP 2003526686 T	09-09-2003
		MX PA02008836 A	10-02-2003
		NO 20024356 A	12-11-2002
		NZ 521117 A	25-02-2005
		PL 363072 A1	15-11-2004
		WO 0168186 A2	20-09-2001
		ZA 200208178 A	11-02-2004
US 6002008	A	14-12-1999	NONE

00107

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2006/015931**Box II Observations where certain claims were found unsearchable (Continuation of Item 2 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of Item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

see annex

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

04/27/2007 16:29 FAX 1 212 218 4551

FITZPATRICK NY

020

International Application No. PCT/US2006/015931

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-5,14,15

Methods for the preparation of compounds of Formula (I)

2. claims: 6-13

An alternative method for the preparation of compounds of Formula (VII)

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

MANDRA, Raymond, R.
FITZPATRICK, CELLA, HARPER & SCINTO
30 Rockefeller Plaza
New York, NY 10112-3801
ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year) 07 July 2006 (07.07.2006)	
Applicant's or agent's file reference 01997.032400	IMPORTANT NOTIFICATION
International application No. PCT/US2006/015931	International filing date (day/month/year) 26 April 2006 (26.04.2006)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 25 May 2005 (25.05.2005)
Applicant WYETH et al	

1. By means of this Form, which replaces any previously issued notification concerning submission or transmittal of priority documents, the applicant is hereby notified of the date of receipt by the International Bureau of the priority document(s) relating to all earlier application(s) whose priority is claimed. Unless otherwise indicated by the letters "NR", in the right-hand column or by an asterisk appearing next to a date of receipt, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. (If applicable) The letters "NR" appearing in the right-hand column denote a priority document which, on the date of mailing of this Form, had not yet been received by the International Bureau under Rule 17.1(a) or (b). Where, under Rule 17.1(a), the priority document must be submitted by the applicant to the receiving Office or the International Bureau, but the applicant fails to submit the priority document within the applicable time limit under that Rule, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

3. (If applicable) An asterisk (*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b) (the priority document was received after the time limit prescribed in Rule 17.1(a) or the request to prepare and transmit the priority document was submitted to the receiving Office after the applicable time limit under Rule 17.1(b)). Even though the priority document was not furnished in compliance with Rule 17.1(a) or (b), the International Bureau will nevertheless transmit a copy of the document to the designated Offices, for their consideration. In case such a copy is not accepted by the designated Office as the priority document, Rule 17.1(c) provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
25 May 2005 (25.05.2005)	60/685,040	US	22 June 2006 (22.06.2006)

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Yolaine Cussac
Facsimile No. +41 22 338 82 70	Facsimile No. +41 22 338 70 80 Telephone No. +41 22 338 90 12

PATENT COOPERATION TREATY

PCT/US2006/015931

From the INTERNATIONAL BUREAU

PCTNOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

To:

MANDRA, Raymond, R.
FITZPATRICK, CELLA, HARPER & SCINTO
30 Rockefeller Plaza
New York, NY 10112-3801
ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year) 01 June 2007 (01.06.2007)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference 01997.032400	
International application No. PCT/US2006/015931	International filing date (day/month/year) 26 April 2006 (26.04.2006)

1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address MCGINNIS, John, Patrick, III 6 Chaparral Road Nanuet, New York 10954 United States of America	State of Nationality US	State of Residence US
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☒ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address MCGINNIS, John, Patrick, II 3 Chaparral Road Nanuet, New York 10954 United States of America	State of Nationality US	State of Residence US
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

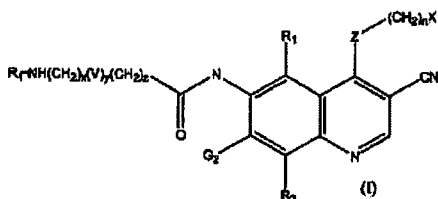
☒ the receiving Office ☒ the designated Offices concerned
☐ the International Searching Authority ☐ the elected Offices concerned
☐ the International Preliminary Examining Authority ☐ other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Ben Helal Najib Facsimile No. +41 22 338 70 80 Telephone No. +41 22 338 74 11
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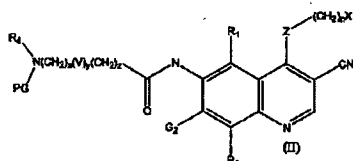
(21) N° de solicitud:		(51) Int Cl:	C07D 215/44, C07C 271/22, C07D 403/12
22) Fecha de solicitud:		(71) Solicitante(s)	WYETH
(30) Prioridad	(31) No. 60/685,040	32) Fecha 25/05/05	(33) País US
		(72) Inventor(es)	CHEW, Warren RABINDRAN, Sridhar Krishna Y otros
		(74) Apoderado:	ALVARO CORREA ORDOÑEZ
(85)	Fecha limite inicio fase nacional: 25/12/07		(87) Publicación internacional
(86)	Datos relativos a la presentación de la solicitud PCT		Fecha: 30/11/06
	Fecha de presentación de la solicitud: 26/04/06		N° publicación: WO/2006/127203
	No. de solicitud PCT/US2006/015931		
(54) Título: MÉTODOS PARA SINTETIZAR DERIVADOS DE 6-ALQUILAMINOQUINOLINA			

Reivindicación(es):

1. Un método para preparar un compuesto de Fórmula (I):



que comprende la etapa de desproteger un compuesto de Fórmula (II):



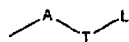
en donde:

X es cicloalquilo de 3 a 7 átomos de carbono, que puede ser opcionalmente sustituido con uno o más alquilo de 1 a 6 grupos de átomos de carbono; o es un anillo de piridinilo, pirimidinilo, o fenilo; en donde el anillo de piridinilo, pirimidinilo, o anillo fenilo puede ser opcionalmente mono- di-, o tri-sustituidos con un sustituyente seleccionado del grupo que consiste de halógeno, alquilo de 1-6 átomos de carbono, alqueno de 2-6 átomos de carbono, alquino de 2-6 átomos de carbono, azido, hidroxialquilo de 1-6 átomos de carbono, halometilo, alcoximetilo de 2-7 átomos de carbono, alcanoloximetilo de 2-7 átomos de carbono, alcoxi de 1-6 átomos de carbono, alquiltio de 1-6 átomos de carbono, hidroxilo, trifluorometilo, ciano, nitro, carboxi, carboalcoxi de 2-7 átomos de carbono, carboalquilo de 2-7 átomos de carbono, fenoxi, fenilo, tiofenoxi, benzoilo, bencilo, amino, alquilamino de 1-6 átomos de carbono, dialquilamino de 2 a 12 átomos de carbono, fenilamino, bencilamino, alcanoilamino de 1-6 átomos de carbono, alquenoilamino de 3-8 átomos de carbono, alquinoilamino de 3-8 átomos de carbono, carboxialquilo de 2-7 átomos de carbono, carboalcoxialquilo de 3-8 átomos de carbono, aminoalquilo de 1-5 átomos de carbono, N- alquilaminoalquilo de 2-9 átomos de carbono, N,N-dialquilaminoalquilo de 3-10 carbonos, átomos, N-alquilaminoalcoxi de 2-9 átomos de carbono, N,N-dialquilaminoalcoxi de 3-10 átomos de carbono, mercapto, y benzoilamino; o

X es un sistema de anillo arilo bicíclico o heteroarilo bicíclico de 8 a 12 átomos en donde el anillo heteroarilo bicíclico contiene 1 a 4 heteroátomos seleccionados de N, O, y S con la condición de que el anillo heteroarilo bicíclico no contenga enlaces O — O, S — S, o S — O y en donde el anillo arilo bicíclico o heteroarilo bicíclico puedan ser opcionalmente mono- di-, tri-, o tetra-sustituídos con un sustituyente seleccionado del grupo que consiste de halógeno, oxo, tio, alquilo de 1-6 átomos de carbono, alquenoilo de 2-6 átomos de carbono, alquinoilo de 2-6 átomos de carbono, azido, hidroxialquilo de 1-6 átomos de carbono, halometilo, alcoximetilo de 2-7 átomos de carbono, alcaniloximetilo de 2-7 átomos de carbono, alcoxi de 1-6 átomos de carbono, alquiltio de 1-6 átomos de carbono, hidroxilo, trifluorometilo, ciano, nitro, carboxi, carboalcoxi de 2-7 átomos de carbono, carboalquilo de 2-7 átomos de carbono, fenoxi, fenilo, tiofenoxi, benzoilo, bencilo, amino, alquilamino de 1-6 átomos de carbono, di alquilo amino de 2 a 12 átomos de carbono, fenilamino, bencilamino, alcanilamino de 1 -6 átomos de carbono, alquenoilamino de 3-8 átomos de carbono, alquililamino de 3-8 átomos de

carbono, carboxialquilo de 2-7 átomos de carbono, carboalcoxialquilo de 3-8 átomos de carbono, aminoalquilo de 1-5 átomos de carbono, N- alquilaminoalquilo de 2-9 átomos de carbono, N,N-dialquilaminoalquilo de 3-10 átomos de carbono, N-alquilaminoalcoxi de 2-9 átomos de carbono, N,N-dialquilaminoalcoxi de 3-10 átomos de carbono, mercapto, y bencilamino; o

X es un radical que tiene la fórmula:



en donde

A es un anillo de piridinilo, pirimidinilo, o fenilo; en donde el anillo de piridinilo, pirimidinilo, o anillo fenilo opcionalmente pueden ser mono- o di-sustituídos con un sustituyente seleccionado del grupo que consiste de halógeno, alquilo de 1-6 átomos de carbono, alquenoilo de 2-6 átomos de carbono, alquinilo de 2-6 átomos de carbono, azido, hidroxialquilo de 1-6 átomos de carbono, halometilo, alcoximetilo de 2-7 átomos de carbono, alcaniloximetilo de 2-7 átomos de carbono, alcoxi de 1-6 átomos de carbono, alquiltio de 1-6 átomos de carbono, hidroxi, trifluorometilo, ciano, nitro, carboxi, carboalcoxi de 2-7 átomos de carbono, carboalquilo de 2-7 átomos de carbono, fenoxi, fenilo, tiofenoxi, benzoilo, bencilo, amino, alquilamino de 1-6 átomos de carbono, dialquilamino de 2 a 12 átomos de carbono, fenilamino, bencilamino, alcanilamino de 1-6 átomos de carbono, alquenoilamino de 3-8 átomos de carbono, alquinoilamino de 3-8 átomos de carbono, carboxialquilo de 2-7 átomos de carbono, carboalcoxialquilo de 3-8 átomos de carbono, aminoalquilo de 1-5 átomos de carbono, N-alquilaminoalquilo de 2-9 átomos de carbono, N₃N- dialquilaminoalquilo de 3-10 átomos de carbono, N- alquilaminoalcoxi de 2-9 átomos de carbono, N,N-dialquilaminoalcoxi de 3-10 átomos de carbono, mercapto, y bencilamino;

T está enlazado con un carbono de A y es:

— NH(CH₂)_m — O(CH₂)_m — S(CH₂)_m — NR(CH₂)_m — (CH₂)_n — (CH₂)_m NH-, — (CH₂)_m O — (CH₂)_m S-, o — (CH₂)_m NR— ;

L es un anillo de fenilo no sustituido o un anillo fenilo mono-, di-, o tri- sustituidos con un sustituyente seleccionado del grupo que consiste de halógeno, alquilo de 1-6 átomos de carbono, alquenoilo de 2-6 átomos de carbono, alquinilo de 2-6 átomos de carbono, azido, hidroxialquilo de 1-6 átomos de carbono, halometilo, alcoximetilo de 2-7 átomos de carbono, alcaniloximetilo de 2-7 átomos de carbono, alcoxi de 1-6 átomos de carbono, alquiltio de 1-6 átomos de carbono, hidroxi, trifluorometilo, ciano, nitro, carboxi, carboalcoxi de 2-7 átomos de carbono, carboalquilo de 2-7 átomos de carbono, fenoxi, fenilo, tiofenoxi, benzoilo, bencilo, amino, alquilamino de 1-6 átomos de carbono, dialquilamino de 2 a 12 átomos de carbono, fenilamino, bencilamino, alcanilamino de 1-6 átomos de carbono, alquenoilamino de 3-8 átomos de carbono, alquinoilamino de 3-8 átomos de carbono, carboxialquilo de 2-7 átomos de carbono, carboalcoxialquilo de 3-8 átomos de carbono, aminoalquilo de 1-5 átomos de carbono, N- alquilaminoalquilo de 2-9 átomos de carbono, N,N-dialquilaminoalquilo de 3-10 átomos de carbono, N- alquilaminoalcoxi de 2-9 átomos de carbono, N,N-dialquilaminoalcoxi de 3-10 átomos de carbono, mercapto, y bencilamino; o

L es un anillo heteroarilo de 5- o 6- miembros en donde el anillo heteroarilo contiene 1 a 3 heteroátomos seleccionados de N, O, y S, con la condición que el anillo heteroarilo no contiene O — O, S — S, o S — O enlaces, y en donde el anillo heteroarilo es opcionalmente mono- o di-sustituídos con un sustituyente seleccionado del grupo que consiste de halógeno, oxo, tio, alquilo de 1-6 átomos de carbono, alquenoilo de 2-6 átomos de carbono, alquinilo de 2-6 átomos de carbono, azido, hidroxialquilo de 1-6 átomos de carbono, halometilo, alcoximetilo de 2-7 átomos de carbono, alcaniloximetilo de 2-7 átomos de carbono, alcoxi de 1-6 átomos de carbono, alquiltio de 1-6 átomos de carbono, hidroxi, trifluorometilo, ciano, nitro, carboxi, carboalcoxi de 2-7 átomos de carbono, carboalquilo de 2-7 átomos de carbono, fenoxi, fenilo, tiofenoxi, benzoilo, bencilo, amino, alquilamino de 1-6 átomos de carbono, dialquilamino de 2 a 12 átomos de carbono, fenilamino, ben2ylamino, alcanilamino de 1-6 átomos de carbono, alquenoilamino de 3-8 átomos de carbono, alquinoilamino de 3-8 átomos de carbono, carboxialquilo de 2-7 átomos de carbono, carboalcoxialquilo de 3-8 átomos de carbono, aminoalquilo de 1-5 átomos de carbono, N- alquilaminoalquilo de 2-9 átomos de carbono, N,N-dialquilaminoalquilo de 3-10 átomos de carbono, N- alquilaminoalcoxi de 2-9 átomos de carbono, N,N-dialquilaminoalcoxi de 3-10 átomos de carbono, mercapto, y benzoilamino;

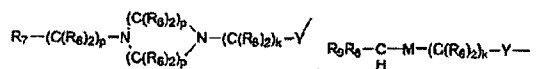
V es etileno o acetileno;

PG es un grupo protector de amina;

R₄ es alquilo de 1 a 6 carbonos;

Z es NR^z, O o S, en donde R^z es H o C₁-C₆ alquil;

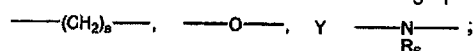
R₁, G₂, y R₃ son cada uno independientemente, hidrógeno, halógeno, alquilo de 1-6 átomos de carbono, alquenoilo de 2-6 átomos de carbono, alquinilo de 2-6 átomos de carbono, alquenoilo de 2-6 átomos de carbono, alquinoilo de 2-6 átomos de carbono, hidroxi, trifluorometilo, trifluorometoxi, ciano, nitro, carboxi, carboalcoxi de 2-7 átomos de carbono, carboalquilo de 2-7 átomos de carbono, fenoxi, ftalimida, fenilo, tiofenoxi, bencilo, amino, hidroxiamino, alcoxiamino de 1-4 átomos de carbono, alquilamino de 1- 6 átomos de carbono, dialquilamino de 2 a 12 átomos de carbono, N-alquilcarbamoilo, N,N- dialquilcarbamoilo, N-alquil-N-alquenoilamino de 4 a 12 átomos de carbono, N,N- dialquenoilamino de 6-12 átomos de carbono, fenilamino, bencilamino,



R₇-(C(R₆)₂)_k-Y-, R₇-(C(R₆)₂)_p-M-(C(R₆)₂)_k-Y-, or Het-(C(R₆)₂)_q-W-(C(R₆)₂)₂-Y-;

o R_1 y R_3 son como se definió anteriormente y G_2 es R_2-NH- ;
o si cualquiera de los sustituyentes R_1 , G_2 o R_3 están localizados en átomos de carbono contiguos entonces ellos pueden tomarse juntos como un radical divalente $-O-C(R_6)_2-O-$;

Y es un radical divalente seleccionado del grupo que consiste de (

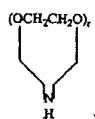


R_7 es $-NR_6R_6$, $-OR_6$, $-J$, $-N(R_6)_3^+$, o $-NR_6(OR_6)$;

M es $>NR_6$, $-O->N-(C(R_6)_p)NR_6R_6$, o $>N-(C(R_6)_p)P-OR_6$;

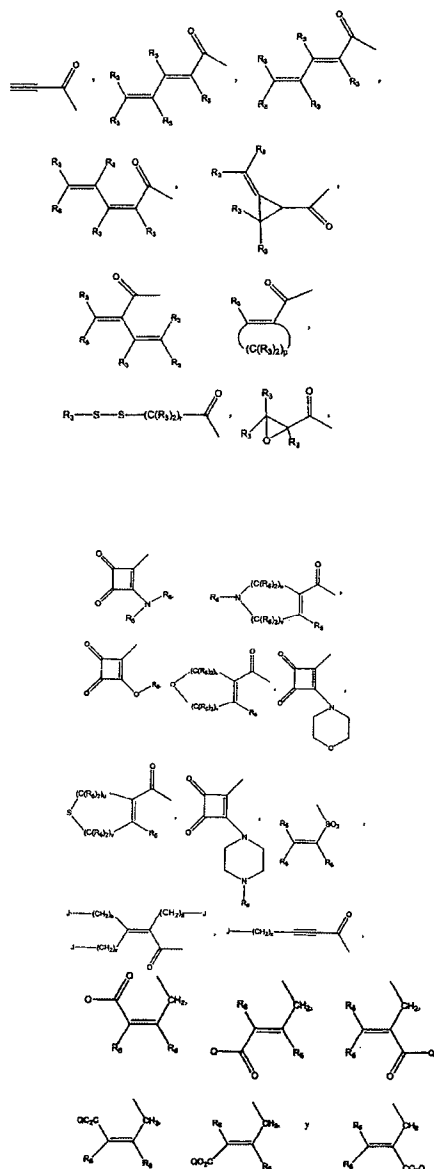
W es $>NR_6$, $-O-o$ es un enlace;

Het es seleccionado del grupo que consiste de morfolina, tiomorfolina, tiomorfolina S-óxido, tiomorfolina S,S-dióxido, piperidina, pirrolidina, aziridina, piridina, imidazol, 1,2,3-triazol, 1,2,4-triazol, tiazol, tiazolidina, tetrazol, piperazina, furano, tiofeno, tetrahidrotiofeno, tetrahydrofurano, dioxano, 1,3-dioxolano, tetrahidropiran, y

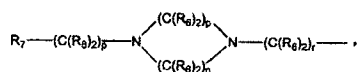


en donde Het es opcionalmente mono- o di-sustituidos en el carbono o nitrógeno con R_6 , opcionalmente mono- o di-sustituidos en carbono con hidroxilo, $-N(R_6)_2$, o $-OR_6$, opcionalmente mono o di-sustituidos en carbono con los radicales mono-valentes $-(C(R_6)_2)_s$, OR_6 o $-(C(R_6)_2)_s N(RO)_2$, y opcionalmente mono o di-sustituidos en un carbono saturado con radicales divalentes $-O-o$ o $O(C(R_6)_2)_s O-$;

R_6 es hidrógeno, alquilo de 1-6 átomos de carbono, alquénilo de 2-6 átomos de carbono, alquínilo de 2-6 átomos de carbono, cicloalquilo de 1-6 átomos de carbono, carboalquilo de 2-7 átomos de carbono, carboxialquilo (2-7 átomos de carbono), fenilo, o fenilo opcionalmente sustituido con uno o más halógeno, alcoxi de 1-6 átomos de carbono, trifluorometilo, amino, alquilamino de 1-3 átomos de carbono, dialquilamino de 2-6 átomos de carbono, nitro, ciano, azido, halometilo, alcoximetilo de 2-7 átomos de carbono, alcanoiloximetilo de 2-7 átomos de carbono, alquiltio de 1-6 átomos de carbono, hidroxilo, carboxilo, carboalcoxi de 2-7 átomos de carbono, fenoxi, fenilo, tiofenoxi, benzoilo, bencilo, fenilamino, bencilamino, alcaoilamino de 1-6 átomos de carbono, o alquilo de 1-6 átomos de carbono; con la condición que la porción de alquénilo o alquínilo se enlaza a un átomo de oxígeno o nitrógeno a través de un átomo de carbono saturado; R_2 , es seleccionado del grupo que consiste de



R_3 es independientemente hidrógeno, alquilo de 1-6 átomos de carbono, carboxi, carboalcoxi de 1-6 átomos de carbono, fenilo, carboalquilo de 2-7 átomos de carbono,



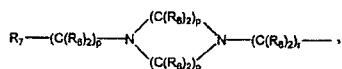
$R_7 - (C(R_6)_2)_s -$

$R_7 - (C(R_6)_2)_p - M - (C(R_6)_2)_r -$, $R_8 R_9 - CH -$

$M - (C(R_6)_2)_r -$, o

$Het - (C(R_6)_2)_q - W - (C(R_6)_2)_r -$;

R_5 es independientemente hidrógeno, alquilo de 1-6 átomos de carbono, carboxi, carboalcoxi de 1-6 átomos de carbono, fenilo carboalquilo de 2-7 átomos de carbono,



$R_7 - (C(R_6)_2)_s -$,

$R_7 - (C(R_6)_2)_p - M - (C(R_6)_2)_r -$, $R_8 R_9 - CH -$

$M - (C(R_6)_2)_r -$, o

$Het - (C(R_6)_2)_q - W - (C(R_6)_2)_r -$;

R_8 , y R_9 son cada uno independientemente $-(C(R_6)_2)_r NR_6 R_6$, o $-(C(R_6)_2)_r OR_6$;
 J es independientemente hidrógeno, cloro, fluor, o bromo;

Q es alquilo de 1-6 átomos de carbono o hidrógeno;

$a=0$ o 1 ;

$g=1-6$;

$k=0-4$;

n es $0-1$;

m es $0-3$;

$p=2-4$;

$q=0-4$;

$r=1-4$;

$s=1-6$;

$u=0-4$ y $v=0-4$, en donde la suma de $u+v$ es $2-4$;

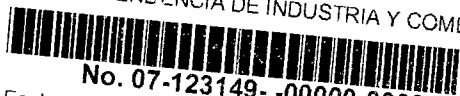
$x=0-3$;

$y=0-1$; y

$z=0-3$;

o una sal farmacéuticamente aceptable de estos.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-123149- -00000-0000

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Tra. 11 PATENTEIYII

Act. 411 PRESENTACION

Dep. 2020 NUECREACIONI

Eve: 378 FASENACIONALI

Folios: 206



Industria y Comercio
SUPERINTENDENCIA

REQUISITOS MINIMOS PARA ADMISION A TRAMITE
PCT

PATENTE DE INVENCION

☒

MODELO DE UTILIDAD

☐

- ◆ Indicación de que se solicita la concesión de una patente ☒
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud ☒
- ◆ Descripción de la invención ☒
- ◆ Dibujos de ser estos pertinentes ☐
- ◆ Comprobante de pago de las tasas establecidas ☒

COMPLETA ☐

INCOMPLETA ☐

DISEÑO INDUSTRIAL ☐

- ◆ Indicación de que se solicita el registro de Diseño Industrial ☐
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud ☐
- ◆ Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño ☐
- ◆ Comprobante de pago de las tasas establecidas ☐

COMPLETA ☐

INCOMPLETA ☐

ESQUEMA DE TRAZADO ☐

- ◆ Indicación de que se solicita el registro de un Esquema de Trazado ☐
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud ☐
- ◆ Representación gráfica del esquema trazado ☐
- ◆ Comprobante de pago de las tasas establecidas ☐

COMPLETA ☐

INCOMPLETA ☐

Claudia M. Neira Corles
Firma Responsable

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REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Folio 208

2020
Bogotá D.C.,

Doctor(a)
CORREA ORDOÑEZ ALVARO
Apoderado(a) y/o Representante de
WYETH

REFERENCIA	Radicación No.	07 123149
	Solicitud internacional	PCT/US2006/015931
	Fecha inicio fase nacional	25/12/2007
	Trámite	11
	Evento	378
	Actuación	416
	Oficio No.	5289
	Folios	1

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en la Decisión 486 de la Comisión de la Comunidad Andina, el Tratado de Cooperación en Materia de Patentes (PCT), el Reglamento y la Circular Única de la Superintendencia de Industria y Comercio, se envía el extracto de la solicitud a la Oficina de Comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial.

Cúmplase
Dado en Bogotá DC,

17 ENE 2008

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

jfernand