



Industria y Comercio

SUPERINTENDENCIA

Organización CSA

Organización CSA Ltda

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENTARIO

Delegatura de Propiedad Industrial

División de Nuevas Creaciones

SOLICITUD

PCT

NOV 22

PATENTE DE INVENCION

07-123653

21. EXPEDIENTE No.

54. TÍTULO "MÉTODO PARA PREPARAR 3-CIANO-QUINOLINAS E INTER-
MEDIOS HECHOS DE ESTA FORMA"

51. CLASIFICACIÓN INTERNACIONAL

71. SOLICITANTE WYETH

DOMICILIO Nueva Jersey, Estados Unidos de América.

74. APODERADO ALVARO CORREA-ORDONEZ T.I.P. 20.281

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

PETITORIO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-123653- -00000-0000

Industria y Comercio
SUPERINTENDENCIA



2007-11-22 16:14:41 Dep. 2020 NUECREACIONE
PATENTEIYII Eve: 378 FASENACIONALI
PRESENTACION Folios: 238

ción

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE PCT ENTRADA EN FASE NACIONAL

25 dic 2007

①

SOLICITUD DE :

☒ X

Patente de Invención

☐

Patente de Modelo de Utilidad

☒ X

Capítulo I.

☐

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 ORDÓÑEZ

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 y PAPAMICHELAKIS, Maria

Dirección: 18071 de Mondeville, Pierrefonds, Quebec, H9K1R9, Canadá y 1030 Emilien Daoust, Montreal, Quebec H4N2Y9, Canadá, respectivamente

Nacionalidad o Domicilio: Canadienses

⑤

PCT (85)

Solicitud Internacional No. PCT/US2006/016019

Fecha 27-ABR-06

Publicación Internacional No. WO/2006/127205

Fecha 30-NOV-06

⑥

Título (54)

MÉTODO PARA PREPARAR 3-CIANO-QUINOLINAS E INTERMEDIOS HECHOS DE ESTA FORMA

⑦

Clasificación Internacional (51)

C07C 251/50, C07D 209/48, C07D 213/30, C07D 215/54, C07D 401/12

⑧

Prioridad

SI ☒ X

NO ☐

(33) País de Origen

US

(32) Fecha

25-MAY-05

(31) Número de Solicitud

60/684,683

⑨

Comprobante de pago No. 07-86109

Fecha 19-OCT-07

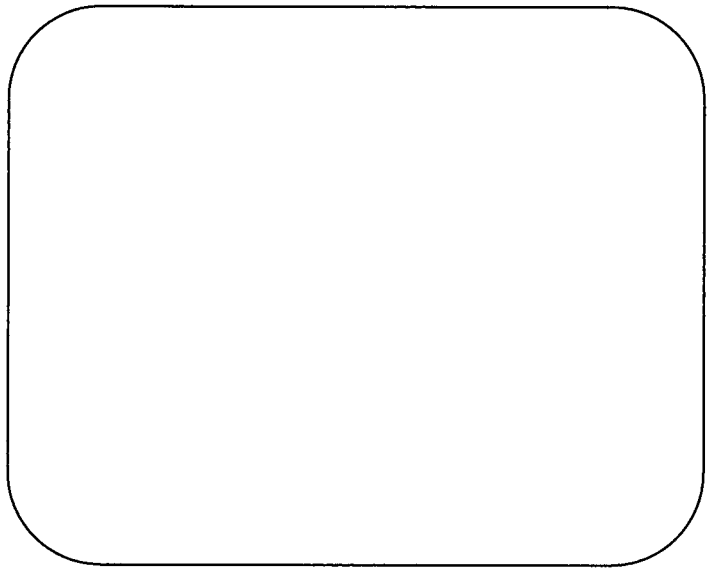
10

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, invitación de corrección de solicitud internacional y respuesta 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

00000021

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-123653- -00000-0000

Fecha: 2007-11-22 16:14:41 Dep. 2020 NUECREACION
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 238

RECIBO OFICIAL DE CAJA : 07 - 86,109
FECHA : OCTUBRE 19 DE 2007

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	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 No. 486/07 de un documento escrito en inglés, el cual para su identificación se sella con el sello del Traductor. Esta es una Traducción Oficial efectuada el día 19 de noviembre de 2007 por la Sra. María Teresa Lara, c.c. 41.568.055 de Bogotá, Traductora Oficial según Resolución No. 01016 del 2 de octubre de 1998, expedida por el Ministerio de Justicia.

= = = = =

Poder otorgado por WYETH respecto de la solicitud de patente titulada "METODO PARA PREPARAR 3-CIANO-QUINOLINAS E INTERMEDIOS HECHOS DE ESTA FORMA". Certificación notarial suscrita por Michelle McGowan, Notario Público del estado de Nueva Jersey, y legalizaciones subsiguientes.

EL PODER Y LA CERTIFICACIÓN NOTARIAL NO SE TRADUCEN POR ENCONTRARSE EN INGLÉS Y ESPAÑOL EN EL DOCUMENTO ORIGINAL.

MARIA TERESA LARA R.
TRADUCTORA OFICIAL
RESOLUCION No. 01016
DE MINISTERIO DE JUSTICIA

MICHELLE L. McGOWAN
Notario Público, Estado de Nueva Jersey
No. 2108903
Habilitada en el Condado de Morris
La comisión expira el 9 de febrero de 2011

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

- 1. País: Estados Unidos de América
- 2. Este documento público ha sido firmado por: Michelle L. McGowan
- 3. actuando en calidad de: Notario Público de Nueva Jersey
- 4. lleva el sello/timbre de: Michelle L. McGowan, Notario

CERTIFICADO

- 5. en Trenton, Nueva Jersey
- 6. el día 1 de mayo de 2007
- 7. por Bradley Abelow, TESORERO DE NUEVA JERSEY
- 8. No. A290271
- 9. Sello/Timbre:
- 10. Firma

(Sello del Estado
de Nueva Jersey)

(Fdo.) Bradley Abelow

= = = = =

La anterior es traducción fiel y completa del documento en referencia, de la cual se deja copia en este archivo para su confrontación.

MARIA TERESA LARA R.
TRADUCTORA OFICIAL
RESOLUCION No. 01016
DE MINISTERIO DE JUSTICIA


María Teresa Lara R.
c.c. 41.568.055 de Bogotá
Traductora Oficial según
Resolución No. 01016 del
2 de octubre de 1998, del
Ministerio de Justicia

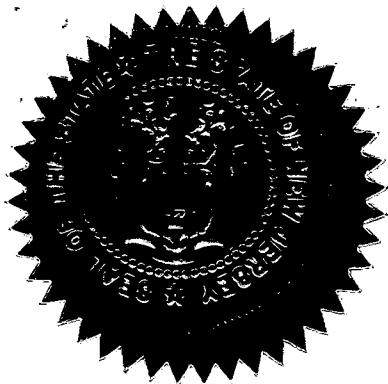
APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA
2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
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. A290271
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/US2006/016019 and entitled "METHODS OF PREPARING 3-CYANO-QUINOLINES AND INTERMEDIATES MADE THEREBY"

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 27th day of April of 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/US2005/016019} ~~METODO PARA PREPARAR 3-CYANO-QUINOLINAS~~ y titulada ~~E INTERMEDIOS HECHOS DE ESTA FORMA"~~

”, 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 27 días del mes de abril de 2007

Firma de la persona que firma el Poder

NOTARIAL CERTIFICATION

On this 27th day of September
2006, the undersigned Notary

CERTIFIES

1. That **William H. Calnan**

of legal age and located at

Five Giralda Faros, Madison, New Jersey 07940 U.S.A.

set his hand on the foregoing document.

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 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.

- 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: The minutes from the Board of Directors Meeting dated April 27, 2006.

CERTIFICACION NOTARIAL

A los 27 días del mes de abril
de 2006, el suscrito Notario

DA FE

- 1 Que **William H. Calnan**

mayor y domiciliado en

**Five Giralda Farms, Madison, Nueva Jersey
07940 Estados Unidos de América**
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 la Junta Directiva
celebrada el 28 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 No. 487/07 de un documento escrito en inglés, el cual para su identificación se sella con el sello del Traductor. Esta es una Traducción Oficial efectuada el día 19 de noviembre de 2007 por la Sra. María Teresa Lara, c.c. 41.568.055 de Bogotá, Traductora Oficial según Resolución No. 01016 del 2 de octubre de 1998, expedida por el Ministerio de Justicia.

= = = = =

Cesión a WYETH del invento titulado "METODO PARA PREPARAR 3-CIANO-QUINOLINAS E INTERMEDIOS HECHOS DE ESTA FORMA". Certificación notarial suscrita por Barbara A. Kiely, Notario Público del estado de Nueva Jersey, y legalizaciones subsiguientes.

AM101519 L1

TERESA LARA R.
TRADUCTORA OFICIAL
RESOLUCION No. 01016
DE MINISTERIO DE JUSTICIA

DECLARACIÓN JURAMENTADA

Yo, Michelle L. McGowan, Asociada para Legalizaciones, Wyeth, certifico por la presente que la copia adjunta ha sido comparada con la Cesión original (para la U.S.S.N. 60/684,683, y cualquier equivalente legal de la misma en un país extranjero, para el invento titulado: "METODO PARA PREPARAR 3-CIANO-QUINOLINAS E INTERMEDIOS HECHOS DE ESTA FORMA"), fechada el 5 de agosto de 2004 de Warren Chew y Maria Papamichelakis a Wyeth y que la citada copia es fiel copia del original.

Dado a los 24 días del mes de abril de 2007, en Madison, Nueva Jersey, Estados Unidos de América.

Wyeth

(Fdo.) Michelle L. McGowan
Michelle L. McGowan
Asociada para Legalizaciones

PARA USO EN COLOMBIA

Estado de Nueva Jersey)
)
Condado de Morris)

MARIA TERESA LARA R.
TRADUCTORA OFICIAL
RESOLUCION No. 01816
DE MINISTERIA

(2) Nombre Completo del Inventor: Maria PAPAMICHELAKIS
Residencia: 1030 Emilien Daoust, Montreal, QC H4N2Y9 Canadá
Ciudadanía: Canadá

por la presente vende, cede y traspasa a la CESIONARIA:

Wyeth
Five Giralda Farms
Madison, Nueva Jersey 07940

y a los sucesores, cesionarios y representantes legales de la CESIONARIA, todo derecho, título e interés para los Estados Unidos y sus posesiones territoriales y en todos los países extranjeros, incluidos todos los derechos a reclamar prioridad, en y sobre el invento titulado:

METODO PARA PREPARAR 3-CIANO-QUINOLINAS E INTERMEDIOS HECHOS DE ESTA FORMA

e inventado por el CEDENTE y los siguientes inventores adicionales, en caso de haberlos:

y el cual se encuentra en la Solicitud Provisional de los E.U. No. 60/684,683 presentada el: 25 de mayo de 2005

[marcar también si se están cediendo solicitud(es) extranjera(s)]

[X] y cualquier equivalente legal de las mismas en un país extranjero,

debiendo insertarse anteriormente la fecha de presentación y número de solicitud de dicha solicitud de los E.U. una vez se conozcan, incluyendo el derecho a reclamar prioridad, incluidas todas y cada una de las mejoras allí divulgadas, y en y sobre todas las Patentes que hayan de obtenerse para dicho invento en virtud de la solicitud anterior o cualquier solicitud provisional, no provisional, de continuación, divisional, de renovación o sustituta de la misma posteriormente presentada, y respecto de Patentes, cualquier reemisión o reexamen de las mismas.

El CEDENTE pacta por el presente que no se ha hecho ni se hará ni se


MARIA TERESA LARA R.
TRADUCTORA OFICIAL
RESOLUCION No. 0787-05
DE MINISTERIO DE JUSTICIA

realizará ninguna cesión, venta, acuerdo o gravamen que pudiese entrar en conflicto con esta cesión.

El CEDENTE autoriza a la CESIONARIA a presentar solicitudes y recibir Patentes para dicho invento en cualquiera de dichos países en su propio nombre, o en nombre del CEDENTE, a su elección.

El CEDENTE pacta y acuerda suscribir u obtener cualquier garantía adicional necesaria del título sobre dicho invento y cualquier Patente que pueda expedirse para el mismo y, en cualquier momento, a solicitud y por cuenta de la CESIONARIA, entregar cualquier testimonio en cualquier interferencia, litigio o proceso relacionado con el mismo y otorgar todos los documentos que puedan ser necesarios o convenientes para perfeccionar el título sobre dicho invento o cualquier Patente que pueda otorgarse para el mismo a la CESIONARIA, sus sucesores, cesionarios u otros representantes legales y, en cualquier momento, a solicitud y por cuenta de la CESIONARIA suscribir cualquier continuación, continuación en parte, solicitud divisional, de renovación o sustituta de la misma, y en cuanto a Patentes y reemisión o reexamen de las mismas, o cualquier otra solicitud adicional de Patente para dicho invento o cualquier parte del mismo, todas las cuales solicitudes y cualesquiera Patentes que se expidan sobre las mismas son por la presente cedidas a la CESIONARIA, y hará todos los juramentos o declaraciones lícitos, y realizará todo los actos lícitos requeridos para adquirir las mismas, sin otra compensación, pero por cuenta de la CESIONARIA, sus sucesores, cesionarios u otros representantes legales.

MARIA TERESA LARA R.
TRADUCTORA OFICIAL
RESOLUCION No. 0146
DE MINISTERIO

El CEDENTE autoriza y solicita al Comisionado de Patentes expedir todas y cada una de las Patentes de los Estados Unidos para dicho invento, resultantes de cualquiera de las anteriores solicitudes a su CESIONARIA.

(Fdo.) Warren Chew
Warren CHEW

5-Ago-2004
Fecha

RECONOCIMIENTO

Estado de CANADA }
 ss:
Provincia de QUEBEC }

A los 5 días del mes de agosto de 2004, compareció personalmente ante mí Warren CHEW, a quien conozco como la misma persona descrita en el instrumento anterior y quien lo otorgó, y reconoció haber otorgado el mismo, por su propia voluntad y para los propósitos allí señalados.

(Fdo.) Line Martin
Notario Público

Line Martin, Notario
Mi comisión es vitalicia

MARIA TERESA LARA R.
TRADUCTORA OFICIAL
RESOLUCION No. 0746
DE MINUTERIA

(Fdo.) Maria Papamichelakis
Maria PAPAMICHELAKIS

5-Ago-2004
Fecha

RECONOCIMIENTO

Estado de CANADA }
 ss:
Provincia de QUEBEC }

A los 5 días del mes de agosto de 2004, compareció personalmente ante mí Maria PAPAMICHELAKIS, a quien conozco como la misma persona descrita en el instrumento anterior y quien lo otorgó, y reconoció haber otorgado el mismo, por su propia voluntad y para los propósitos allí señalados.

(Fdo.) Line Martin
Notario Público

Line Martin, Notario
Mi comisión es vitalicia

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

- 1. País: Estados Unidos de América
- 2. Este documento público ha sido firmado por: Barbara A. Kiely
- 3. actuando en calidad de: Notario Público de Nueva Jersey
- 4. lleva el sello/timbre de: Barbara A. Kiely, Notario

CERTIFICADO

- 5. en Trenton, Nueva Jersey
- 6. el día 1 de mayo de 2007
- 7. por Bradley Abelow, TESORERO DE NUEVA JERSEY
- 8. No. A290288
- 9. Sello/Timbre:
- 10. Firma

(Sello del Estado
de Nueva Jersey)

(Fdo.) Bradley Abelow

TERESA LARA R.
TRADUCTORA OFICIAL
RESOLUCION No. 01016
DE MINISTERIO DE JUSTICIA

= = = = =

La anterior es traducción fiel y completa del documento en referencia, de la cual se deja copia en este archivo para su confrontación.


María Teresa Lara R.
c.c. 41.568.055 de Bogotá
Traductora Oficial según
Resolución No. 01016 del
2 de octubre de 1998, del
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 1ST DAY OF MAY 2007
7. BY: Bradley Abelow, NEW JERSEY TREASURER
8. NO. A290288
9. SEAL/STAMP:
10. SIGNATURE

*Bradley Abelow*

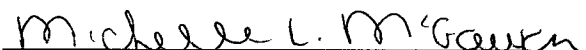
AM101519 L1

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. 60/684,683, and any legal equivalent thereof in a foreign country, for the invention entitled: "METHOD OF PREPARING 3-CYANO-QUINOLINES AND INTERMEDIATES MADE THEREBY) dated August 5, 2004 from Warren Chew and Maria Papamichelakis to Wyeth and that the said copy is a true copy of the original.

Dated this 24th day of April, 2007, at Madison, New Jersey, United States of America.

Wyeth

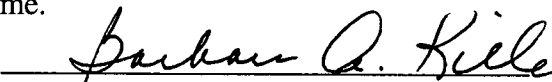

Michelle L. McGowan
Legalization Associate

TO BE USED IN COLOMBIA

ACKNOWLEDGMENT

State of New Jersey)
)
County of Morris)

On this 24th day of April, 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 she acknowledged to me that she executed the same.


Notary Public

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

Assignment of Invention

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 H2V3W8 Canada
Citizenship: Canada

(2) Full Name of Inventor: Maria PAPAMICHELAKIS
Residence: 1030 Emilien Daoust, Montreal, QC H4N2Y9 Canada
Citizenship: Canada

hereby sells, assigns and transfers to ASSIGNEE:

Wyeth
Five Giralda Farms
Madison, New Jersey 07940

18
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:

METHOD OF PREPARING 3-CYANO-QUINOLINES AND INTERMEDIATES MADE THEREBY

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

and which is found in U.S. Provisional Application No. 60/684,683 filed on: May 25, 2005

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

☒ and any legal equivalent thereof in a foreign country,

the date of filing and application number of said U.S. application when known, to be inserted above, 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.

19

5-AUG-2004
Date

ACKNOWLEDGMENT

State of CANADA }
Province of QUEBEC }

On the 5th day of August 2004, 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.

I elect to vote.
 Notary Public
 LINE MARTIN NOTARY
 my commission is for life

M. Papamichelis
Maria PAPAMICHELAKIS

05-Aug-2004

Date

ACKNOWLEDGMENT

State of CANADA }
Province of QUEBEC }

On the 5th day of August 2004, Maria PAPAMICHELAKIS 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.

John Martin
Notary Public
My commission is for life

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(57) Abstract: The present invention relates to methods for preparing substituted 3-cyanoquinolines and intermediates obtained by the methods of the present invention. The methods of the invention comprise reacting an N-aryl-2-propanimide with phosphoryl chloride to produce the substituted 3-cyanoquinolines. The methods further comprise reacting arylamines, orthoformates and active methylenes to produce the N-aryl-2-propenamide.



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WO 2006/127205 A2

- 1 -

**METHOD OF PREPARING 3-CYANO-QUINOLINES
AND INTERMEDIATES MADE THEREBY**

BACKGROUND OF THE INVENTION

Field of the Invention

[0001] The invention relates to a method for the preparation of substituted 3-cyanoquinolines. The 3-cyanoquinolines are made by two separate pathways which include the reaction of arylamines, orthoformates and active methylenes. Both pathways result in the production of N-aryl-2-propene derivatives.

[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 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 Wissner et al. patents are all incorporated herein by reference in their entirety.

[0005] Known methods of making quinolines utilize the thermal cyclization reaction. See, R.W. Sabnis and D.W. Rangnekar, *J. Hetero. Chem.* 29:65 (1992); N.C. Mehta and C.M. Desai, *J. Ind. Chem. Soc.* 55:193 (1978); H. Bredereck, F. Effenberger, H. Botsch and H. Rehn, *Chem. Ber.* 98:1081 (1965); J. Salon, V. Milita, N. Pronayova and J. Lesko, *Monatsh. fur Chem.* 131:293 (2000). Such thermal cyclization reactions require high temperatures (> 240 °C) which limit their practicality for large scale production. In addition, such processes also require high dilution conditions resulting in decreased overall throughput and production. The yields in the thermal cyclization reaction are typically 50% or less but are variable and can range from 19-94%.

- 3 -

[0006] A microwave-assisted methodology for the production of quinolines from aromatic amines has also been described. See C.G. Dave and H.M. Joshipura, *Ind. J. Chem.* 41B:650 (2002).

[0007] Subsequent functionality of hydroxyquinolines typically requires chlorination or halogenation. Chlorination reactions of hydroxyquinolines suffer from the generation of viscous tars and decomposition products that are difficult to remove. The yields in chlorination reaction are variable and range from 24-60%.

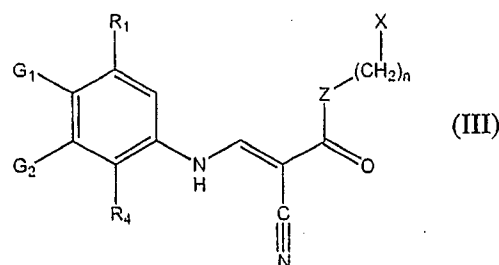
[0008] To date there has not been any description in the art to a catalytic or milder method of preparing quinolines that does not require high temperatures. The present invention provides a novel milder synthesis that overcomes the scale-up issues of the prior art.

SUMMARY OF THE INVENTION

[0009] The present invention provides improved methods of making such substituted 3-cyanoquinolines, intermediates obtained by the methods of the invention, and the substituted 3-cyanoquinolines made by the methods of the invention.

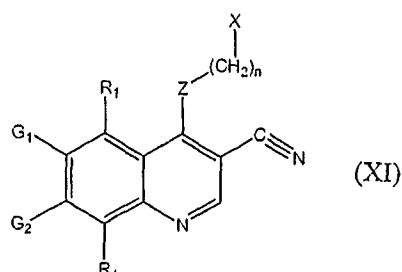
[0010] The methods of making the 3-cyanoquinolines utilize two separate pathways. Both pathways result in the production of N-aryl-2-propene derivatives which are then treated with phosphoryl chloride to provide 3-cyanoquinolines.

[0011] A first embodiment of this invention is directed to a method of preparing a substituted 3-cyanoquinoline which comprises the step of treating an N-aryl-2-propene represented by formula III:



with POCl_3 to form a substituted 3-cyanoquinoline represented by formula XI:

- 4 -



wherein:

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 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 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

- 5 -

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, and benzoylamino; or

X is a radical having the formula: ---A---T---L

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

- 6 -

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; provided that L can be an unsubstituted phenyl ring only when $m > 0$ and T is not -CH₂NH- or -CH₂O-; 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;

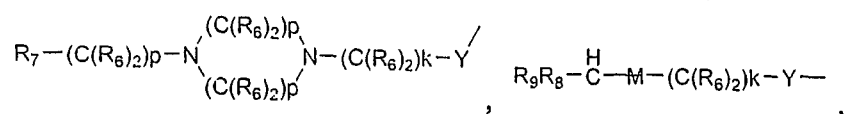
Z is -NH-, -O-, -S-, or -NR-;

R is alkyl of 1-6 carbon atoms, or carboalkyl of 2-7 carbon atoms;

G₁, G₂, R₁, and R₄ 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

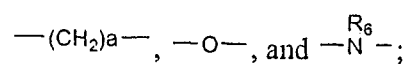
- 7 -

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, 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 optionally G_1 and/or G_2 are independently selected from a protected amino group and R_2-NH- ;

or if any of the substituents R_1 , G_1 , G_2 , or R_4 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



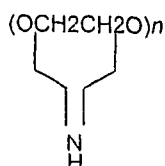
R_7 is $-NR_6R_7$, $-OR_6$, $-J$, $-N(R_6)_3^+$, or $-NR_7(OR_6)$;

M is $>NR_6$, $-O-$, $>N-(C(R_6)_2)_p-NR_6R_6$, 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

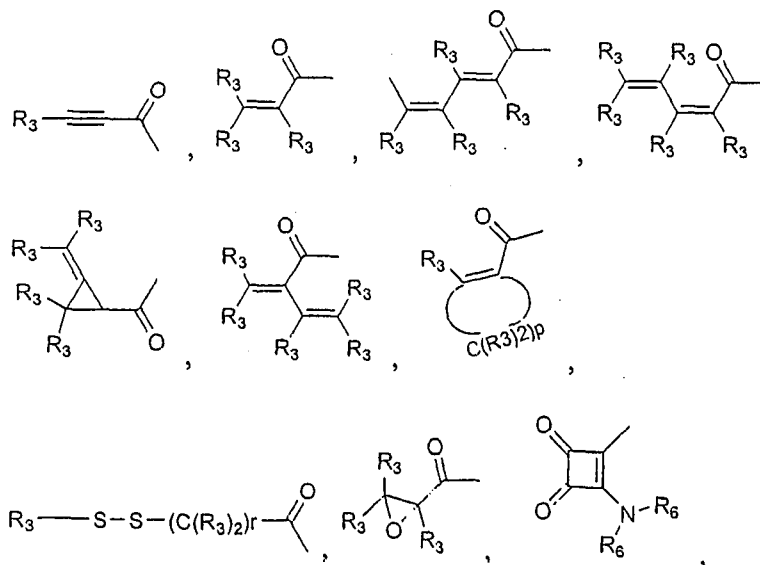
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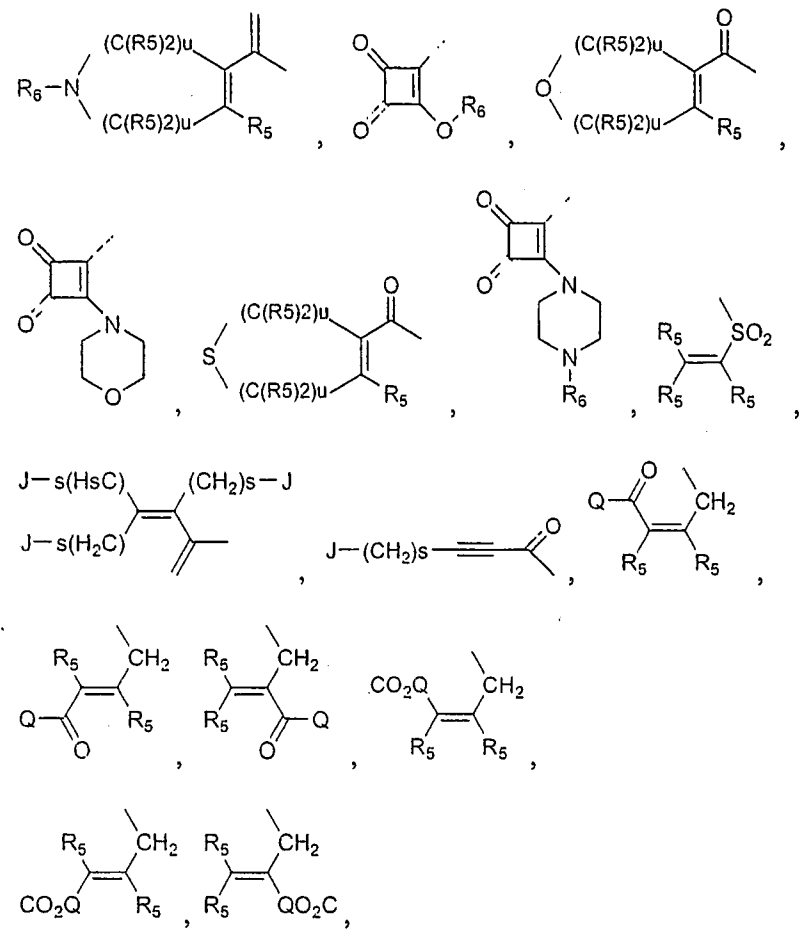


wherein Het is optionally mono- or di-substituted on carbon or nitrogen with R_6 , optionally mono- or di-substituted on carbon with hydroxy, $-N(R_6)_2$, or $-OR_6$, optionally mono or di-substituted on carbon with the mono-valent radicals $-(C(R_6)_2)_sOR_6$ or $-(C(R_6)_2)_sN(R_6)_2$, and optionally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

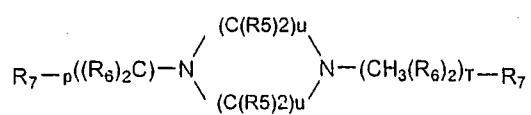
R₆ is hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, cycloalkyl of 1-6 carbon atoms, carboalkyl of 2-7 carbon atoms, carboxyalkyl (2-7 carbon atoms), phenyl, or phenyl optionally substituted with one or more halogen, alkoxy of 1-6 carbon atoms, trifluoromethyl, 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;

R_2 , is selected from the group consisting of



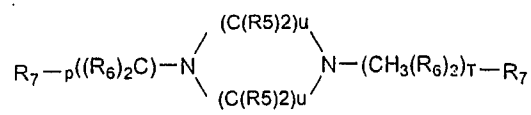


R₃ is independently hydrogen, alkyl of 1-6 carbon atoms, carboxy, carboalkoxy of 1-6 carbon atoms, phenyl, carboalkyl of 2-7 carbon atoms,



R₇-(C(R₆)₂)_s-, R₇-(C(R₆)₂)_p-M-(C(R₇)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,



$R_7-(C(R_6)_2)_s-$, $R_7-(C(R_6)_2)_p-M-(C(R_6)_2)_r-$, $R_8R_9-CH-M-(C(R_6)_2)_r-$, or
Het-(C(R₆)₂)_q-W-(C(R₆)₂)_r-; R₈, and R₉ are each, independently, -(C(R₆)₂)_r NR₆
R₆, 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;

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;

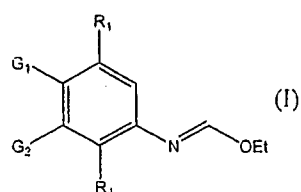
or a pharmaceutically acceptable salt thereof, provided that

when R₆ 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; and provided that when Y is -NR₆- and R₇ is -NR₆R₆--
N(R₆)₃⁺, or -NR₆(OR₆), then g=2-6; when M is -O- and R₇ is -OR₆ then p=1-4;
when Y is -NR₆- 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 and
when W is a bond with Het bonded through a nitrogen atom and Y is --O-- or -
NR₆- then k=2-4.

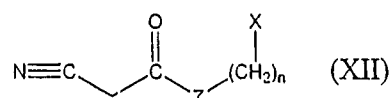
[0012] Unless stated otherwise herein, all variables set forth above, e.g. G₁, G₂,
R₁, R₄, Z, X and n, apply to the formula and schemes set forth throughout this
application.

[0013] In another embodiment of this invention the N-aryl-2-propene compound
of formula III may be formed by condensing an N-arylformimide of formula I

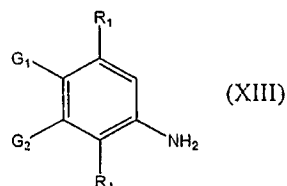
- 11 -



with an active methylene of formula XII

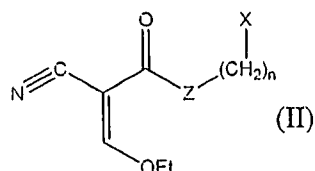


[0014] In yet another embodiment, the N-arylformimidate of formula I may be formed by reacting an arylamine of formula (XIII).

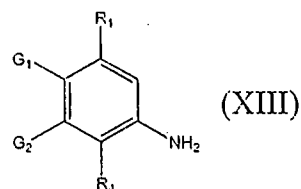


with $\text{CH}(\text{OEt})_3$

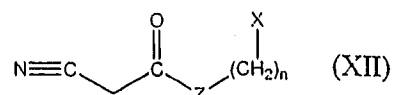
[0015] In another embodiment of the invention the N-aryl-2-propene of formula III may be formed by reacting an alkoxymethylene derivative of formula II.



with an arylamine of formula XIII



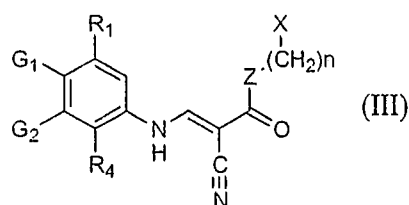
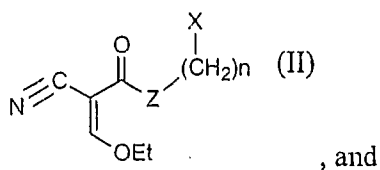
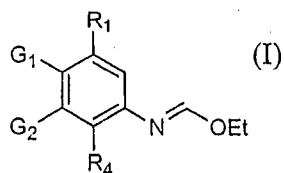
[0016] In a further embodiment of the invention, the alkoxymethylene of formula II may be formed by condensing an active methylene of formula XII



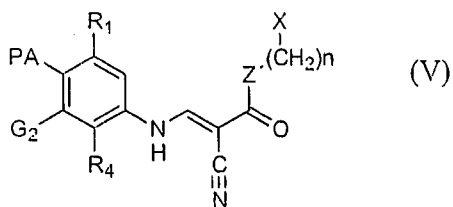
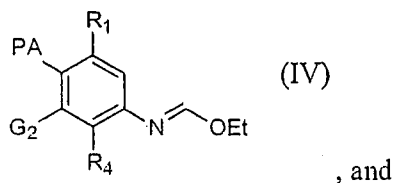
- 12 -

with $\text{CH}(\text{OEt})_3$.

[0017] The present invention also provides for the intermediates produced by the methods of the present invention. In one embodiment of the invention, the intermediates are of formulas I, II and III below.



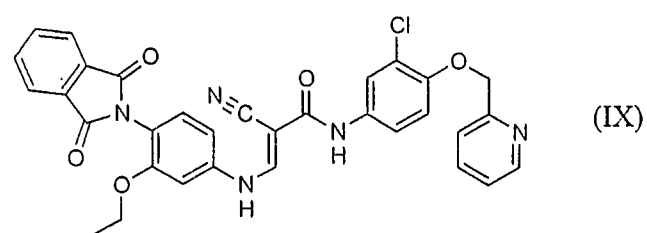
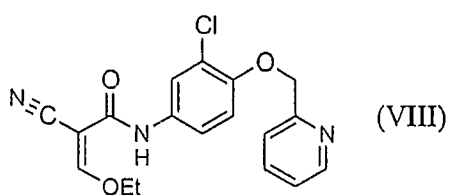
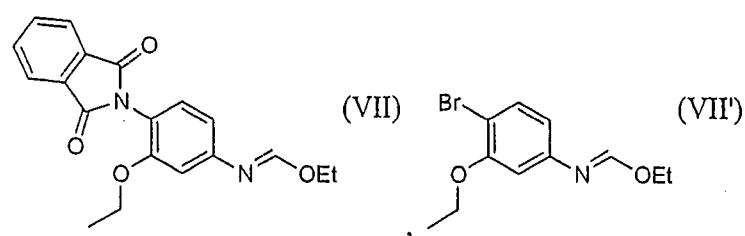
[0018] In another embodiment of the invention, the intermediates are of formulas IV and V below:



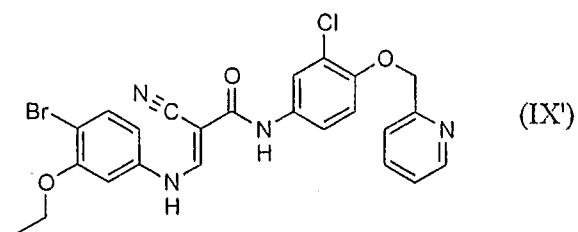
wherein PA is a protected amino group.

[0019] In a further embodiment of the invention, the intermediates are of formulas VII, VII', VIII, IX and IX' below:

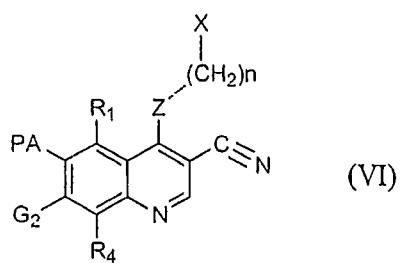
- 13 -



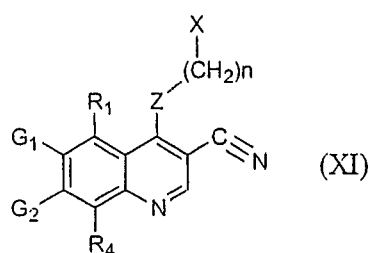
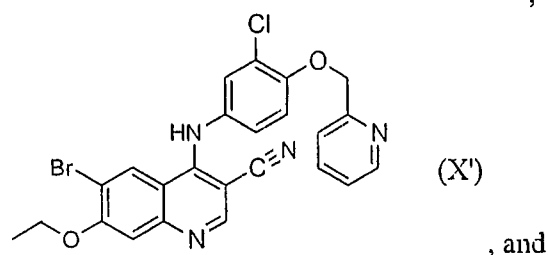
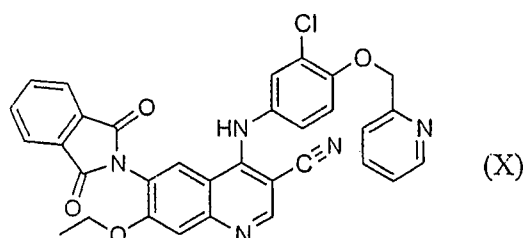
and



[0020] The present invention also provides for 3-cyanoquinoline derivatives produced by the methods of the present invention. Accordingly, the invention provides a 3-cyanoquinoline of formulas VI, X, X' and XI produced by the methods of the present invention:



- 14 -



DETAILED DESCRIPTION OF THE INVENTION

[0021] The present invention provides improved methods of making substituted 3-cyanoquinolines, intermediates obtained by the methods of the invention, and substituted 3-cyanoquinolines made by the methods of the invention.

[0022] As noted above, the methods of making the 3-cyanoquinolines utilize two separate pathways. Both pathways include the reaction of arylamines, orthoformates and active methylenes and both pathways result in the production of N-aryl-2-propene derivatives. The methods of the present invention avoid many of the hindrances of the prior synthetic pathways, since they do not involve heating to high temperatures or using microwave irradiation. Thus, the current methods can be easily adapted to large-scale preparation of 3-cyanoquinolines. Also, the chlorination step used in prior synthetic methods is avoided. This is an improvement because the chlorination of quinolines are known to suffer from the formation of viscous tars and decomposition products, which result in lower yields of the desired product and impurities that are difficult to remove.

- 15 -

Therefore, syntheses involving chlorination of quinolines are not very practical for use in large-scale synthesis of 3-cyanoquinolines. The current method is also advantageous because it readily allows for the synthesis of many 3-cyanoquinolines derivatives with varying moieties substituted at the 4-position of the quinoline ring system.

[0023] In one embodiment of the invention, the arylamine includes a protected amino group such as phthalimide, cyclic imides, maleimide, 2,3-dichloromaleamide, succinimide, dihydrophthalimide, and 2,5-dimethylpyrrole. Arylamines which may be used in the methods of the present invention are described, for example, in United States Patent No. 4,873,338 of Wiesen et al., and United States Patent No. 4,617,316 of Plummer et al., all of which are incorporated herein by reference in their entirety.

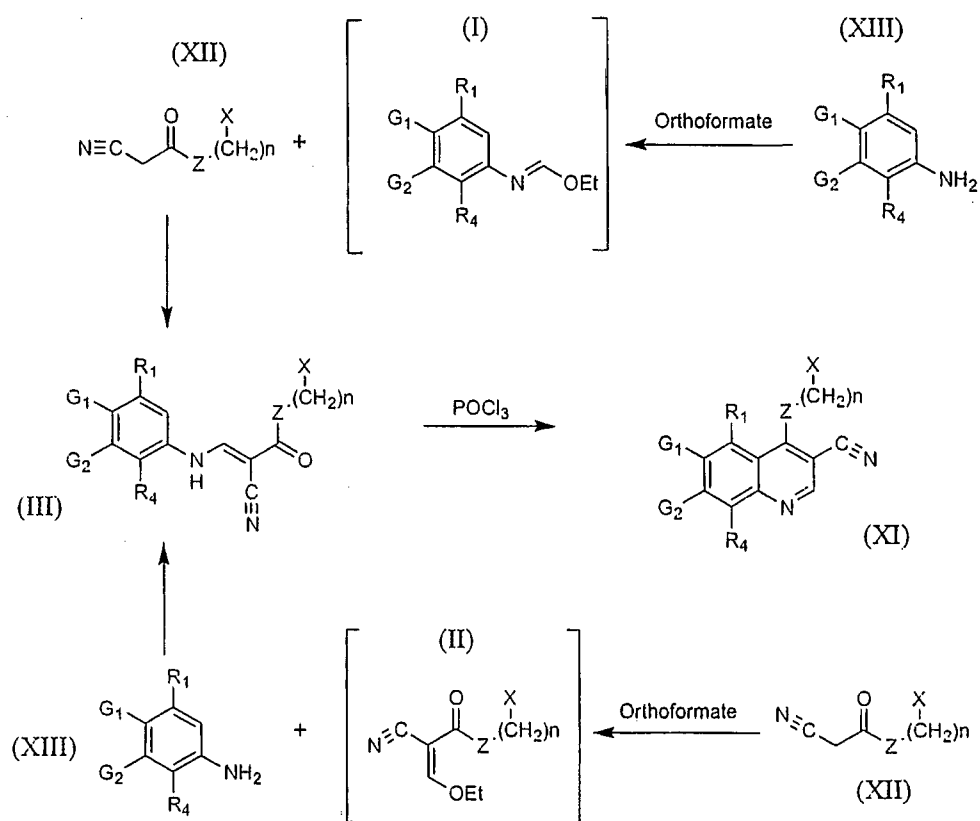
[0024] In one embodiment of the invention, an arylamine is reacted with an orthoformate to produce an N-arylformimidate, which is then condensed with an active methylene to produce an N-aryl-2-propene.

[0025] In another embodiment of the invention, an active methylene compound is condensed with an orthoformate to produce an alkoxymethylene derivative which is then reacted with an arylamine to give an N-aryl-2-propene. As mentioned above, in both schemes, the N-aryl-2-propene is then treated with phosphoryl chloride to produce the 3-cyanoquinolines of the present invention. In yet another embodiment, the arylamine includes at least one protected amino group.

[0026] One embodiment of the invention is depicted in Scheme 1 below which shows both pathways of the methods of the invention.

- 16 -

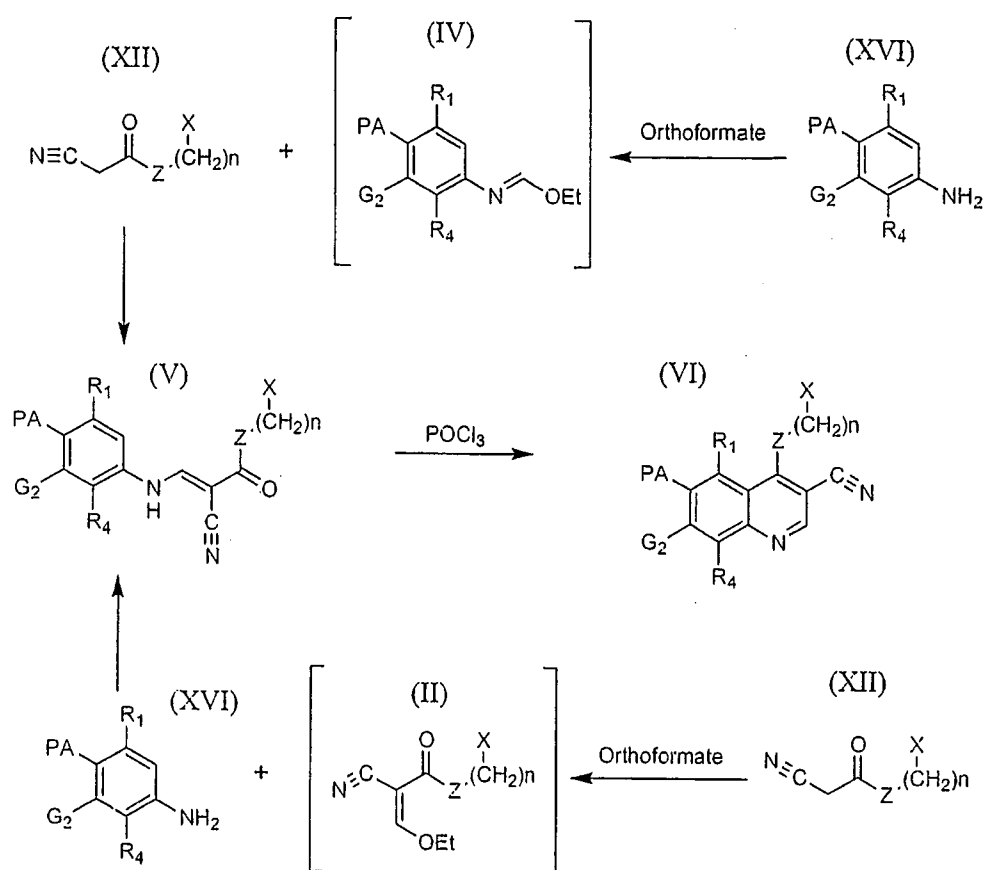
Scheme 1



[0027] Another embodiment of the invention is depicted by Scheme 2 below which shows the embodiments of the two pathways of the methods of the present invention.

- 17 -

Scheme 2

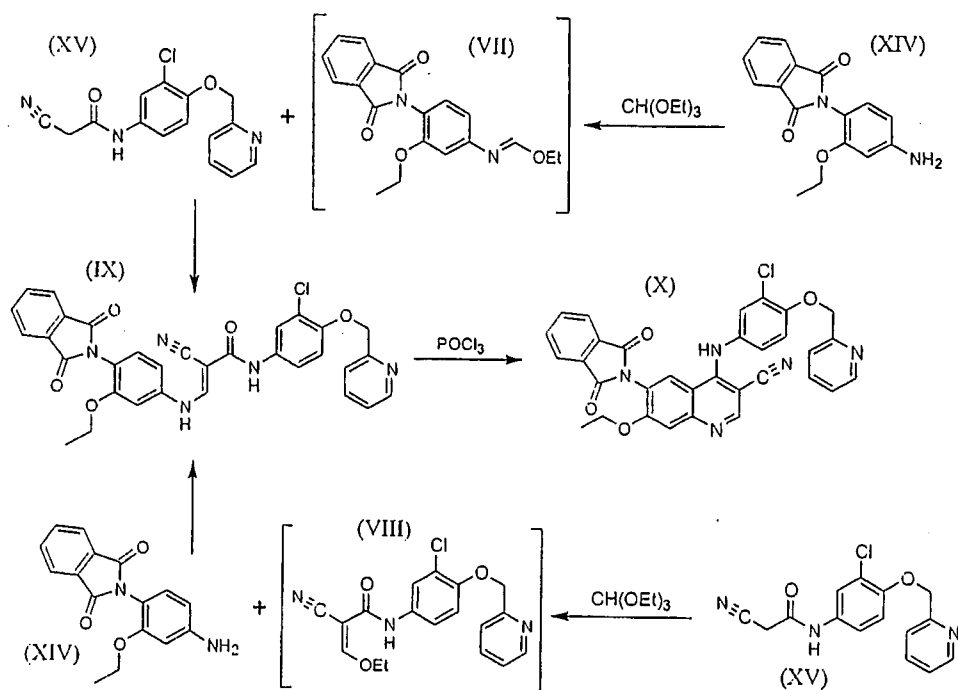


where PA represents a protected amino group.

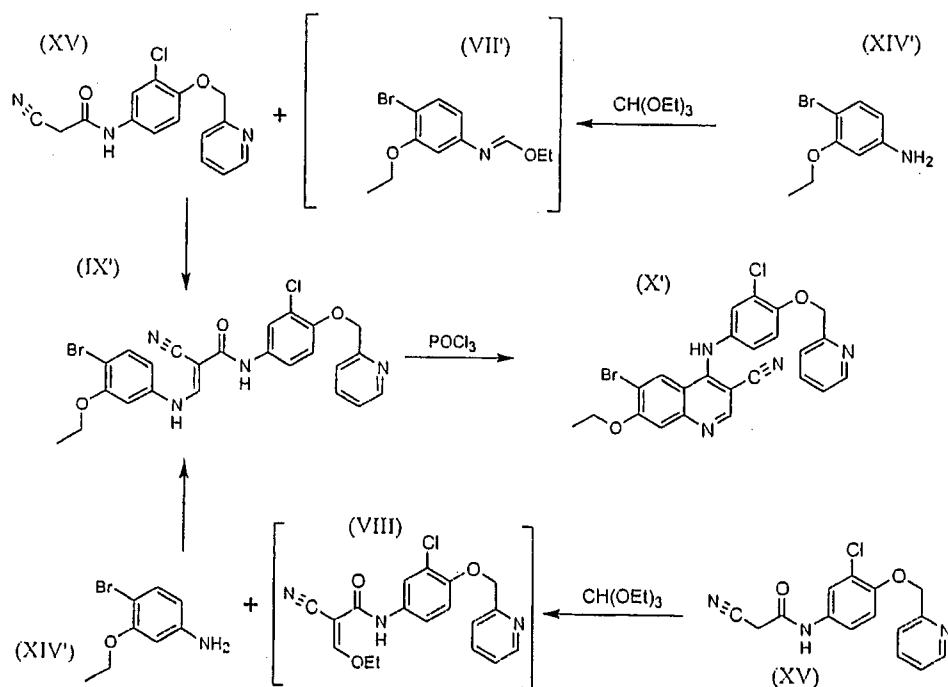
[0028] Specific embodiments of the present invention are depicted in Schemes 3a and 3b below which show embodiments of the two pathways of the methods of the present invention. In scheme 3a, G_1 is a protected amine. Scheme 3b illustrates where G_1 is bromo. Compounds with halogens at the 6-position can be readily reacted with reagents, such as amines and alcohols, to form other derivatives encompassed within the present invention.

- 18 -

Scheme 3a

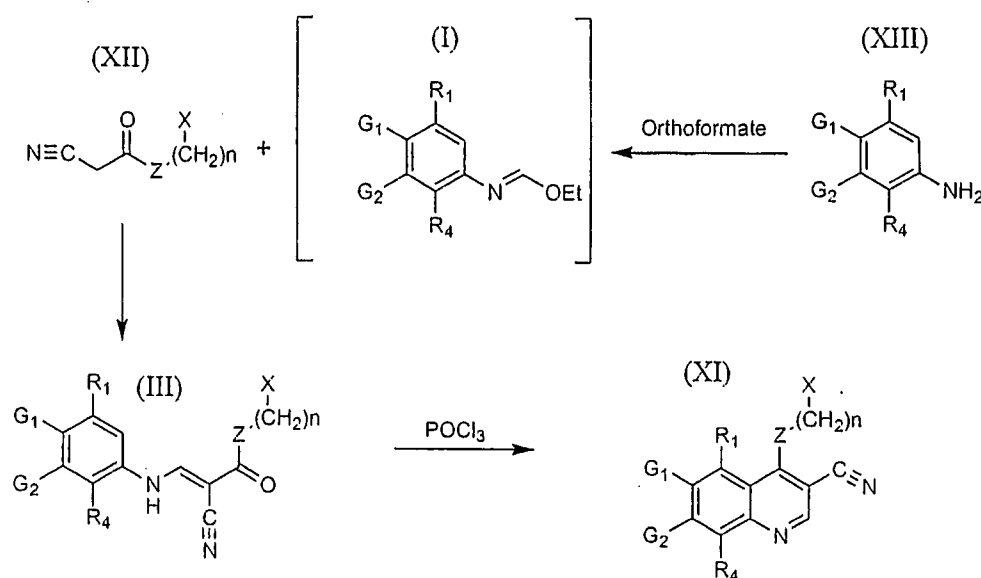


Scheme 3b



[0029] Scheme 1 includes two embodiments of the invention, which represent the two separate pathways, a first of which is depicted by Scheme 4 below.

Scheme 4



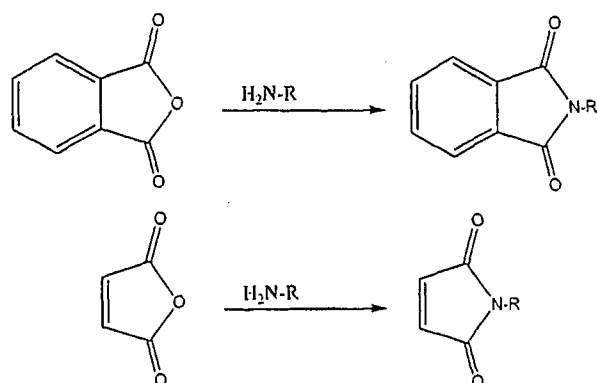
wherein X, Z, G₁, G₂, R₁ and R₄ are as described previously.

[0030] The term protected amino group (PA) refers to an amine or amino group having or forming a “protecting group” which 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. Exemplary protected amino groups include acetamides, benzamides, cyclic imides (e.g., phthalimide, maleimide, 2,3-dichloromaleimide, succinimide, dihydrophthalimide), pyrroles (e.g. 2,5-dimethylpyrrole), tert-butoxycarbonyl protected amine and benzyloxycarbonyl protected amide.

[0031] Cyclicimides are particularly useful protecting groups for masking primary amines. They are formed by reacting primary amine to be masked with a

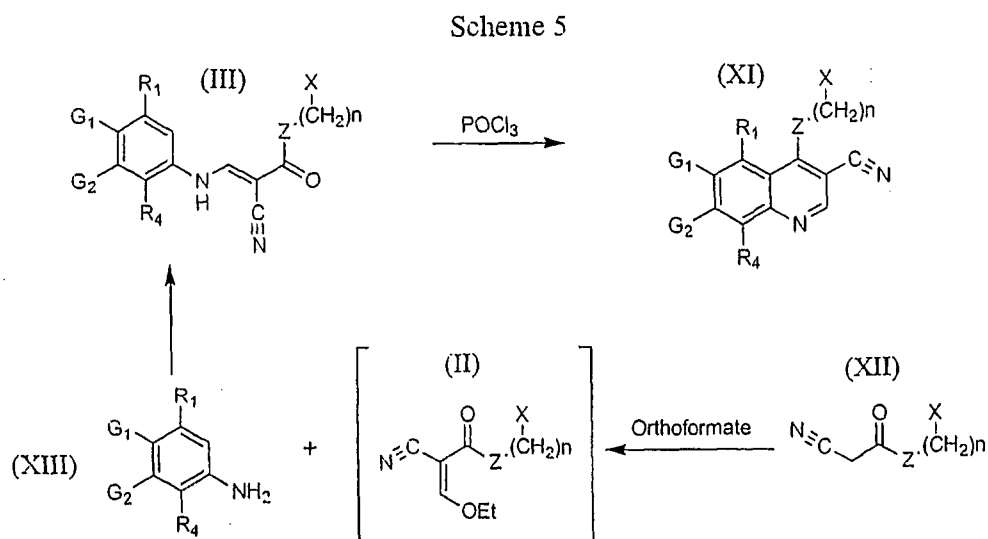
- 20 -

reagent such as phthalic anhydride or maleamic anhydride, thereby incorporating the amine into the cyclicimide, as shown below.



[0032] Thereafter, the cyclicimides can be cleaved under a variety of conditions, such as NH_4OH , to give the primary amine in good yield. See *Green* at pp. 358-359. In one embodiment of the present invention NH_4OH is used to cleave the phthalimide protecting group. This is best accomplished using multiple equivalents of NH_4OH relative to the protected compound, wherein 10 equivalents are effective, with 25 equivalents being even more efficient. 2,5-Dimethylpyrrole operates similarly.

[0033] The second embodiment of Scheme 1 is depicted in Scheme 5 below.



wherein X, Z, G_1 , G_2 , R_1 and R_4 are as described previously.

- 21 -

[0034] In another embodiment of Schemes 4 and 5, 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 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, and benzoylamino.

[0035] In another embodiment of the invention, X is a radical having the

formula: —A—T—L

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;

- 22 -

[0036] T is bonded to a carbon of A and is:

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

[0037] 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; provided that L can be an unsubstituted phenyl ring only when $m > 0$ and T is not $-\text{CH}_2\text{NH}-$ or $-\text{CH}_2\text{O}-$; or

[0038] 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,

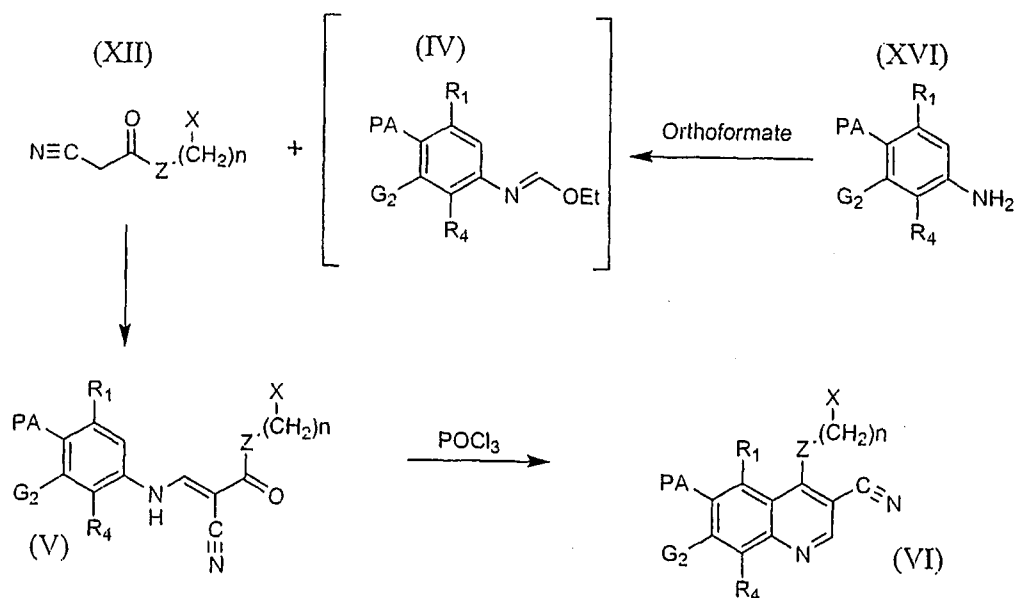
- 23 -

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.

[0039] In a further embodiment of the methods depicted by Schemes 4 and 5, G_1 is a protected amino group (PA). In a yet another embodiment of the invention, the protected amino group is phthalimide.

[0040] The two embodiments of the pathways shown in Scheme 2 above, are depicted in Scheme 6 and 7 below.

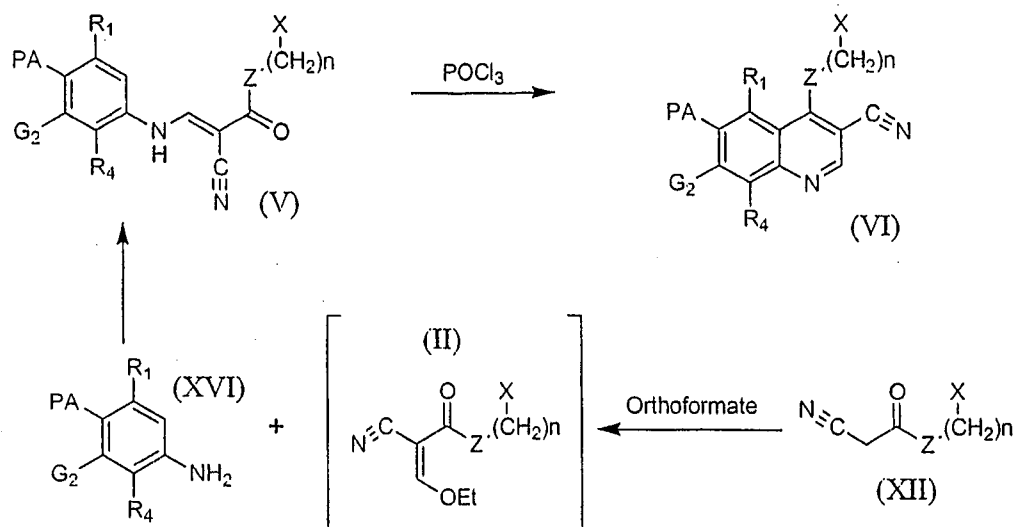
Scheme 6



and

- 24 -

Scheme 7

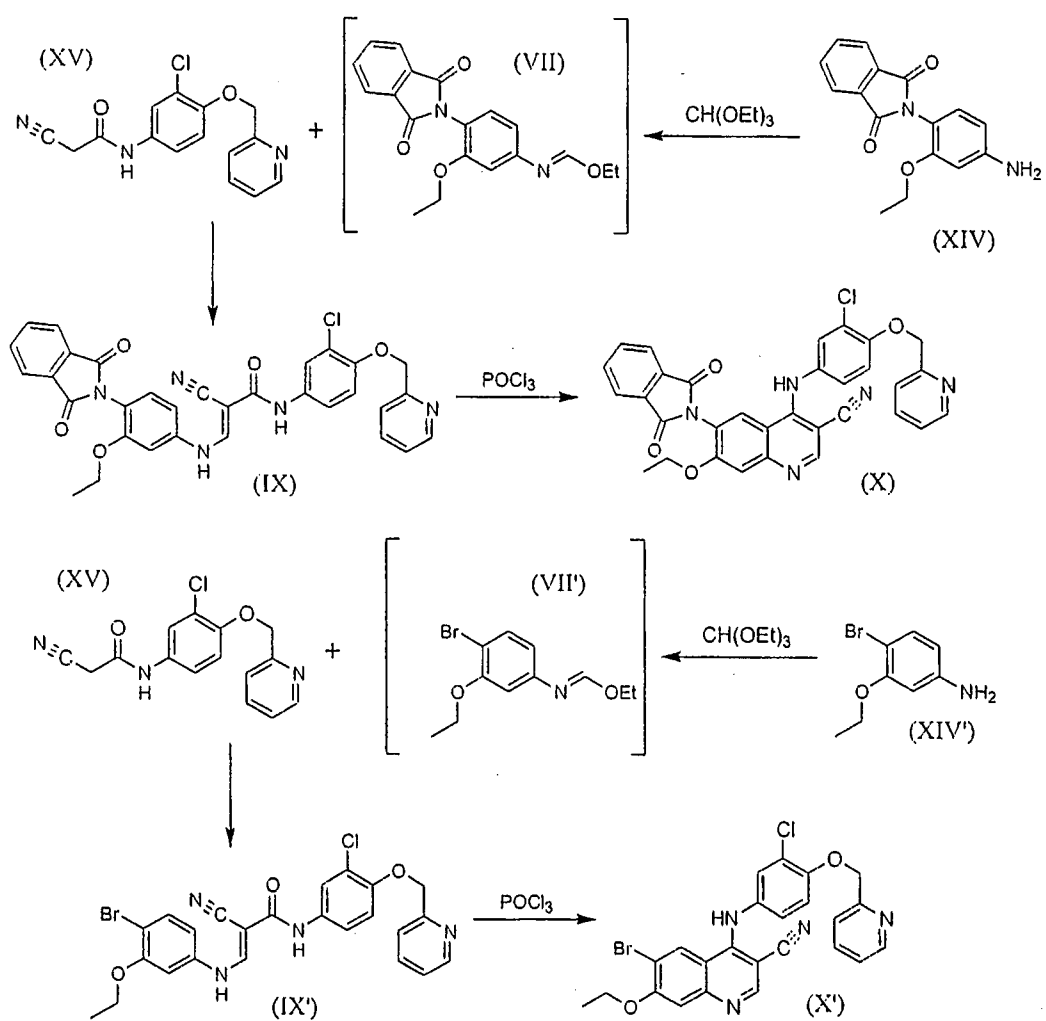


wherein X, Z, G_2 , R_1 and R_4 are as described above for Schemes 4 and 5, and wherein PA is a protected amino group. In a particularly preferred embodiment of Schemes 6 and 7, PA is phthalimide.

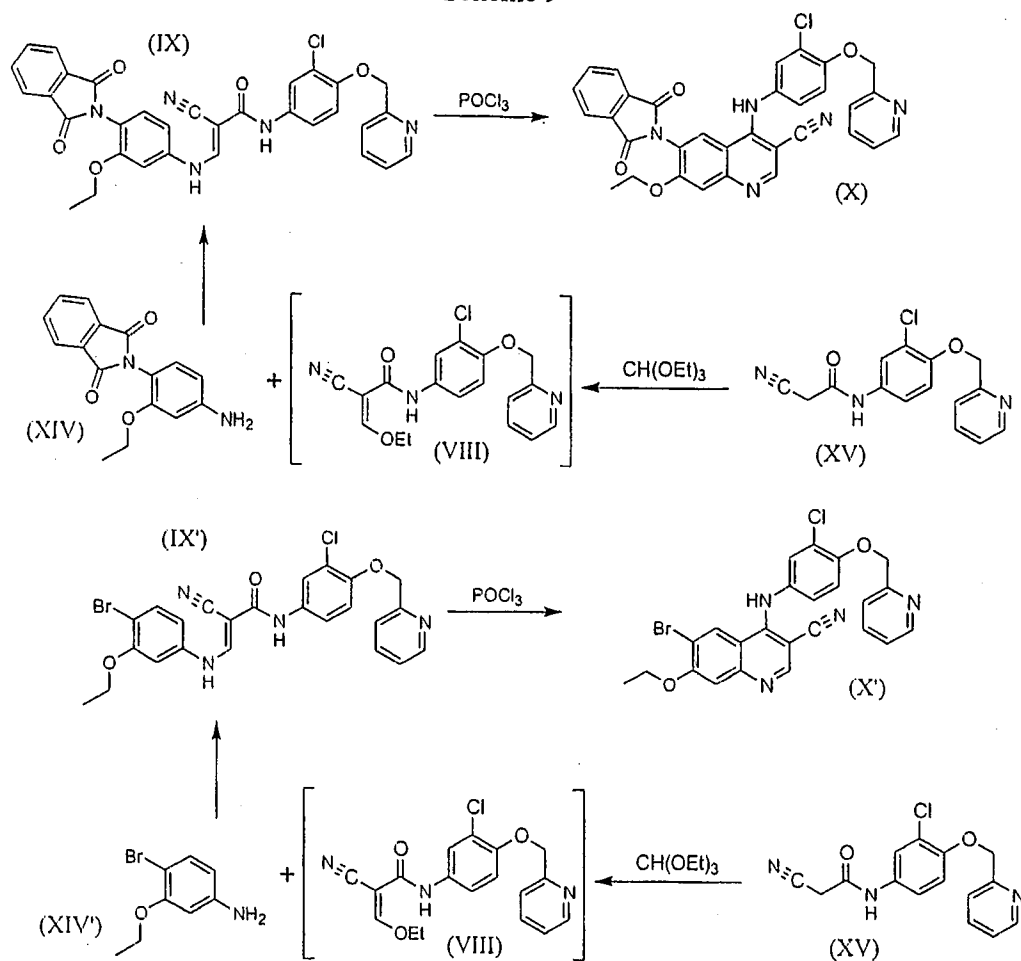
[0041] The four embodiments depicted in Schemes 3a and 3b above are separately depicted in Schemes 8 and 9 below.

- 25 -

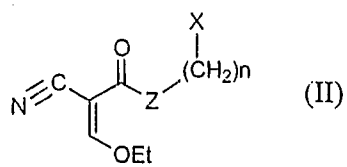
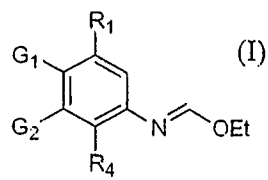
Scheme 8



Scheme 9

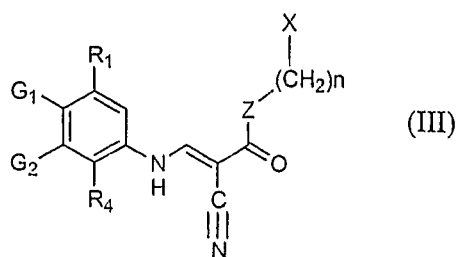


[0042] The present invention also provides for the intermediates produced by the methods of the present invention. In one embodiment of the invention, the intermediates are of formulas I, II and III below.



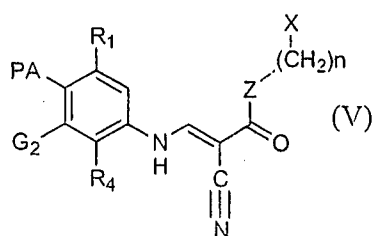
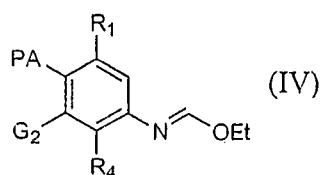
, and

- 27 -



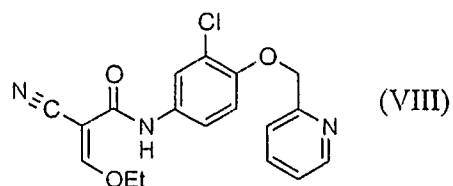
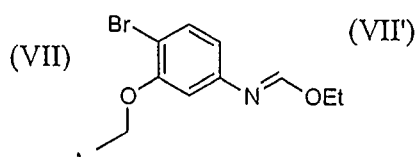
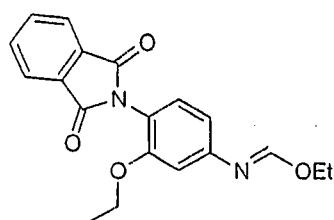
wherein X, Z, G₁, G₂, R₁ and R₄ are as previously described.

[0043] In another embodiment of the invention, the intermediates are of Formulas IV and V below:

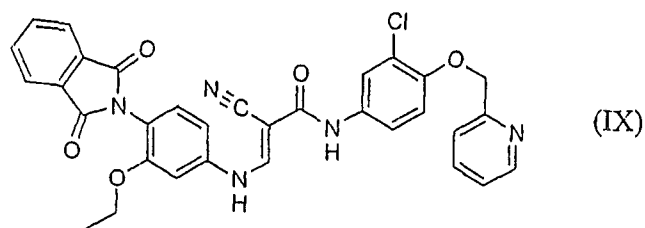


wherein X, Z, PA, G₂, R₁ and R₄ are as defined previously.

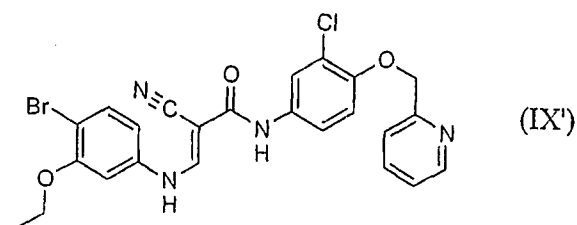
[0044] In a further embodiment of the invention, the intermediates are compounds represented by the Formulas VII, VII', VIII, IX and IX' below:



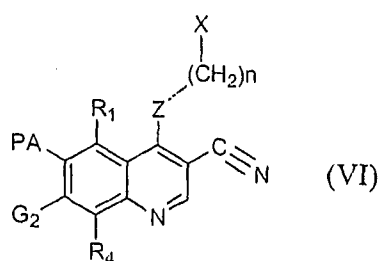
- 28 -



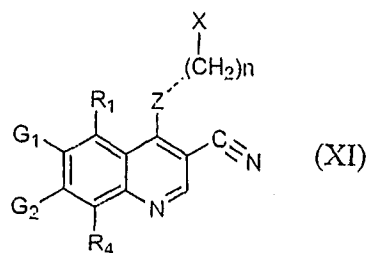
, and



[0045] The present invention also provides for 3-cyanoquinoline derivatives produced by the methods of the present invention. Accordingly, the invention provides a 3-cyanoquinoline of Formula VI, produced by the methods depicted in Schemes 6 and 7 above, and a 3-cyanoquinoline of Formula XI produced by the methods depicted in Schemes 4 and 5 above:



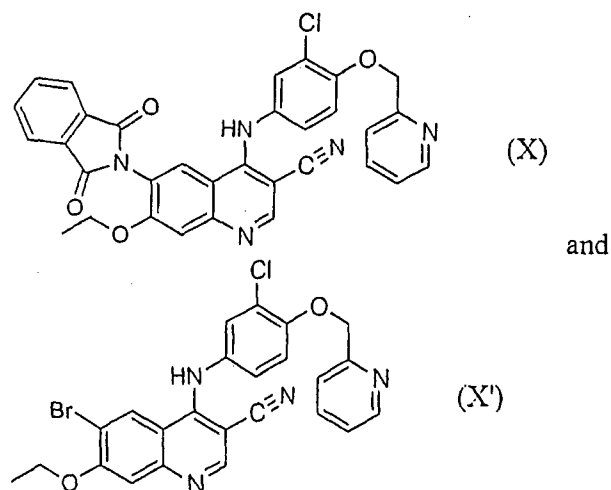
wherein X, Z, PA, G₂, R₁ and R₄ are as previously described;



wherein X, G₁, G₂, R₁ and R₄ are as previously described.

[0046] Specific 3-cyanoquinolines of the invention are represented by the compounds of formula X and X'.

- 29 -

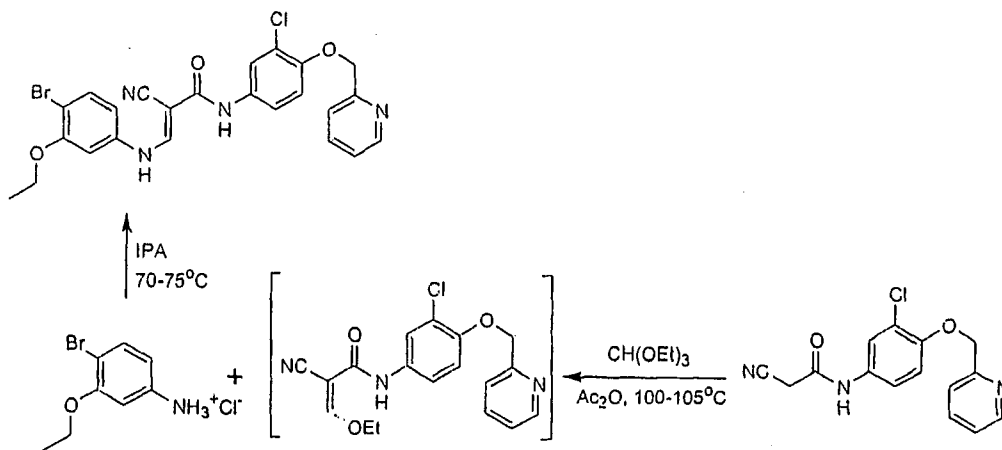


EXAMPLES

[0047] The following examples are offered to illustrate, but not to limit the present invention.

Example 1

Preparation of (E/Z)-3-(4-bromo-3-ethoxyanilino)-N-[3-chloro-4-(2-pyridinylmethoxy)phenyl]-2-cyano-2-propenamide.



[0048] To a 3-necked 50 ml flask was charged cyanoacetamide (0.50 g, 1.7 mmole) in triethylorthoformate (2.45g, 2.75 ml, d=0.89 g/ml). The mixture was heated to 50-60 °C and acetic anhydride (0.42g, 0.39 ml, 4.1 mmole, 2.5 eq, d=1.08 g/ml) was added. The flask was heated to 100-105 °C and held for a

- 50 -

minimum of 4 h and then cooled to 70-75°C. A solution of 3-ethoxy-4-bromoaniline hydrochloride (0.42g, 1.67 mmole) in isopropanol (5 ml) was added. The mixture was stirred for 3 h and cooled to room temperature. Water was added and the mixture extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate and stripped to dryness. The residue was dissolved in acetonitrile (10 ml) and water (10 ml) was added dropwise to precipitate the product. The product was filtered on a Buchner funnel to give 0.11g of the title compound.

Example 2

Preparation of 3-ethoxy-4-(N-phthalimidyl)nitrobenzene.

[0049] To a 5-L multi-necked flask equipped with mechanical stirrer, temperature probe, condenser and nitrogen protection was charged 2-amino-5-nitrophenol (116 g, 0.75 mole) and phthalic anhydride (223 g, 1.51 mol, 2.0 eq) followed by glacial acetic acid (1.13 L). The reaction mixture was heated to (115-120 °C) and held for 2.5-3 hr until the reaction was complete by HPLC or TLC. The mixture was cooled to room temperature and water was added (0.5 L) over 10 mins. The mixture was held for 1 h and the solids were filtered on a 15 cm diameter Buchner funnel and washed with water (2 x 0.5 L). The solids were transferred back to the 5-L flask, water was added (2.32 L) and the mixture stirred at room temperature for a minimum of 30 mins. The mixture was filtered and washed with water (2 x 0.5 L). The product was dried at 60 °C for 23 hr in a vacuum oven to give 210 g (99%) as a tan solid. ¹H NMR: δ (DMSO-d₆) 10.98 (s, 1H, OH), 8.10-7.85 (m, 4H, phthalimide), 7.82 (d, 1H, Ar), 7.80 (d, 1H, Ar), 7.63 (dd, 1H, Ar).

[0050] To a 5-L multi-necked flask equipped with mechanical stirrer, temperature probe, condenser and nitrogen protection was charged N-(2-hydroxy-4-nitrophenyl)phthalimide (208 g, 0.73 mol) and DMF (1.04 L). The mixture was stirred at room temperature until a solution was obtained. Potassium carbonate (0.15 kg, 1.5 eq.) was added in portions until the pH of the mixture was 9. The suspension was heated to 60-65 °C and ethyl bromide (88 g, 0.80 mol, 1.1 eq.) was added dropwise over 20 min. After complete addition, the mixture was held

- 51 -

for a minimum of 30 mins and then cooled to room temperature. Water (2.08 L) was added over 30 mins while maintaining the pot temperature at 20-25 °C and the mixture was held for an additional 1hr. The mixture was filtered on a 15 cm diameter Buchner funnel and washed with warm (45-50 °C) water (3 x 0.2 L). The wet cake was transferred back to the 5-L flask, water (2.08 L) was added and the mixture slurried for a minimum of 30 mins at 45-50 °C. The mixture was filtered and washed with water (0.2 L). The product was dried at 60 °C for 20 hr in a vacuum oven to give the titled compound (154 g, 67%). ¹H NMR: δ (DMSO-d₆) 8.10-7.92 (m, 6H, Ar), 7.73 (d, 1H, Ar), 4.23 (q, 2H, CH₃CH₂O), 1.21 (t, 3H, CH₃CH₂O).

Example 3

Preparation of N-[3-Chloro-4-(2-pyridinylmethoxy)]phenyl-2-cyanoacetamide.

[0051] In a 12-L multi-necked flask, 2-pyridyl carbinol (0.13 kg, 1.19 mole, 1.05 eq) was dissolved in acetonitrile (0.88 L) and to it was added potassium hydroxide flakes (85%) (80 g, 1.25 eq). The resulting suspension was warmed to 35 °C. A solution of 3-chloro-4-fluoronitrobenzene (0.20 kg, 1.14 mol) in acetonitrile (1.0 L) was added at 35-40 °C. The mixture was held for 18 h until reaction completion. The mixture was then cooled back to 20-25 °C, quenched with water (4 L) and the resulting slurry was filtered and washed with water (3 x 200 mL). The resulting product was isolated as a tan solid (251 g, 84% yield).

[0052] A mixture of 3-chloro-4-(2-pyridylmethoxy)nitrobenzene (0.149 kg, 0.56 mole) and 2% (w/w) of 5% Pt/C (6.0 g, 50% water wet) in tetrahydrofuran (0.895 L) was hydrogenated in a 2-L stainless steel Parr reactor at 25 psi, 25 °C for a minimum of 8 h. The mixture was filtered through a celite pad (50 g, 15 cm diameter) and washed with tetrahydrofuran (0.45 L). The filtrate was distilled to a volume of ~0.30 L and the concentrate was transferred to a 2-L multi-neck flask and used as is in the next step.

[0053] To the 2-L flask equipped with mechanical stirrer, temperature probe, claisen head and condenser was added ethylcyanoacetate (0.421 kg, 3.72 mole, 6.6 eq.). The reaction mixture was heated to (100-115 °C) while removing tetrahydrofuran and ethanol. The temperature was raised to ~125 °C and the

- 32 -

mixture was held for a minimum of 24 h until the aniline starting material was consumed and no distillate was collected. The mixture was cooled to room temperature over 1 h. At 50-60 °C, solids crystallized out and ethyl acetate (0.15 L) was added. The mixture was further cooled to 0-10 °C and held for 1 h. The mixture was filtered on a 15 cm diameter Buchner funnel and washed with 50 mL of the filtrate followed by pre-cooled (0-10 °C) ethyl acetate (0.15 L). The product was dried at 60 °C for a minimum of 16 h in a vacuum oven to give the titled compound (0.12 kg, 71%) as a brown solid. The product was purified by slurrying in cold ethyl acetate (1-1.3 volumes) for 1 hr. ¹H NMR: δ (DMSO-d₆) 10.31 (s, 1H, NH), 8.58 (dd, 1H, Ar), 7.86 (dt, 1H, Ar), 7.75 (d, 1H, Ar), 7.55 (d, 1H, Ar), 7.39-7.32 (m, 2H, Ar), 7.21 (d, 1H, Ar), 5.25 (s, 2H, OCH₂Pyr), 3.88 (s, 2H, NCCH₂CO).

Example 4

Preparation of (E/Z) 3-[3-ethoxy-4-(N-phthalimidyl)]anilino-N-[3-chloro-4-(2-pyridinylmethoxy)]phenyl-2-cyano-2-propenamide.

[0054] A mixture of 3-ethoxy-4-(N-phthalimidyl)nitrobenzene (0.135 kg, 0.43 mole) and 4% (w/w) of 10% Pd/C (5.42 g, 50% water wet) in tetrahydrofuran (1.08 L) was hydrogenated in a 2-L stainless steel Parr reactor at 70 psi, 50 °C for a minimum of 10 h. The mixture was filtered through a celite pad (100 g, 15 cm diameter) into a 1-neck 3-L flask and washed with tetrahydrofuran (3 x 0.14 L). The filtrate was distilled to a volume of ~0.55 L and to the concentrate was added n-propanol (0.75 L). The mixture was distilled to a volume of ~0.41 L and the concentrate was used as is in the next step. Taking an aliquot and concentrating to dryness obtained an analytical reference sample.

[0055] The concentrate was transferred to a 3-L multi-necked flask equipped with an agitator, temperature probe, condenser and nitrogen protection. The flask was charged with n-propanol (0.91 L) followed by N-[3-Chloro-4-(2-pyridinylmethoxy)]phenyl-2-cyanoacetamide (119 g, 0.39 mole, 0.91 eq.). The mixture was heated to 75-80 °C. The first of three portions of triethylorthoformate (64.3 g, 72 ml, 0.43 mole, d=0.89 g/ml) was added and the mixture heated to reflux (95-100 °C). After 2.5 h, the second portion of

- 33 -

triethylorthoformate was added (64.3 g, 72 ml, 0.43 mole). After 19.5 hr, the third portion of triethylorthoformate was added (64.3 g, 72 ml, 0.43 mole). The third portion may be added 2.5 hr after the second portion. The mixture was held for a minimum of 6.5 hr at 95 °C (total of 28.5 h). The mixture was cooled to 0-10 °C and held for 1 hr. The mixture was filtered on an 18 cm diameter Buchner funnel and washed with filtrate (150 ml) followed by chilled (0-10 °C) n-propanol (4 x 0.15 L). The weight of the wet cake was 252 g. (estimated LOD of ~12%).

[0056] The wet cake was purified from acetonitrile. The wet cake (186 g) was transferred to a 5-L multi-necked flask equipped with mechanical stirrer, condenser, temperature probe and nitrogen protection. The flask was charged with acetonitrile (2.42 L), heated to 65-70 °C and held for a minimum of 30 min. The mixture was cooled to 60 °C, filtered on a 15 cm diameter Buchner funnel and washed with acetonitrile (3 x 0.18 L). The product was dried at 60 °C, full vacuum for 18 h to give 3-[3-ethoxy-4-(N-phthalimidyl)]anilino-N-[3-chloro-4-(2-pyridinylmethoxy)]phenyl-2-cyano-2-propenamide (122 g, 75% recovery based on dry weight) as a beige solid. Overall yield over 2 steps: 53%. ¹H NMR (aniline): δ (DMSO-d₆) 7.96-7.86 (m, 4H, phthalimide), 6.90 (d, 1H, Ar), 6.34 (d, 1H, Ar), 6.22 (dd, 1H, Ar), 5.37 (d, 2H, NH₂), 3.90 (q, 2H, CH₃CH₂O), 1.11 (t, 3H, CH₃CH₂O). ¹H NMR (propenamide): δ (DMSO-d₆) 11.45 (d, 1H, NHCH=C), 9.58 (d, 1H, CONH), 8.59 (m, 1H, Ar), 8.54 (d, 1H, NHCH=C), 8.00-7.84 (m, 6H, Ar), 7.57 (d, 1H, Ar), 7.52 (dd, 1H, Ar), 7.39-7.34 (m, 3H, Ar), 7.21 (d, 1H, Ar), 7.11 (dd, 1H, Ar), 5.27 (s, 2H, OCH₂Pyr), 4.11 (q, 2H, OCH₂CH₃), 1.16 (t, 3H, OCH₂CH₃).

Example 5

Preparation of 3-cyano-4-[3-chloro-4-(2-pyridinylmethoxy)]anilino-7-ethoxy-N-phthalimidylquinoline.

[0057] To a 5-L multi-necked flask equipped with an agitator, temperature probe, condenser and nitrogen protection was charged 3-[3-ethoxy-4-(N-phthalimidyl)]anilino-N-[3-chloro-4-(2-pyridinylmethoxy)]phenyl-2-cyano-2-propenamide (0.12 kg, 0.20 mole) and suspended in acetonitrile (1.20 L) and

- 34 -

methanol (0.06 L). A sodium hydroxide (40 g in 1 L water) scrubber system was set up. The mixture was heated to 60-65 °C and phosphorus oxychloride (0.31 kg, 0.19 L, 10.0 eq, d=1.645 g/ml) was added dropwise keeping the pot temperature at 60-70 °C. The mixture eventually became thinner and deep red (after ~6 hr). The mixture was held for a minimum of 18 h and then cooled to 0-10 °C. Water (0.60 L) was added keeping the pot temperature < 20 °C. The pH of the mixture was adjusted to 8-10 using 28% ammonium hydroxide (~0.95 L). The 2-phase mixture was filtered on a 15 cm diameter Buchner funnel and washed with 2:1 acetonitrile:water (2 x 0.12 L). The wet cake was transferred to the 3-L flask, water (1.20 L) was added and the mixture slurried for a minimum of 30 mins at 45-50 °C. The mixture was filtered at 45 °C on a 15 cm diameter Buchner funnel and washed with water (3 x 0.20 L) until the pH of the final wash was 7-8. The solid was dried at 60 °C, in a vacuum oven for 24 hr to give the desired compound (88 g, 76%) as an orange solid. ¹H NMR: δ (DMSO-d₆) 9.72 (s, 1H, Ar), 8.58 (m, 2H, Ar), 8.53 (s, 1H, Ar), 8.08-7.96 (m, 4H, phthalimide), 7.87 (m, 1H, Ar), 7.55 (m, 3H, Ar), 7.37 (m, 1H, Ar), 7.28 (s, 1H, Ar), 5.29 (s, 2H, OCH₂Pyr), 4.24 (q, 2H, OCH₂CH₃), 1.22 (t, 3H, OCH₂CH₃).

Example 6

Preparation of 6-amino-4-[3-chloro-4-(2-pyridinylmethoxy)]anilino-3-cyano-7-ethoxyquinoline.

[0058] To a 3-L multi-necked flask equipped with an agitator, temperature probe, condenser and nitrogen protection was charged 3-cyano-4-[3-chloro-4-(2-pyridinylmethoxy)]anilino-7-ethoxy-N-phthalimidylquinoline (0.085 kg, 0.147 mole) and suspended in ethanol (ASDQ #2, 0.68 L). Next, 28% ammonium hydroxide (0.5 L of a 7.4 M solution, 25 eq.) was added. The suspension was heated to 62-68 °C and held for a minimum of 2 hr. The reaction was cooled to room temperature, filtered on a 15 cm diameter Buchner funnel, and washed with ethanol (2 x 85 ml). The solid was dried at 65 °C, in a vacuum oven for 20 hr to give the titled compound (61 g, 92% uncorrected for strength) as an orange solid. ¹H NMR: δ (DMSO-d₆) 9.08 (s, 1H, NH), 8.59 (d, 1H, Ar), 8.31 (s, 1H, Ar), 7.90-7.84 (m, 1H, Ar), 7.58 (s, 1H, Ar), 7.40-7.34 (m, 1H, Ar), 7.26-7.19 (m, 4H,

- 35 -

Ar), 7.09-7.05 (m, 1H, Ar), 5.40 (d, 2H, NH₂), 5.25 (s, 2H, OCH₂Pyr), 4.23 (q, 2H, OCH₂CH₃), 1.45 (t, 3H, OCH₂CH₃).

Example 7

Preparation of (E)-N-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinoliny]-4-(dimethylamino)-2-butenamide free base.

[0059] A solution of 4-N,N-dimethylaminocrotonic acid hydrochloride (22.3 g, 0.135 mol, 2.0 eq.) in tetrahydrofuran (0.225 L) and a catalytic amount of dimethylformamide (0.5 mL) was cooled to 0-5 °C. Oxalyl chloride (11.4 mL, 0.131 mol, 1.95 eq) was added dropwise over 15 min. The mixture was then warmed to 25-30 °C and stirred for 2 h then cooled to 0-5 °C. N-Methyl-2-pyrrolidinone (15 ml) was added. A filtered solution of warm (30 °C) 6-amino-4-[3-chloro-4-(2-pyridylmethoxy)]anilino-3-cyano-7-ethoxy-quinoline (30 g, 0.067 mole, 1.0 eq.) in N-methyl-2-pyrrolidinone (0.27 L) was added dropwise over 30 min keeping the temperature 0-10 °C. The mixture was stirred for a minimum of 20 h. Upon completion, the reaction was quenched with water (0.36 L), held for 30 min and then warmed to 40-45 °C. Aqueous sodium hydroxide (19 g in 0.15 L water) was added over 30 min to bring the pH to 9-10 followed by adding water (0.39 L). The mixture was stirred for 1 hr, then cooled to room temperature. The resulting precipitates were filtered and washed with water (3 x 60 mL) until the pH of the washes were 7-8. The wet solids were heated to reflux (70-75 °C) in 1.5:1 acetonitrile:tetrahydrofuran (0.33 L) and the solution cooled over 2 h to room temperature. The product was filtered and washed with cold 1.5:1 acetonitrile:tetrahydrofuran (3 x 0.01 L). The product was dried (60 °C, 10 mm Hg, 24 h) to give the titled compound (19.4 g, 52% uncorrected for strength).

¹H NMR : δ (DMSO-d₆) 9.59 (s, 1H, NH), 9.47 (s, 1H, NH), 8.96 (s, 1H, Ar), 8.60 (dd, 1H, Ar), 8.47 (s, 1H, Ar), 7.87 (dd, 1H, Ar), 7.58 (d, 1H, Ar), 7.39-7.34 (m, 3H, Ar), 7.27-7.20 (m, 2H, Ar), 6.81-6.73 (m, 1H, CH₂-CH=CH-), 6.59 (d, 1H, CH₂-CH=CH-), 5.28 (s, 2H, OCH₂Pyr), 4.31 (q, 2H, OCH₂CH₃), 3.09 (d, 2H, NCH₂), 2.18 (s, 6H, N(CH₃)₂), 1.47 (t, 3H, OCH₂CH₃).

Example 8

Preparation of (E)-N-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinoliny]-4-(dimethylamino)-2-butenamide maleate.

[0060] (E)-N-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinoliny]-4-di-methylamino)-2-butenamide crude free base (17 g, 0.027 mole, 88% strength) and maleic acid (3.60 g, 0.031 mole) were dissolved at 50-60 °C in a 5% water/n-propanol mixture (0.12 L) and stirred for 15 min. To the hot solution was added charcoal (1.7 g) and the mixture stirred for 20 min. The hot solution was clarified and cooled to room temperature and held for 12-15 hr. The product was filtered and washed with 5% water/n-propanol (3 x 0.017 L). The product was dried (60 °C, 10 mm Hg, 24 h) to give the titled compound (9.83 g, 54%, uncorrected for strength). The product (7.0 g) was recrystallized from 7.5% water/propanol to give 5.7g. DSC: 196 °C (single crystal form). ¹H NMR : δ (DMSO-d₆) 9.74 (s, 1H, NH), 9.63 (s, 1H, NH), 8.94 (s, 1H, Ar), 8.60 (dd, 1H, Ar), 8.50 (s, 1H, Ar), 7.88 (dd, 1H, Ar), 7.59 (d, 1H, Ar), 7.42-7.35 (m, 3H, Ar), 7.28-7.19 (m, 2H, Ar), 6.76 (d, 2H, -CH=CH-), 6.05 (s, 2H, HOOC-CH=CH-COOH), 5.29 (s, 2H, OCH₂Pyr), 4.33 (q, 2H, OCH₂CH₃), 3.91 (d, 2H, NCH₂), 2.77 (s, 6H, N(CH₃)₂), 1.45 (t, 3H, OCH₂CH₃). ¹³C NMR : δ (DMSO-d₆) 167.3, 162.4, 156.1, 153.4, 152.5, 151.2, 150.5, 149.1, 147.7, 137.0, 135.8, 134.0, 132.6, 131.6, 127.3, 125.9, 124.2, 123.0, 121.5, 121.4, 117.1, 115.6, 114.3, 113.2, 108.7, 87.3, 71.3, 64.6, 57.0, 42.3, 14.2.

Example 9

Preparation of N-[3-Chloro-4-(3-fluorobenzyloxy)]phenyl-2-cyanoacetamide.

[0061] 3-Fluorobenzyl alcohol (0.30 kg, 2.39 mole, 1.05 eq) was dissolved in acetonitrile (6.0 L) and to it was added potassium hydroxide flakes (85%) (0.16 kg, 1.25 eq). The resulting suspension was warmed to 35 °C. A solution of the 3-chloro-4-fluoronitrobenzene (0.40 kg, 2.28 mol) in acetonitrile (2.0 L) was added at 35-40 °C. The mixture was held for 18 h. The mixture was then cooled to ambient temperature, quenched with water (8 L) and the resulting slurry was filtered and washed with water (2 x 0.40 L). The resulting product was dried (45 °C, 10 mmHg, 25 h) to give 0.59 kg (92% yield).

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[0062] A mixture of 3-chloro-4-(3-fluorobenzyloxy)nitrobenzene (20 g, 0.071 mole) and ethanol (195 ml) was added zinc (23.2 g, 5.0 eq.). The mixture was heated to 55-60 °C. A solution of ammonium chloride (7.6 g) in water (40 ml) was added over 20 min keeping the pot temperature 55-65 °C (small exotherm). The mixture was stirred for 2 h, filtered over a celite pad and washed with ethanol (2 x 20 ml). The filtrate was distilled to essentially dryness and 2-methyltetrahydrofuran (100 ml) was added to dissolve the product. Water (40 ml) and brine (5.2 g in 15 ml water) were added, mixed and the layers were separated. The organic layer was washed with water (30 ml) and then transferred to a 500 ml multi-necked flask.

[0063] To the 500 ml flask equipped with mechanical stirrer, temperature probe, claisen head and condenser was added ethylcyanoacetate (53.2g, 0.47 mole, 6.6 eq.). The reaction mixture was heated to (120-125 °C) while removing 2-methyltetrahydrofuran and residual ethanol atmospherically. The mixture was held for a minimum of 24 h until the aniline starting material was consumed and no distillate was collected. The mixture was cooled to ambient temperature and isopropyl acetate (75 ml) and heptane (75 ml) were added. The mixture was mixed for 2 hr. The mixture was filtered on a 5.5 cm diameter Buchner funnel and washed with heptane. The product was dried at 45 °C overnight in a vacuum oven to give the titled compound (6.45 g, 29%) as a greyish solid (WC26280-77).
¹H NMR: δ (DMSO-d₆) 10.31 (s, 1H, NH), 7.73 (d, 1H, Ar), 7.46-7.19 (m, 6H, Ar), 5.20 (s, 2H, OCH₂Ph), 3.87 (s, 2H, NCCH₂CO).

Example 10

Preparation of (E/Z) 3-[3-ethoxy-4-(N-phthalimidyl)]anilino-N-[3-chloro-4-(3-fluorobenzyloxy)]phenyl-2-cyano-2-propenamide.

[0064] A mixture of 3-ethoxy-4-(N-phthalimidyl)nitrobenzene (9.99 g, 0.032 mole, 1.1 eq.) and 4% (w/w) of 10% Pd/C (0.40 g, 50% water wet) in tetrahydrofuran (80 ml) was hydrogenated in a 0.2 L stainless steel Parr reactor at 70 psi, 50 °C for a minimum of 10 h. The mixture was filtered through a celite pad into a 1-neck 0.5 L flask and washed with tetrahydrofuran (3 x 10 ml). The filtrate was distilled to a volume of 40 ml and to the concentrate was added n-

propanol (60 ml). The mixture was distilled to a volume of 40 ml and the concentrate was used as is in the next step.

[0065] The concentrate was transferred to a 0.5 L multi-necked flask equipped with an agitator, temperature probe, condenser and nitrogen protection. The flask was charged with n-propanol (60 ml) followed by N-[3-Chloro-4-(3-fluorobenzyloxy)]phenyl-2-cyanoacetamide (9.0 g, 0.029 mole, 1.0 eq.). The mixture was heated to 75-80 °C. The first of three portions of triethylorthoformate (4.4 g, 4.7 ml, 0.029 mole, d=0.89 g/ml) was added and the mixture heated to reflux (95-100 °C). After 2 hr, the second portion of triethylorthoformate was added (4.4 g, 4.7 ml, 0.029 mole). After another 2 hr, the third portion of triethylorthoformate was added (4.4 g, 4.7 ml, 0.029 mole). The mixture was held for a minimum of 20 hr at 95 °C. The mixture was cooled to 0-10 °C and held for 1 hr. The mixture was filtered on a Buchner funnel and washed with filtrate (10 ml) followed by chilled (0-10 °C) n-propanol (3 x 10 ml). The weight of the wet cake was ~25.6 g. The product was dried at 60 °C, full vacuum for 20 h to give the titled compound (15.7 g, 88% overall yield over 2 steps). ¹H NMR: δ (DMSO-d₆) 11.46 (d, 1H, NHCH=C), 9.58 (d, 1H, CONH), 8.54 (d, 1H, NHCH=C), 7.95-7.86 (m, 5H, Ar), 7.55-7.10 (m, 9H, Ar), 5.22 (s, 2H, OCH₂Ph), 4.10 (q, 2H, OCH₂CH₃), 1.16 (t, 3H, OCH₂CH₃).

Example 11

Preparation of 3-cyano-4-[3-chloro-4-(3-fluorobenzyloxy)]anilino-7-ethoxy-N-phthalimidylquinoline.

[0066] To a 1-L multi-necked flask equipped with an agitator, temperature probe, condenser and nitrogen protection was charged 3-[3-ethoxy-4-(N-phthalimidyl)]anilino-N-[3-chloro-4-(3-fluorobenzyloxy)]phenyl-2-cyano-2-propenamide (15 g, 0.0245 mole) and suspended in acetonitrile (150 ml) and methanol (3.0 ml). A sodium hydroxide (40 g in 1 L water) scrubber system was set up. The mixture was heated to 65-70 °C and phosphorus oxychloride (37.6 g, 22.8 ml, 10.0 eq, d=1.645 g/ml) was added dropwise keeping the pot temperature at 70-75 °C. The mixture eventually became thinner. The mixture was held for a minimum of 20 h and then cooled to 0-10 °C. Water (75 ml) was added keeping

- 39 -

the pot temperature < 20 °C. The pH of the mixture was adjusted to 8-10 using 28% ammonium hydroxide (~115 ml) keeping the pot temperature 10-15 °C. The 2-phase mixture was filtered on a Buchner funnel and washed with warm water (120 ml). The solid was dried at 60 °C, in a vacuum oven for 25 hr to give the titled compound (11.29 g, 78% uncorrected for strength) as an orange solid. ¹H NMR: δ (DMSO-d₆) 8.59 (s, 1H, Ar), 8.53 (s, 1H, Ar), 8.07-7.96 (m, 4H, phthalimide), 7.53-7.42 (m, 3H, Ar), 7.34-7.16 (m, 5H, Ar), 5.26 (s, 2H, OCH₂Ph), 4.24 (q, 2H, OCH₂CH₃), 1.22 (t, 3H, OCH₂CH₃).

Example 12

Preparation of 6-amino-4-[3-chloro-4-(3-fluorobenzyloxy)]anilino-3-cyano-7-ethoxyquinoline.

[0067] To a 250 ml multi-necked flask equipped with an agitator, temperature probe, condenser and nitrogen was charged 3-cyano-4-[3-chloro-4-(3-fluorobenzyloxy)]anilino-7-ethoxy-N-phthalimidylquinoline (10 g, 0.0169 mole) and suspended in ethanol (80 ml). Next, 28% ammonium hydroxide (22.8 ml of a 7.4 M solution, 25 eq.) was added. The suspension was heated to 65-70 °C and held for a minimum of 2 hr. The reaction was cooled to room temperature, filtered on a Buchner funnel, and washed with ethanol (2 x 10 ml) and heptanes (2 x 10 ml). The solid was dried at 60 °C, in a vacuum oven for 24 hr to give the titled compound (5.78 g, 74%) as an orange-red solid. ¹H NMR: δ (DMSO-d₆) 9.10 (s, 1H, NH), 8.31 (s, 1H, Ar), 7.51-7.05 (m, 9H, Ar), 5.36 (s, 2H, NH₂), 5.22 (s, 2H, OCH₂Ph), 4.23 (q, 2H, OCH₂CH₃), 1.45 (t, 3H, OCH₂CH₃).

Example 13

Preparation of N-(3-Chloro-4-fluoro)phenyl-2-cyanoacetamide.

[0068] 3-Chloro-4-fluoroaniline (1.00 kg, 6.87 mole) and cyanoacetic acid (0.602 kg, 7.08 mole) were reacted together in the presence of 1,3-diisopropylcarbodiimide (0.893 kg, 1.108 L, 7.08 mole) in refluxing THF (2.67 kg, 3.0 L), similar to that reported by R. Westwood et. al. [*J. Med. Chem.*, 39, 4608, (1996)]. The urea byproduct precipitated from the THF solution and was removed after chilling to 13 ± 2 °C and filtration. The precipitates were washed

with THF (3 x 1.0 L). The filtrate was then added slowly to a large volume of water (17 L) to precipitate the product. The resulting slurry of crystals was filtered, washed with water (2 x 0.50 L) and dried under vacuum at 45°C for a minimum of 24 hrs to give the desired compound as an off white solid (1.25 kg, 86%). ¹H NMR: δ (DMSO-d₆) 10.48 (s, 1H, NH), 7.83 (dd, 1H, Ar), 7.45-7.32 (m, 2H, Ar), 3.90 (s, 2H, NCCH₂CO).

Example 14

Preparation of (E/Z) 3-[3-ethoxy-4-(N-phthalimidyl)]anilino-N-(3-chloro-4-fluoro)phenyl-2-cyano-2-propenamide.

[0069] A mixture of 3-ethoxy-4-(N-phthalimidyl)nitrobenzene (20.0 g, 0.064 mole, 1.1 eq.) and 4% (w/w) of 10% Pd/C (0.80 g, 50% water wet) in tetrahydrofuran (160 ml) was hydrogenated in a 0.2 L stainless steel Parr reactor at 70 psi, 50 °C for a minimum of 10 h. The mixture was filtered through a celite pad into a 1-neck 0.5 L flask and washed with tetrahydrofuran (2 x 20 ml). The filtrate was distilled to a volume of ~80 ml and to the concentrate was added n-propanol (110 ml). The mixture was distilled to a volume of 80 ml and the concentrate was used as is in the next step.

[0070] The concentrate was transferred to a 0.5 L multi-necked flask equipped with an agitator, temperature probe, condenser and nitrogen protection. The flask was charged with n-propanol (120 ml) followed by N-(3-Chloro-4-fluoro)phenyl-2-cyanoacetamide (12.4 g, 0.058 mole, 1.0 eq.). The mixture was heated to 75-80 °C. The first of three portions of triethylorthoformate (8.6 g, 9.7 ml, 0.058 mole, d=0.89 g/ml) was added and the mixture heated to reflux (95-100 °C). After 2 hr, the second portion of triethylorthoformate was added (8.6 g, 9.7 ml, 0.058 mole). After another 2 hr, the third portion of triethylorthoformate was added (8.6 g, 9.7 ml, 0.058 mole). The mixture was held for a minimum of 20 hr at 95 °C. The mixture was cooled to ambient temperature. The mixture was filtered on a Buchner funnel and washed with filtrate (20 ml) followed by chilled (0-10 °C) n-propanol (3 x 20 ml). The weight of the wet cake was ~40 g.

[0071] The wet cake can be purified from acetonitrile. The wet cake was transferred to a 1-L multi-necked flask equipped with mechanical stirrer,

condenser, temperature probe and nitrogen protection. The flask was charged with acetonitrile (390 ml), heated to 65-70 °C and held for a minimum of 20 min.

The mixture was cooled to 60 °C, filtered on a Buchner funnel and washed with acetonitrile (2 x 15 ml). The product was dried at 60 °C, full vacuum for 20 h to give the titled compound (19.65 g, 67% overall yield over 2 steps). ¹H NMR: δ (DMSO-d₆) 11.43, (d, 1H, NHCH=C), 9.74, (s, 1H, NH), 8.56 (d, 1H, NHCH=C), 7.99-7.88 (m, 5H, Ar), 7.64-7.56 (m, 1H, Ar), 7.39-7.29 (m, 3H, Ar), 7.15-7.10 (m, 1H, Ar), 4.10 (q, 2H, OCH₂CH₃), 1.18 (t, 3H, OCH₂CH₃).

Example 15

Preparation of 3-cyano-4-(3-chloro-4-fluoroanilino)-7-ethoxy-N-phthalimidyl-quinoline.

[0072] To a 1-L multi-necked flask equipped with an agitator, temperature probe, condenser and nitrogen was charged 3-[3-ethoxy-4-(N-phthalimidyl)]anilino-N-(3-chloro-4-fluoro)phenyl-2-cyano-2-propenamide (18 g, 0.0356 mole) and suspended in acetonitrile (180 ml) and methanol (7.2 ml). A sodium hydroxide (40 g in 1 L water) scrubber system was set up. The mixture was heated to 65-70 °C and phosphorus oxychloride (54.6 g, 33.2 ml, 10.0 eq, d=1.645 g/ml) was added dropwise keeping the pot temperature at 65-70 °C. The mixture eventually became thinner. The mixture was held for a minimum of 22 h and then cooled to 0-10 °C. Water (90 ml) was added keeping the pot temperature < 20 °C. The pH of the mixture was adjusted to 8-10 using 28% ammonium hydroxide (~140 ml) keeping the pot temperature at 5-10 °C. The 2-phase mixture was filtered on a Buchner funnel and washed with warm water. The solid was dried at 60 °C, in a vacuum oven for 18 hr to give the titled compound (14.44 g, 83% uncorrected for strength) as an orange solid. ¹H NMR: δ (DMSO-d₆) 8.64 (s, 1H, Ar), 8.52 (m, 2H, Ar), 8.06-7.95 (m, 4H, phthalimide), 7.59-7.55 (m, 2H, Ar), 7.43 (m, 1H, Ar), 7.33 (m, 1H, Ar), 4.24 (q, 2H, OCH₂CH₃), 1.22 (t, 3H, OCH₂CH₃).

Example 16

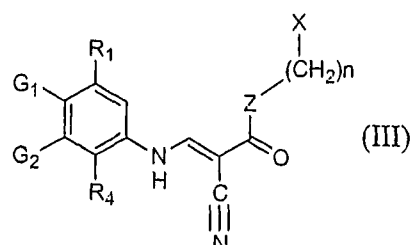
Preparation of 6-amino-4-(3-chloro-4-fluoroanilino)-3-cyano-7-ethoxyquinoline.
[0073] To a 500 ml multi-necked flask equipped with an agitator, temperature probe, condenser and nitrogen was charged 3-cyano-4-(3-chloro-4-fluoroanilino)-7-ethoxy-N-phthalimidyl-quinoline (12 g, 0.0246 mole) and suspended in ethanol. Next, 28% ammonium hydroxide (83 ml of a 7.4 M solution, 25 eq.) was added. The suspension was heated to 65-70 °C and held for a minimum of 2 hr. The reaction was cooled to room temperature, filtered on a Buchner funnel, and washed with water (3 x 15 ml) until the washes were colorless. The solid was dried at 60 °C, in a vacuum oven for 25 hr to give the desired compound (4.13 g). A second crop (2.05 g) was obtained from acetonitrile recrystallization. (Overall yield 6.18 g, 70% uncorrected for strength). ¹H NMR: δ (DMSO-d₆) 9.22 (s, 1H, NH), 8.39 (s, 1H, Ar), 7.37-7.03 (m, 5H, Ar), 5.51 (s, 2H, NH₂), 4.24 (q, 2H, OCH₂CH₃), 1.45 (t, 3H, OCH₂CH₃).

Analytical Methods

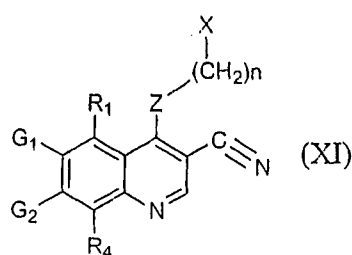
[0074] NMR spectra were recorded on a Varian Inova 300 at 300 MHz (¹H and ¹³C) and chemical shifts were identified in ppm relative to TMS internal standard.

WHAT IS CLAIMED IS:

1. A method of preparing a substituted 3-cyanoquinoline comprising the step of treating an N-aryl-2-propene represented by formula III:



with POCl_3 to form a substituted 3-cyanoquinoline represented by formula XI:



wherein:

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

-44-

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 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 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, and benzoylamino;

or

X is a radical having the formula: ---A-T-L

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:

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

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

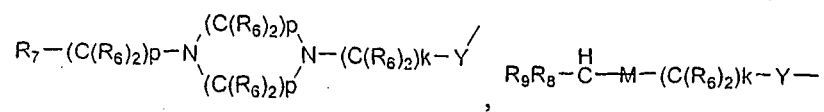
L is a 5- or 6-membered heteroaryl ring where the heteroaryl ring contains 1 to 3 heteroatoms selected from N, O, and S, with the proviso that the heteroaryl ring does not contain O-O, S-S, or S-O bonds, and where the heteroaryl ring is optionally mono- or di-substituted with a substituent selected from 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;

Z is -NH-, -O-, -S-, or -NR-;

R is alkyl of 1-6 carbon atoms, or carboalkyl of 2-7 carbon atoms;

G₁, G₂, R₁, and R₄ 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, 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)_qW-(C(R₆)₂)₂-Y-; or optionally G₁ and/or G₂ are independently selected from a protected amino group and R₂-NH-;

-47-

or if any of the substituents R_1 , G_1 , G_2 , or R_4 are located on contiguous carbon atoms then they may be taken together as the divalent radical $-O-C(R_6)_2-O-$;

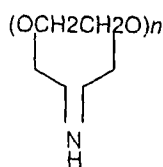
Y is a divalent radical selected from the group consisting of $-(CH_2)_a-$, $-O-$, and $-\overset{R_6}{N}-$;

R_7 is $-NR_6R_7$, $-OR_6$, $-J$, $-N(R_6)_3^+$, or $-NR_7(OR_6)$;

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

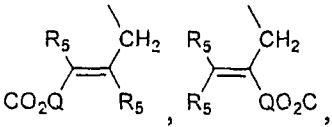
W is $>NR_6$, $-O-$ or is a bond;

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

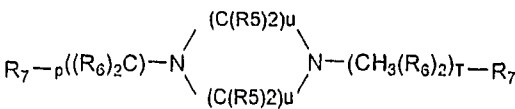


wherein Het is optionally mono- or di-substituted on carbon or nitrogen with R_6 , optionally mono- or di-substituted on carbon with hydroxy, $-N(R_6)_2$, or $-OR_6$, optionally mono or di-substituted on carbon with the mono-valent radicals $-(C(R_6)_2)_sOR_6$ or $-(C(R_6)_2)_sN(R_6)_2$, and optionally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

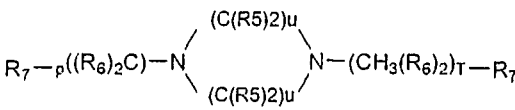


R₃ is independently hydrogen, alkyl of 1-6 carbon atoms, carboxy, carboalkoxy of 1-6 carbon atoms, phenyl, carboalkyl of 2-7 carbon atoms,



R₇-(C(R₆)₂)_s-, R₇-(C(R₆)₂)_p-M-(C(R₇)₂)_r-, R₈R₉-CH-M-(C(R₆)₂)_r-, Het-(C(R₆)₂)_q-W-(C(R₆)₂)_r-; aminoalkyl of 1-6 carbon atoms, N-alkylaminoalkyl of 2-9 carbon atoms, N,N-dialkylaminoalkyl of 3-12 carbon atoms, N-cycloalkylaminoalkyl of 4-12 carbon atoms, N-cycloalkyl-N-alkylaminoalkyl of 5-18 carbon atoms, N,N-dicycloalkylaminoalkyl of 7-18 carbon atoms, morpholino-N-alkyl wherein the alkyl group is 1-6 carbon atoms, piperidino-N-alkyl wherein the alkyl group is 1-6 carbon atoms, N-alkyl-piperidino-N-alkyl wherein either alkyl group is 1-6 carbon atoms;

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;

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;

or a pharmaceutically acceptable salt thereof, provided that

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;

and further provided that

when Y is $-NR_6-$ and R_7 is $-NR_6R_6--N(R_6)_3^+$, or $-NR_6(OR_6)$, then $g=2-6$;

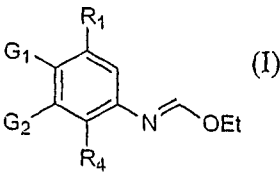
when M is $-O-$ and R_7 is $-OR_6$ then $p=1-4$;

when Y is $-NR_6-$ then $k=2-4$;

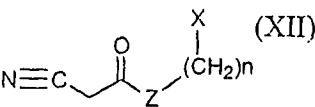
when Y is $-O-$ and M or W is $-O-$ then $k=1-4$

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 $-NR_6-$ then $k=2-4$.

2. The method according to claim 1, further comprising the step of forming the N-aryl-2-propene compound of formula III by condensing an N-arylformimide of formula I:

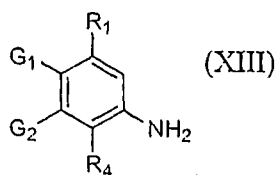


with an active methylene of formula XII:

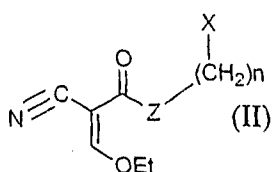


3. The method according to claim 2, further comprising the step of forming the N-arylformimide of formula I by reacting an arylamine of formula XIII:

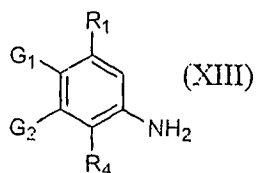
-51-

with $\text{CH}(\text{OEt})_3$.

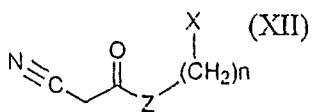
4. The method according to claim 1 further comprising the step of forming the N-aryl-2-propene of formula III by reacting an alkoxymethylene derivative of formula II:



with an arylamine of formula XIII:



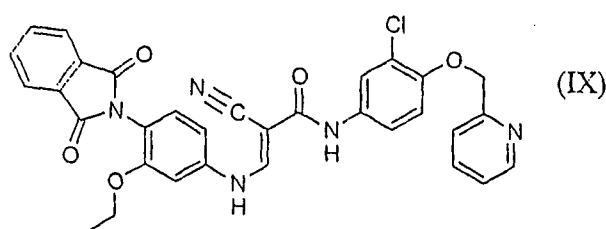
5. The method according to claim 4, further comprising the step of forming an alkoxymethylene of formula II by condensing an active methylene of formula XII:

with $\text{CH}(\text{OEt})_3$.

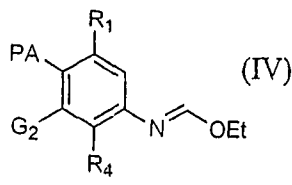
6. The method according to claims 1, 2, 3, 4, and 5, wherein Z is selected from the group consisting of NH, O and S.

-52-

7. The method according to claim 1, 2, 3, 4, and 5, wherein G_1 is a protected amino group selected from the group consisting of acetamides, benzamides, cyclic imides, pyrroles, tert-butoxycarbonyl amine and benzyloxycarbonyl amide.
8. The method according to claim 7, wherein G_1 is phthalimide.
9. A method according to claims 1, 2, 3, 4, and 5, 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 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, and benzoylamino.
10. The method according to claims 1, 2, 3, 4, and 5, wherein the N-aryl-2-propene of formula III is the compound represented by formula IX:

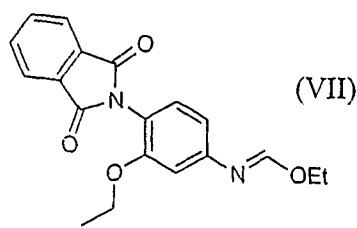


11. The method according to claims 2 and 3, wherein the N-arylformimidate of formula I is a compound represented by formula IV:

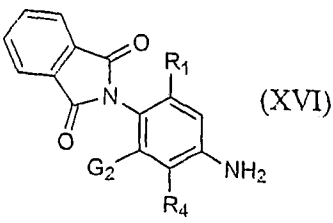


wherein PA is a protected amino group.

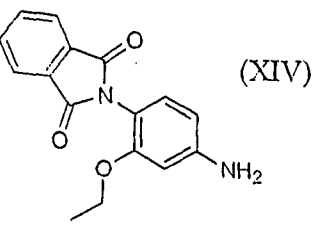
12. The method according to claim 11, wherein the N -arylformimidate of formula IV is a compound represented by formula VII:



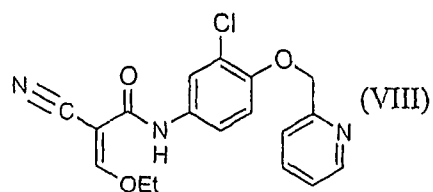
13. The method according to claims 3, 4 and 5, wherein the arylamine of formula XIII is a compound represented by formula XVI:



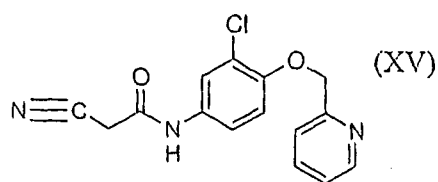
14. The method according to claim 13, wherein the arylamine of formula XVI is a compound represented by formula XIV:



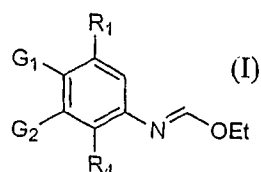
15. The method according to claims 4 and 5, wherein the alkoxyethylene of formula II is a compound represented by formula VIII:



16. The method according to claims 2, 3 and 5, wherein the active methylene of formula XII is the compound represented by formula XV:



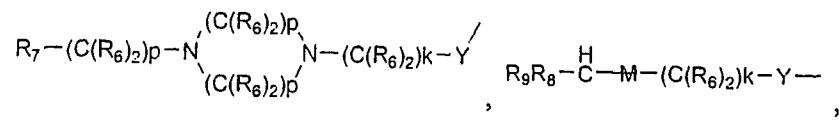
17. A compound represented by formula I:



wherein

G_1 , G_2 , R_1 , and R_4 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, 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 $Het-(C(R_6)_2)_qW-(C(R_6)_2)_s-Y-$; or optionally G_1 and/or G_2 are independently selected from a protected amino group and R_2-NH- ;

or if any of the substituents R_1 , G_1 , G_2 , or R_4 are located on contiguous carbon atoms then they may be taken together as the divalent radical $-O-C(R_6)_2-O-$;

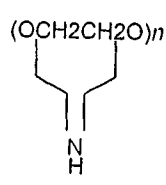
Y is a divalent radical selected from the group consisting of $-(CH_2)_a-$, $-O-$, and $-\overset{R_6}{N}-$;

R_7 is $-NR_6R_7$, $-OR_6$, $-J$, $-N(R_6)_3^+$, 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



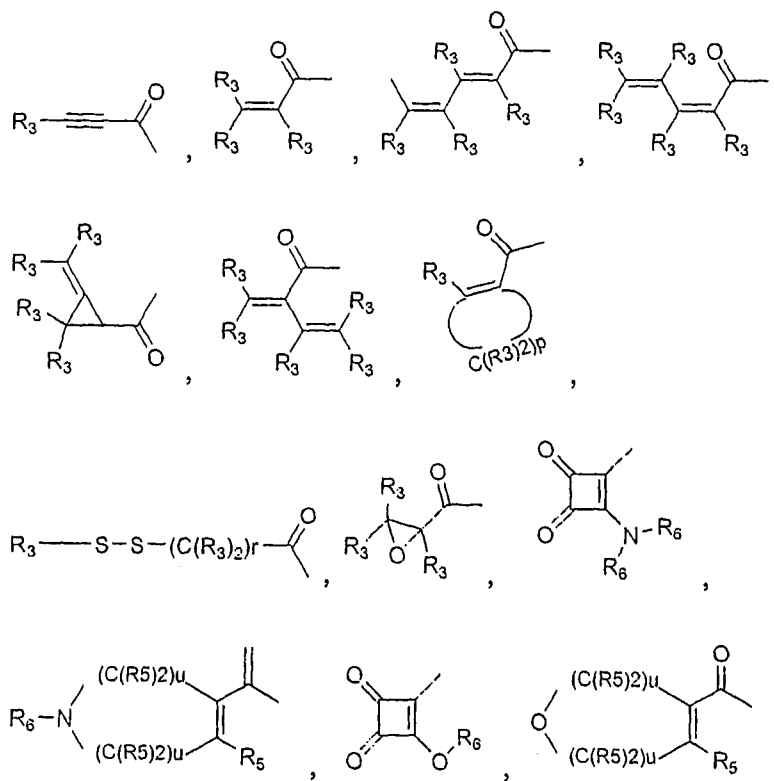
wherein Het is optionally mono- or di-substituted on carbon or nitrogen with R_6 , optionally mono- or di-substituted on carbon with hydroxy, $-N(R_6)_2$, or $-OR_6$, optionally mono or di-substituted on carbon with the mono-valent radicals $-(C(R_6)_2)_sOR_6$ or

$-(C(R_6)_2)_sN(R_6)_2$, and optionally mono or di-substituted on a saturated carbon with divalent radicals $-O-$ or $-O(C(R_6)_2)_sO-$;

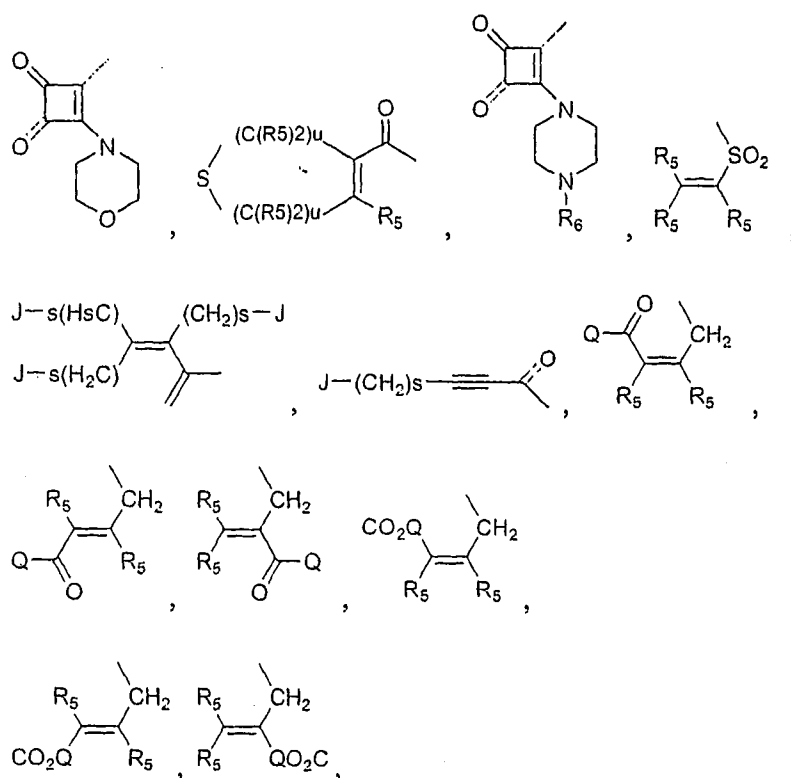
-56-

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;

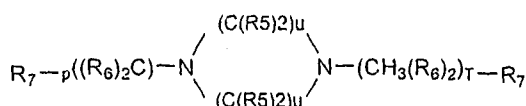
R_2 , is selected from the group consisting of



-57-

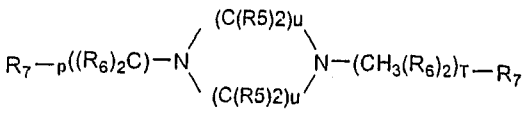


R_3 is independently hydrogen, alkyl of 1-6 carbon atoms, carboxy, carboalkoxy of 1-6 carbon atoms, phenyl, carboalkyl of 2-7 carbon atoms,



$R_7-(C(R_6)_2)_s-$, $R_7-(C(R_6)_2)_p-M-(C(R_7)_2)_r-$, $R_8R_9-CH-M-(C(R_6)_2)_r-$, $Het-(C(R_6)_2)_q-W-(C(R_6)_2)_r-$; aminoalkyl of 1-6 carbon atoms, N-alkylaminoalkyl of 2-9 carbon atoms, N,N-dialkylaminoalkyl of 3-12 carbon atoms, N-cycloalkylaminoalkyl of 4-12 carbon atoms, N-cycloalkyl-N-alkylaminoalkyl of 5-18 carbon atoms, N,N-dicycloalkylaminoalkyl of 7-18 carbon atoms, morpholino-N-alkyl wherein the alkyl group is 1-6 carbon atoms, piperidino-N-alkyl wherein the alkyl group is 1-6 carbon atoms, N-alkyl-piperidino-N-alkyl wherein either alkyl group is 1-6 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,



$R_7 - (C(R_6)_2)_s$ -, $R_7 - (C(R_6)_2)_p - M - (C(R_6)_2)_r$ -, $R_8R_9 - CH - M - (C(R_6)_2)_r$ -, or
 Het- $(C(R_6)_2)_q - W - (C(R_6)_2)_r$ -;

R_8 , and R_9 are each, independently, $-(C(R_6)_2)_r NR_6 R_6$, or $-(C(R_6)_2)_r OR_6$;

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;

or a pharmaceutically acceptable salt thereof, provided that

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;

and further provided that

when Y is $-NR_6$ - and R_7 is $-NR_6R_6$ -- $N(R_6)_3^+$, or $-NR_6(OR_6)$, then g=2-6;

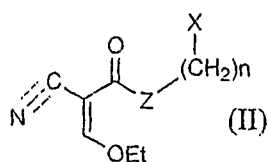
when M is -O- and R_7 is $-OR_6$ then p=1-4;

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

18. A compound represented by formula II:



wherein:

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 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 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

-60-

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, and benzoylamino;

or

X is a radical having the formula: ---A---T---L

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,

-61-

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

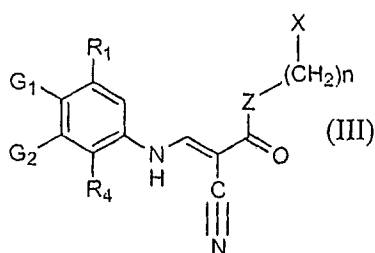
L is a 5- or 6-membered heteroaryl ring where the heteroaryl ring contains 1 to 3 heteroatoms selected from N, O, and S, with the proviso that the heteroaryl ring does not contain O-O, S-S, or S-O bonds, and where the heteroaryl ring is optionally mono- or di-substituted with a substituent selected from 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;

Z is $-\text{NH}-$, $-\text{O}-$, $-\text{S}-$, or $-\text{NR}-$; and

R is alkyl of 1-6 carbon atoms, or carboalkyl of 2-7 carbon atoms.

19. A compound represented by formula III:

-62-



wherein:

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 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 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,

-63-

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, and benzoylamino;

or

X is a radical having the formula: ---A---T---L

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,

-64-

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

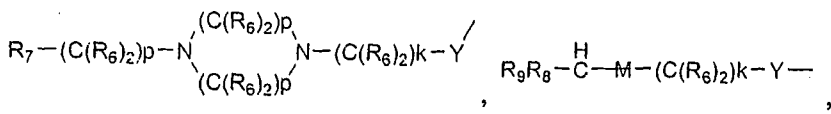
L is a 5- or 6-membered heteroaryl ring where the heteroaryl ring contains 1 to 3 heteroatoms selected from N, O, and S, with the proviso that the heteroaryl ring does not contain O-O, S-S, or S-O bonds, and where the heteroaryl ring is optionally mono- or di-substituted with a substituent selected from 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;

Z is $-\text{NH}-$, $-\text{O}-$, $-\text{S}-$, or $-\text{NR}-$;

R is alkyl of 1-6 carbon atoms, or carboalkyl of 2-7 carbon atoms;

G_1 , G_2 , R_1 , and R_4 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, 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 $Het-(C(R_6)_2)_qW-(C(R_6)_2)_l-Y$; or optionally G_1 and/or G_2 are independently selected from a protected amino group and R_2-NH ;

or if any of the substituents R_1 , G_1 , G_2 , or R_4 are located on contiguous carbon atoms then they may be taken together as the divalent radical $-O-C(R_6)_2-O-$;

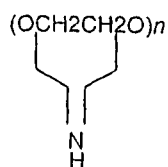
Y is a divalent radical selected from the group consisting of $-(CH_2)_a-$, $-O-$, and $-\overset{R_6}{N}-$;

R_7 is $-NR_6R_7$, $-OR_6$, $-J$, $-N(R_6)_3^+$, or $-NR_7C(OR_6)$;

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

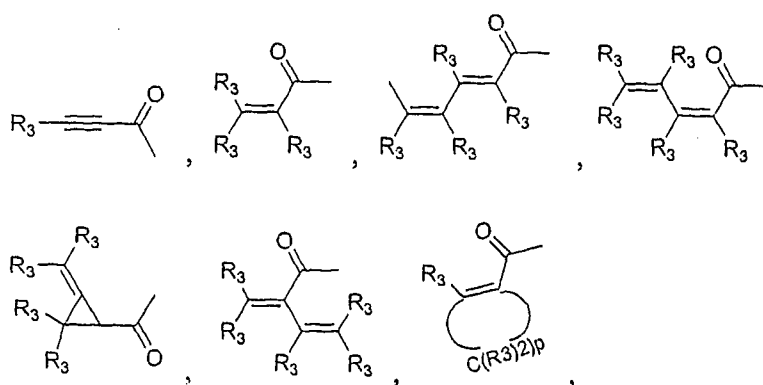


wherein Het is optionally mono- or di-substituted on carbon or nitrogen with R_6 , optionally mono- or di-substituted on carbon with hydroxy, $-N(R_6)_2$, or $-OR_6$, optionally mono or di-substituted on carbon with the mono-valent radicals $-(C(R_6)_2)_sOR_6$ or

$-(C(R_6)_2)_sN(R_6)_2$, 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;

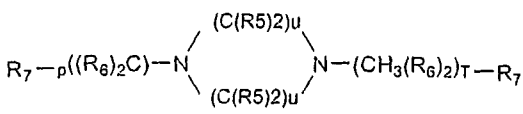
R_2 , is selected from the group consisting of



R₇-(C(R₆)₂)_s-, R₇-(C(R₆)₂)_p-M-(C(R₇)₂)_r-, R₈R₉-CH-M-(C(R₆)₂)_r-,
Het-(C(R₆)₂)_q-W-(C(R₆)₂)_r-, aminoalkyl of 1-6 carbon atoms, N-alkylaminoalkyl
of 2-9 carbon atoms, N,N-dialkylaminoalkyl of 3-12 carbon atoms,
N-cycloalkylaminoalkyl of 4-12 carbon atoms, N-cycloalkyl-N-alkylaminoalkyl of

5-18 carbon atoms, N,N-dicycloalkylaminoalkyl of 7-18 carbon atoms, morpholino-N-alkyl wherein the alkyl group is 1-6 carbon atoms, piperidino-N-alkyl wherein the alkyl group is 1-6 carbon atoms, N-alkyl-piperidino-N-alkyl wherein either alkyl group is 1-6 carbon atoms;

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;

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;

or a pharmaceutically acceptable salt thereof, provided that

when R₆ 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;

and further provided that

when Y is -NR₆- and R₇ is -NR₆R₆ -N(R₆)₃⁺, or -NR₆(OR₆), then g=2-6;

when M is -O- and R₇ is -OR₆ then p=1-4;

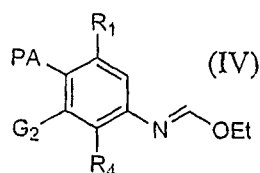
when Y is -NR₆- then k=2-4;

-69-

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

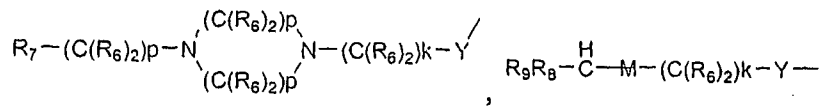
when W is not a bond with Het bonded through a nitrogen atom then q=2-4
and when W is a bond with Het bonded through a nitrogen atom and Y is --O-- or
-NR₆- then k=2-4.

20. Compound represented by formula IV:



wherein PA is a protected amino group;

wherein G₂, R₁, and R₄ 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,



-70-

$R_7-(C(R_6)_2)_g-Y-$, $R_7-(C(R_6)_2)_p-M-(C(R_6)_2)_k-Y-$, or
 $Het-(C(R_6)_2)_q-W-(C(R_6)_2)_l-Y-$; or optionally G_2 is selected from a protected amino
 group and R_2-NH- ;

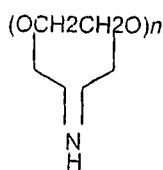
Y is a divalent radical selected from the group consisting of $-(CH_2)_a-$,
 $-O-$, and $-\overset{R_6}{N}-$;

R_7 is $-NR_6R_7$, $-OR_6$, $-J$, $-N(R_6)_3^+$, or $-NR_6(OR_6)$;

M is $>NR_6$, $-O-$, $>N-(C(R_6)_2)_p-NR_6R_6$, or $>N-(C(R_6)_2)_p-OR_6$;

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

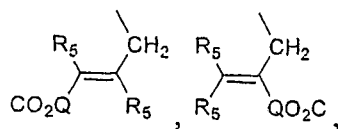
Het is selected from the group consisting of morpholine, thiomorpholine,
 thiomorpholine S-oxide, thiomorpholine S,S-dioxide, piperidine, pyrrolidine,
 aziridine, pyridine, imidazole, 1,2,3-triazole, 1,2,4-triazole, thiazole, thiazolidine,
 tetrazole, piperazine, furan, thiophene, tetrahydrothiophene,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



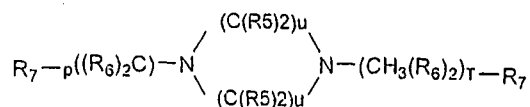
wherein Het is optionally mono- or di-substituted on carbon or nitrogen
 with R_6 , optionally mono- or di-substituted on carbon with hydroxy, $-N(R_6)_2$, or
 $-OR_6$, optionally mono or di-substituted on carbon with the mono-valent radicals
 $-(C(R_6)_2)_sOR_6$ or $-(C(R_6)_2)_sN(R_6)_2$, and optionally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

-72-

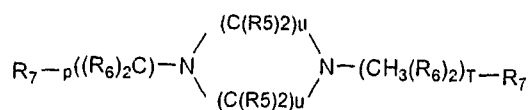


R₃ is independently hydrogen, alkyl of 1-6 carbon atoms, carboxy, carboalkoxy of 1-6 carbon atoms, phenyl, carboalkyl of 2-7 carbon atoms,



R₇-(C(R₆)₂)_s-, R₇-(C(R₆)₂)_p-M-(C(R₇)₂)_r-, R₈R₉-CH-M-(C(R₆)₂)_r-, Het-(C(R₆)₂)_q-W-(C(R₆)₂)_r-; aminoalkyl of 1-6 carbon atoms, N-alkylaminoalkyl of 2-9 carbon atoms, N,N-dialkylaminoalkyl of 3-12 carbon atoms, N-cycloalkylaminoalkyl of 4-12 carbon atoms, N-cycloalkyl-N-alkylaminoalkyl of 5-18 carbon atoms, N,N-dicycloalkylaminoalkyl of 7-18 carbon atoms, morpholino-N-alkyl wherein the alkyl group is 1-6 carbon atoms, piperidino-N-alkyl wherein the alkyl group is 1-6 carbon atoms, N-alkyl-piperidino-N-alkyl wherein either alkyl group is 1-6 carbon atoms;

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;

m is 0-3;p=2-4;

q=0-4;

r=1-4;

-73-

$s=1-6; u=0-4$ and $v=0-4$, wherein the sum of $u+v$ is 2-4;

or a pharmaceutically acceptable salt thereof, provided that

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;

and further provided that

when Y is $-NR_6-$ and R_7 is $-NR_6R_6$, $-N(R_6)_3^+$, or $-NR_6(OR_6)$, then $g=2-6$;

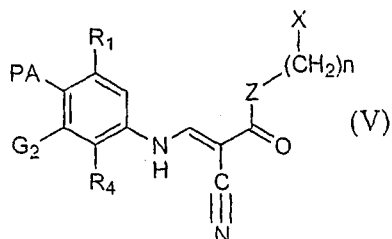
when M is $-O-$ and R_7 is $-OR_6$ then $p=1-4$;

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

21. A compound represented by formula V:



wherein PA is a protected amino group;

wherein 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,

-74-

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 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 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, and benzoylamino;

or

X is a radical having the formula: ---A---T---L

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:

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

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

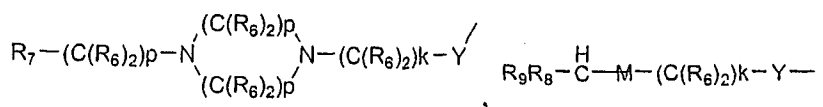
-76-

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;

Z is -NH-, -O-, -S-, or -NR-;

R is alkyl of 1-6 carbon atoms, or carboalkyl of 2-7 carbon atoms;

G₂, R₁, and R₄ 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, 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,



-77-

$R_7-(C(R_6)_2)_g-Y-$, $R_7-(C(R_6)_2)_p-M-(C(R_6)_2)_k-Y-$, or
 $Het-(C(R_6)_2)_q-W-(C(R_6)_2)_p-Y-$; or optionally G_2 is selected from a protected amino
 group and R_2-NH- ;

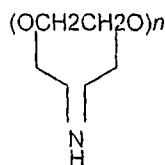
Y is a divalent radical selected from the group consisting of $-(CH_2)_a-$,
 $-O-$, and $-\overset{R_6}{N}-$;

R_7 is $-NR_6R_7$, $-OR_6$, $-J$, $-N(R_6)_3^+$, or $-NR_6(OR_6)$;

M is $>NR_6$, $-O-$, $>N-(C(R_6)_2)_p-NR_6R_6$, 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

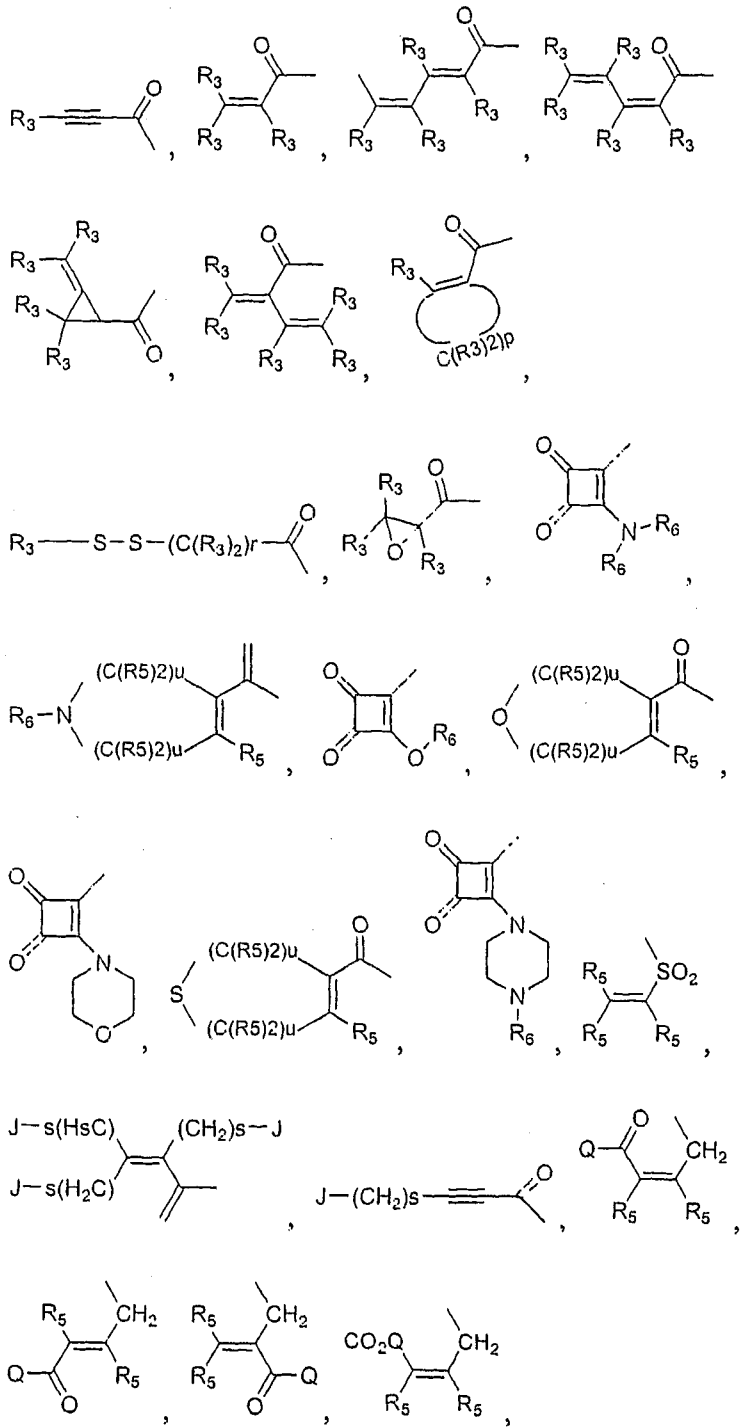


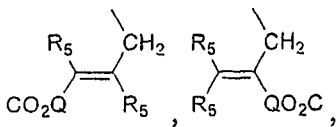
wherein Het is optionally mono- or di-substituted on carbon or nitrogen
 with R_6 , optionally mono- or di-substituted on carbon with hydroxy, $-N(R_6)_2$, or
 $-OR_6$, optionally mono or di-substituted on carbon with the mono-valent radicals
 $-(C(R_6)_2)_sOR_6$ or $-(C(R_6)_2)_sN(R_6)_2$, and optionally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

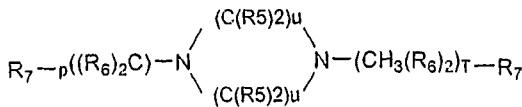
carbon atoms; with the proviso that the alkenyl or alkynyl moiety is bound to a nitrogen or oxygen atom through a saturated carbon atom;

R₂, is selected from the group consisting of



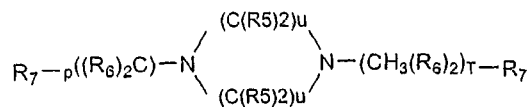


R₃ is independently hydrogen, alkyl of 1-6 carbon atoms, carboxy, carboalkoxy of 1-6 carbon atoms, phenyl, carboalkyl of 2-7 carbon atoms,



R₇-(C(R₆)₂)_s-, R₇-(C(R₆)₂)_p-M-(C(R₇)₂)_r-, R₈R₉-CH-M-(C(R₆)₂)_r-, Het-(C(R₆)₂)_q-W-(C(R₆)₂)_r-; aminoalkyl of 1-6 carbon atoms, N-alkylaminoalkyl of 2-9 carbon atoms, N,N-dialkylaminoalkyl of 3-12 carbon atoms, N-cycloalkylaminoalkyl of 4-12 carbon atoms, N-cycloalkyl-N-alkylaminoalkyl of 5-18 carbon atoms, N,N-dicycloalkylaminoalkyl of 7-18 carbon atoms, morpholino-N-alkyl wherein the alkyl group is 1-6 carbon atoms, piperidino-N-alkyl wherein the alkyl group is 1-6 carbon atoms, N-alkyl-piperidino-N-alkyl wherein either alkyl group is 1-6 carbon atoms;

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;

m is 0-3;

p=2-4;

q=0-4;

-80-

$r=1-4$;

$s=1-6$;

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

or a pharmaceutically acceptable salt thereof, provided that

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;

and further provided that

when Y is $-NR_6-$ and R_7 is $-NR_6R_6$, $-N(R_6)_3^+$, or $-NR_6(OR_6)$, then $g=2-6$;

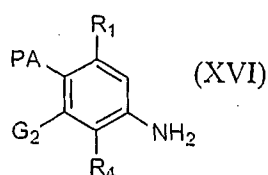
when M is $-O-$ and R_7 is $-OR_6$ then $p=1-4$;

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

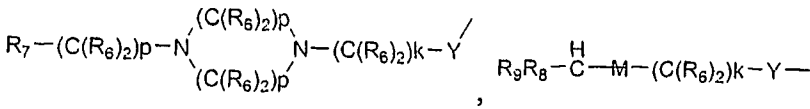
22. A compound represented by formula XVI:



wherein PA is a protected amino group;

G_2 , R_1 , and R_4 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, N,N-dialkenylamino of 6-12 carbon atoms, phenylamino, benzylamino,

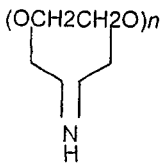


$R_7-(C(R_6)_2)_g-Y-$, $R_7-(C(R_6)_2)_p-M-(C(R_6)_2)_k-Y-$, or $Het-(C(R_6)_2)_q-W-(C(R_6)_2)_2-Y-$; or optionally G_2 is selected from a protected amino group and R_2-NH- ;

Y is a divalent radical selected from the group consisting of $-(CH_2)_a-$, $-O-$, and $-\overset{R_6}{N}-$;

R_7 is $-NR_6R_7$, $-OR_6$, $-J$, $-N(R_6)_3^+$, or $-NR_7C(OR_6)$;
 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

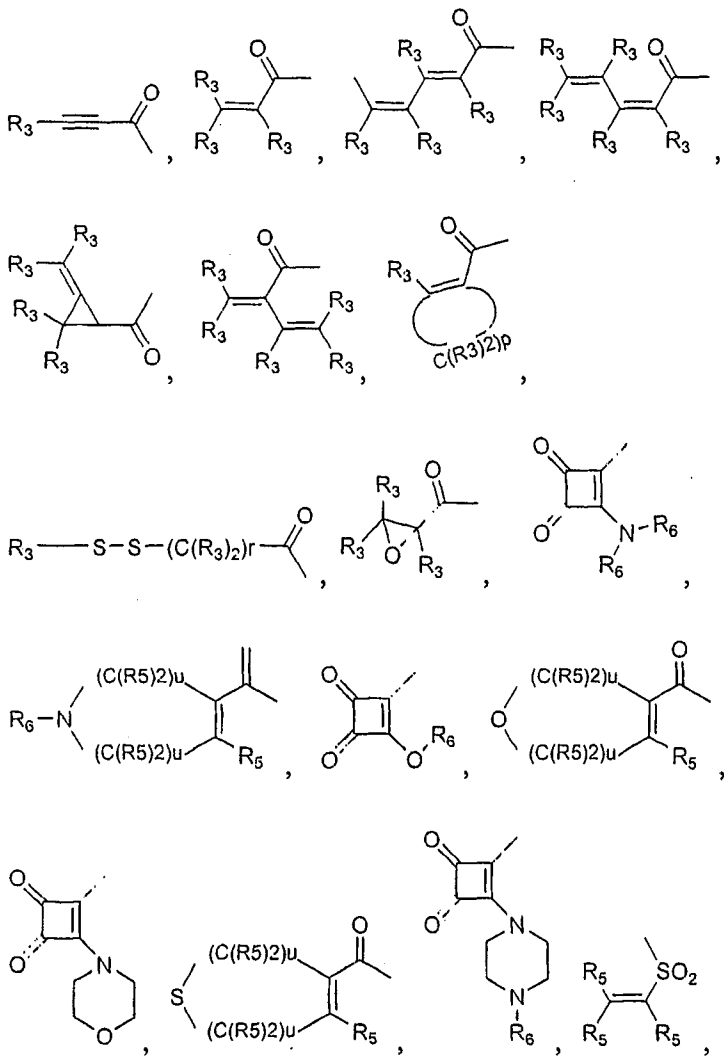


wherein Het is optionally mono- or di-substituted on carbon or nitrogen with R_6 , optionally mono- or di-substituted on carbon with hydroxy, $-N(R_6)_2$, or $-OR_6$, optionally mono or di-substituted on carbon with the mono-valent radicals $-(C(R_6)_2)_sOR_6$ or $-(C(R_6)_2)_sN(R_6)_2$, and optionally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

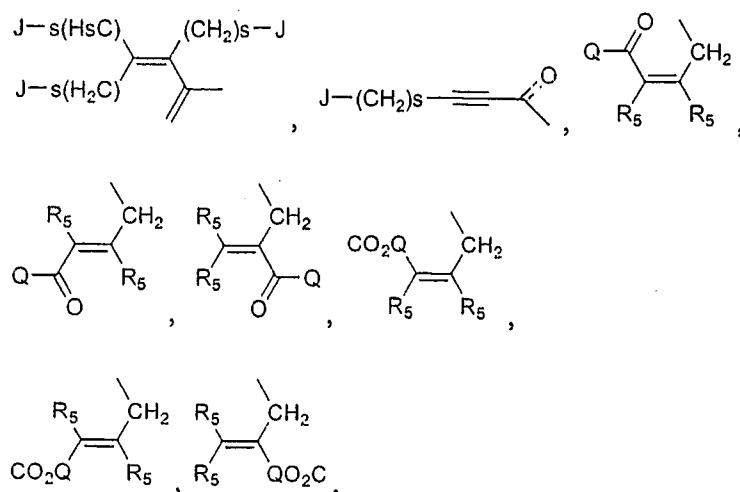
R_6 is hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, cycloalkyl of 1-6 carbon atoms, carboalkyl of 2-7

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;

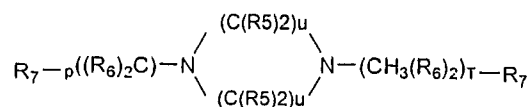
R₂, is selected from the group consisting of



-83-

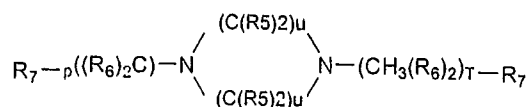


R_3 is independently hydrogen, alkyl of 1-6 carbon atoms, carboxy, carboalkoxy of 1-6 carbon atoms, phenyl, carboalkyl of 2-7 carbon atoms,



$R_7-(C(R_6)_2)_s$ -, $R_7-(C(R_6)_2)_p-M-(C(R_7)_2)_r$ -, $R_8R_9-CH-M-(C(R_6)_2)_r$ -,
 Het- $(C(R_6)_2)_q-W-(C(R_6)_2)_r$ -, aminoalkyl of 1-6 carbon atoms, N-alkylaminoalkyl
 of 2-9 carbon atoms, N,N-dialkylaminoalkyl of 3-12 carbon atoms,
 N-cycloalkylaminoalkyl of 4-12 carbon atoms, N-cycloalkyl-N-alkylaminoalkyl of
 5-18 carbon atoms, N,N-dicycloalkylaminoalkyl of 7-18 carbon atoms,
 morpholino-N-alkyl wherein the alkyl group is 1-6 carbon atoms, piperidino-
 N-alkyl wherein the alkyl group is 1-6 carbon atoms, N-alkyl-piperidino-N-alkyl
 wherein either alkyl group is 1-6 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,



$R_7-(C(R_6)_2)_s$ -, $R_7-(C(R_6)_2)_p-M-(C(R_6)_2)_r$ -, $R_8R_9-CH-M-(C(R_6)_2)_r$ -, 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;

-84-

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;

or a pharmaceutically acceptable salt thereof, provided that

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;

and further provided that

when Y is $-NR_6-$ and R_7 is $-NR_6R_6$, $-N(R_6)_3^+$, 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 $-NR_6-$ then k=2-4;

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

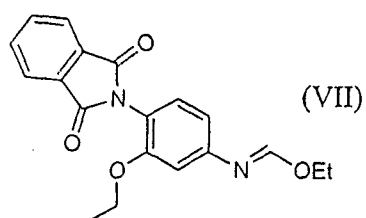
when W is not a bond with Het bonded through a nitrogen atom then q=2-4, and when W is a bond with Het bonded through a nitrogen atom and Y is $-O-$ or $-NR_6-$ then k=2-4.

23. The compound according to claims 20, 21 and 22, wherein the protected amino group is selected from the group consisting of acetamides, benzamides, cyclic imides, pyrroles, tert-butoxycarbonyl amine and benzyloxycarbonyl amide.

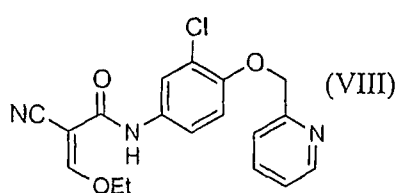
24. The compound according to claim 23, wherein the protected amino group is phthalimide.

25. A compound represented by formula VII:

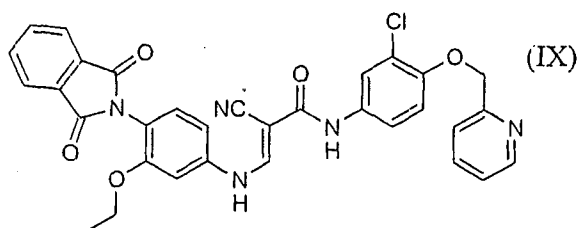
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26. A compound represented by formula VIII:

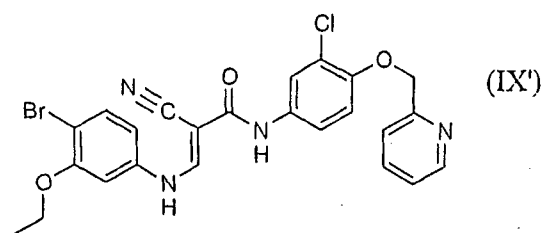


27. A compound represented by formula IX:

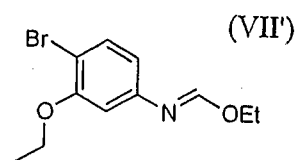


28. The method according to claim 1, 2, 3, 4, and 5, wherein G_1 is a halogen selected from the group consisting of F, Cl, Br, or I.

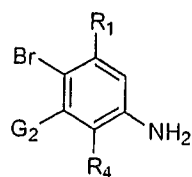
29. The method according to claims 1, 2, 3, 4, and 5, wherein the N-aryl-2-propene of formula III is the compound represented by formula IX':



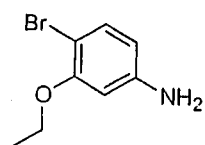
30. The method according to claims 1, 2, 3, 4 and 5, wherein the N-arylformimidate of formula I is a compound represented by formula VII':



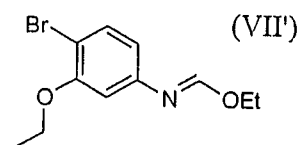
31. The method according to claims 3, 4 and 5, wherein the arylamine of formula XIII is a compound represented by the structure:



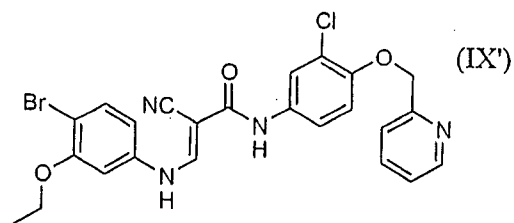
32. The method according to claim 31, wherein the arylamine is:



33. A compound of formula VII':



34. A compound of formula IX':



MÉTODO PARA PREPARAR 3-CIANO-QUINOLINAS E INTERMEDIOS

HECHOS DE ESTA FORMA

ANTECEDENTES DE LA INVENCION

5

Campo de la Invención

[0001] La invención se relaciona con un método para la preparación de 3-cianoquinolinas sustituidas. Las 3-cianoquinolinas se hacen mediante dos rutas separadas que incluyen la reacción de arilaminas, ortoformatos y metilenos activos. Ambas rutas resultan en la producción de derivados de N-aril-2-propeno.

[0002] Las cinasas proteínicas son una clase de enzimas que 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 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 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 sobreexpresión, estos RTK se 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) and Parsons, J. T.; Parsons, S. J., Important Advances in Oncology, DeVita, V. T. Ed., J. B. Lippincott Co., Phila., 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) and 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 antineoplásicos potenciales [some recent reviews: Traxler, P., Exp. Opin. Ther. Patents, 8, 1599 (1998) and 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. La patentes de Wissner et al. se incorporan aquí todas como referencia en su totalidad.

[0005] Los métodos conocidos para elaborar quinolinas utilizan la reacción de ciclización térmica. Ver, R.W. Sabnis and D.W. Rangnekar, J. Hetero. Chem. 29:65 (1992); N.C. Mehta and CM. Desai, J. Ind. Chem. Soc. 55: 193 (1978); H. Bredereck, F. Effenberger, H. Botsch and H. Rehn, Chem. Ber. 98: 1081 (1965); J. Salon, V. Milita, N. Pronayova y J. Lesko, Monatsh.fur Chem. 131:293 (2000). Tales reacciones de ciclización térmica requieren altas temperaturas (> 240 °C) que limitan su practicidad para la producción a gran escala. Adicionalmente, tales procesos también requieren condiciones de alta dilución que resultan en producción y rendimiento general reducidos. Los rendimientos en la reacción de ciclización térmica son típicamente del 50% o menos pero son variables y pueden cambiar de 19-94%.

[0006] También se ha descrito una metodología asistida por microondas para la producción de quinolinas a partir de aminas aromáticas. Ver CG. Dave and H.M. Joshipura, *Intl. J Chem.* 41B:650 (2002).

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[0007] La funcionalidad posterior de las hidroxiquinolinas requiere típicamente clorinación o halogenación. Las reacciones de clorinación de hidroxiquinolinas sufren la generación de alquitranes viscosos y productos de descomposición que son difíciles de remover. Los rendimientos en la reacción de clorinación son variables y cambian de 24-
10 60%.

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[0008] Hasta la fecha no ha existido ninguna descripción en la técnica para un método catalítico o más suave para preparar quinolinas que no requiera altas temperaturas. La presente invención proporciona una síntesis novedosa más suave que supera los problemas de la producción a escala de la técnica anterior.

RESUMEN DE LA INVENCION

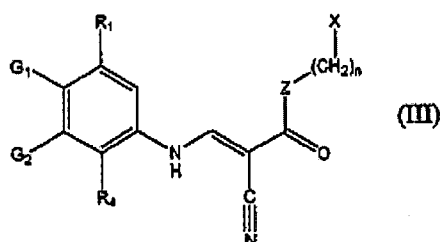
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[0009] La presente invención proporciona métodos mejorados para elaborar tales 3-cianoquinolinas sustituidas, intermedios obtenidos por los métodos de la invención, y las 3-cianoquinolinas sustituidas elaboradas por los métodos de la invención.

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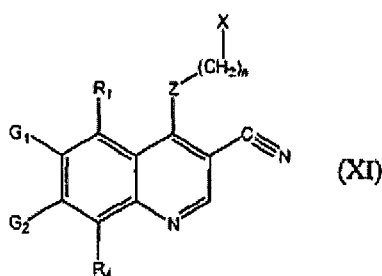
[0010] Los métodos de elaboración de las 3-cianoquinolinas utilizan dos rutas separadas. Ambas rutas resultan en la producción de derivados N-aril-2-propeno que se tratan luego con cloruro de fosforilo para proporcionar 3-cianoquinolinas.

[0011] Una primer modalidad de esta invención se dirige a un método para preparar una 3-cianoquinolina sustituida que comprende la etapa de tratar un N-aril-2-propeno representado por la fórmula III:



5

con POCl_3 para formar una 3-cianoquinolina sustituida representada por la fórmula XI:



en donde:

- 10 X es un sistema de anillo heteroarilo bicíclico o arilo bicíclico de 8 a 12 átomos en donde el anillo heteroarilo bicíclico contiene de 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 heteroarilo bicíclico o arilo bicíclico puede ser opcionalmente
- 15 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, alcanoiloximetilo 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
- 20 carbono, carboalquilo de 2-7 átomos de carbono, fenoxi, fenilo, tiofenoxi, benzoilo, bencilo, amino, alquilamino de 1-6 átomos de carbono, dialquil amino 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 átomos de carbono, N-alquilaminoalcoxi de 2-9 átomos de carbono, N,N-dialquilaminoalcoxi de 3-10 átomos de carbono, mercapto, y benzoilamino; o X es cicloalquilo de 3 a 7 átomos de carbono, que pueden ser opcionalmente sustituidos con uno o más grupos alquilo de 1 a 6 átomos de carbono; o es un anillo piridinilo, pirimidinilo, o fenilo; en donde el anillo piridinilo, pirimidinilo, o fenilo opcionalmente mono- di-, o tri-sustituido 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, alcanoiloximetilo 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, y benzoilamino; o

X es un radical que tiene la fórmula: ---A---T---L

en donde A es un anillo piridinilo, pirimidinilo, o fenilo; en donde el anillo piridinilo, pirimidinilo, o fenilo puede ser opcionalmente mono- o di-sustituido 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, alcanoiloximetilo 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 átomos de carbono, N-alquilaminoalcoxi de 2-9 átomos de carbono, N,N-dialquilaminoalcoxi de 3-10 átomos de carbono, mercapto, y benzoilamino;

T se une a un carbono de A y es:

10 -NH(CH₂)_m-, -O(CH₂)_m-, -S(CH₂)_m-, -NR CH₂)_m-, -(CH₂)_m-, -(CH₂)_mNH-, - (CH₂)_mO, - (CH₂)_mS-, o -(CH₂)_mNR-;

L es un anillo fenilo no sustituido o un anillo fenilo mono-, di-, o tri-sustituido 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, alcanoiloximetilo 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, 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 átomos de carbono, N-alquilaminoalcoxi de 2-9 átomos de carbono, N,N-dialquilaminoalcoxi de 3-10 átomos de carbono, mercapto, y benzoilamino; dado que L puede ser un anillo fenilo no sustituido solo cuando ;m>0 y T no es - CH₂ NH- o -CH₂O-; o

L es un anillo heteroarilo de 5- o 6-miembros en donde al anillo heteroarilo contiene de 1 a 3 heteroátomos seleccionados de N, O, y S, con la condición que al 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 un sustituyente seleccionado del grupo que

5 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, alcanoiloximetilo de 2-7 átomos de carbono, alcoxi de 1-6 átomos de carbono, alquiltio de 1-6 átomos de carbono, hidroxil, trifluorometilo, ciano, nitro, carboxi, carboalcoxi de 2-

10 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,

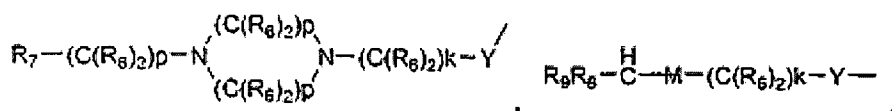
15 aminoalquilo de 1-5 átomos de carbono, N-alquilaminoalquilo de 2-9 átomos de carbono, N,N-dialquilaininoalquilo de 3-10 átomos de carbono, N-alquilaminoalcoxi de 2-9 átomos de carbono, N,N-dialquilaminoalcoxi de 3-10 átomos de carbono, mercapto, y benzoilamino;

Z es -NH-, -O-, -S-, o -NR-;

20 R es alquilo de 1-6 átomos de carbono, o carboalquilo de 2-7 átomos de carbono; G₁, G₂, R₁, y R₄ 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, alcanoiloxi de 1-6 átomos de carbono, alquenoiloxi de 3-8

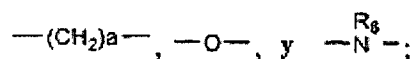
25 átomos de carbono, alquinoiloxi de 3-8 átomos de carbono, alcanoiloximetilo de 2-7 átomos de carbono, alquenoiloximetilo de 4-9 átomos de carbono, alquinoiloximetilo de 4-9 átomos de carbono, alcoximetilo de 2-7 átomos de carbono, alcoxi de 1-6 átomos de carbono, alquiltio de 1-6 átomos de carbono, alquilsulfinilo de 1-6 átomos de carbono,

alquilsulfonilo de 1-6 átomos de carbono, alquilsulfonamido de 1-6 átomos de carbono, alquenilsulfonamido de 2-6 átomos de carbono, alquinilsulfonamido de 2-6 átomos de carbono, hidroxilo, trifluorometilo, trifluorometoxi, ciano, nitro, carboxi, carboalcoxi de 2-7 átomos de carbono, carboalquilo de 2-7 átomos de carbono, fenoxi, ftalimida, fenilo, tienofenoxi, 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-alquilcarbamoilo, N,N-dialquilcarbamoilo, N-alquil-N-alquenilamino de 4 a 12 átomos de carbono, N,N-dialquenilamino de 6-12 átomos de carbono, fenilamino, bencilamino,



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

opcionalmente G_1 y/o G_2 se seleccionan independientemente de un grupo amino protegido y R_2-NH ; o si cualquiera de los sustituyentes R_1 , G_1 , G_2 , o R_4 se localizan en átomos de carbono contiguos entonces ellos pueden ser tomados juntos como el radical divalente $-O-C(R_6)_2-O$; Y es un radical divalente seleccionado del grupo que consiste de

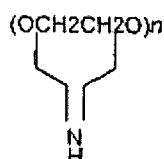


R_7 es $-NR_6R_7$, $-OR_6$, $-J$, $-N(R_6)_3^+$, o $-NR_7(OR_6)$;

M es $>NR_6$, $-O-$, $>N-(C(R_6)_2)_p-NR_6R_6$, o $>N-(C(R_6)_2)_p-OR_6$;

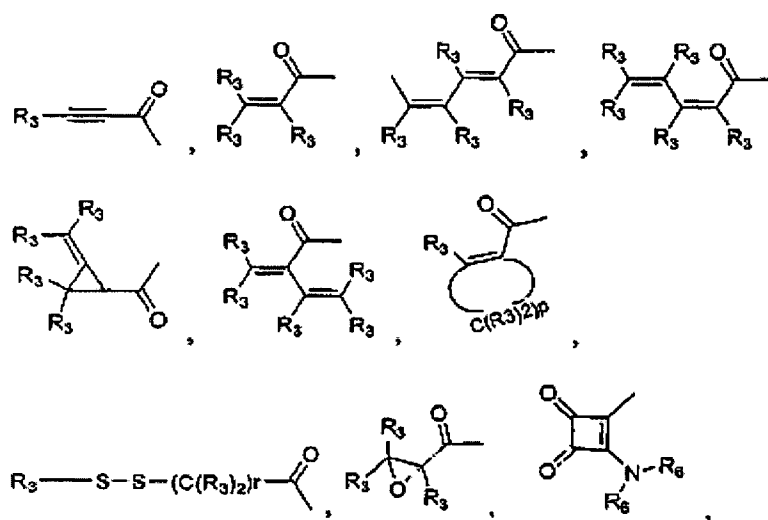
W es $>NR_6$, $-O-$ o es un enlace;

Het se selecciona del grupo que consiste de morfolina, tiomorfolina, S-óxido de tiomorfolina, S,S-dióxido de tiomorfolina, piperidina, pirrolidina, aziridina, piridina, imidazol, 1,2,3-triazol, 1,2,4-triazol, tiazol, tiazolidina, tetrazol, piperazina, furano, tiofeno, tetrahidrotiofeno, tetrahidrofurano, dioxano, 1,3-dioxolano, tetrahidropirano, y



en donde Het es opcionalmente mono- o di-sustituido en carbono o nitrógeno con R_6 ,
 opcionalmente mono- o di-sustituido en carbono con hidroxilo, $-N(R_6)_2$, o $-OR_6$,
 opcionalmente mono o di-sustituido en carbono con los radicales mono-valentes -
 $(C(R_6)_2)_sOR_6$ o $-(C(R_6)_2)_sN(R_6)_2$ y opcionalmente mono o di-sustituido en un carbono
 5 saturado con radicales divalentes $-O-$ o $-O(C(R_6)_2)_sO-$;

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, carboxialquil (2-7 átomos de carbono), fenilo, o
 fenilo opcionalmente sustituido con uno o más halógenos, alcoxi de 1-6 átomos de
 10 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, alcanoilamino de 1-6 átomos de
 15 carbono, o alquilo de 1-6 átomos de carbono; con la condición que la porción alquenilo
 o alquinilo está unida a un átomo de nitrógeno u oxígeno a través de un átomo de
 carbono saturado; R_2 , se selecciona del grupo que consiste de



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;

1=1-4;

s=1-6;

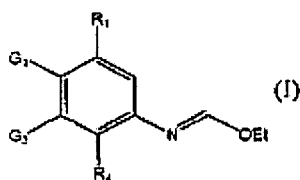
10 u=0-4 y v=0-4, en donde la suma de u+v es 2-4; o una sal farmacéuticamente aceptable de estos, dado que cuando R_6 es alquenilo de 2-7 átomos de carbono o alquinilo de 2-7 átomos de carbono, tal porción alquenilo o alquinilo está unida a un átomo de nitrógeno u oxígeno a través de un átomo de carbono saturado; y dado que cuando Y es $-NR_6-$ y R_7 es $-NR_6R_6 - N(R_6)_3^+$, o $-NR_6(OR_6)$, entonces g=2-6; cuando M es $-O-$ y R_7 es $-OR_6$

15 entonces p=1-4; cuando Y es $-NR_6-$ entonces k=2-4; cuando Y es $-O-$ y M o W es $-O-$ entonces k=1-4 cuando W no es un enlace con Het unido a través de un átomo de nitrógeno entonces q=2-4 y cuando W es un enlace con Het unido a través de un átomo de nitrógeno y Y es $-O--$ o $-NR_6-$ entonces k=2-4.

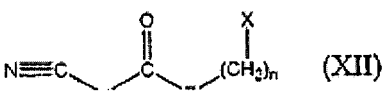
20 [0012]A menos que aquí se establezca de otra manera, todas las variables establecidas anteriormente, por ejemplo G_1 , G_2 , R_1 , R_4 , Z, X y n, aplican a la fórmula y esquemas establecidos a través de esta solicitud.

[0013]En otra modalidad de esta invención el compuesto N-aril-2-propeno de fórmula III

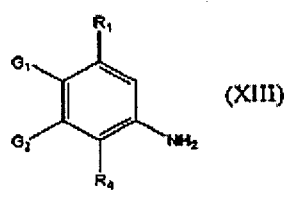
25 se puede formar al condensar un N-arilformimidato de fórmula I



con un metileno activo de fórmula XII o x

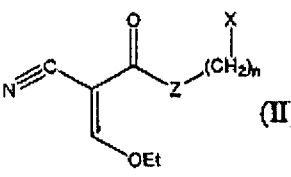


[0014] En otra modalidad, el N-arilformimidato de fórmula I se puede formar al hacer
5 reaccionar una arilamina de fórmula (XIII).

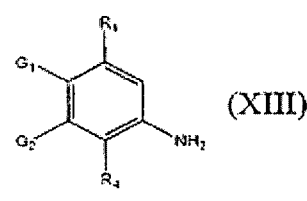


con CH(OEt)₃

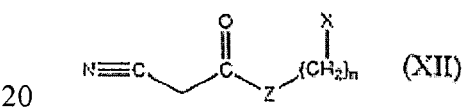
10 [0015] En otra modalidad de la invención el N-aril-2-propeno de fórmula III se puede formar al hacer reaccionar un derivado de alcoximetileno de fórmula II.



con una arilamina de fórmula XIII

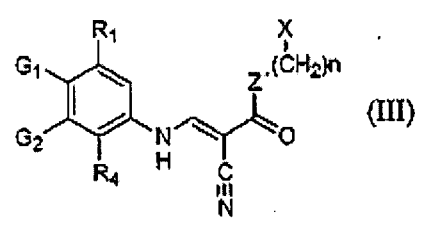
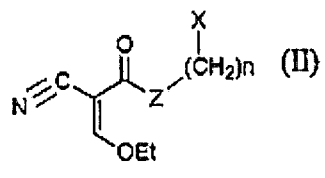
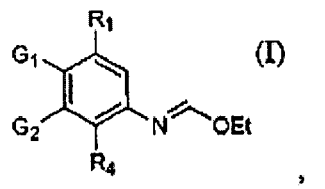


15 [0016] En una modalidad adicional de la invención, el alcoximetileno de fórmula II se puede formar al condensar un metileno activo de fórmula XII



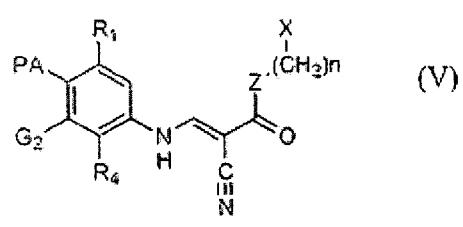
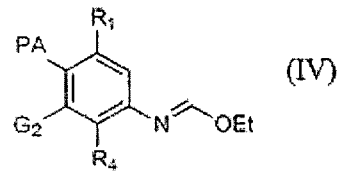
20 con CH(OEt)₃.

[0017] La presente invención también suministra para los intermediarios producidos por los métodos de la presente invención. En una modalidad de la invención, los intermediarios son de las fórmulas I, II y III adelante.



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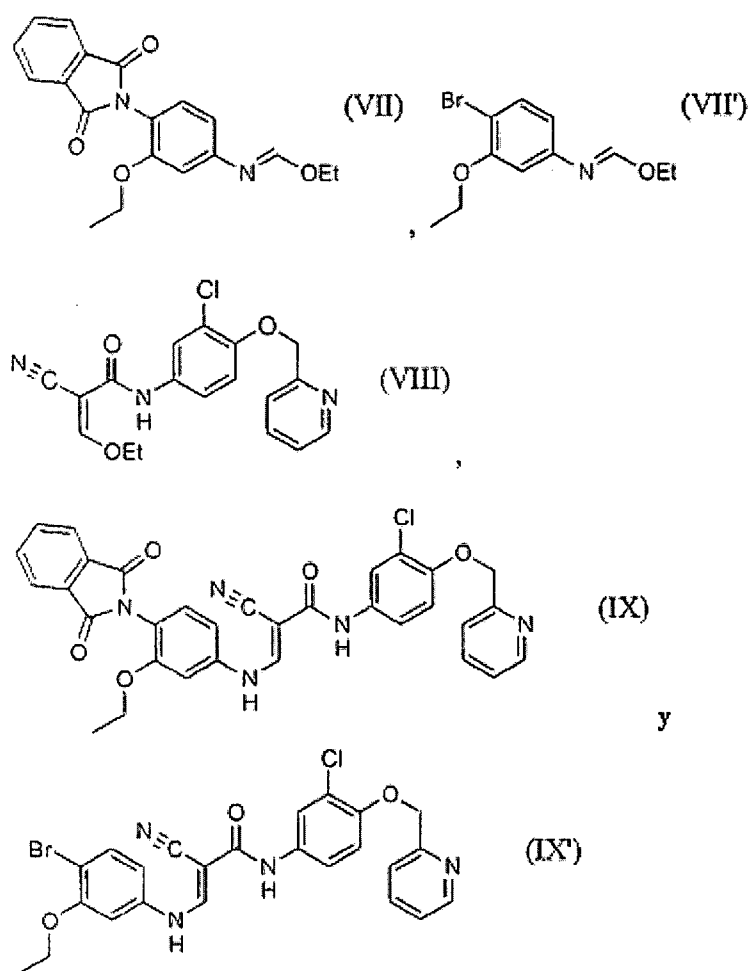
[0018] En otra modalidad de la invención, los intermediarios son de fórmulas IV y V adelante:



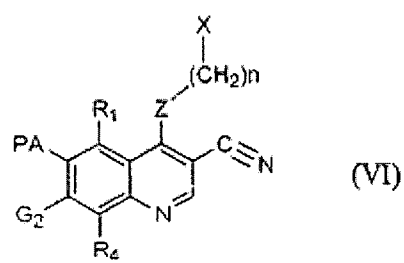
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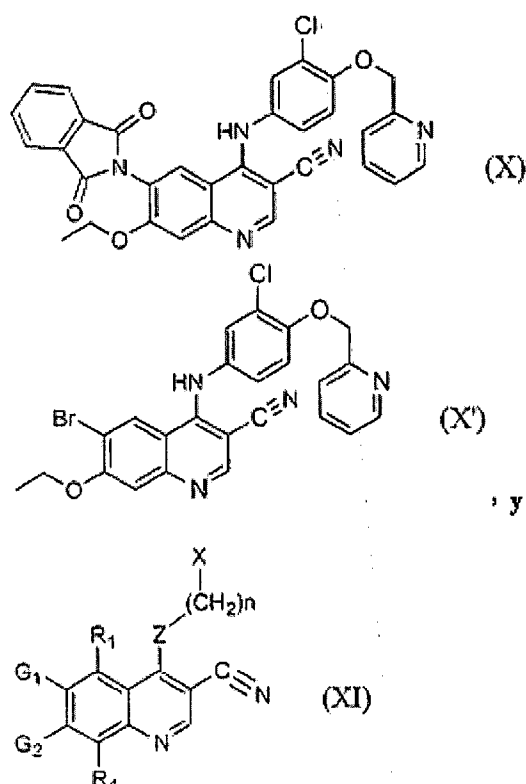
en donde PA es un grupo amino protegido.

[0019] En una modalidad adicional de la invención, los intermediarios son de fórmulas VII, VII', VIII, IX y IX' adelante:



[0020] La presente invención también se suministra para derivados de 3-cianoquinolina producidos por los métodos de la presente invención. De acuerdo con esto, la invención se suministra una 3-cianoquinolina de fórmulas VI, X, X' y XI producidas por los métodos de la presente invención:





DETALLADA DESCRIPCIÓN DE LA INVENCION

5 [0021] La presente invención proporciona métodos mejorados de elaboración de 3-cianoquinolinas sustituidas, intermedios obtenidos por los métodos de la invención, y 3-cianoquinolinas sustituidas elaboradas por los métodos de la invención.

[0022] Como se estableció anteriormente, los métodos de elaboración de las 3-cianoquinolinas utilizan dos rutas separadas. Ambas rutas incluyen la reacción de arilaminas, ortoformatos y metilenos activos y ambas rutas resultan en la producción de derivados de N-aril-2-propeno. Los métodos de la presente invención evitan muchos de los obstáculos de las rutas sintéticas de la técnica anterior, en razón a que ellas no involucran calentar a altas temperaturas o utilizar radiación de microondas. Así, los métodos actuales se pueden adaptar fácilmente para la preparación a gran escala de 3-cianoquinolinas. También, se evita la etapa de clorinación utilizada en los métodos de la técnica anterior. Esta también es una mejora en razón a que la clorinación de las quinolinas se sabe que se sufre a partir de la formación de alquitranes viscosos y

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15

productos de descomposición, que resulta en rendimientos inferiores de los productos deseados e impurezas que son difíciles de remover. Por lo tanto, la síntesis que involucra la clorinación de quinolinas no son muy practicas para uso en la síntesis a gran escala de 3-cianoquinolinas. El método actual también es ventajoso en razón a que este facilita la síntesis de muchos derivados de 3-cianoquinolinas con porciones variantes sustituidas en la posición 4 del sistema de anillo quinolina.

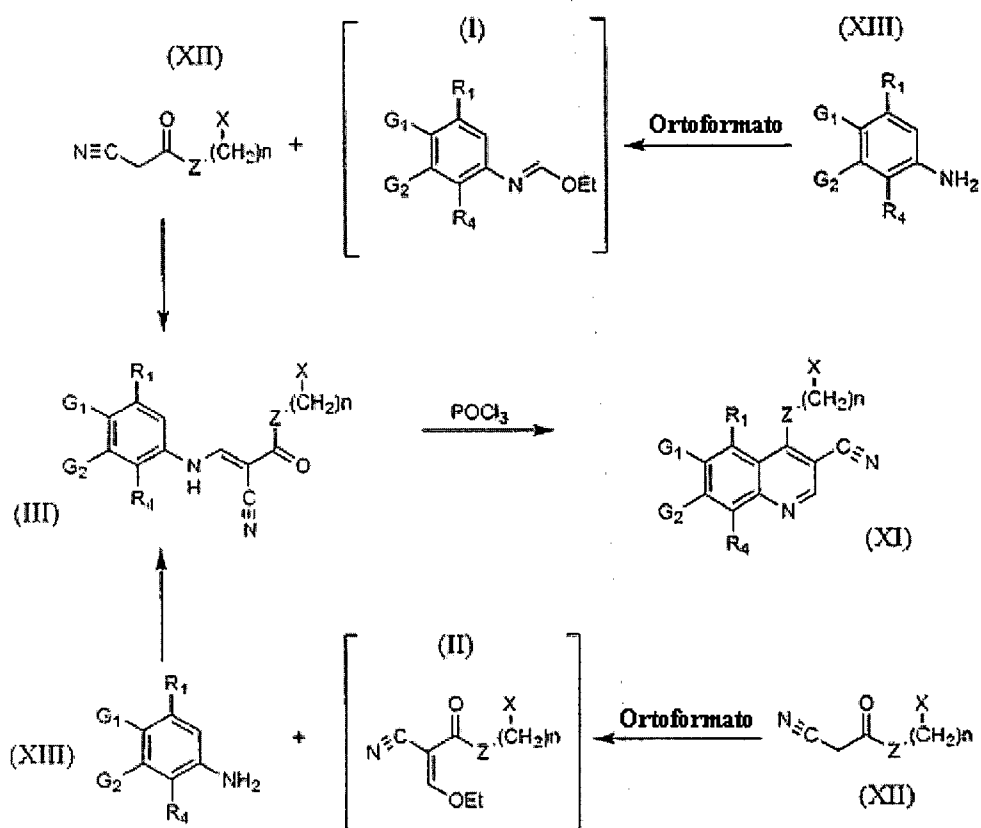
[0023] En una modalidad de la invención, las arilamina incluyen un grupo amino protegido tal como ftalimida, imidas cíclicas, maleimida, 2,3-dicloromaleamida, succinimida, dihidroftalimida, y 2,5-dimetilpirrol. Las arilaminas que se pueden utilizar en los métodos de la presente invención se describen, por ejemplo, en la Patente Estadounidense No. 4,873,338 de Wiesen et al., y la Patente Estadounidense No. 4,617,316 de Plummet et al., todas las cuales se incorporan aquí como referencia en su totalidad.

[0024] En una modalidad de la invención, una arilamina se hace reaccionar con un ortoformato para producir un N-arilformimidato, que luego se condensa con un metileno activo para producir un N-aril-2-propeno.

[0025] En otra modalidad de la invención, un compuesto de metileno activo se condensa con un ortoformato para producir un derivado de alcoximetileno que luego se hace reaccionar con una arilamina para dar un N-aril-2-propeno. Como se menciono anteriormente, en ambos esquemas, el N-aril-2-propeno se hace reaccionar luego con cloruro de fosforilo para producir las 3-cianoquinolinas de la presente invención. En aún otra modalidad, las arilaminas incluyen por lo menos un grupo amino protegido.

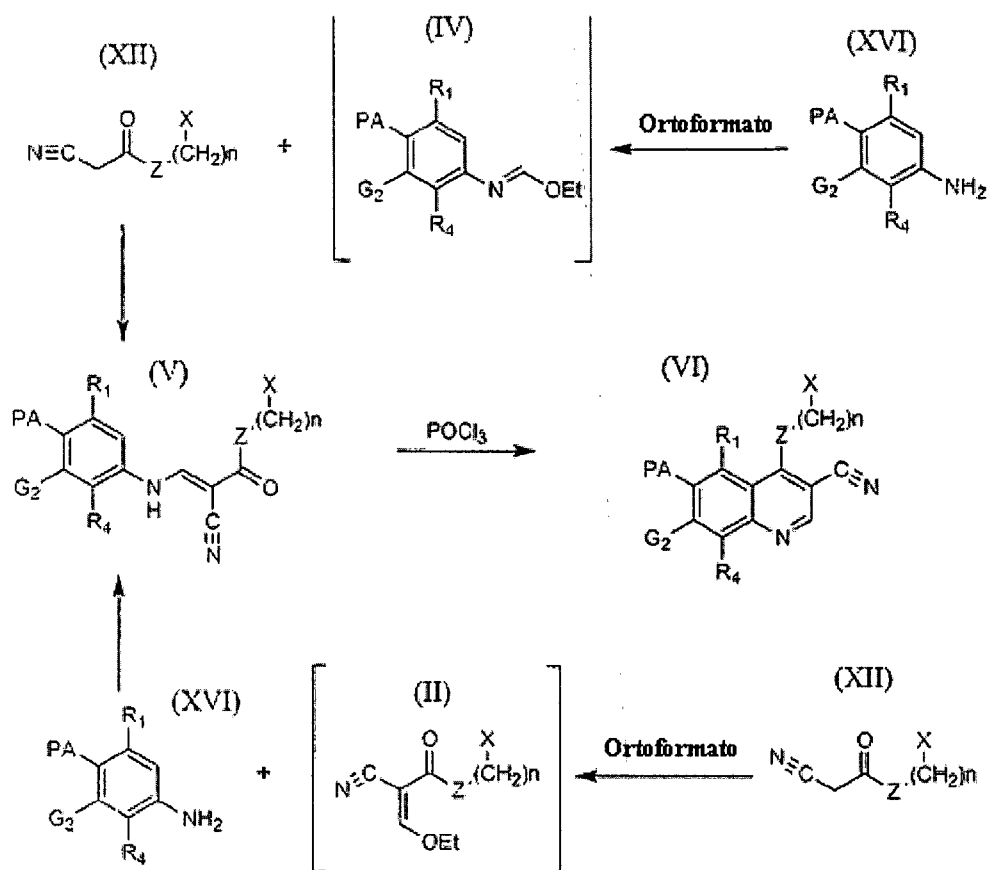
[0026] Una modalidad de la invención se representa en el Esquema 1 adelante que muestra ambas rutas de los métodos de la invención.

Esquema 1



- 5 [0027] Otra modalidad de la invención se representa por el Esquema 2 adelante que muestra las modalidades de las dos rutas de los métodos de la presente invención.

Esquema 2



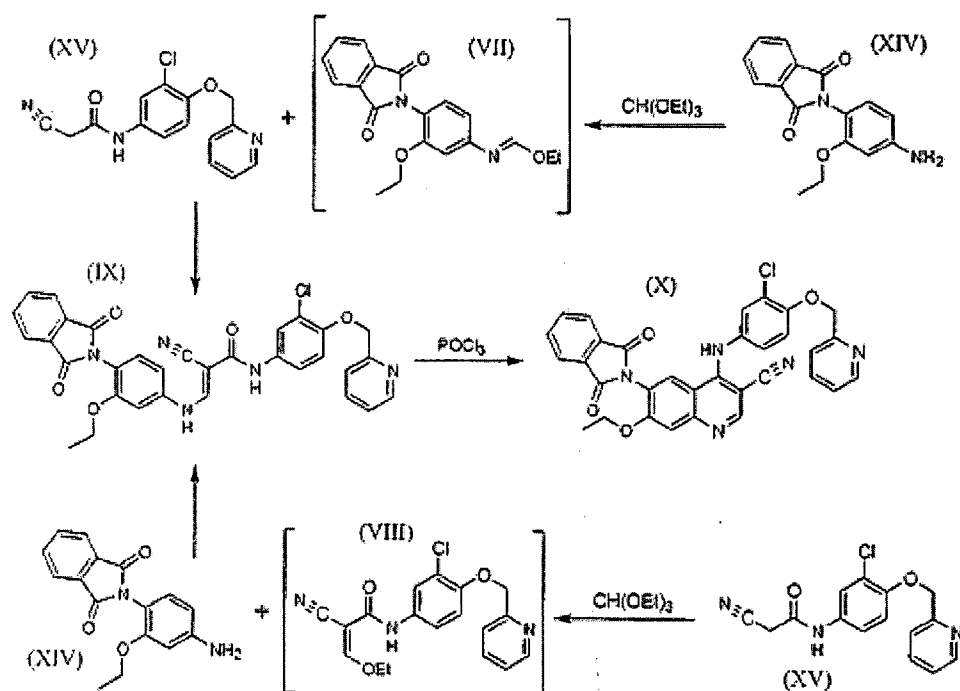
5

en donde PA representa un grupo amino protegido.

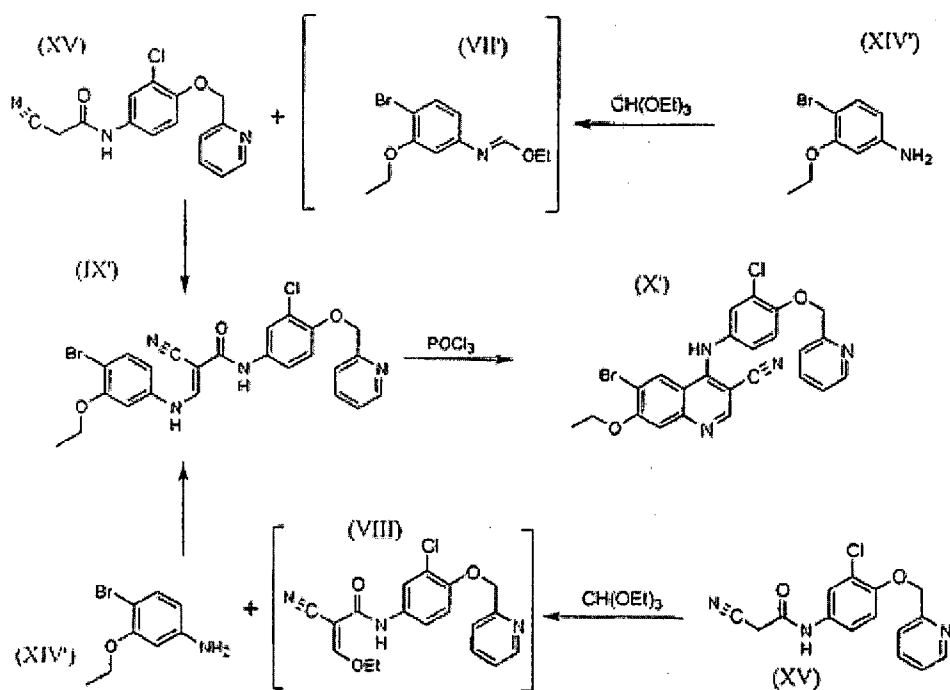
[0028] Modalidades específicas de la presente invención se describen en los Esquemas 3a y 3b adelante que muestran modalidades de las dos rutas de los métodos de la presente invención. En el esquema 3a, G_1 es una amina protegida. El Esquema 3b ilustra en donde G_1 es bromo. Los compuestos con halógenos en la posición 6 se pueden hacer reaccionar fácilmente con reactivos, tales como aminas y alcoholes, para formar otros derivados abarcados dentro de la presente invención.

15

Esquema 3a

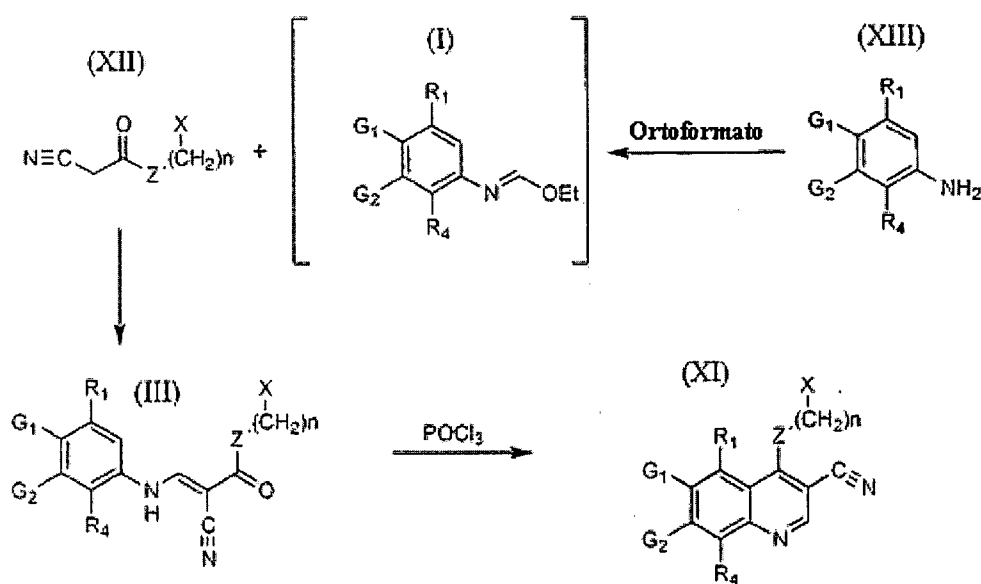


Esquema 3b



[0029] En el Esquema 1 se incluye dos modalidades de la invención, que representan las dos rutas separadas, una primera que se representa por el Esquema 4 adelante.

Esquema 4



5 en donde X, Z, G_1 , G_2 , R_1 y R_4 son como se describió previamente.

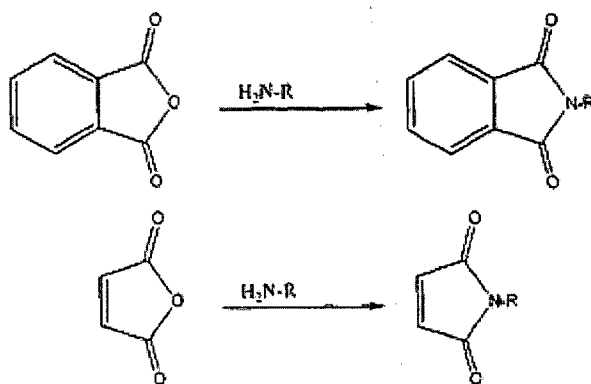
[0030] El término grupo amino protegido se refiere (PA) se refiere a un grupo amina o amino que tiene o forma un "grupo protector" que se refiere a un grupo introducido en una molécula para proteger un grupo funcional sensible o posición específica en la

10 molécula de reaccionar cuando la molécula se expone a reactivos o condiciones para transformar o reaccionar con otra parte de la molécula. Después de esto se puede remover el grupo protector. Los grupos protectores adecuados son bien conocidos en la técnica e incluyen ácido lábil, base lábil, fotoremovible, o removible bajo condiciones neutras. Ver, por ejemplo, Green, Protecting Groups in Organic Synthesis, Wiley 1991,

15 2da ed., pp. 309-405, que se incorpora aquí como referencia. Grupos amino protegidos de ejemplo incluyen acetamidas, benzamidas, imidas cíclicas (por ejemplo, ftalimida, maleimida, 2,3-dicloromaleimida, succinimida, dihidroftalimida), pirroles (por ejemplo 2,5-dimetilpirrol), amina terc-butoxicarbonilo protegido y amida benciloxicarbonilo protegida.

20 [0031] Las ciclimidas son grupos protectores particularmente útiles para enmascarar aminas primarias. Ellas se forman al hacer reaccionar amina primaria para ser

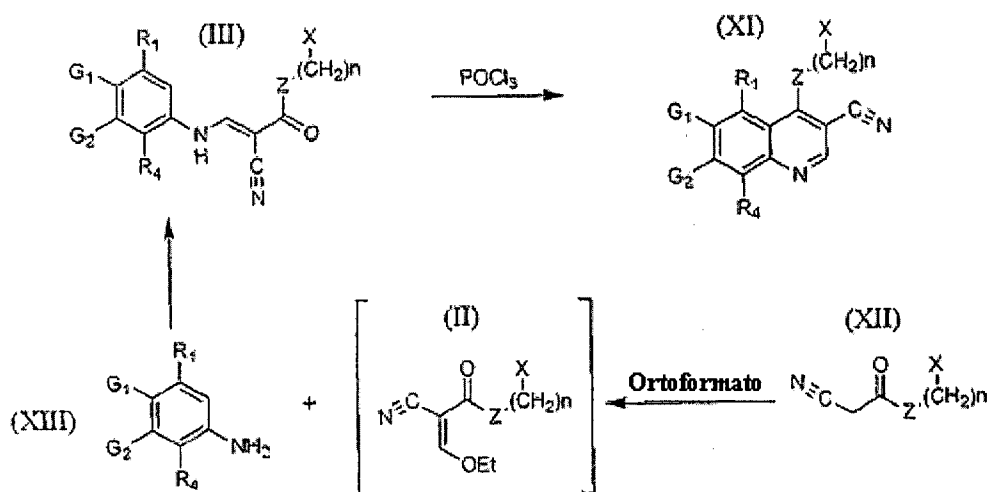
enmascarada con un reactivo tal como anhídrido ftálico o anhídrido meleámico, de tal modo incorporar la amina en la ciclicimida, como se muestra adelante.



- 5 [0032] Después, las ciclímidas se pueden clivar bajo una variedad de condiciones, tales como NH_4OH , para dar la amina primaria en buen rendimiento. Ver *Green* at pp. 358-359. En una modalidad de la presente invención NH_4OH se utiliza para clivar el grupo protector ftalimida. Esto se logra mejor utilizando equivalentes múltiples de NH_4OH relativos al compuesto protector, en donde 10 equivalentes son efectivos, siendo aún
- 10 más eficientes 25 equivalentes. 2,5-Dimetilpirrol opera similarmente.

[0033] La segunda modalidad del Esquema 1 se representa en el Esquema 5 adelante.

Esquema 5



en donde X, Z, G_1 , G_2 , R_1 y R_4 son como se describió previamente.

[0034] En otra modalidad de los Esquemas 4 y 5, X es cicloalquilo de 3 a 7 átomos de carbono, que puede ser opcionalmente sustituido con uno o más grupos alquilo de 1 a 6 átomos de carbono; o es un anillo piridinilo, pirimidinilo, o fenilo; en donde el anillo piridinilo, pirimidinilo, o fenilo opcionalmente mono- di-, o tri-sustituido 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, alcanoiloximetilo 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, y benzoilamino.

[0035] En otra modalidad de la invención, X es un radical que tiene la fórmula: A-T-L en donde A es un anillo piridinilo, pirimidinilo, o fenilo; en donde el anillo piridinilo, pirimidinilo, o fenilo puede ser opcionalmente mono- o di-sustituido 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, alcanoiloximetilo 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 átomos de carbono, N-
 alquilaminoalcoxi de 2-9 átomos de carbono, N,N-dialquilaminoalcoxi de 3-10 átomos de
 5 carbono, mercapto, y benzoilamino;

[0036] T se une a un carbono de A y es:

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

[0037] L es un anillo fenilo no sustituido o un anillo fenilo mono-, di-, o tri- sustituido 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
 15 de carbono, alcanoiloximetilo de 2-7 átomos de carbono, alcoxi de 1-6 átomos de
 carbono, alquiltio de 1-6 átomos de carbono, hidroxil, 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
 20 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
 25 carbono, mercapto, y benzoilamino; dado que L puede ser un anillo fenilo no sustituido
 solo cuando $m > 0$ y T no es -CH₂ NH- o -CH₂O-; o

[0038] L es un anillo heteroarilo de 5- o 6-miembros en donde al anillo heteroarilo contiene de 1 a 3 heteroátomos seleccionados de N, O, y S, con la condición que al anillo heteroarilo no contiene enlaces O-O, S-S, o S-O, y en donde al anillo heteroarilo es opcionalmente mono- o di-sustituido con un sustituyente seleccionado del grupo que

5 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, alcanoiloximetilo 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-

10 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,

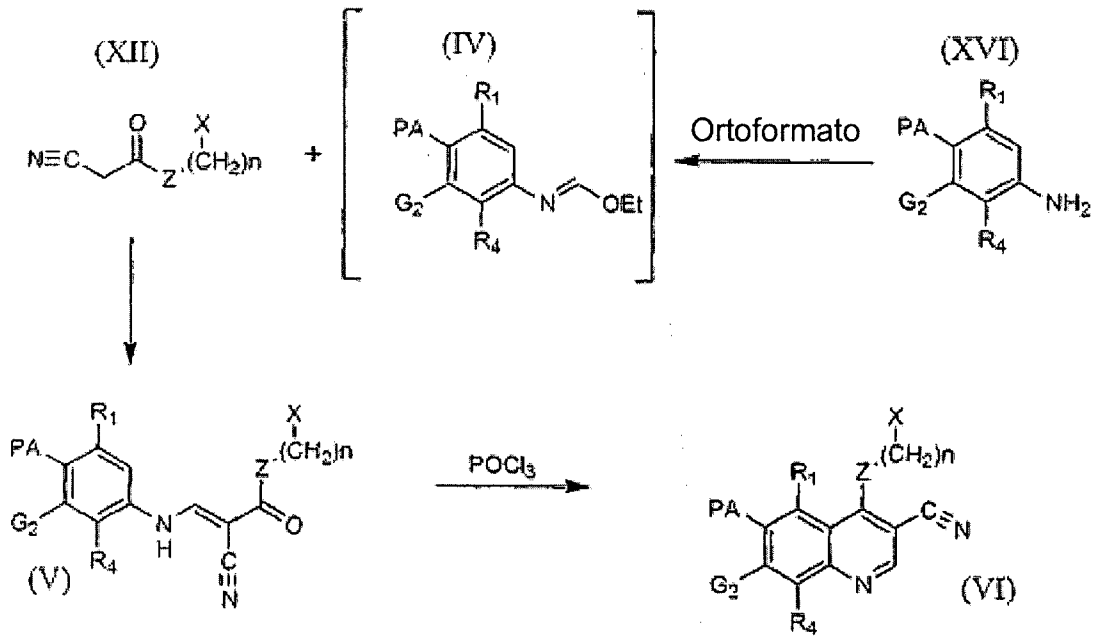
15 aminoalquilo de 1-5 átomos de carbono, N-alquilaminoalquilo de 2-9 átomos de carbono, N,N-dialquilaminoalquilo de 3-10 átomos de carbono, N-alquilaminoalcoxi de 2-9 átomos de carbono, N,N-dialquilaminoalcoxi de 3-10 átomos de carbono, mercapto, y benzoilamino.

20 [0039] En una modalidad adicional de los métodos descritos por los Esquemas 4 y 5, G₁ es un grupo amino protegido (PA). En aún otra modalidad de la invención, el grupo amino protegido es ftalimida.

[0040] Las dos modalidades de las rutas mostradas en el Esquema 2 anterior, se

25 representan en el Esquema 6 y 7 adelante.

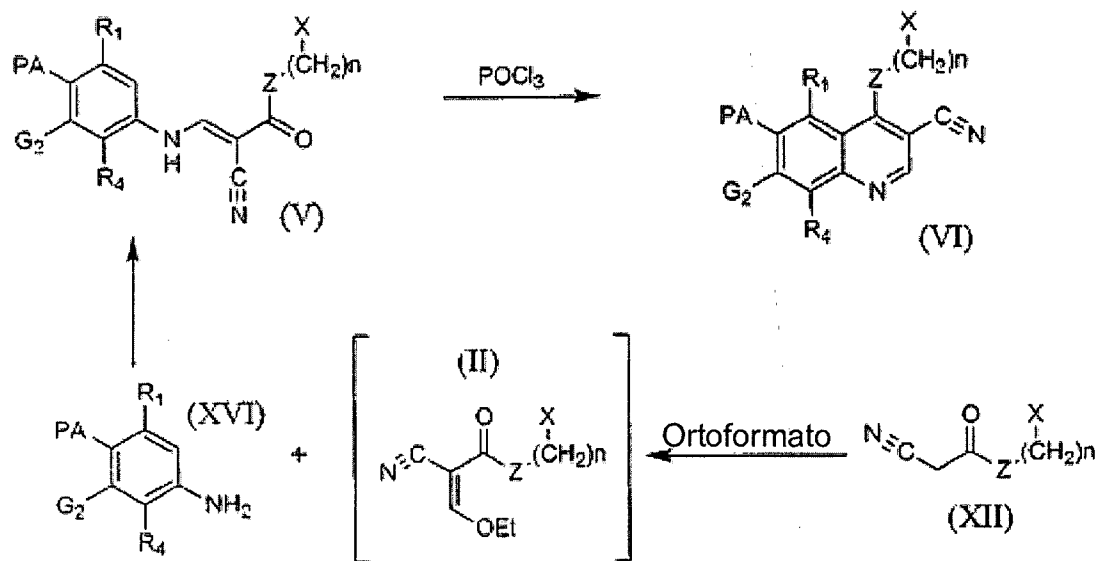
Esquema 6



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Y

Esquema 7

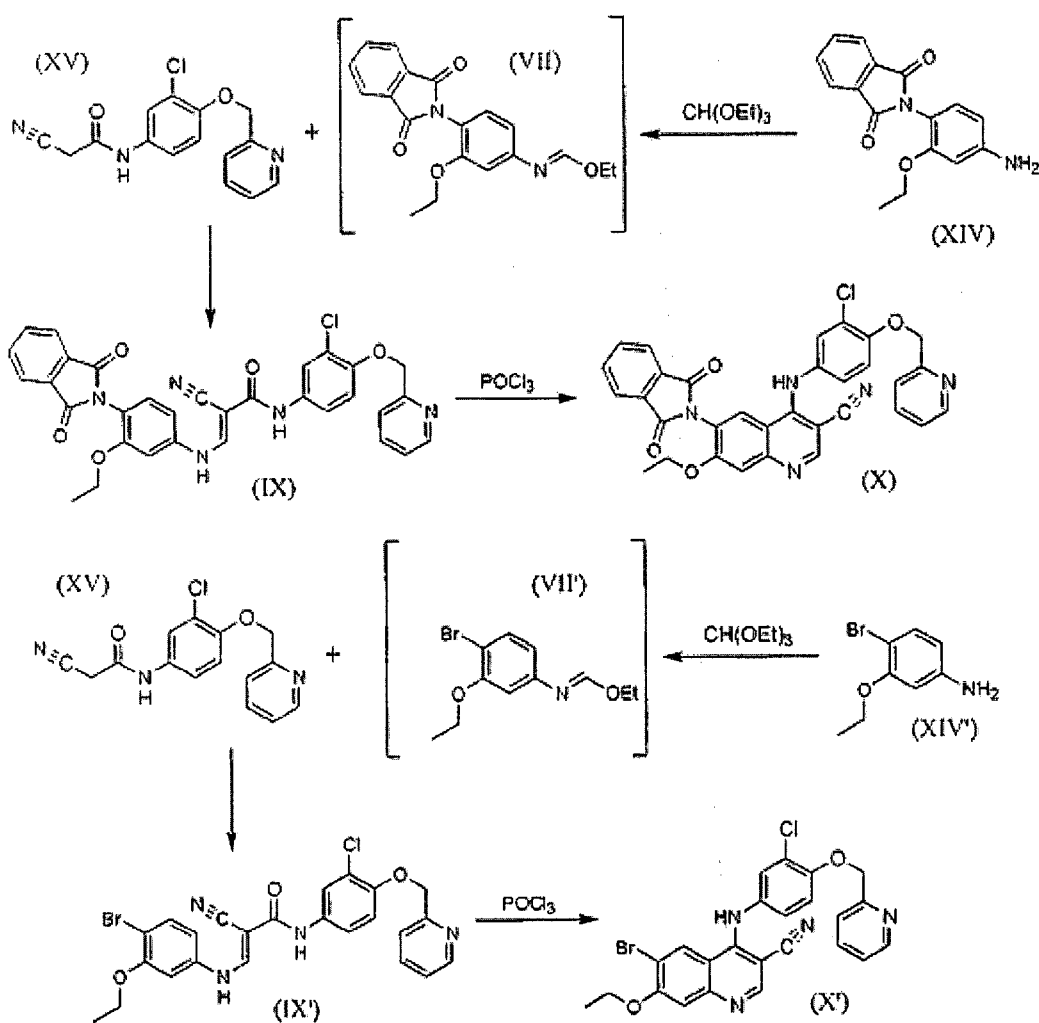


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en donde X, Z, G₂, R₁ y R₄ son como se describieron anteriormente por los Esquemas 4 y 5, y en donde PA es un grupo amino protegido. En una modalidad preferida particularmente de los Esquemas 6 y 7, PA es ftalimida.

- 5 [0041] Las cuatro modalidades representadas en los Esquemas 3a y 3b anteriores son representadas separadamente en los Esquemas 8 y 9 adelante.

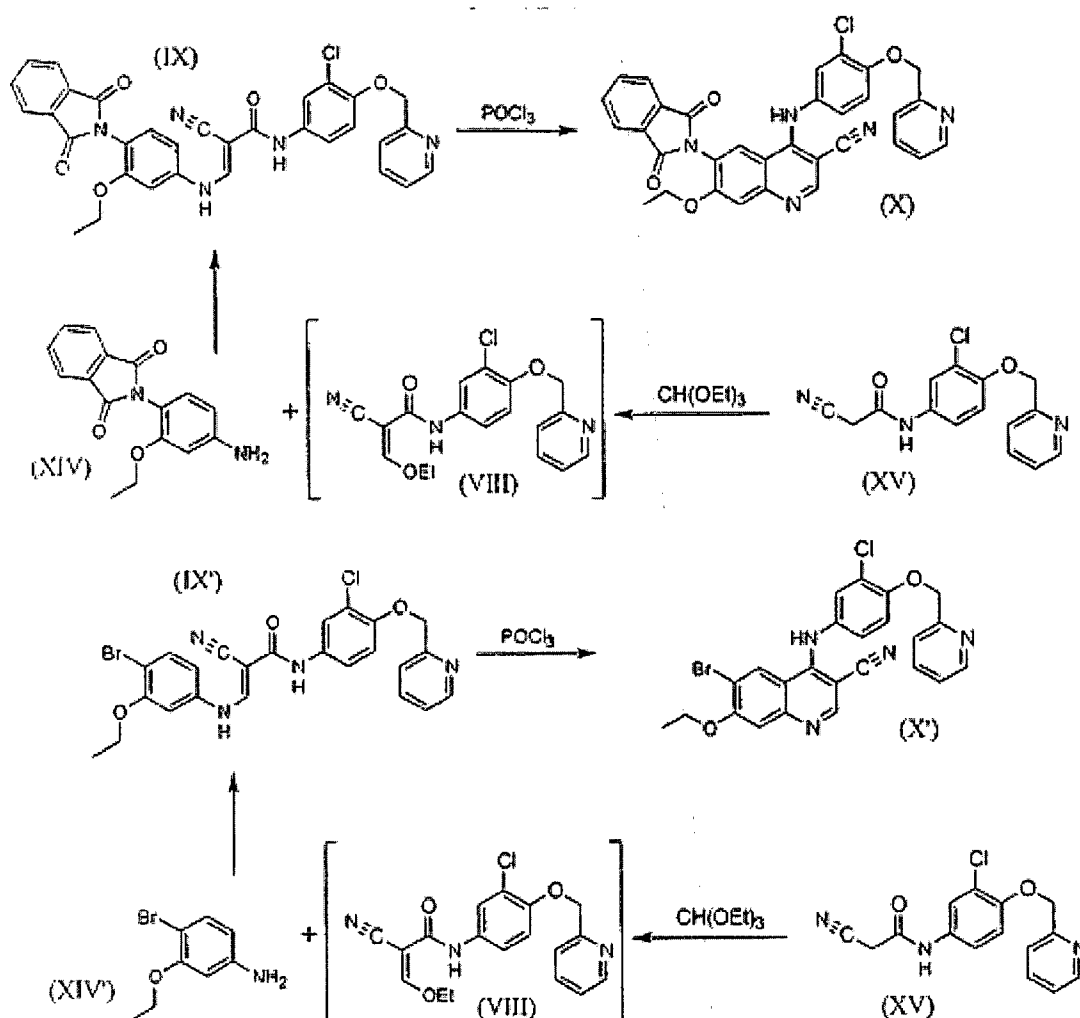
Esquema 8



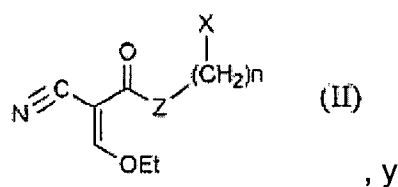
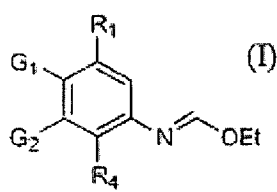
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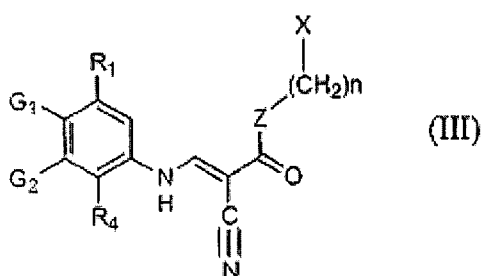
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Esquema 9



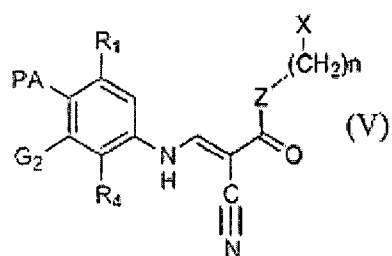
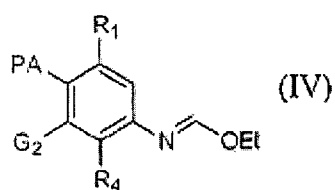
[0042] La presente invención también suministra para los intermediarios producidos por los métodos de la presente invención. En una modalidad de la invención, los intermediarios son de fórmulas I, II y III adelante.





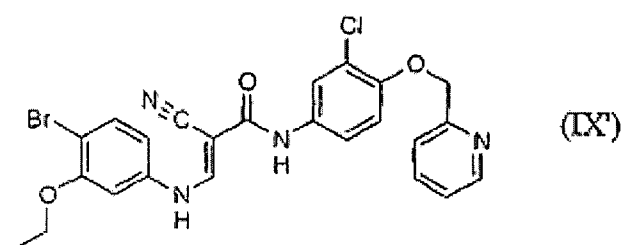
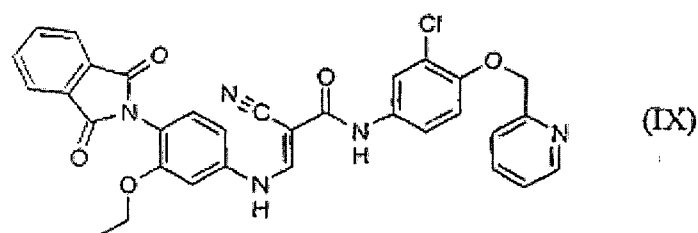
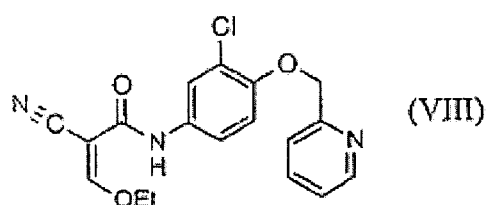
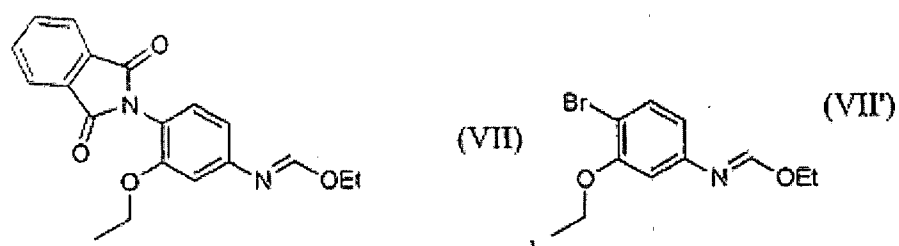
en donde X, Z, G₁, G₁, R₁ y R₄ son como se describió previamente.

- 5 [0043] En otra modalidad de la invención, los intermediarios son de Fórmulas IV y V adelante:



- 10 en donde X, Z, PA, G₂, R₁ y R₄ son como de definió previamente.

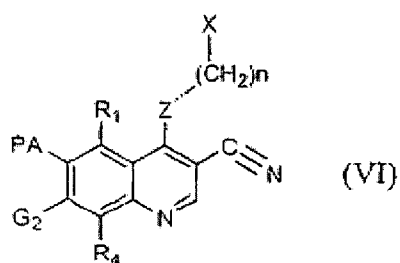
[0044] En una modalidad adicional de la invención, los intermediarios son los compuestos representados por las Fórmulas VII, VII', VIII, IX y IX' adelante:



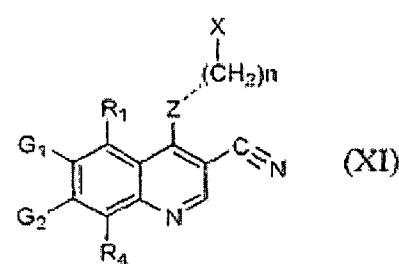
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[0045] La presente invención también suministra para derivados de 3-cianoquinolina producidos por los métodos de la presente invención. De acuerdo con esto, la invención suministra a 3-cianoquinolina de fórmula VI, producida por los métodos representados en los Esquemas 6 y 7 anteriores, y un 3-cianoquinolina de fórmula XI producida por los métodos representados en los Esquemas 4 y 5 anteriores:

10



en donde X, Z, PA, G₂, R₁ y R₄ son como se describió previamente;

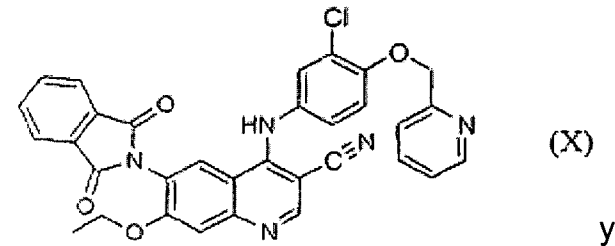


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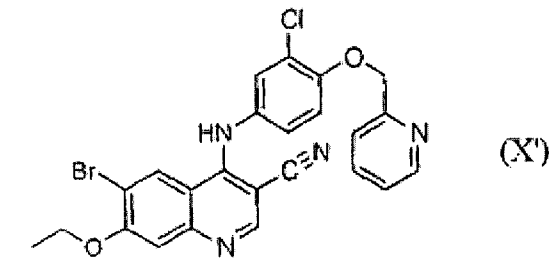
en donde X, G₁, G₂, R₁ y R₄ son como se describió previamente.

[0046] Las 3-cianoquinolinas específicas de la invención son representadas por los compuestos de fórmula X y X'.

10



y



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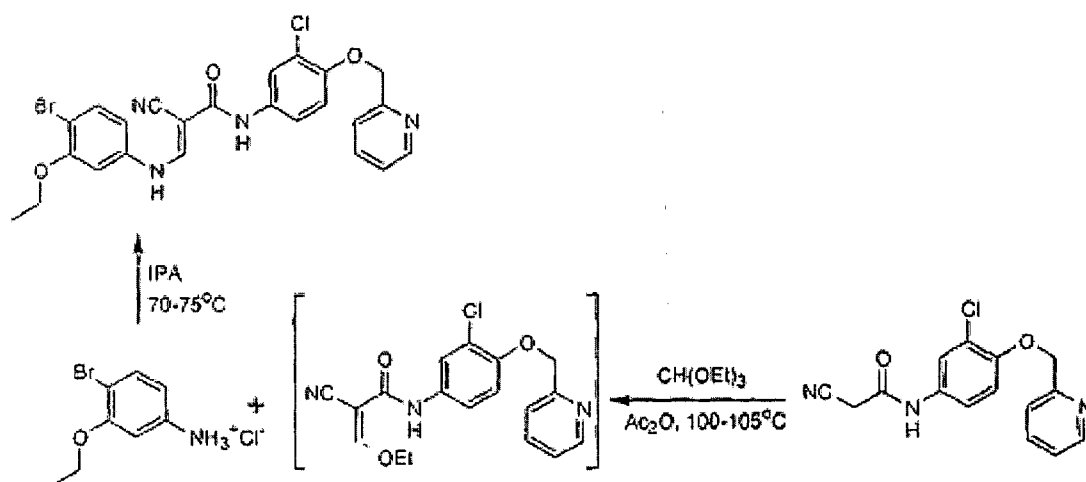
EJEMPLOS

[0047] Se ofrecen los siguientes ejemplos para ilustrar, pero no limitar la presente invención.

Ejemplo 1

Preparación de (E/Z)-3-(4-bromo-3-etoxianilino)-N-[3-cloro-4-(2-piridinil-metoxi)fenil]-2-ciano-2-propenamida.

5



[0048] A un frasco de 3 cuellos de 50 ml se carga cianoacetamida (0.50 g, 1.7 mmol) en trietilortoformato (2.45g, 2.75 ml, d=0.89 g/ml). La mezcla se calienta a 50-60 °C y se
 10 agrega anhídrido acético (0.42g, 0.39 ml, 4.1 mmol, 2.5 eq, d=1.08 g/ml). El frasco se calienta a 100-105 °C y se mantiene durante un mínimo de 4 h y luego se enfría a 70-75°C. Se agrega una solución de hidrocloreuro de 3-etoxi-4-bromoanilina (0.42g, 1.67 mmol) en isopropanol (5 ml) . La mezcla se agita durante 3 h y se enfría a temperatura ambiente. Se agrega agua y la mezcla se extrae con acetato de etilo. La capa orgánica
 15 se lava con solución salina, se seca sobre sulfato de sodio y se depura hasta secado. El residuo se disuelve en acetonitrilo (10 ml) y agua (10 ml) se agrega en forma de gotas para precipitar el producto. El producto se filtra en un túnel Buchner para dar 0.11 g del compuesto del título.

20 Ejemplo 2

Preparación de 3-etoxi-4-(N-ftalimidil)nitrobencono.

[0049] A un frasco multi-cuello de 5-L equipado con un agitador mecánico, sonda de temperatura, condensada y protección de nitrógeno se carga 2-amino-5-nitrofenol (116 g, 0.75 mol) y anhídrido ftálico (223 g, 1.51 mol, 2.0 eq) seguido por ácido acético glacial (1.13 L). La mezcla de reacción se calienta a (1 15-120 °C) y se mantiene durante 2.5-3 h hasta que la reacción se completa mediante HPLC o TLC. La mezcla se enfría a temperatura ambiente y se agrega agua (0.5 L) sobre 10 minutos. La mezcla se mantiene durante 1 h y los sólidos se filtran en un túnel de Buchner de 15 cm de diámetro y se lava con agua (2 x 0.5 L). Los sólidos se transfieren de regreso a un frasco de 5-L, se agrega agua (2.32 L) y la mezcla se agita a temperatura ambiente durante un mínimo de 30 mins. La mezcla se filtra y se lava con agua (2 x 0.5 L). El producto se seca a 60 °C durante 23 hr en un horno de vacío para dar 210 g (99%) como un sólido tostado. ¹H NMR: δ (DMSO-d₆) 10.98 (s, 1H, OH), 8.10-7.85 (m, 4H, ftalimida), 7.82 (d, 1H, Ar), 7.80 (d, 1H, Ar), 7.63 (dd, 1H, Ar).

[0050] A un frasco multi-cuello de 5-L equipado con un agitador mecánico, sonda de temperatura, condensada y protección de nitrógeno se carga N-(2-hidroxi-4-nitrofenil)ftalimida (208 g, 0.73 mol) y DMF (1.04 L). La mezcla se agita a temperatura ambiente hasta que se obtiene una solución. Se agrega carbonato de potasio (0.15 kg, 1.5 eq.) en porciones hasta que el pH de la mezcla fue 9. La suspensión se calienta a 60-65 °C y y bromuro de etilo (88 g, 0.80 mol, 1.1 eq.) se agrega en forma de gotas sobre 20 min. Después de completa la adición, la mezcla se mantiene durante un mínimo de 30 mins y luego se enfría a temperatura ambiente. Se agrega agua (2.08 L) sobre 30 min. mientras mantiene la temperatura de crisol a 20-25 °C y la mezcla se mantiene durante 1 hr adicional. La mezcla se filtra en un túnel de Buchner de 15 cm y se lava con agua caliente (45-50 °C) (3 x 0.2 L). La torta húmeda se transfiere de regreso a un frasco de 5-L, se agrega agua (2.08 L) y la mezcla se coloca en forma de suspensión durante un mínimo de 30 mins a 45-50 °C. La mezcla se filtra y se lava con

agua (0.2 L). El producto se seca a 60 °C durante 20 hr en un horno de vacío para dar el compuesto del título (154 g, 67%). ¹H NMR: δ (DMSO-d₆) 8.10-7.92 (m, 6H, Ar), 7.73 (d, 1H, Ar), 4.23 (q, 2H, CH₃CH₂O), 1.21 (t, 3H, CH₃CH₂O).

5 Ejemplo 3

Preparación de N-[3-Cloro-4-(2-piridinilmetoxi)]fenil-2-cianoacetamida.

[0051] En un frasco multi-cuello de 12-L, 2-piridilo carbinol (0.13 kg, 1.19 mol, 1.05 eq) se disuelve en acetonitrilo (0.88 L) y para esto se agrega hidróxido de potasio en hojuelas (85%) (80 g, 1.25 eq). La suspensión resultante se calienta a 35 °C. Se agrega una solución de 3-cloro-4-fluoronitrobenzo (0.20 kg, 1.14 mol) en acetonitrilo (1.0 L) a 35-40 °C. La mezcla se mantiene durante 18 h hasta completar la reacción. La mezcla luego se enfría a 20-25 °C, se apaga con agua (4 L) y la suspensión resultante se filtra y se lava con agua (3 x 200 mL). El producto resultante se aísla como un sólido tostado (251 g, 84% rendimiento).

[0052] Una mezcla de 3-cloro-4-(2-piridinilmetoxi)nitrobenzo (0.149 kg, 0.56 mol) y 2% (p/p) de 5% Pt/C (6.0 g, 50% se humecta) en tetrahidrofurano (0.895 L) se hidrogena en un reactor Parr de 2-L de acero inoxidable a 25 psi, 25 °C durante un mínimo de 8 h. La mezcla se filtra a través de una almohadilla de celita (50 g, 15 cm de diámetro) y se lava con tetrahidrofurano (0.45 L). El filtrado se destila a un volumen de -0.30 L y el concentrado se transfiere a un frasco multi-cuello de 2-L y como se utiliza en la siguiente etapa.

[0053] A un frasco de 2-L equipado con un agitador mecánico, sonda de temperatura, cabezal claisen y condensador se agrega etilcianoacetato (0.421 kg, 3.72 mol, 6.6 eq.). La mezcla de reacción se calienta a (100-115 °C) mientras se remueve tetrahidrofurano

y etanol. La temperatura se aumenta a ~125 °C y la mezcla se mantiene durante un mínimo de 24 h hasta que se consume el material de partida anilina y no se recolecta destilado. La mezcla se enfría a temperatura ambiente sobre 1h. A 50-60 °C, los sólidos se cristalizan y se agrega acetato de etilo (0.15 L). La mezcla se enfría adicionalmente a 0-10 °C y se mantiene durante 1h. La mezcla se filtra en un túnel de Buchner de 15 cm de diámetro y se lava con 50 mL del filtrado seguido por pre-enfriado (0-10 °C) acetato de etilo (0.15 L). El producto se seca a 60 °C durante un mínimo de 16 h en un horno de vacío para dar el compuesto del título (0.12 kg, 71%) como un sólido café. El producto se purifica al colocar en suspensión en acetato de etilo frío (1-1.3 volúmenes) durante 1 hr. ¹H NMR: δ (DMSO_d₆) 10.31 (s, 1H, NH), 8.58 (dd, 1H, Ar), 7.86 (dt, 1H, Ar), 7.75 (d, 1H, Ar), 7.55 (d, 1H, Ar), 7.39-7.32 (m, 2H, Ar), 7.21 (d, 1H, Ar), 5.25 (s, 2H, OCH₂Pir), 3.88 (s, 2H, NCCH₂CO).

Ejemplo 4

Preparación de (E/Z) 3-[3-etoxi-4-(N-ftalimidil)]anilino-N-[3-cloro-4-(2-piridinilmetoxi)]fenil-2-ciano-2-propenamida.

[0054] Una mezcla de 3-etoxi-4-(N-ftalimidil)nitrobencono (0.135 kg, 0.43 mol) y 4% (p/p) de 10% Pd/C (5.42 g, 50% se humecta) en tetrahidrofurano (1.08 L) se hidrogena en un reactor Parr de 2-L de acero inoxidable a 70 psi, 50 °C durante un mínimo de 10 h. La mezcla se filtra a través de una almohadilla de celita (100 g, 15 cm de diámetro) en un frasco de 1 cuello de 3-L y se lava con tetrahidrofurano (3 x 0.14 L). El filtrado se destila a un volumen de ~0.55 L y para el concentrado se agrega n-propanol (0.75 L). La mezcla se destila a un volumen de ~0.41 L y el concentrado como se utiliza en la siguiente etapa. Tomando una alícuota y concentrando hasta secado se obtiene una muestra de referencia analítica.

[0055] El concentrado se transfiere a un frasco multi-cuello de 3-L equipado con un agitador, sonda de temperatura, condensada y protección de nitrógeno. El frasco se carga con n-propanol (0.91 L) seguido por N-[3-Cloro-4-(2-piridinilmetoxi)]fenil-2-cianoacetamida (1 19 g, 0.39 mol, 0.91 eq.). La mezcla se calienta a 75-80 °C. La primera de tres porciones de trietilortoformato (64.3 g, 72 ml, 0.43 mol, d=0.89 g/ml) se agrega y la mezcla calentada a reflujo (95-100 °C). Después de 2.5 h, se agrega la segunda porción de trietilortoformato (64.3 g, 72 ml, 0.43 mol). Después 19.5 hr, se agrega la tercera porción de trietilortoformato (64.3 g, 72 ml, 0.43 mol). Se puede agregar la tercera porción 2.5 hr después de la segunda porción. La mezcla se mantiene durante un mínimo de 6 .5 hr a 95 °C (total de 28.5 h). La mezcla se enfría a 0- 10 °C y se mantiene durante 1 hr. La mezcla se filtra en un túnel de Buchner de 18 cm de diámetro y se lava con el filtrado (150 ml) seguido por molido (0-10 °C) n-propanol (4 x 0.15 L). El peso de la torta húmeda es 252 g. (estimado de LOD -12%).

[0056] La torta húmeda se purifica de acetonitrilo. La torta húmeda (186 g) se transfiere a un frasco multi-cuello de 5-L equipado con un agitador mecánico, condensador, sonda de temperatura y protección de nitrógeno. El frasco se carga con acetonitrilo (2.42 L), calentado a 65-70 °C y se mantiene durante un mínimo de 30 min. La mezcla se enfría a 60 °C, filtrado en un túnel de Buchner de 15 cm y se lava con acetonitrilo (3 x 0.18 L).

El producto se seca a 60 °C, vacío total durante 18 h para dar 3-[3-etoxi-4-(N-ftalimidil)]anilino-N-[3-cloro-4-(2-piridinilmetoxi)]fenil-2-ciano-2-propenamida (122 g, 75% se recupera con base en peso seco) como un sólido beige. Rendimiento general durante 2 etapas: 53%. ¹H RMN (anilina): δ (DMSO-d₆) 7.96-7.86 (m, 4H, ftalimida), 6.90 (d, 1H, Ar), 6.34 (d, 1H, Ar), 6.22 (dd, 1H, Ar), 5.37 (d, 2H, NH₂), 3.90 (q, 2H, CH₃CH₂O), 1.1 1 (t, 3H, CH₃CH₂O). ¹H RMN (propenamida): δ (DMSO-d₆) 11.45 (d, 1H, NHCH=C), 9.58 (d, 1H, CONH), 8.59 (m, 1H, Ar), 8.54 (d, 1H, NHCH=C), 8.00-7.54 (m, 6H, Ar), 7.57 (d, 1H, Ar), 7.52 (dd, 1H, Ar), 7.39-7.34 (m, 3H, Ar), 7.21 (d, 1H, Ar), 7.11 (dd, 1H, Ar), 5.27 (s, 2H, OCH₂Pir), 4.11 (q, 2H, OCH₂CH₃), 1.16 (t, 3H, OCH₂CH₃).

Ejemplo 5

5 Preparación de 3-ciano-4-[3-cloro-4-(2-piridinilmetoxi)]anilino-7-etoxi-N-ftalimidilquinolina.

[0057] A un frasco multi-cuello de 5-L equipado con un agitador, sonda de temperatura, condensada y protección de nitrógeno se carga 3-[3-etoxi-4-(N-ftalimidil)]anilino-N-[3-cloro-4-(2-piridinilmetoxi)]fenil-2-ciano-2- propenamida (0.12 kg, 0.20 mol) y suspendido en acetonitrilo (1.20 L) y metanol (0.06 L). Se configura un sistema lavador de hidróxido de sodio (40 g en 1 L de agua). La mezcla se calienta a 60-65 °C y oxiclورو de fósforo (0.31 kg, 0.19 L, 10.0 eq, d=1.645 g/ml) se agrega en forma de gotas manteniendo la temperatura de crisol a 60-70 °C. Eventualmente la mezcla llega a ser más delgada y roja oscura (después ~6 hr). La mezcla se mantiene durante un mínimo de 18 h y luego se enfría a 0-10 °C. Se agrega agua (0.60 L) mantiene la temperatura del crisol < 20 °C. El pH de la mezcla se ajusta a 8-10 utilizando 28% de hidróxido de amonio (-0.95 L). La 2 fase de la mezcla se filtra en un túnel de Buchner de 15 cm y se lava con 2:1 acetonitrilo: agua (2 x 0.12 L). La torta húmeda se transfiere a el frasco de 3-L, agua (1.20 L) se agrega y la mezcla en forma de suspensión durante un mínimo de 30 mins a 45-50 °C. La mezcla se filtra a 45 °C en un túnel de Buchner de 15 cm y se lava con agua (3 x 0.20 L) hasta que el pH del lavado final es 7-8. El sólido se seca a 60 °C, en un horno de vacío durante 24 hr para dar el compuesto deseado (88 g, 76%) como un sólido naranja. ¹H NMR: δ (DMSOd₆) 9.72 (s, 1H, Ar), 8.58 (m, 2H, Ar), 8.53 (s, 1H, Ar), 8.08-7.96 (m, 4H, ftalimida), 7.87 (m, 1H, Ar), 7.55 (m, 3H, Ar), 7.37 (m, 1H, Ar), 7.28 (s, 1H, Ar), 5.29 (s, 2H, OCH₂Pyr), 4.24 (q, 2H, OCH₂CH₃), 1.22 (t, 3H, OCH₂CH₃).

Ejemplo 6

Preparación de 6-amino-4-[3-cloro-4-(2-piridinilmetoxi)]anilino-3-ciano-7-etoxiquinolina.

- 5 [0058] Un frasco multi-cuello 3-L equipado con un agitador, sonda de temperatura, condensada y protección de nitrógeno se carga 3-ciano-4-[3-cloro-4-(2-piridinilmetoxi)]anilino-7-etoxi-N-ftalimidilquinolina (0.085 kg, 0.147 mol) y etanol suspendido en (ASDQ #2, 0.68 L). Siguiendo, se agrega 28% de hidróxido de amonio (0.5 L de una solución de 7.4 M, 25 eq.). La suspensión se calienta a 62-68 °C y se
- 10 mantiene durante un mínimo de 2 hr. La reacción se enfría a temperatura ambiente, filtrado en un túnel de Buchner de 15 cm, y se lava con etanol (2 x 85 ml). El sólido se seca a 65 °C, en un horno de vacío durante 20 hr para dar el compuesto del título (61 g, 92% no corregido para resistencia) como un sólido naranja. ¹H NMR: δ (DMSO-d₆) 9.08 (s, 1H, NH), 8.59 (d, 1H, Ar), 8.31 (s, 1H, Ar), 7.90-7.84 (m, 1H, Ar), 7.58 (s, 1H, Ar),
- 15 7.40-7.34 (m, 1H, Ar), 7.26-7.19 (m, 4H, Ar), 7.09-7.05 (m, 1H, Ar), 5.40 (d, 2H, NH₂), 5.25 (s, 2H, OCH₂Pyr), 4.23 (q, 2H, OCH₂CH₃), 1.45 (t, 3H, OCH₂CH₃).

Ejemplo 7

- 20 Preparación de (E)-N-(4-[3-cloro-4-(2-piridinilmetoxi)]anilino]-3-ciano-7-etoxi-6-quinolinil)-4-(dimetilamino)-2-butenamida libre de base.

- [0059] Una solución de clorhidrato de ácido 4-N,N-dimetilaminocrotonico (22.3 g, 0.135 mol, 2.0 eq.) en tetrahidrofurano (0.225 L) y una cantidad catalítica de dimetilformamida
- 25 (0.5 mL) se enfría a 0-5 °C. Se agrega cloruro de oxalilo (1.4 mL, 0.131 mol, 1.95 eq) en forma de gotas durante 15 min. La mezcla luego se calienta a 25-30 °C y se agita durante 2 h luego se enfría a 0-5 °C. Se agrega N-Metil-2-pirrolidinona (15 ml). A una solución filtrada caliente de (30 °C) 6-amino-4-[3-cloro-4-(2-piridinilmetoxi)]anilino-3-ciano-

7-etoxi-quinolina (30 g, 0.067 mol, 1.0 eq.) en N-metil-2-pirrolidinona (0.27 L) se agrega en forma de gotas sobre 30 min manteniendo la temperatura de 0-10 °C. La mezcla se agita durante un mínimo de 20 h. Luego de terminación, la reacción se apaga con agua (0.36 L), mantenido durante 30 min y luego se calienta a 40-45 °C. Se agrega hidróxido de sodio acuoso (19 g en 0.15 L de agua) sobre 30 min para llevar el pH a 9-10 seguido por adición de agua (0.39 L). La mezcla se agita durante 1 hr, luego se enfría a temperatura ambiente. El precipitado resultante se filtra y se lava con agua (3 x 60 mL) hasta el pH de las lavadas fue 7-8. Los sólidos húmedos se calientan hasta reflujo (70-75 °C) en 1.5:1 acetonitrilo:tetrahidrofurano (0.33 L) y la solución se enfría sobre 2 h a temperatura ambiente. El producto se filtra y se lava con 1.5:1 acetonitrilo:tetrahidrofurano frío (3 x 0.01 L). El producto se seca (60 °C, 10 mm Hg, 24 h) para dar el compuesto del título (19.4 g, 52% no corregido para resistencia). ¹H RMN : δ (DMSO-d₆) 9.59 (s, 1H, NH), 9.47 (s, 1H, NH), 8.96 (s, 1H, Ar), 8.60 (dd, 1H, Ar), 8.47 (s, 1H, Ar), 7.87 (dd, 1H, Ar), 7.58 (d, 1H, Ar), 7.39-7.34 (m, 3H, Ar), 7.27-7.20 (m, 2H, Ar), 6.81-6.73 (m, 1H, CH₂-CH=CH-), 6.59 (d, 1H, CH₂-CH=CH-), 5.28 (s, 2H, OCH₂Pir), 4.31 (q, 2H, OCH₂CH₃), 3.09 (d, 2H, NCH₂), 2.18 (s, 6H, N(CH₃)₂), 1.47 (t, 3H, OCH₂CH₃).

Ejemplo 8

Preparación de maleato de (E)-N-{4-[3-cloro-4-(2-piridinilmetoxi)anilino]-3-ciano-7-etoxi-6-quinolinil}-4-(dimetilamino)-2-butenamida.

[0060] (E)-N-{4-[3-cloro-4-(2-piridinilmetoxi)anilino]-3-ciano-7-etoxi-6-quinolinil}-4-di-

metilamino)-2-butenamido crudo libre de base (17 g, 0.027 mol, 88% resistencia) y ácido maleico (3.60 g, 0.031 mol) se disuelve a 50-60 °C en una mezcla de 5% agua/n-propanol (0.12 L) y agitado durante 15 min. A la solución caliente se agrega carbón (1.7 g) y la mezcla se agita durante 20 min. La solución caliente se depura y se enfría a

temperatura ambiente y se mantiene durante 12-15 hr. El producto se filtra y se lava con 5% agua/n-propanol (3 x 0.017 L). El producto se seca (60 °C, 10 mm Hg, 24 h) para dar el compuesto del título (9.83 g, 54%, no corregido para resistencia). El producto (7.0 g) se recrystaliza de 7.5% agua/propanol para dar 5.1%. DSC: 196 °C (forma de cristal
5 única). ¹H RMN: δ (DMSO-d6) 9.74 (s, 1H, NH), 9.63 (s, 1H, NH), 8.94 (s, 1H, Ar), 8.60 (dd, 1H, Ar), 8.50 (s, 1H, Ar), 7.88 (dd, 1H, Ar), 7.59 (d, 1H, Ar), 7.42-7.35 (m, 3H, Ar), 7.28-7.19 (m, 2H, Ar), 6.76 (d, 2H, -CH=CH-), 6.05 (s, 2H, HOOC-CH=CH-COOH), 5.29 (s, 2H, OCH₂Pir), 4.33 (q, 2H, OCH₂CH₃), 3.91 (d, 2H, NCH₂), 2.77 (s, 6H, N(CH₃)₂), 1.45 (t, 3H, OCH₂CH₃). ¹³C RMN: δ (DMSO-d6) 167.3, 162.4, 156.1, 153.4, 152.5,
10 151.2, 150.5, 149.1, 147.7, 137.0, 135.8, 134.0, 132.6, 131.6, 127.3, 125.9, 124.2, 123.0, 121.5, 121.4, 117.1, 115.6, 114.3, 113.2, 108.7, 87.3, 71.3, 64.6, 57.0, 42.3, 14.2.

Ejemplo 9

15 Preparación de N-[3-Cloro-4-(3-fluorobenciloxi)]fenil-2-cianoacetamida.

[0061] Alcohol 3-Fluorobencilo (0.30 kg, 2.39 mol, 1.05 eq) se disuelve en acetonitrilo (6.0 L) y para esto se agrega hidróxido de potasio en hojuelas (85%) (0.16 kg, 1.25 eq).

20 La suspensión resultante se calienta a 35 °C. Una solución de 3-cloro-4-fluoronitrobenceno (0.40 kg, 2.28 mol) en acetonitrilo (2.0 L) se agrega a 35-40 °C. La mezcla se mantiene durante 18 h. La mezcla luego se enfría a temperatura ambiente, se apaga con agua (8 L) y la suspensión resultante se filtra y se lava con agua (2 x 0.40 L). El producto resultante se seca (45 °C, 10 mmHg, 25 h) para dar 0.59 kg (92%
25 rendimiento).

[0062] Una mezcla de 3-cloro-4-(3-fluorobenciloxi)nitrobenceno (20 g, 0.071 mol) y etanol (195 ml) se agrega zinc (23.2 g, 5.0 eq.). La mezcla se calienta a 55-60 °C. Una

solución de cloruro de amonio (7.6 g) en agua (40 ml) se agrega sobre 20 min mantiene la temperatura del crisol 55-65 °C (exoterma pequeña). La mezcla se agita durante 2 h, filtrada sobre una almohadilla de celita y se lava con etanol (2 x 20 ml). El filtrado se destila esencialmente hasta secado y 2-metiltetrahidrofurano (100 ml) se agrega para
5 disolver el producto. Se agrega agua (40 ml) y solución salina (5.2 g en 15 ml de agua), se mezclan y las capas se separan. La capa orgánica se lava con agua (30 ml) y luego se transfiere a un frasco multi-cuello de 500 ml.

[0063] A el frasco de 500 ml equipado con un agitador mecánico, sonda de temperatura,
10 cabezal claisen y condensador se agrega etilcianoacetato (53.2 g, 0.47 mol, 6.6 eq.). La mezcla de reacción se calienta a (120-125 °C) mientras se remueve 2-metiltetrahidrofurano y etanol atmosférico residual. La mezcla se mantiene durante un mínimo de 24 h hasta que se consume el material de partida anilina y no se recolecta destilado. La mezcla se enfría a temperatura ambiente y acetato de isopropilo (75 ml) y
15 se agrega heptano (75 ml). La mezcla se mezcla durante 2 h. La mezcla se filtra en un túnel Buchner de 5.5 cm de diámetro y se lava con heptano. El producto se seca a 45 °C durante la noche en un horno de vacío para dar el compuesto del título (6.45 g, 29%) como un sólido grisoso (WC262S0-77). ¹H NMR: δ (DMSO_d₆) 10.31 (s, 1H, NH), 7.73 (d, 1H, Ar), 7.46-7.19 (m, 6H, Ar), 5.20 (s, 2H, OCH₂Ph), 3.87 (s, 2H, NCCH₂CO).

Ejemplo 10

Preparación de (E/Z) 3-[3-etoxi-4-(N-ftalimidil)]anilino-N-[3-cloro-4-(3-fluorobenciloxi)]fenil-2-ciano-2-propenamida.

[0064] Una mezcla de 3-etoxi-4-(N-ftalimidil)nitrobencono (9.99 g, 0.032 mol, 1.1 eq.) y 4% (p/p) de 10% Pd/C (0.40 g, 50% se humecta) en tetrahidrofurano (80 ml) se hidrogena en un reactor Parr de 0.2 L de acero inoxidable a 70 psi, 50 °C durante un

mínimo de 10 h. La mezcla se filtra a través de una almohadilla de celita en un frasco de 1-cuello de 0.5 L y se lava con tetrahidrofurano (3 x 10 ml). El filtrado se destila a un volumen de 40 ml y al concentrado se agrega n-propanol (60 ml). La mezcla se destila a un volumen de 40 ml y el concentrado como se utiliza en la siguiente etapa.

5

[0065] El concentrado se transfiere a un frasco multi-cuello 0.5 L equipado con un agitador, sonda de temperatura, condensada y protección de nitrógeno. El frasco se carga con n-propanol (60 ml) seguido por N-[3-Cloro-4-(3-fluorobenciloxi)]fenil-2-cianoacetamida (9.0 g, 0.029 mol, 1.0 eq.). La mezcla se calienta a 75-80 °C. La primera de tres porciones de trietilortofornato (4.4 g, 4.7 ml, 0.029 mol, d=0.89 g/ml) se agrega y la mezcla calentada a reflujo (95-100 °C). Después de 2 h, se agrega la segunda porción de trietilortofornato (4.4 g, 4.7 ml, 0.029 mol). Después de otras 2 h, se agrega la tercera porción de trietilortofornato (4.4 g, 4.7 ml, 0.029 mol). La mezcla se mantiene durante un mínimo de 20 h a 95 °C. La mezcla se enfría a 0-10 °C y se mantiene durante 1 h. La mezcla se filtra un túnel Buchner y se lava con el filtrado (10 ml) seguido por molido (0-10 °C) n-propanol (3 x 10 ml). El peso de la torta húmeda es - 25.6 g. El producto se seca a 60 °C, vacío total durante 20 h para dar el compuesto del título (15.7 g, 88% rendimiento general durante 2 etapas). ¹H NMR: δ (DMSOd₆) 11.46 (d, 1H, NHCH=C), 9.58 (d, 1H, CONH), 8.54 (d, 1H, NHCH=C), 7.95-7.86 (m, 5H, Ar), 7.55-7.10 (m, 9H, Ar), 5.22 (s, 2H, OCH₂Ph), 4.10 (q, 2H, OCH₂CH₃), 1.16 (t, 3H, OCH₂CH₃).

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Ejemplo 11

25 Preparación de 3-ciano-4-[3-cloro-4-(3-fluorobenciloxi)]anilino-7-etoxi-N-ftalimidilquinolina.

[0066] A un frasco multi-cuello 1-L equipado con un agitador, sonda de temperatura, condensada y protección de nitrógeno se carga 3-[3-etoxi-4-(N-ftalimidil)]anilino-N-[3-cloro-4-(3-fluorobenciloxi)]fenil-2-ciano-2-propenamida (15 g, 0.0245 mol) y suspendido en acetonitrilo (150 ml) y metanol (3.0 ml). A un hidróxido de sodio (40 g en 1 L de agua) se configura un sistema lavador. La mezcla se calienta a 65-70 °C y oxiclورو de fósforo (37.6 g, 22.8 ml, 10.0 eq, d=1.645 g/ml) se agrega en forma de gotas manteniendo la temperatura de crisol a 70-75 °C. La mezcla eventualmente llega a ser más delgada. La mezcla se mantiene durante un mínimo de 20 h y luego se enfría a 0-10 °C. Se agrega agua (75 ml) manteniendo la temperatura del crisol < 20 °C. El pH de la mezcla se ajusta a 8-10 utilizando 28% de hidróxido de amonio (~115 ml) mantiene la temperatura del crisol 10-15 °C. La 2 fase de la mezcla se filtra en un túnel Buchner y se lava con agua caliente (120 ml). El sólido se seca a 60 °C, en un horno de vacío durante 25 h para dar el compuesto del título (1 1.29 g, 78% no corregido para resistencia) como un sólido naranja. ¹H NMR: δ (DMSO_{d6}) 8.59 (s, 1H, Ar), 8.53 (s, 1H, Ar), 8.07-7.96 (m, 4H, ftalimida), 7.53-7.42 (m, 3H, Ar), 7.34-7.16 (m, 5H, Ar), 5.26 (s, 2H, OCH₂Ph), 4.24 (q, 2H, OCH₂CH₃), 1.22 (t, 3H, OCH₂CH₃).

Ejemplo 12

20 Preparación de 6-amino-4-[3-cloro-4-(3-fluorobenciloxi)]anilino-3-ciano-7-etoxiquinolona.

[0067] A un frasco multi-cuello de 250 ml equipado con un agitador, sonda de temperatura, condensador y nitrógeno se carga 3-ciano-4-[3-cloro-4-(3-fluorobenciloxi)]anilino-7-etoxi-N-ftalimidilquinolona (10 g, 0.0169 mol) y etanol suspendido en (80 ml). Luego, se agrega 28% de hidróxido de amonio (22.8 ml de una solución de 7.4 M, 25 eq.). La suspensión se calienta a 65-70 °C y se mantiene durante un mínimo de 2 h. La reacción se enfría a temperatura ambiente, filtrado en un túnel Buchner, y se lava con etanol (2 x 10 ml) y heptano (2 x 10 ml). El sólido se seca a 60

°C, en un horno de vacío durante 24 h para dar el compuesto del título (5.78 g, 74%) como un sólido rojo-anaranjado. ¹H NMR: δ (DMSO-d₆) 9.10 (s, 1H, NH), 8.31 (s, 1H, Ar), 7.51-7.05 (m, 9H, Ar), 5.36 (s, 2H, NH₂), 5.22 (s, 2H, OCH₂Ph), 4.23 (q, 2H, OCH₂CH₃), 1.45 (t, 3H, OCH₂CH₃).

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Ejemplo 13

Preparación de N-(3-Cloro-4-fluoro)fenil-2-cianoacetamida.

10 [0068] 3-Cloro-4-fluoroanilina (1.00 kg, 6.87 mol) y ácido cianoacético (0.602 kg, 7.08 mol) reaccionan en la presencia de 1,3-diisopropilcarbodiimida (0.893 kg, 1.108 L, 7.08 mol) en reflujo THF (2.67 kg, 3.0 L), similar a lo reportado por R. Westwood et. al. [*J. Med. Chew.*, 39, 4608, (1996)]. El subproducto de urea precipitado de la solución de THF y se remueve después de molido a 13 ± 2 °C y filtración. El precipitado se lava con
15 THF (3 x 1.0 L). El filtrado luego se agrega lentamente a un volumen grande de agua (17 L) para precipitar el producto. La suspensión resultante de los cristales se filtra, se lava con agua (2 x 0.50 L) y se seca bajo vacío a 45°C durante un mínimo de 24 h para dar el compuesto deseado como un sólido blanco (1.25 kg, 86%). ¹H NMR: δ (DMSO-d₆) 10.48 (s, 1H, NH), 7.83 (dd, 1H, Ar), 7.45-7.32 (m, 2H, Ar), 3.90 (s, 2H, NCCH₂CO).

20

Ejemplo 14

Preparación de (E/Z) 3-[3-etoxi-4-(N-ftalimidil)]anilino-N-(3-cloro-4-fluoro)fenil-2-ciano-2-propenamida.

25

[0069] Una mezcla de 3-etoxi-4-(N-ftalimidil)nitrobencono (20.0 g, 0.064 mol, 1.1 eq.) y 4% (p/p) de 10% Pd/C (0.80 g, 50% se humecta) en tetrahidrofurano (160 ml) se hidrogeno en a reactor Parr de 0.2 L de acero inoxidable a 70 psi, 50 °C durante un

mínimo de 10 h. La mezcla se filtra a través de una almohadilla de celita en un frasco de 1-cuello de 0.5 L y se lava con tetrahidrofurano (2 x 20 ml). El filtrado se destila a un volumen de -80 ml y el concentrado se agrega n-propanol (110 ml). La mezcla se destila a un volumen de 80 ml y el concentrado como se utiliza en la siguiente etapa.

5

[0070] El concentrado se transfiere a un frasco multi-cuello 0.5 L equipado con un agitador, sonda de temperatura, condensada y protección de nitrógeno. El frasco se carga con n-propanol (120 ml) seguido por N-(3-Cloro-4-fluoro)fenil-2-cianoacetamida (12.4 g, 0.058 mol, 1.0 eq.). La mezcla se calienta a 75-80 °C. La primera de tres
10 porciones de trietilortoformato (8.6 g, 9.7 ml, 0.058 mol, d=0.89 g/ml) se agrega y la mezcla calentada a reflujo (95-100 °C). Después de 2 h, la segunda porción de trietilortoformato se agrega (8.6 g, 9.7 ml, 0.058 mol). Después de otras 2 h, la tercera porción de trietilortoformato se agrega (8.6 g, 9.7 ml, 0.058 mol). La mezcla se mantiene durante un mínimo de 20 h a 95 °C. La mezcla se enfría a temperatura ambiente. La
15 mezcla se filtra en un túnel Buchner y se lava con el filtrado (20 ml) seguido por molido (0-10 °C) n-propanol (3 x 20 ml). El peso de la torta húmeda es -40 g.

[0071] La torta húmeda puede ser purificada de acetonitrilo. La torta húmeda se transfiere a un frasco multi-cuello 1-L equipado con un agitador mecánico, condensador,
20 sonda de temperatura y protección de nitrógeno. El frasco se carga con acetonitrilo (390 ml), calentado a 65-70 °C y se mantiene durante un mínimo de 20 min. La mezcla se enfría a 60 °C, filtrado en un túnel Buchner y se lava con acetonitrilo (2 x 15 ml). El producto se seca a 60 °C, vacío total durante 20 h para dar el compuesto del título (19.65 g, 67% rendimiento general durante 2 etapas). ¹H NMR: δ (DMSOd₆) 1 1.43, (d, 1H, NHCH=C), 9.74, (s, 1H, NH), 8.56 (d, 1H, NHCH=C), 7.99-7.88 (m, 5H, Ar), 7.64-7.56 (m, 1H, Ar), 7.39-7.29 (m, 3H, Ar), 7.15-7.10 (m, 1H, Ar), 4.10 (q, 2H, OCH₂CH₃),
25 1.18 (t, 3H, OCH₂CH₃).

Ejemplo 15

Preparación de 3-ciano-4-(3-cloro-4-fluoroanilino)-7-etoxi-N-ftalimidil-quinolina.

- 5 [0072] A un frasco multi-cuello de 1-L equipado con un agitador, sonda de temperatura, condensador y nitrógeno se carga 3-[3-etoxi-4-(N-ftalimidil)]anilino-N-(3-cloro-4-fluoro)fenil-2-ciano-2-propenamida (18 g, 0.0356 mol) y suspendido en acetonitrilo (180 ml) y metanol (7.2 ml). A un hidróxido de sodio (40 g en 1 L de agua) se configura un sistema lavador. La mezcla se calienta a 65-70 °C y oxiclورو de fósforo (54.6 g, 33.2
- 10 ml, 10.0 eq, d=1.645 g/ml) se agrega en forma de gotas manteniendo la temperatura de crisol a 65-70 °C. La mezcla eventualmente llega a ser más delgada. La mezcla se mantiene durante un mínimo de 22 h y luego se enfría a 0-10 °C. Se agrega agua (90 ml) mantiene la temperatura del crisol < 20 °C. El pH de la mezcla se ajusta a 8-10 utilizando 28% de hidróxido de amonio (~140 ml) manteniendo la temperatura de crisol
- 15 a 5-10 °C. La mezcla de 2 fase se filtra en un túnel Buchner y se lava con agua caliente. El sólido se seca a 60 °C, en un horno de vacío durante 18 h para dar el compuesto del título (14.44 g, 83% no corregido para resistencia) como un sólido naranja. ¹H NMR: δ (DMSO-d₆) 8.64 (s, 1H, Ar), 8.52 (m, 2H, Ar), 8.06-7.95 (m, 4H, ftalimida), 7.59-7.55 (m, 2H, Ar), 7.43 (m, 1H, Ar), 7.33 (m, 1H, Ar), 4.24 (q, 2H, OCH₂CH₃), 1.22 (t, 3H,
- 20 OCH₂CH₃).

Ejemplo 16

Preparación de 6-amino-4-(3-cloro-4-fluoroanilino)-3-ciano-7-etoxiquinolina.

- 25 [0073] A un frasco multi-cuello de 500 ml equipado con un agitador, sonda de temperatura, condensador y nitrógeno se carga 3-ciano-4-(3-cloro-4-fluoroanilino)-7-etoxi-N-ftalimidil-quinolina (12 g, 0.0246 mol) y etanol suspendido en etanol. Luego, se

agrega 28% de hidróxido de amonio (83 ml de una solución 7.4 M, 25 eq.). La suspensión se calienta a 65-70 °C y se mantiene durante un mínimo de 2 h. La reacción se enfría a temperatura ambiente, filtrada en un túnel Buchner, y se lava con agua (3 x 15 ml) hasta que los lavados sean incoloros. El sólido se seca a 60 °C, en un horno de vacío durante 25 h para dar el compuesto deseado (4.13 g). Se obtiene un segundo cultivo (2.05 g) de recristalización de acetonitrilo. (Rendimiento general 6.18 g, 70% no corregido para resistencia). ¹H NMR: δ (DMSOd₆) 9.22 (s, 1H, NH), 8.39 (s, 1H, Ar), 7.37-7.03 (m, 5H, Ar), 5.51 (s, 2H, NH₂), 4.24 (q, 2H, OCH₂CH₃), 1.45 (t, 3H, OCH₂CH₃).

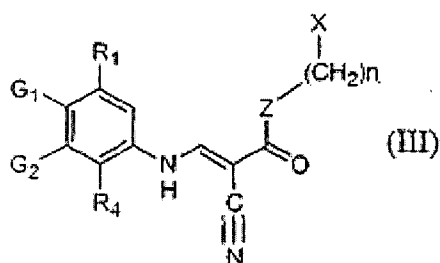
10 Métodos Analíticos

[0074] Se registra el espectro RMN en un Varian Inova a 300 a 300 MHz (¹H y ¹³C) y se identifican cambios químicos en ppm con relación al estándar interno TMS.

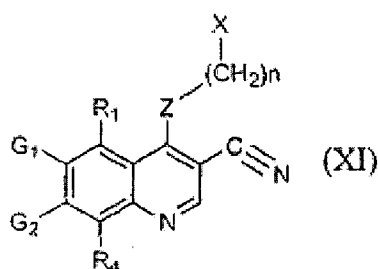
REIVINDICACIONES

LO QUE SE REIVINDICA ES:

- 5 1. Un método para preparar una 3-cianoquinolina sustituida comprende la etapa de tratar un N-aril-2-propeno representado por la fórmula III:



- 10 con POCl_3 para formar una 3-cianoquinolina sustituida representada por la fórmula XI:



- 15 en donde:

X es un sistema de anillo heteroarilo bicíclico o arilo bicíclico de 8 a 12 átomos en donde el anillo heteroarilo bicíclico contiene de 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 puede ser opcionalmente

20 mono- di-, tri, o tetra-sustituido 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, alcanoiloximetilo 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, dialquil amino 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 carbón, 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; o

X es cicloalquilo de 3 a 7 átomos de carbono, que pueden ser opcionalmente sustituidos con uno o más grupos alquilo de 1 a 6 átomos de carbono; o es un anillo piridinilo, pirimidinilo, o fenilo; en donde el anillo piridinilo, pirimidinilo, o fenilo opcionalmente mono- di-, o tri-sustituido 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, alcanoiloximetilo 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, alcanoilamino de 1-6 átomos de carbono, alquenoilamino de 3-8 átomos de carbono, alquinoilamino de 3-8 átomos de carbono, y benzoilamino;

o

X es un radical que tiene la fórmula: ---A---T---L

en donde

A es un anillo piridinilo, pirimidinilo, o fenilo; en donde el anillo piridinilo, pirimidinilo, o fenilo puede ser opcionalmente mono- o di-sustituido 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, alcanoiloximetilo 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 átomos de carbono, N-alquilaminoalcoxi de 2-9 átomos de carbono, N,N-dialquilaminoalcoxi de 3-10 átomos de carbono, mercapto, y benzoilamino;

T se une a un carbono de A y es:

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

L es un anillo fenilo no sustituido o un anillo fenilo mono-, di-, o tri- sustituido 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, alcanoiloximetilo 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,

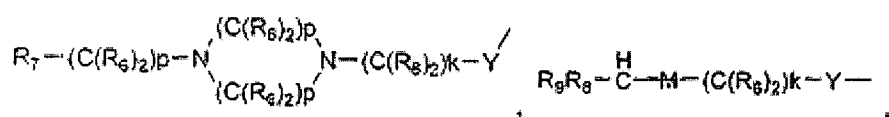
dialquilamino de 2 a 12 átomos de carbono, fenilamino, bencilamino, alcanoilamino de 1-6 átomos de carbono, alquenoilamino de 3-8 átomos de carbono, alquinoilamino de 3-8 átomos de carbono, carboxialquilo de 2-7 átomos de carbono, carboalcoxialquilo de 3-8 átomos de carbono, aminoalquilo de 1-5 átomos de carbono, N-alquilaminoalquilo de 2-9 átomos de carbono, N,N-dialquilaminoalquilo de 3-10 átomos de carbono, N-alquilaminoalcoxi de 2-9 átomos de carbono, N,N-dialquilaminoalcoxi de 3-10 átomos de carbono, mercapto, y benzoilamino; dado que L puede ser un anillo fenilo no sustituido solo cuando $m > 0$ y T no es $-\text{CH}_2\text{NH}-$ o $-\text{CH}_2\text{O}-$; o

L es un anillo heteroarilo de 5- o 6-miembros en donde al anillo heteroarilo contiene de 1 a 3 heteroátomos seleccionados de N, O, y S, con la condición que al anillo heteroarilo no contiene enlaces O-O, S-S, o S-O, y en donde al anillo heteroarilo es opcionalmente mono- o di-sustituido 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, alcanoiloximetilo 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 átomos de carbono, N-alquilaminoalcoxi de 2-9 átomos de carbono, N,N-dialquilaminoalcoxi de 3-10 átomos de carbono, mercapto, y benzoilamino;

Z es $-\text{NH}-$, $-\text{O}-$, $-\text{S}-$, o $-\text{NR}-$;

R es alquilo de 1-6 átomos de carbono, o carboalquilo de 2-7 átomos de carbono;

G₁, G₂, R₁, y R₄ 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, alquenilo de 2-6 átomos de carbono, alquinoxilo de 2-6 átomos de carbono, alquinoxilo de 2-6 átomos de carbono, hidroximetilo, halometilo, alcanilo de 1-6 átomos de carbono, alquinoxilo de 3-8 átomos de carbono, alquinoxilo de 3-8 átomos de carbono, alcaniloximetilo de 2-7 átomos de carbono, alquinoxilometilo de 4-9 átomos de carbono, alquinoxilometilo 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, alquilsulfonilo de 1-6 átomos de carbono, alquilsulfonamido de 1-6 átomos de carbono, alquilsulfonamido de 2-6 átomos de carbono, alquilsulfonamido de 2-6 átomos de carbono, hidroxilo, 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-alquenilamino de 4 a 12 átomos de carbono, N,N-dialquenilamino de 6-12 átomos de carbono, fenilamino, bencilamino,



R₇-(C(R₆)₂)_g-Y-, R₇-(C(R₆)₂)_p-M-(C(R₆)₂)_r-Y-, o Het-(C(R₆)₂)_qW-(C(R₆)₂)-Y-; o opcionalmente G₁ y/o G₂ se seleccionan independientemente de un grupo amino protegido y R₂-NH-;

o si cualquiera de los sustituyentes R₁, G₁, G₂, o R₄ se localizan en átomos de carbono contiguos entonces ellos pueden ser tomados juntos como el radical divalente -O-C(R₆)₂-O-;

Y es un radical divalente seleccionado del grupo que consiste de $-(CH_2)_a-$,
 $-O-$, y $-N^{R_6}-$;

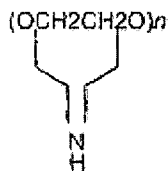
R_7 es $-NR_6R_7$, $-OR_6$, $-J$, $-N(R_6)_3^+$, o $-NR_7(OR_6)$;

M es $>NR_6$, $--O--$, $>N-(C(R_6)_2)_p NR_6R_6$, o $>N-(C(R_6)_2)_p-OR_6$;

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

Het se selecciona del grupo que consiste de morfolina, tiomorfolina, S-óxido de tiomorfolina, S,S-dióxido de tiomorfolina, piperidina, pirrolidina, aziridina, piridina, imidazol, 1,2,3-triazol, 1,2,4-triazol, tiazol, tiazolidina, tetrazol, piperazina, furano, tiofeno, tetrahidrotiofeno, tetrahidrofurano, dioxano, 1,3-dioxolano, tetrahidropirano, y

10



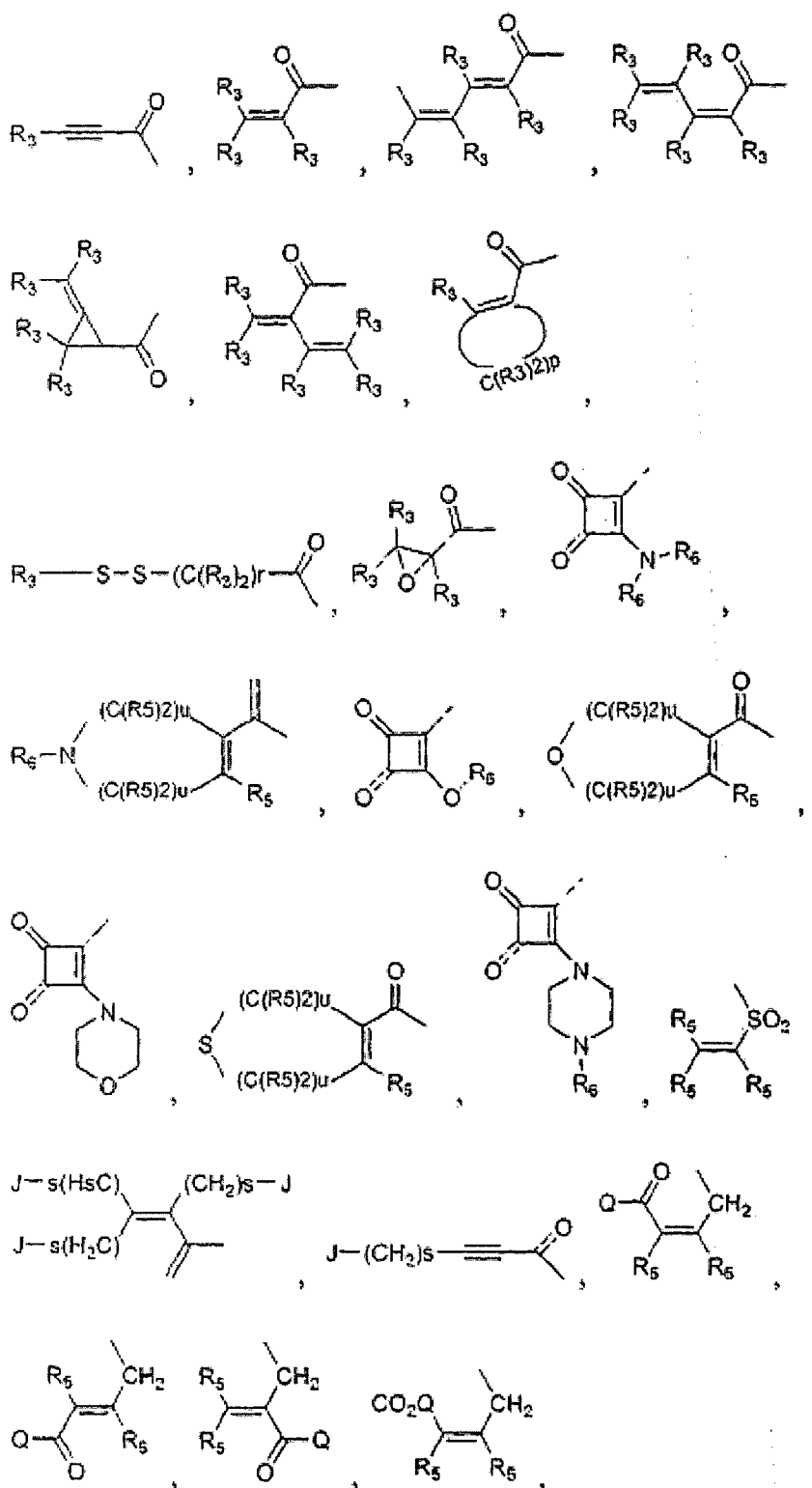
en donde Het es opcionalmente mono- o di-sustituido en carbono o nitrógeno con R_6 , opcionalmente mono- o di-sustituido en carbono con hidroxilo, $-N(R_6)_2$, o $-OR_6$,
 15 opcionalmente mono o di-sustituido en carbono con los radicales mono-valentes $-(C(R_6)_2)_sOR_6$ o $-(C(R_6)_2)_sN(R_6)_2$, y opcionalmente mono o di-sustituido en un carbono saturado con radicales divalentes $-O-$ o $-O(C(R_6)_2)_sO-$;

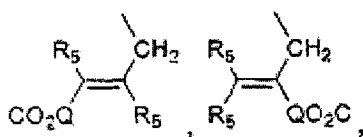
R_6 es hidrógeno, alquilo de 1-6 átomos de carbono, alquenilo de 2-6 átomos de carbono, alquinilo de 2-6 átomos de carbono, cicloalquilo de 1-6 átomos de carbono, carboalquilo de 2-7 átomos de carbono, carboxialquil (2-7 átomos de carbono), fenilo, o fenil opcionalmente sustituido con uno o más halógenos, 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
 25 carbono, hidroxilo, carboxilo, carboalcoxi de 2-7 átomos de carbono, fenoxi, fenilo, tiofenoxi, benzoilo, bencilo, fenilamino, bencilamino, alcanoilamino de 1-6 átomos de

carbono, o alquilo de 1-6 átomos de carbono; con la condición que la porción alquenoil o alquinilo está unida a un átomo de nitrógeno u oxígeno a través de un átomo de carbono saturado;

R_2 , se selecciona del grupo que consiste de

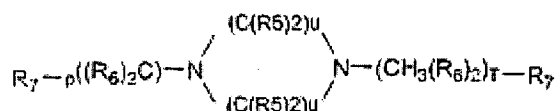
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R₃ es independientemente hidrógeno, alquilo de 1-6 átomos de carbono, carboxi, carboalcoxi de 1-6 átomos de carbono, fenilo, carboalquilo de 2-7 átomos de carbono,

5



R₇-(C(R₆)₂)_s-, R₇-(C(R₆)₂)_p-M-(C(R₇)₂)_r-, R₈R₉-CH-M-(C(R₆)₂)_r-, Het-(C(R₆)₂)_q-W-(C(R₆)₂)_r-; aminoalquilo de 1-6 átomos de carbono, N-alquilaminoalquilo de 2-9 átomos de carbono, N,N-dialquilaminoalquilo de 3-12 átomos de carbono, N-cicloalquilaminoalquilo de 4-12 átomos de carbono, N-cicloalquil-N-alquilaminoalquilo de 5-18 átomos de carbono, N,N-dicicloalquilaminoalquilo de 7-18 átomos de carbono, morfolino-N-alquilo en donde el grupo alquilo es 1-6 átomos de carbono, piperidino-N-alquil en donde el grupo alquilo es 1-6 átomos de carbono, N-alquil-piperidino-N-alquil en donde el otro grupo alquilo es 1-6 átomos de carbono;

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(R₆)₂)_r-, o Het-(C(R₆)₂)_q-W-(C(R₆)₂)_r-;

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

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

25

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;

10 u=0-4 y v=0-4, en donde la suma de u+v es 2-4;

o una sal farmacéuticamente aceptable de estos, dado que cuando R_6 es alqueno de 2-7 átomos de carbono o alquino de 2-7 átomos de carbono, tal porción alqueno o alquino está unida a un átomo de nitrógeno u oxígeno a través de un átomo de carbono saturado;

15 y dado que

cuando Y es $-NR_6-$ y R_7 es $-NR_6R_6 - N(R_6)_3^+$, o $-NR_6(OR_6)$, entonces g=2-6;

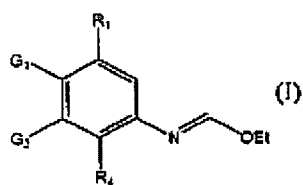
cuando M es $-O-$ y R_7 es $-OR_6$ entonces p=1-4;

cuando Y es $-NR_6-$ entonces k=2-4;

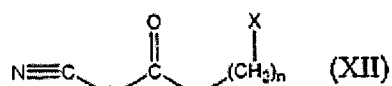
cuando Y es $-O-$ y M o W es $-O-$ entonces k=1-4

20 cuando W no es un enlace con Het unido a través de un átomo de nitrógeno entonces q=2-4 y cuando W es un enlace con Het unido a través de un átomo de nitrógeno y Y es $-O-$ o $-NR_6-$ entonces k=2-4.

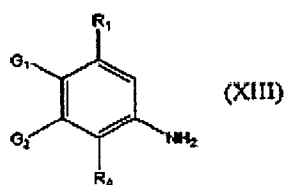
2. El método de acuerdo con la reivindicación 1, adicionalmente comprende la
25 etapa de formar el N-aril-2-propeno compuesto de fórmula III al condensar un N-arilformimidato de fórmula I:



con un metileno activo de fórmula XII:



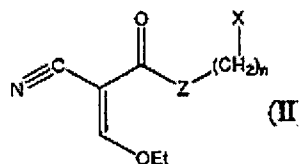
- 5 3. El método de acuerdo con la reivindicación 2, adicionalmente comprende la etapa de formar el N-arilformimidato de fórmula I al hacer reaccionar una arilamina de fórmula XIII:



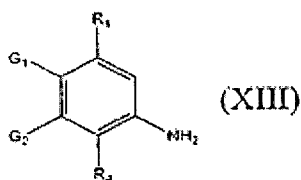
10 con $\text{CH}(\text{OEt})_3$

4. El método de acuerdo con la reivindicación 1 adicionalmente comprende la etapa de formar el N-aril-2-propeno de fórmula III al hacer reaccionar un derivado de alcoximetileno de fórmula II:

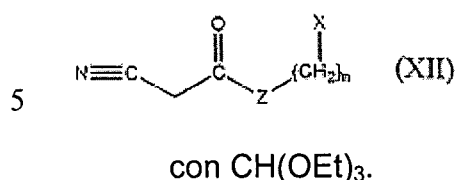
15



con una arilamina de fórmula XIII



5. El método de acuerdo con la reivindicación 4, adicionalmente comprende la etapa de formar un alcoximetileno de fórmula II al condensar un metileno activo de fórmula XII:



6. El método de acuerdo con las reivindicaciones 1, 2, 3, 4, y 5, en donde Z es seleccionados del grupo que consiste de NH, O y S.

10

7. El método de acuerdo con la reivindicación 1, 2, 3, 4, y 5, en donde G_1 es un grupo amino protegido seleccionado del grupo que consiste de acetamidas, benzamidas, imidas cíclicas, pirroles, amina terc-butoxicarbonilo y amida benciloxicarbonilo.

15

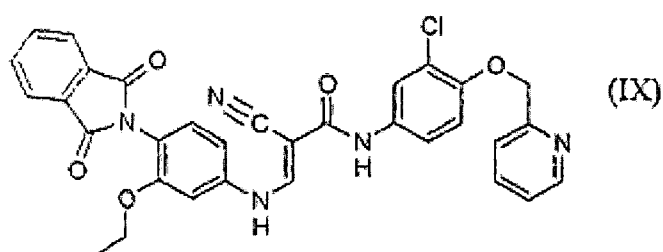
8. El método de acuerdo con la reivindicación 7, en donde G_1 es ftalimida.

9. Un método de acuerdo con las reivindicaciones 1, 2, 3, 4, y 5, en donde X es cicloalquilo de 3 a 7 átomos de carbono, que pueden ser opcionalmente sustituidos con uno o más grupos alquilo de 1 a 6 átomos de carbono; o es un anillo piridinilo, pirimidinilo, o fenilo; en donde el anillo piridinilo, pirimidinilo, o fenilo opcionalmente mono- di-, o tri-sustituido 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, alcanoiloximetilo 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, y benzoilamino.

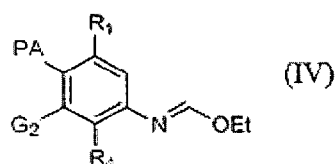
5

10. El método de acuerdo con las reivindicaciones 1, 2, 3, 4, y 5, en donde el N-aril-2-propeno de fórmula III es el compuesto representado por la fórmula IX:



10

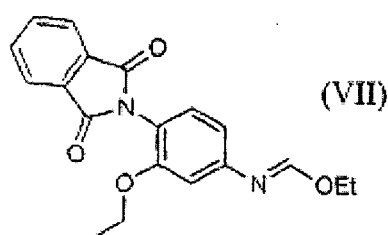
11. El método de acuerdo con las reivindicaciones 2 y 3, en donde la N-arilformimidato de fórmula I es un compuesto representado por la fórmula IV:



15

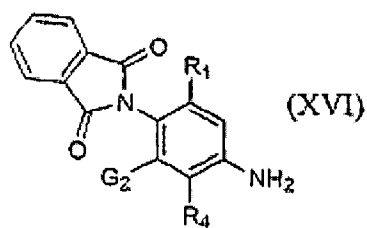
en donde PA es un grupo amino protegido.

12. El método de acuerdo con la reivindicación 11, en donde el N-arilformimidato de fórmula IV es un compuesto representado por la fórmula VII:

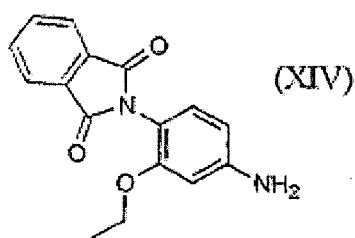


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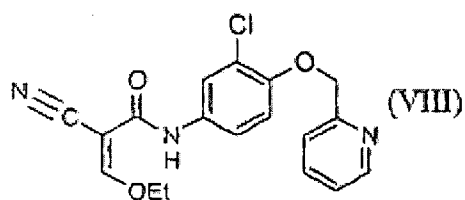
13. El método de acuerdo con las reivindicaciones 3, 4 y 5, en donde la arilamina de fórmula XIII es un compuesto representado por la fórmula XVI:



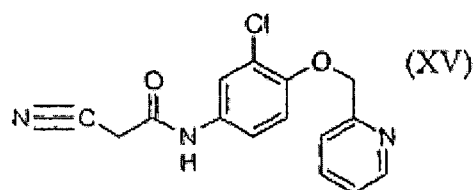
14. El método de acuerdo con la reivindicación 13, en donde la arilamina de fórmula XVI es un compuesto representado por la fórmula XIV:



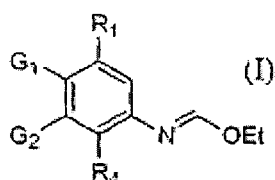
15. El método de acuerdo con las reivindicaciones 4 y 5, en donde el alcoximetileno de fórmula II es un compuesto representado por la fórmula VIII:



16. El método de acuerdo con las reivindicaciones 2, 3 y 5, en donde el metileno activo de fórmula XII es el compuesto representado por la fórmula XV:



17. Un compuesto representado por la fórmula I:

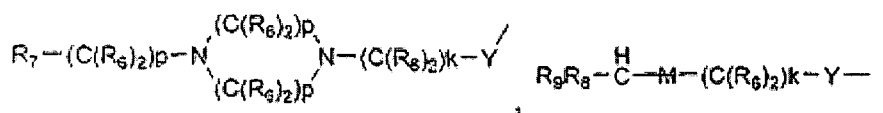


5

en donde

G_1 , G_2 , R_1 , y R_4 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, alcanoiloxi de 1-6 átomos de carbono, alquenoiloxi de 3-8 átomos de carbono, alquinoiloxi de 3-8 átomos de carbono, alcanoiloximetilo de 2-7 átomos de carbono, alquenoiloximetilo de 4-9 átomos de carbono, alquinoiloximetilo 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, alquilsulfínilo de 1-6 átomos de carbono, alquilsulfonilo de 1-6 átomos de carbono, alquilsulfonamido de 1-6 átomos de carbono, alquenilsulfonamido de 2-6 átomos de carbono, alquinilsulfonamido de 2-6 átomos de carbono, hidroxilo, 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, alcoxi-amino 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-alquenilamino de 4 a 12 átomos de carbono, N,N-dialquenilamino de 6-12 átomos de carbono, fenilamino, bencilamino,

10
15
20



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

5 opcionalmente G_1 y/o G_2 se seleccionan independientemente de un grupo amino protegido y R_2-NH- ;

o si cualquiera de los sustituyentes R_1 , G_1 , G_2 , o R_4 se localizan en átomos de carbono contiguos entonces ellos pueden ser tomados juntos como el radical divalente -
 $O-C(R_6)_2-O-$;

10 Y es un radical divalente seleccionado del grupo que consiste de $-(CH_2)_a-$,

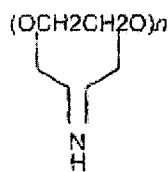
$-O-$, y $-\overset{R_4}{N}-$;

R_7 es $-NR_6R_7$, $-OR_6$, $-J$, $-N(R_6)_3^+$, o $-NR_7(OR_6)$;

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

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

15 Het se selecciona del grupo que consiste de morfolina, tiomorfolina, S-óxido de tiomorfolina, S,S-dióxido de tiomorfolina, piperidina, pirrolidina, aziridina, piridina, imidazol, 1,2,3-triazol, 1,2,4-triazol, tiazol, tiazolidina, tetrazol, piperazina, furano, tiofeno, tetrahidrotiofeno, tetrahidrofurano, dioxano, 1,3-dioxolano, tetrahidropirano, y



20

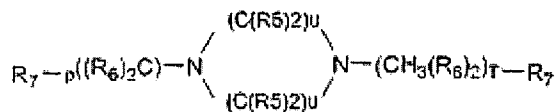
en donde Het es opcionalmente mono- o di-sustituido en carbono o nitrógeno con R_6 , opcionalmente mono- o di-sustituido en carbono con hidroxí, $-N(R_6)_2$, o $-OR_6$, opcionalmente mono o di-sustituido en carbono con los radicales mono-valentes -

25 $(C(R_6)_2)_sOR_6$ o

$-(C(R_6)_2)_sN(R_6)_2$, y opcionalmente mono o di-sustituido en un carbono saturado con radicales divalentes $-O-$ o $-O(C(R_6)_2)_sO-$;

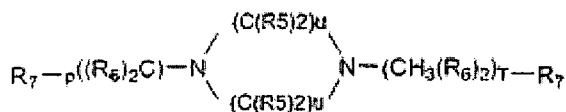
5 R_6 es hidrógeno, alquilo de 1-6 átomos de carbono, alquenilo de 2-6 átomos de carbono, alquinilo de 2-6 átomos de carbono, cicloalquilo de 1-6 átomos de carbono, carboalquilo de 2-7 átomos de carbono, carboxialquil (2-7 átomos de carbono), fenilo, o fenil opcionalmente sustituido con uno o más halógenos, alcoxi de 1-6 átomos de carbono, trifluorometilo, amino, alquilamino de 1-3 átomos de carbono, dialquilamino de 10 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, alcanoilamino de 1-6 átomos de carbono, o alquilo de 1-6 átomos de carbono; con la condición que la porción alquenilo 15 o alquinilo está unida a un átomo de nitrógeno u oxígeno a través de un átomo de carbono saturado;

R_2 , se selecciona del grupo que consiste de



$R_7 - (C(R_6)_2)_s$ -, $R_7 - (C(R_6)_2)_p - M - (C(R_7)_2)_r$ -, $R_8 R_9 - CH - M - (C(R_6)_2)_r$ -, $Het - (C(R_6)_2)_q - W - (C(R_6)_2)_r$;- aminoalquilo de 1-6 átomos de carbono, N-alquilaminoalquilo de 2-9 átomos
 5 de carbono, N,N-dialquilaminoalquilo de 3-12 átomos de carbono, N-cicloalquilaminoalquilo de 4-12 átomos de carbono, N-cicloalquil-N-alquilaminoalquilo de 5-18 átomos de carbono, N,N-dicicloalquilaminoalquilo de 7-18 átomos de carbono, morfolino-N-alquilo en donde el grupo alquilo es 1-6 átomos de carbono, piperidino-N-alquil en donde el grupo alquilo es 1-6 átomos de carbono, N-alquil-piperidino-N-alquil
 10 en donde el otro grupo alquilo es 1-6 átomos de carbono;

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,



15

$R_7 - (C(R_6)_2)_s$ -, $R_7 - (C(R_6)_2)_p - M - (C(R_6)_2)_r$ -, $R_8 R_9 - CH - M - (C(R_6)_2)_r$ -, 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, flúor, o bromo;

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

$a=0$ o 1 ;

$g=1-6$;

$k=0-4$;

n es $0-1$;

25 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;

5 o una sal farmacéuticamente aceptable de estos, dado que cuando R_6 es alqueno de 2-7 átomos de carbono o alquino de 2-7 átomos de carbono, tal porción alqueno o alquino está unida a un átomo de nitrógeno u oxígeno a través de un átomo de carbono saturado;

y dado que adicionalmente

10 cuando Y es $-NR_6-$ y R_7 es $-NR_6R_6 - N(R_6)_3^+$, o $-NR_6(OR_6)$, entonces g=2-6;

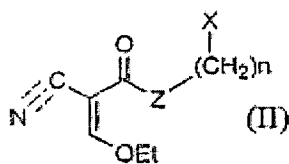
cuando M es $-O-$ y R_7 es $-OR_6$ entonces p=1-4;

cuando Y es $-NR_6-$ entonces k=2-4;

cuando Y es $-O-$ y M o W es $-O-$ entonces k=1-4

15 cuando W no es un enlace con Het unido a través de un átomo de nitrógeno entonces q=2-4 y cuando W es un enlace con Het unido a través de un átomo de nitrógeno y Y es $-O-$ o $-NR_6-$ entonces k=2-4.

18. Un compuesto representado por la fórmula II:



en donde:

X es un sistema de anillo heteroarilo bicíclico o arilo bicíclico de 8 a 12 átomos en donde el anillo heteroarilo bicíclico contiene de 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, 25 o S-O y en donde el anillo arilo bicíclico o heteroarilo bicíclico puede ser opcionalmente

mono- di-, tri, o tetra-sustituido 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, fenilo, tiofenoxi, benzoilo, bencilo, amino, alquilamino de 1-6 átomos de carbono, dialquil amino 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 carbón, 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; o

X es cicloalquilo de 3 a 7 átomos de carbono, que pueden ser opcionalmente sustituidos con uno o más grupos alquilo de 1 a 6 átomos de carbono; o es un anillo piridinilo, pirimidinilo, o fenilo; en donde el anillo piridinilo, pirimidinilo, o fenilo opcionalmente mono- di-, o tri-sustituido 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, 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,

alquenoilamino de 3-8 átomos de carbono, alquinoilamino de 3-8 átomos de carbono, y benzoilamino;

o

X es un radical que tiene la fórmula: ---A---T---L

5 en donde

A es un anillo piridinilo, pirimidinilo, o fenilo; en donde el anillo piridinilo, pirimidinilo, o fenilo puede ser opcionalmente mono- o di-sustituido 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, alcanoiloximetilo 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 átomos de carbono, N-alquilaminoalcoxi de 2-9 átomos de carbono, N,N-dialquilaminoalcoxi de 3-10 átomos de carbono, mercapto, y benzoilamino;

T se une a un carbono de A y es:

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

25 L es un anillo fenilo no sustituido o un anillo fenilo mono-, di-, o tri- sustituido 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, alcanoiloximetilo 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, 5 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 átomos de carbono, N- 10 alquilaminoalcoxi de 2-9 átomos de carbono, N,N-dialquilaminoalcoxi de 3-10 átomos de carbono, mercapto, y benzoilamino; dado que L puede ser un anillo fenilo no sustituido solo cuando $m > 0$ y T no es $-\text{CH}_2\text{NH}-$ o $-\text{CH}_2\text{O}-$; o

L es un anillo heteroarilo de 5- o 6-miembros en donde el anillo heteroarilo contiene de 1 a 3 heteroátomos seleccionados de N, O, y S, con la condición que el 15 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 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 de 2-7 átomos de carbono, 20 alcanoiloximetilo 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, 25 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

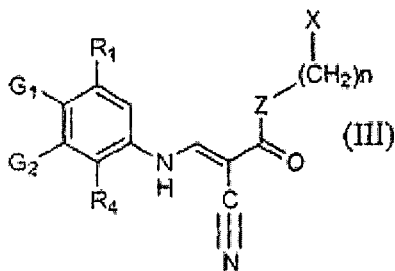
2-9 átomos de carbono, N,N-dialquilaminoalcoxi de 3-10 átomos de carbono, mercapto, y benzoilamino;

Z es -NH-, -O-, -S-, o -NR-;

R es alquilo de 1-6 átomos de carbono, o carboalquilo de 2-7 átomos de carbono;

5

19. Un compuesto representado por la fórmula III:



10 en donde:

X es un sistema de anillo heteroarilo bicíclico o arilo bicíclico de 8 a 12 átomos en donde el anillo heteroarilo bicíclico contiene de 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 puede ser opcionalmente

15 mono- di-, tri, o tetra-sustituido 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, alcanoiloximetilo de 2-7 átomos de carbono, alcoxi de 1-6 átomos de carbono, alquiltio de 1-6 átomos de

20 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, dialquil amino 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,

25 carboxialquilo de 2-7 átomos de carbón, 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; o

5 X es cicloalquilo de 3 a 7 átomos de carbono, que pueden ser opcionalmente sustituidos con uno o más grupos alquilo de 1 a 6 átomos de carbono; o es un anillo piridinilo, pirimidinilo, o fenilo; en donde el anillo piridinilo, pirimidinilo, o fenilo opcionalmente mono- di-, o tri-sustituido 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, alcanoiloximetilo 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, 15 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, y benzoilamino;

o

20 X es un radical que tiene la fórmula: $\text{---}^{\text{A}}\text{---}^{\text{T}}\text{---}^{\text{L}}$

en donde

A es un anillo piridinilo, pirimidinilo, o fenilo; en donde el anillo piridinilo, pirimidinilo, o fenilo puede ser opcionalmente mono- o di-sustituido 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, alcanoiloximetilo 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, 25

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 átomos de carbono, N-alquilaminoalcoxi de 2-9 átomos de carbono, N,N-dialquilaminoalcoxi de 3-10 átomos de carbono, mercapto, y benzoilamino;

10 T se une a un carbono de A y es:

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

L es un anillo fenilo no sustituido o un anillo fenilo mono-, di-, o tri- sustituido 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, alcanoiloximetilo 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 átomos de carbono, N-alquilaminoalcoxi de 2-9 átomos de carbono, N,N-dialquilaminoalcoxi de 3-10 átomos de carbono, mercapto, y benzoilamino; dado que L puede ser un anillo fenilo no sustituido solo cuando m>0 y T no es -CH₂ NH- o -CH₂O-; o

L es un anillo heteroarilo de 5- o 6-miembros en donde al anillo heteroarilo contiene de 1 a 3 heteroátomos seleccionados de N, O, y S, con la condición que al anillo heteroarilo no contiene enlaces O-O, S-S, o S-O, y en donde al anillo heteroarilo es opcionalmente mono- o di-sustituido con un sustituyente seleccionado del grupo que

5 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, alcanoiloximetilo 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-

10 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,

15 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;

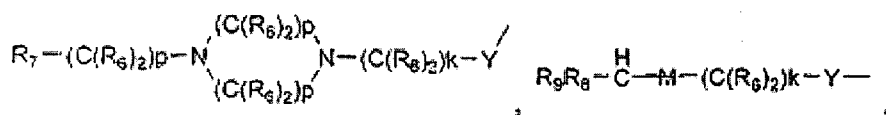
Z es -NH-, -O-, -S-, o -NR-;

20 R es alquilo de 1-6 átomos de carbono, o carboalquilo de 2-7 átomos de carbono;

G₁, G₂, R₁, y R₄ 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, alcanoiloxi de 1-6 átomos de carbono, alquenoiloxi de 3-8 átomos de carbono, alquinoiloxi de 3-8 átomos de carbono, alcanoiloximetilo de 2-7 átomos de carbono, alquenoiloximetilo de 4-9 átomos de carbono, alquinoiloximetilo 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, alquilsulfinilo de 1-6 átomos de

25

carbono, alquilsulfonilo de 1-6 átomos de carbono, alquilsulfonamido de 1-6 átomos de carbono, alquenilsulfonamido de 2-6 átomos de carbono, alquinilsulfonamido de 2-6 átomos de carbono, hidroxilo, 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, alcoxi-amino 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-alquenilamino de 4 a 12 átomos de carbono, N,N-dialquenilamino de 6-12 átomos de carbono, fenilamino, bencilamino,



$R_7-(C(R_6)_2)_g-Y-$, $R_7-(C(R_6)_2)_p-M-(C(R_6)_2)_r-Y-$, o $Het-(C(R_6)_2)_qW-(C(R_6)_2)_2-Y-$; o opcionalmente G_1 y/o G_2 se seleccionan independientemente de un grupo amino protegido y R_2-NH- ;

o si cualquiera de los sustituyentes R_1 , G_1 , G_2 , o R_4 se localizan en átomos de carbono contiguos entonces ellos pueden ser tomados juntos como el radical divalente - $O-C(R_6)_2-O-$;

Y es un radical divalente seleccionado del grupo que consiste de $-(CH_2)_a-$,

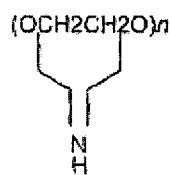
$-O-$, y $-\overset{R_8}{N}-$;

R_7 es $-NR_6R_7$, $-OR_6$, $-J$, $-N(R_6)_3^+$, o $-NR_7(OR_6)$;

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

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

Het se selecciona del grupo que consiste de morfolina, tiomorfolina, S-óxido de tiomorfolina, S,S-dióxido de tiomorfolina, piperidina, pirrolidina, aziridina, piridina, imidazol, 1,2,3-triazol, 1,2,4-triazol, tiazol, tiazolidina, tetrazol, piperazina, furano, tiofeno, tetrahidrotiofeno, tetrahidrofurano, dioxano, 1,3-dioxolano, tetrahidropirano, y



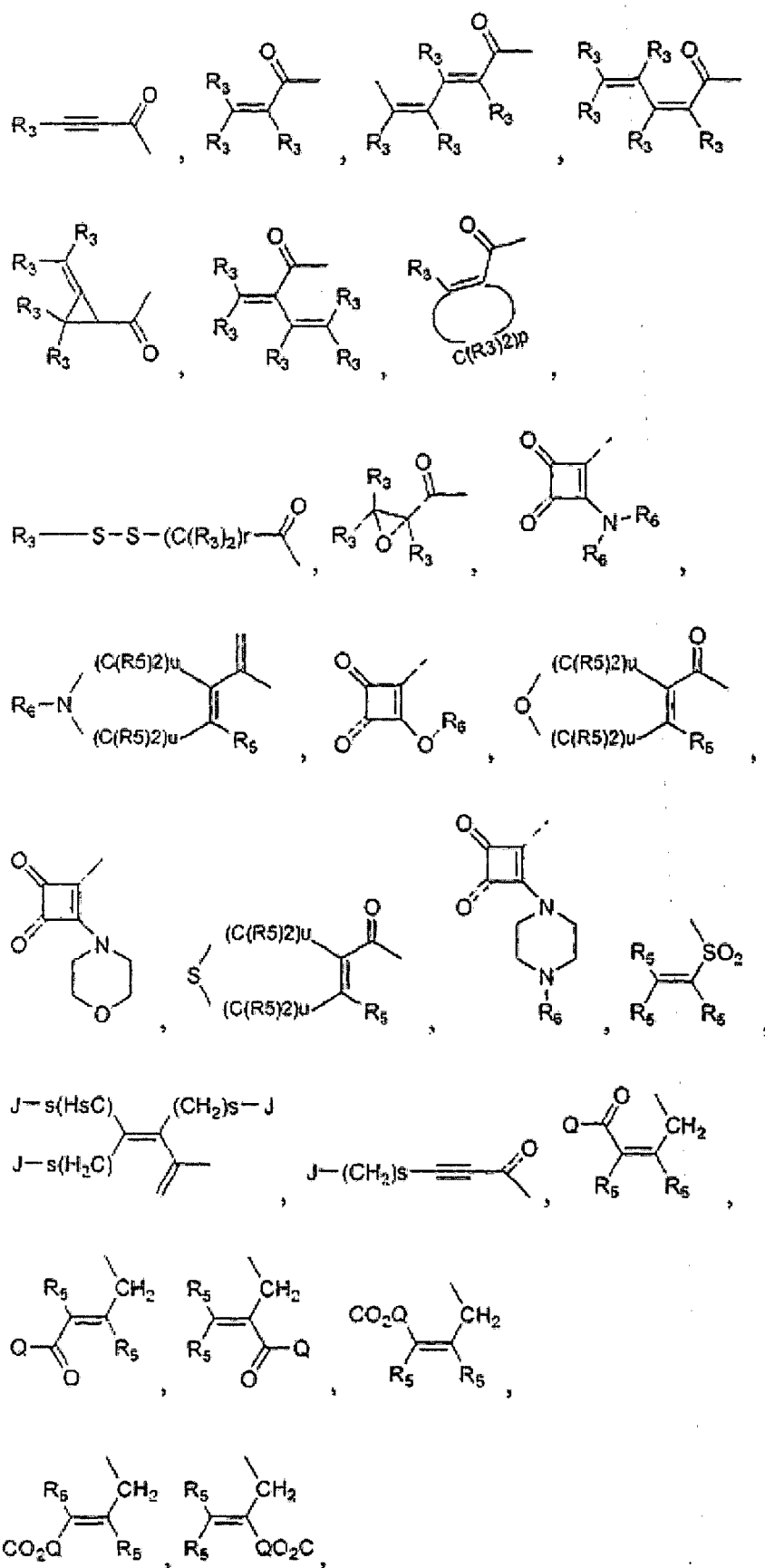
en donde Het es opcionalmente mono- o di-sustituido en carbono o nitrógeno con

5 R_6 , opcionalmente mono- o di-sustituido en carbono con hidroxilo, $-\text{N}(\text{R}_6)_2$, o $-\text{OR}_6$,
opcionalmente mono o di-sustituido en carbono con los radicales mono-valentes -
 $(\text{C}(\text{R}_6)_2)_s\text{OR}_6$ o

$-(\text{C}(\text{R}_6)_2)_s\text{N}(\text{R}_6)_2$, y opcionalmente mono o di-sustituido en un carbono saturado
con radicales divalentes $-\text{O}-$ o $-\text{O}(\text{C}(\text{R}_6)_2)_s\text{O}-$;

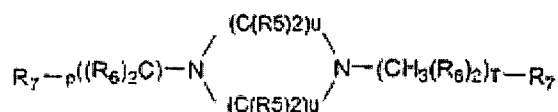
10 R_6 es hidrógeno, alquilo de 1-6 átomos de carbono, alquenilo de 2-6 átomos de
carbono, alquinilo de 2-6 átomos de carbono, cicloalquilo de 1-6 átomos de carbono,
carboalquilo de 2-7 átomos de carbono, carboxialquil (2-7 átomos de carbono), fenilo, o
fenil opcionalmente sustituido con uno o más halógenos, alcoxi de 1-6 átomos de
carbono, trifluorometilo, amino, alquilamino de 1-3 átomos de carbono, dialquilamino de
15 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, alcanoilamino de 1-6 átomos de
carbono, o alquilo de 1-6 átomos de carbono; con la condición que la porción alquenilo
20 o alquinilo está unida a un átomo de nitrógeno u oxígeno a través de un átomo de
carbono saturado;

R_2 , se selecciona del grupo que consiste de



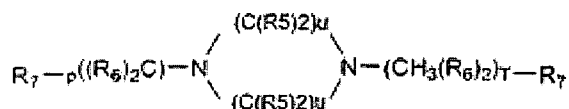
R_3 es independientemente hidrógeno, alquilo de 1-6 átomos de carbono, carboxi,

5 carboalcoxi de 1-6 átomos de carbono, fenilo, carboalquilo de 2-7 átomos de carbono,



$R_7 - (C(R_6)_2)_s$ -, $R_7 - (C(R_6)_2)_p - M - (C(R_7)_2)_r$ -, $R_8 R_9 - CH - M - (C(R_6)_2)_r$ -, $Het - (C(R_6)_2)_q - W - (C(R_6)_2)_r$;- aminoalquilo de 1-6 átomos de carbono, N-alquilaminoalquilo de 2-9 átomos
 5 de carbono, N,N-dialquilaminoalquilo de 3-12 átomos de carbono, N-cicloalquilaminoalquilo de 4-12 átomos de carbono, N-cicloalquil-N-alquilaminoalquilo de 5-18 átomos de carbono, N,N-dicicloalquilaminoalquilo de 7-18 átomos de carbono, morfolino-N-alquilo en donde el grupo alquilo es 1-6 átomos de carbono, piperidino-N-alquil en donde el grupo alquilo es 1-6 átomos de carbono, N-alquil-piperidino-N-alquil
 10 en donde el otro grupo alquilo es 1-6 átomos de carbono;

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, flúor, o bromo;

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

$a=0$ o 1 ;

$g=1-6$;

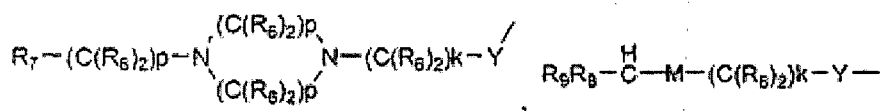
$k=0-4$;

n es $0-1$;

m es $0-3$;

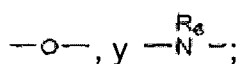
$p=2-4$;

de 3-8 átomos de carbono, alquinoiloxi de 3-8 átomos de carbono, alcanoiloximetilo de 2-7 átomos de carbono, alquenoiloximetilo de 4-9 átomos de carbono, alquinoiloximetilo 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, alquilsulfinilo de 1-6 átomos de carbono, alquilsulfonilo de 1-6 átomos de carbono, alquilsulfonamido de 1-6 átomos de carbono, alquenilsulfonamido 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, ftalimida, 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-alquilcarbamoilo, N,N-dialquilcarbamoilo, N-alquil-N-alquenilamino de 4 a 12 átomos de carbono, N,N-dialquenilamino de 6 -12 átomos de carbono, fenilamino, bencilamino,



$R_7-(C(R_6)_2)_g-Y-$, $R_7-(C(R_6)_2)_p-M-(C(R_6)_2)_r-Y-$, o $Het-(C(R_6)_2)_qW-(C(R_6)_2)_2-Y-$; o opcionalmente G_2 se seleccionan independientemente de un grupo amino protegido y R_2-NH- ;

Y es un radical divalente seleccionado del grupo que consiste de $-(CH_2)_a-$,

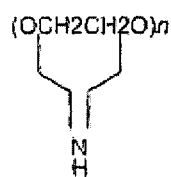


R_7 es $-NR_6R_7$, $-OR_6$, $-J$, $-N(R_6)_3^+$, o $-NR_7(OR_6)$;

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

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

Het se selecciona del grupo que consiste de morfolina, tiomorfolina, S-óxido de tiomorfolina, S,S-dióxido de tiomorfolina, piperidina, pirrolidina, aziridina, piridina, imidazol, 1,2,3-triazol, 1,2,4-triazol, tiazol, tiazolidina, tetrazol, piperazina, furano, tiofeno, tetrahidrotiofeno, tetrahidrofurano, dioxano, 1,3-dioxolano, tetrahidropirano, y

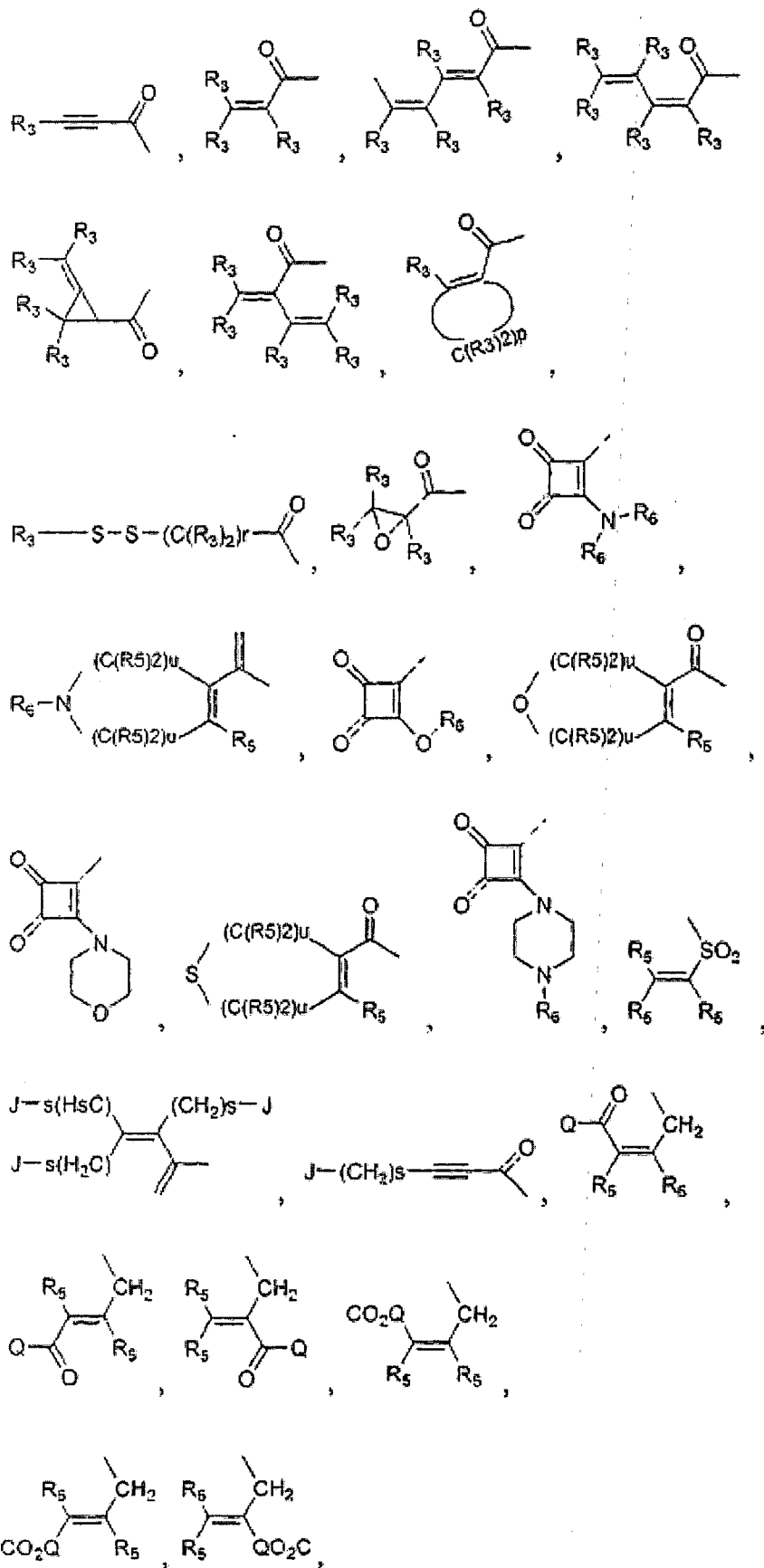


en donde Het es opcionalmente mono- o di-sustituido en carbono o nitrógeno con

- 5 R_6 , opcionalmente mono- o di-sustituido en carbono con hidroxilo, $-N(R_6)_2$, o $-OR_6$,
opcionalmente mono o di-sustituido en carbono con los radicales mono-valentes -
 $(C(R_6)_2)_sOR_6$ o $-(C(R_6)_2)_sN(R_6)_2$, y opcionalmente mono o di-sustituido en un carbono
saturado con radicales divalentes $-O-$ o $-O(C(R_6)_2)_sO-$;

- R_6 es hidrógeno, alquilo de 1-6 átomos de carbono, alquenilo de 2-6 átomos de
10 carbono, alquinilo de 2-6 átomos de carbono, cicloalquilo de 1-6 átomos de carbono,
carboalquilo de 2-7 átomos de carbono, carboxialquil (2-7 átomos de carbono), fenilo, o
fenil opcionalmente sustituido con uno o más halógenos, 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
15 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, alcanoilamino de 1-6 átomos de
carbono, o alquilo de 1-6 átomos de carbono; con la condición que la porción alquenilo
o alquinilo está unida a un átomo de nitrógeno u oxígeno a través de un átomo de
20 carbono saturado;

R_2 , se selecciona del grupo que consiste de



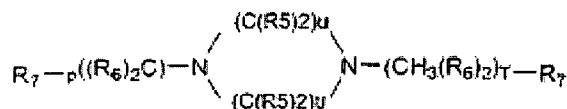
R_3 es independientemente hidrógeno, alquilo de 1-6 átomos de carbono, carboxi,

5 carboalcoxi de 1-6 átomos de carbono, fenilo, carboalquilo de 2-7 átomos de carbono,



$R_7 - (\text{C(R}_6\text{)}_2)_s$ -, $R_7 - (\text{C(R}_6\text{)}_2)_p - \text{M} - (\text{C(R}_7\text{)}_2)_r$ -, $R_8 R_9 - \text{CH} - \text{M} - (\text{C(R}_6\text{)}_2)_r$ -, $\text{Het} - (\text{C(R}_6\text{)}_2)_q - \text{W} - (\text{C(R}_6\text{)}_2)_r$;- aminoalquilo de 1-6 átomos de carbono, N-alquilaminoalquilo de 2-9 átomos
 5 de carbono, N,N-dialquilaminoalquilo de 3-12 átomos de carbono, N-cicloalquilaminoalquilo de 4-12 átomos de carbono, N-cicloalquil-N-alquilaminoalquilo de 5-18 átomos de carbono, N,N-dicicloalquilaminoalquilo de 7-18 átomos de carbono, morfolino-N-alquilo en donde el grupo alquilo es 1-6 átomos de carbono, piperidino-N-alquil en donde el grupo alquilo es 1-6 átomos de carbono, N-alquil-piperidino-N-alquil
 10 en donde el otro grupo alquilo es 1-6 átomos de carbono;

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,



$R_7 - (\text{C(R}_6\text{)}_2)_s$ -, $R_7 - (\text{C(R}_6\text{)}_2)_p - \text{M} - (\text{C(R}_6\text{)}_2)_r$ -, $R_8 R_9 - \text{CH} - \text{M} - (\text{C(R}_6\text{)}_2)_r$ -, o $\text{Het} - (\text{C(R}_6\text{)}_2)_q - \text{W} - (\text{C(R}_6\text{)}_2)_r$;-

R_8 , y R_9 son cada uno, independientemente, $-(\text{C(R}_6\text{)}_2)_r \text{NR}_6 \text{R}_6$, o $-(\text{C(R}_6\text{)}_2)_r \text{OR}_6$;

J es independientemente hidrógeno, cloro, flúor, 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;

- 5 o una sal farmacéuticamente aceptable de estos, dado que cuando R_6 es alqueno de 2-7 átomos de carbono o alquino de 2-7 átomos de carbono, tal porción alqueno o alquino está unida a un átomo de nitrógeno u oxígeno a través de un átomo de carbono saturado;

y dado que

- 10 cuando Y es $-NR_6-$ y R_7 es $-NR_6R_6 - N(R_6)_3^+$, o $-NR_6(OR_6)$, entonces $g=2-6$;

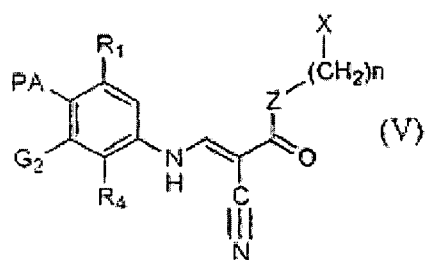
cuando M es $-O-$ y R_7 es $-OR_6$ entonces $p=1-4$;

cuando Y es $-NR_6-$ entonces $k=2-4$;

cuando Y es $-O-$ y M o W es $-O-$ entonces $k=1-4$

- 15 cuando W no es un enlace con Het unido a través de un átomo de nitrógeno entonces $q=2-4$ y cuando W es un enlace con Het unido a través de un átomo de nitrógeno y Y es $-O-$ o $-NR_6-$ entonces $k=2-4$.

21. Un compuesto representado por la fórmula V:



20

en donde PA es un grupo amino protegido;

- 25 en donde X es un sistema de anillo heteroarilo bicíclico o arilo bicíclico de 8 a 12 átomos en donde el anillo heteroarilo bicíclico contiene de 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 puede ser opcionalmente mono- di-, tri, o tetra-sustituido 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, alcanoiloximetilo 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, dialquil amino 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 carbón, 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; o

X es cicloalquilo de 3 a 7 átomos de carbono, que pueden ser opcionalmente sustituidos con uno o más grupos alquilo de 1 a 6 átomos de carbono; o es un anillo piridinilo, pirimidinilo, o fenilo; en donde el anillo piridinilo, pirimidinilo, o fenilo opcionalmente mono- di-, o tri-sustituido 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, alcanoiloximetilo 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, alcanoilamino de 1-6 átomos de carbono,

alquenoilamino de 3-8 átomos de carbono, alquinoilamino de 3-8 átomos de carbono, y benzoilamino; o

X es un radical que tiene la fórmula: ---A---T---L

en donde

5 A es un anillo piridinilo, pirimidinilo, o fenilo; en donde el anillo piridinilo, pirimidinilo, o fenilo puede ser opcionalmente mono- o di-sustituido 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, alcanoiloximetilo 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 15 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; 20

T se une a un carbono de A y es:

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

L es un anillo fenilo no sustituido o un anillo fenilo mono-, di-, o tri- sustituido con 25 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, alcanoiloximetilo 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, alcanoilamino de 5 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 10 carbono, mercapto, y benzoilamino; dado que L puede ser un anillo fenilo no sustituido solo cuando $m > 0$ y T no es $-\text{CH}_2\text{NH}-$ o $-\text{CH}_2\text{O}-$; o

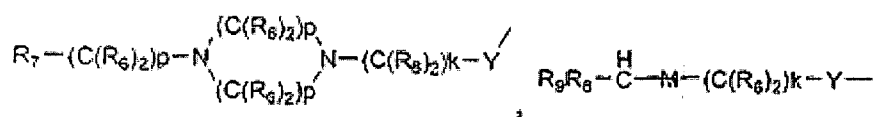
L es un anillo heteroarilo de 5- o 6-miembros en donde al anillo heteroarilo contiene de 1 a 3 heteroátomos seleccionados de N, O, y S, con la condición que al anillo heteroarilo no contiene enlaces O-O, S-S, o S-O, y en donde al anillo heteroarilo es opcionalmente mono- o di-sustituido con un sustituyente seleccionado del grupo que 15 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, alcanoiloximetilo de 2-7 átomos de carbono, alcoxi de 1-6 átomos de carbono, alquiltio 20 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, alcanoilamino de 1-6 átomos de carbono, alquenoilamino de 3-8 átomos de carbono, alquinoilamino de 3-8 átomos de carbono, 25 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;

Z es -NH-, -O-, -S-, o -NR-;

R es alquilo de 1-6 átomos de carbono, o carboalquilo de 2-7 átomos de carbono;

5 G₁, R₁, y R₄ 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, alcanoioloxi de 1-6 átomos de carbono, alquenoiloxi de 3-8 átomos de carbono, alquinoiloxi de 3-8 átomos de carbono, alcanoiloximetilo de 2-7 átomos de carbono, alquenoiloximetilo de 4-9 átomos de carbono, alquinoiloximetilo 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, alquilsulfinilo de 1-6 átomos de carbono, alquilsulfonilo de 1-6 átomos de carbono, alquilsulfonamido de 1-6 átomos de carbono, alquenilsulfonamido de 2-6 átomos de carbono, alquinilsulfonamido de 2-6 átomos de carbono, hidroxilo, 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-alquenilamino de 4 a 12 átomos de carbono, N,N-dialquenilamino de 6-12 átomos de carbono, fenilamino, bencilamino,



25 R₇-(C(R₆)₂)_g-Y-, R₇-(C(R₆)₂)_p-M-(C(R₆)₂)_r-Y-, o Het-(C(R₆)₂)_q-W-(C(R₆)₂)-Y-; o opcionalmente G₂ se seleccionan independientemente de un grupo amino protegido y R₂-NH-;

Y es un radical divalente seleccionado del grupo que consiste de $-(CH_2)_a-$,
 $-O-$, y $-N^{R_6}-$;

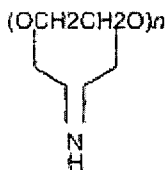
R_7 es $-NR_6R_7$, $-OR_6$, $-J$, $-N(R_6)_3^+$, o $-NR_7(OR_6)$;

M es $>NR_6$, $--O--$, $>N-(C(R_6)_2)_p NR_6R_6$, o $>N-(C(R_6)_2)_p-OR_6$;

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

Het se selecciona del grupo que consiste de morfolina, tiomorfolina, S-óxido de tiomorfolina, S,S-dióxido de tiomorfolina, piperidina, pirrolidina, aziridina, piridina, imidazol, 1,2,3-triazol, 1,2,4-triazol, tiazol, tiazolidina, tetrazol, piperazina, furano, tiofeno, tetrahidrotiofeno, tetrahidrofurano, dioxano, 1,3-dioxolano, tetrahidropirano, y

10



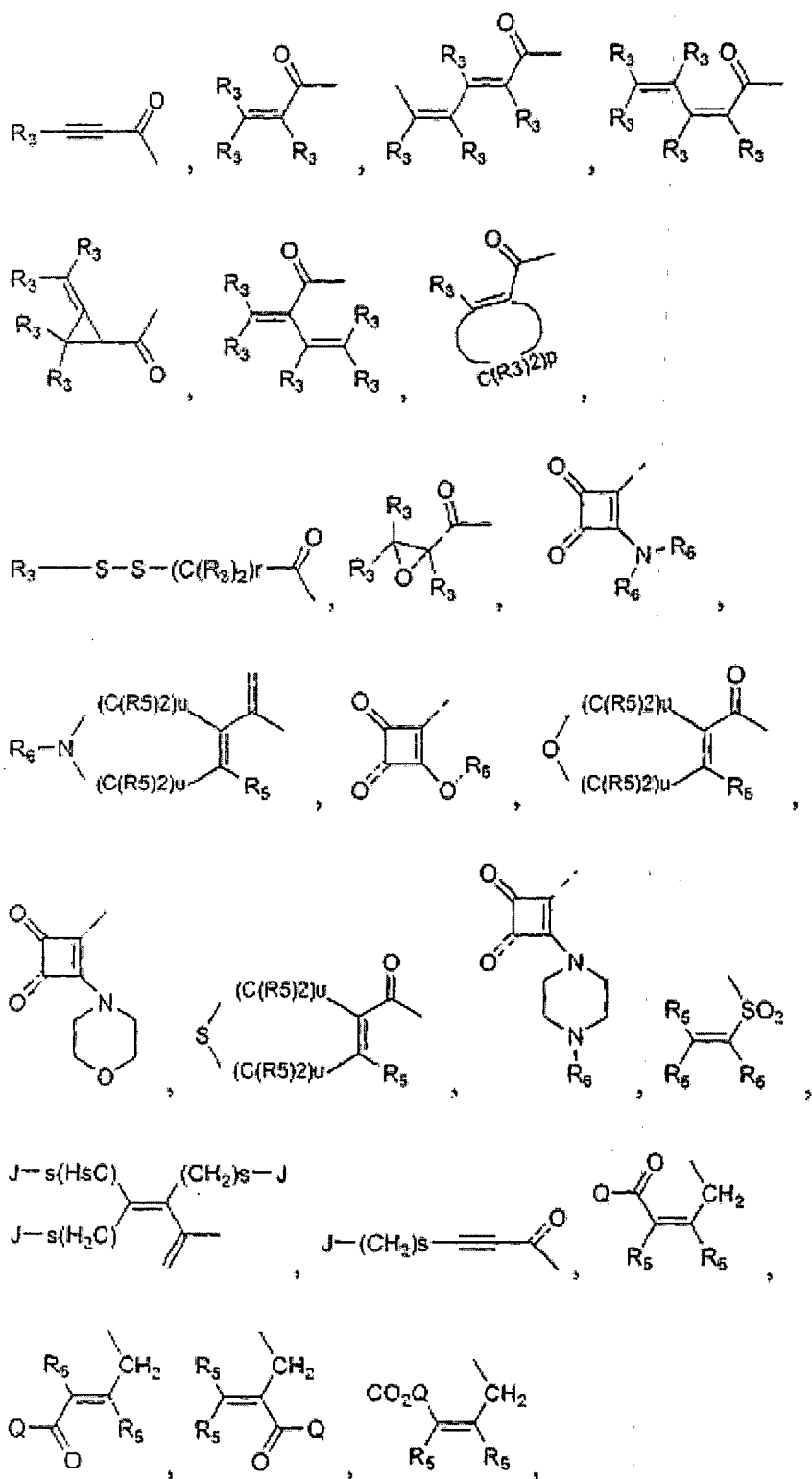
en donde Het es opcionalmente mono- o di-sustituido en carbono o nitrógeno con R_6 , opcionalmente mono- o di-sustituido en carbono con hidroxilo, $-N(R_6)_2$, o $-OR_6$,
 15 opcionalmente mono o di-sustituido en carbono con los radicales mono-valentes $-(C(R_6)_2)_sOR_6$ o $-(C(R_6)_2)_sN(R_6)_2$, y opcionalmente mono o di-sustituido en un carbono saturado con radicales divalentes $-O-$ o $-O(C(R_6)_2)_sO-$;

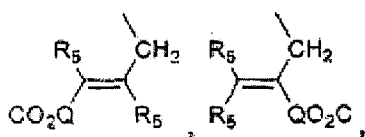
R_6 es hidrógeno, alquilo de 1-6 átomos de carbono, alquenilo de 2-6 átomos de carbono, alquinilo de 2-6 átomos de carbono, cicloalquilo de 1-6 átomos de carbono, carboalquilo de 2-7 átomos de carbono, carboxialquil (2-7 átomos de carbono), fenilo, o
 20 fenil opcionalmente sustituido con uno o más halógenos, 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
 25 carbono, hidroxilo, carboxilo, carboalcoxi de 2-7 átomos de carbono, fenoxi, fenilo, tiofenoxi, benzoilo, bencilo, fenilamino, bencilamino, alcanoilamino de 1-6 átomos de

carbono, o alquilo de 1-6 átomos de carbono; con la condición que la porción alquenilo o alquinilo está unida a un átomo de nitrógeno u oxígeno a través de un átomo de carbono saturado:

R_2 , se selecciona del grupo que consiste de

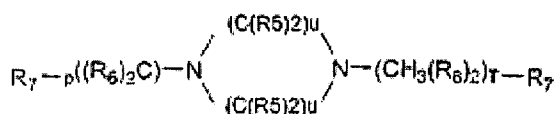
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R_3 es independientemente hidrógeno, alquilo de 1-6 átomos de carbono, carboxi, carboalcoxi de 1-6 átomos de carbono, fenilo, carboalquilo de 2-7 átomos de carbono,

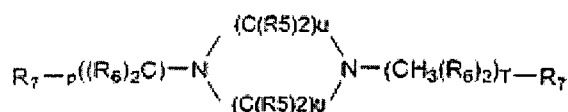
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$\text{R}_7 - (\text{C}(\text{R}_6)_2)_s$ -, $\text{R}_7 - (\text{C}(\text{R}_6)_2)_p - \text{M} - (\text{C}(\text{R}_7)_2)_r$ -, $\text{R}_8\text{R}_9 - \text{CH} - \text{M} - (\text{C}(\text{R}_6)_2)_r$ -, $\text{Het} - (\text{C}(\text{R}_6)_2)_q - \text{W} - (\text{C}(\text{R}_6)_2)_r$ -, aminoalquilo de 1-6 átomos de carbono, N-alquilaminoalquilo de 2-9 átomos de carbono, N,N-dialquilaminoalquilo de 3-12 átomos de carbono, N-cicloalquilaminoalquilo de 4-12 átomos de carbono, N-cicloalquil-N-alquilaminoalquilo de 5-18 átomos de carbono, N,N-dicicloalquilaminoalquilo de 7-18 átomos de carbono, morfolino-N-alquilo en donde el grupo alquilo es 1-6 átomos de carbono, piperidino-N-alquil en donde el grupo alquilo es 1-6 átomos de carbono, N-alquil-piperidino-N-alquil en donde el otro grupo alquilo es 1-6 átomos de carbono;

15

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,



20

$\text{R}_7 - (\text{C}(\text{R}_6)_2)_s$ -, $\text{R}_7 - (\text{C}(\text{R}_6)_2)_p - \text{M} - (\text{C}(\text{R}_6)_2)_r$ -, $\text{R}_8\text{R}_9 - \text{CH} - \text{M} - (\text{C}(\text{R}_6)_2)_r$ -, o $\text{Het} - (\text{C}(\text{R}_6)_2)_q - \text{W} - (\text{C}(\text{R}_6)_2)_r$;

R_8 , y R_9 son cada uno, independientemente, $-(\text{C}(\text{R}_6)_2)_r \text{NR}_6$ R_6 , o $-(\text{C}(\text{R}_6)_2)_r \text{OR}_6$;

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

25

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;

10 u=0-4 y v=0-4, en donde la suma de u+v es 2-4;

o una sal farmacéuticamente aceptable de estos, dado que cuando R_6 es alqueno de 2-7 átomos de carbono o alquino de 2-7 átomos de carbono, tal porción alqueno o alquino está unida a un átomo de nitrógeno u oxígeno a través de un átomo de carbono saturado;

15 y dado que

cuando Y es $-NR_6-$ y R_7 es $-NR_6R_6 - N(R_6)_3^+$, o $-NR_6(OR_6)$, entonces g=2-6;

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

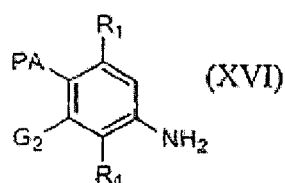
cuando Y es $-NR_6-$ entonces k=2-4;

cuando Y es $-O-$ y M o W es $-O-$ entonces k=1-4

20 cuando W no es un enlace con Het unido a través de un átomo de nitrógeno entonces q=2-4 y cuando W es un enlace con Het unido a través de un átomo de nitrógeno y Y es $-O-$ o $-NR_6-$ entonces k=2-4.

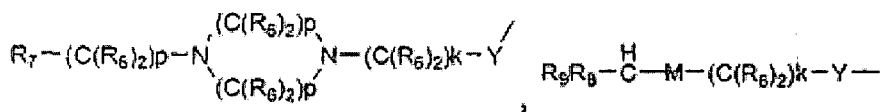
22. Un compuesto representado por la fórmula XVI:

25



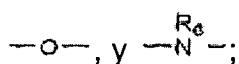
en donde PA es un grupo amino protegido;

en donde G_2 , R_1 , y R_4 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, alquenilo de 2-6 átomos de carbono, alquinoxilo de 2-6 átomos de carbono, alquinoxilo de 2-6 átomos de carbono, hidroximetilo, halometilo, alcanilo de 1-6 átomos de carbono, alquinoxilo de 3-8 átomos de carbono, alquinoxilo de 3-8 átomos de carbono, alcanilo de 2-7 átomos de carbono, alquinoxilo de 4-9 átomos de carbono, alquinoxilo de 4-9 átomos de carbono, alcoximetilo de 2-7 átomos de carbono, alcoxilo de 1-6 átomos de carbono, alquilo de 1-6 átomos de carbono, alquilsulfonilo de 1-6 átomos de carbono, alquilsulfonamido de 1-6 átomos de carbono, alquilsulfonamido de 2-6 átomos de carbono, alquilsulfonamido de 2-6 átomos de carbono, hidroxilo, trifluorometilo, trifluorometoxi, ciano, nitro, carboxi, carboalcoxilo 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-alquencilamino de 4 a 12 átomos de carbono, N,N-dialquencilamino de 6 -12 átomos de carbono, fenilamino, bencilamino,



$R_7-(C(R_6)_2)_g-Y-$, $R_7-(C(R_6)_2)_p-M-(C(R_6)_2)_r-Y-$, o $Het-(C(R_6)_2)_qW-(C(R_6)_2)_2-Y-$; o opcionalmente G_2 se seleccionan independientemente de un grupo amino protegido y R_2-NH- ;

Y es un radical divalente seleccionado del grupo que consiste de $-(CH_2)_a-$,

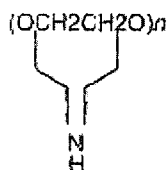


R_7 es $-NR_6R_7$, $-OR_6$, $-J$, $-N(R_6)_3^+$, o $-NR_7(OR_6)$;

M es $>NR_6$, $--O--$, $>N-(C(R_6)_2)_p NR_6R_6$, o $>N-(C(R_6)_2)_p -OR_6$;

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

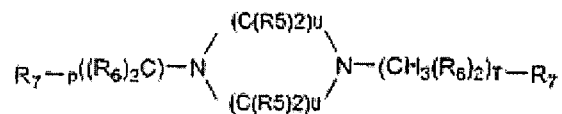
Het se selecciona del grupo que consiste de morfolina, tiomorfolina, S-óxido de tiomorfolina, S,S-dióxido de tiomorfolina, piperidina, pirrolidina, aziridina, piridina, imidazol, 1,2,3-triazol, 1,2,4-triazol, tiazol, tiazolidina, tetrazol, piperazina, furano, 5 tiofeno, tetrahidrotiofeno, tetrahidrofurano, dioxano, 1,3-dioxolano, tetrahidropirano, y



10 en donde Het es opcionalmente mono- o di-sustituido en carbono o nitrógeno con R_6 , opcionalmente mono- o di-sustituido en carbono con hidroxil, $-N(R_6)_2$, o $-OR_6$, opcionalmente mono o di-sustituido en carbono con los radicales mono-valentes $-(C(R_6)_2)_s OR_6$ o $-(C(R_6)_2)_s N(R_6)_2$, y opcionalmente mono o di-sustituido en 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, alqueno de 2-6 átomos de carbono, alquino de 2-6 átomos de carbono, cicloalquilo de 1-6 átomos de carbono, carboalquilo de 2-7 átomos de carbono, carboxialquil (2-7 átomos de carbono), fenilo, o fenil opcionalmente sustituido con uno o más halógenos, alcoxi de 1-6 átomos de carbono, trifluorometilo, amino, alquilamino de 1-3 átomos de carbono, dialquilamino de 20 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, fenilamino, bencilamino, alcanilamino de 1-6 átomos de carbono, o alquilo de 1-6 átomos de carbono; con la condición que la porción alqueno 25 o alquino está unida a un átomo de nitrógeno u oxígeno a través de un átomo de carbono saturado;

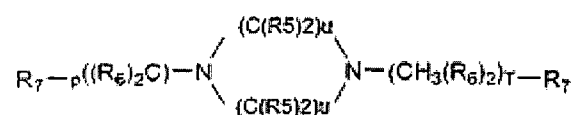
R_3 es independientemente hidrógeno, alquilo de 1-6 átomos de carbono, carboxi, carboalcoxi de 1-6 átomos de carbono, fenilo, carboalquilo de 2-7 átomos de carbono,



5

$R_7 - (C(R_6)_2)_s$ -, $R_7 - (C(R_6)_2)_P - M - (C(R_7)_2)_r$ -, $R_8 R_9 - CH - M - (C(R_6)_2)_r$ -, $Het - (C(R_6)_2)_q - W - (C(R_6)_2)_r$ -, aminoalquilo de 1-6 átomos de carbono, N-alquilaminoalquilo de 2-9 átomos de carbono, N,N-dialquilaminoalquilo de 3-12 átomos de carbono, N-cicloalquilaminoalquilo de 4-12 átomos de carbono, N-cicloalquil-N-alquilaminoalquilo de 5-18 átomos de carbono, N,N-dicicloalquilaminoalquilo de 7-18 átomos de carbono, morfolino-N-alquilo en donde el grupo alquilo es 1-6 átomos de carbono, piperidino-N-alquil en donde el grupo alquilo es 1-6 átomos de carbono, N-alquil-piperidino-N-alquil en donde el otro grupo alquilo es 1-6 átomos de carbono;

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 $Het - (C(R_6)_2)_q - W - (C(R_6)_2)_r$;

20

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, flúor, o bromo;

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

$a=0$ o 1 ;

25 $g=1-6$;

$k=0-4$;

n es 0-1;

m es 0-3;

p=2-4;

q=0-4;

5 r=1-4;

s=1-6;

u=0-4 y v=0-4, en donde la suma de u+v es 2-4;

10 o una sal farmacéuticamente aceptable de estos, dado que cuando R_6 es alqueno de 2-7 átomos de carbono o alquino de 2-7 átomos de carbono, tal porción alqueno o alquino está unida a un átomo de nitrógeno u oxígeno a través de un átomo de carbono saturado;

y dado que

cuando Y es $-NR_6-$ y R_7 es $-NR_6R_6 - N(R_6)_3^+$, o $-NR_6(OR_6)$, entonces g=2-6;

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

15 cuando Y es $-NR_6-$ entonces k=2-4;

cuando Y es $-O-$ y M o W es $-O-$ entonces k=1-4

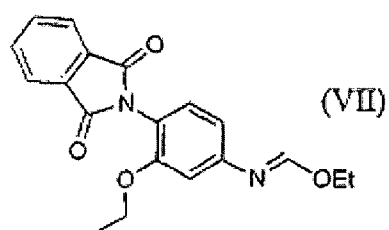
cuando W no es un enlace con Het unido a través de un átomo de nitrógeno entonces q=2-4 y cuando W es un enlace con Het unido a través de un átomo de nitrógeno y Y es $-O-$ o $-NR_6-$ entonces k=2-4.

20

23. El compuesto de acuerdo a las reivindicaciones 20, 21 y 22, en donde el grupo amino protegido se selecciona del grupo que consiste de acetamidas, benzamidas, imidas cíclicas, pirroles, amina terc-butoxicarbonilo y amida benciloxicarbonilo.

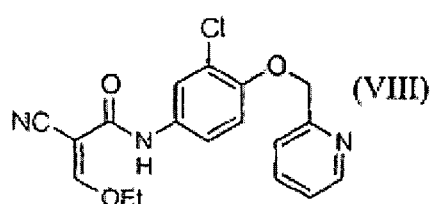
25 24. El compuesto de acuerdo a la reivindicación 23, en donde el grupo amino protegido es ftalimida.

25. Un compuesto representado por la fórmula VII:

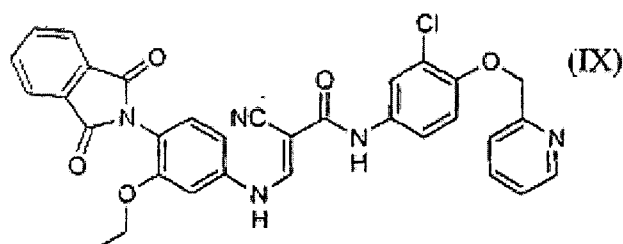


26. Un compuesto representado por la fórmula VIII:

5



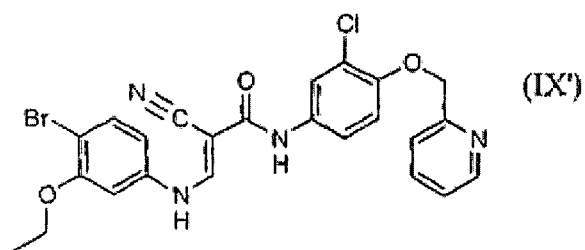
27. Un compuesto representado por la fórmula IX:



10

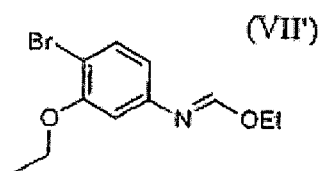
28. El método de acuerdo con la reivindicación 1, 2, 3, 4, y 5, en donde G₁ es un halógeno seleccionado del grupo que consiste de F, Cl, Br, o I.

15 29. El método de acuerdo con las reivindicaciones 1, 2, 3, 4, y 5, en donde el N-aril-2-propeno de fórmula III es el compuesto representado por la fórmula IX':



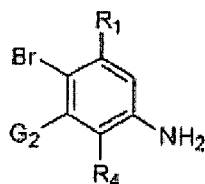
30. El método de acuerdo con las reivindicaciones 1, 2, 3, 4 y 5, en donde el N-arilformimidato de fórmula I es un compuesto representado por la fórmula VII':

5

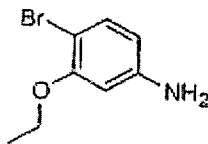


31. El método de acuerdo con las reivindicaciones 3, 4 y 5, en donde la arilamina de fórmula XIII es un compuesto representado por la estructura:

10

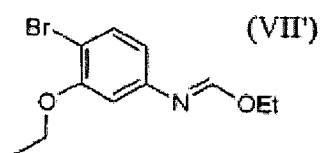


32. El método de acuerdo con la reivindicación 31, en donde la arilamina es:

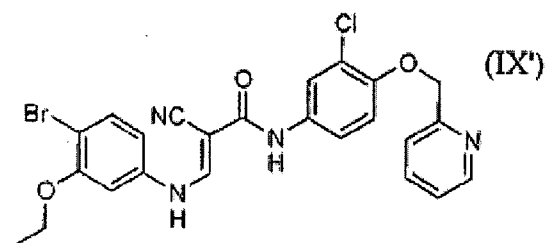


15

33. Un compuesto de fórmula VII':



34. Un compuesto de fórmula IX':



RESUMEN

La presente invención se relaciona con métodos para preparar 3-cianoquinolinas
5 sustituidas e intermedios obtenidos por los métodos de la presente invención. Los
métodos de la invención comprenden hacer reaccionar un N-aril-2-propanimida con
cloruro de fosforilo para producir las 3-cianoquinolinas sustituidas. Los métodos
comprenden hacer reaccionar adicionalmente las arilaminas, ortoformatos y metilenos
activos para producir los N-aril-2-propenamida.

PATENT COOPERATION TREATY

PCT/US2006/016019

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, New York 10112-3801
ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year) 20 July 2006 (20.07.2006)	
Applicant's or agent's file reference 01997.032200	IMPORTANT NOTIFICATION
International application No. PCT/US2006/016019	International filing date (day/month/year) 27 April 2006 (27.04.2006)
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)	60/684,683	US	22 June 2006 (22.06.2006)

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Simin Baharlou
Facsimile No. +41 22 338 82 70	Facsimile No. +41 22 338 71 30 Telephone No. +41 22 338 99 32

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To: FITZPATRICK CELLA HARPER & SCINTO Attn. Mandra, Raymond R. 30 Rockefeller Plaza New York, NY 10112-3801 ETATS-UNIS D'AMERIQUE FITZPATRICK, CELLA, HARPER & SCINTO FILE NO. <u>01997.032200.PC</u> ATTORNEY <u>SV</u> DUE DATE <u>3/29/07</u> DOCKETED <u>VMG 2/1/07</u>	RECEIVED 2007 JAN 32 A 9:09 NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION (PCT Rule 44.1) <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%;">Date of mailing (day/month/year)</td> <td style="width: 50%;">29/01/2007</td> </tr> </table> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%;">Applicant's or agent's file reference 01997.032200.</td> <td style="width: 50%;">FOR FURTHER ACTION See paragraphs 1 and 4 below</td> </tr> <tr> <td style="width: 50%;">International application No. PCT/US2006/016019</td> <td style="width: 50%;">International filing date (day/month/year) 27/04/2006</td> </tr> </table> Applicant WYETH	Date of mailing (day/month/year)	29/01/2007	Applicant's or agent's file reference 01997.032200.	FOR FURTHER ACTION See paragraphs 1 and 4 below	International application No. PCT/US2006/016019	International filing date (day/month/year) 27/04/2006
Date of mailing (day/month/year)	29/01/2007						
Applicant's or agent's file reference 01997.032200.	FOR FURTHER ACTION See paragraphs 1 and 4 below						
International application No. PCT/US2006/016019	International filing date (day/month/year) 27/04/2006						

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.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patehtlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Jaap Hurenkamp SHEILA McBRIDE
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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.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 01997.032200.	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/US2006/016019	International filing date (day/month/year) 27/04/2006	(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/US2006/016019

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07C251/50 C07D209/48 C07D213/30 C07D215/54 C07D401/12

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)

C07C C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PRICE C C ET AL: "A SYNTHESIS OF SUBSTITUTED 4-AMINOQUINOLINES" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, US, vol. 68, August 1946 (1946-08), pages 1246-1250, XP002072256 ISSN: 0002-7863 Scheme on left-hand column and compounds III-IV; scheme on right-hand column, page 1246.	1,2, 6-12,16, 19,28-30
X	E. B. KNOTT AND R. A. JEFFREYS: "The strucutre of the solid reaction product of anilines and ethyl orthoformate" JOURNAL OF ORGANIC CHEMISTRY, vol. 14, 1949, pages 879-886, XP002396497 Paragraph 4 (Experimental), page 884. ----- -/--	17

☒ 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.

G document member of the same patent family

Date of the actual completion of the international search

17 January 2007

Date of mailing of the international search report

29/01/2007

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. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Menchaca, Roberto

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/016019

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	V. D. DYACHENKO AND R. P. TKACHEV: "3-Amino-3-thiopropylamide in the synthesis of functionally substituted nicotinamides" RUSSIAN JOURNAL OF ORGANIC CHEMISTRY, vol. 39, no. 8, 2003, pages 1174-1179, XP002396496 Compound IIId, scheme, page 1175.	18
X	J. VAMECO, P. BAC, C. HERRENKNECHT, P. MAUROIS, P. DELCOURT AND J. P. STABLES: "Synthesis and anticonvulsant and neurotoxic properties of substituted N-phenyl derivatives of the phthalimide pharmacophore" JOURNAL OF THE MEDICINAL CHEMISTRY, vol. 43, 2000, pages 1311-1319, XP008065485 Compounds 1, 6 and 17, figure 2, page 1313.	22
X	US 2005/043537 A1 (SUTHERLAND KAREN WIGGINS ET AL) 24 February 2005 (2005-02-24) Synthetic route 1, bottom-page 4. Example 14, page 8	1, 2, 6-9, 19
X	DESAI P R ET AL: "BROMINATION OF .BETA.-ARYLAMINO (-CYANO- AND .ACETYL-) ACRYLOANILIDES" JOURNAL OF THE INSTITUTION OF CHEMISTS (INDIA), CALCUTTA,, IN, vol. 62, no. 4, July 1990 (1990-07), page 173, XP008068397 ISSN: 0020-3254 page 173, paragraph 1	19
A	US 6 002 008 A (WISSNER ET AL) 14 December 1999 (1999-12-14) cited in the application Flowsheet C, column 12.	1, 17-22, 25-27, 33, 34

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2006/016019**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.:

1-2, 4, 6-16 (in part), 19, 21, 23-24 (in part), 27, 28-32 (in part), 34

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

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, 6-10 (in part), 28-29 (in part)

Processes for the preparation of compounds of formula (XI).

2. claims: 2, 6-12 (in part), 16 (in part), 28-30 (in part)

Processes for the preparation of known compounds (III); this problem being solved by using starting compounds (I) and (XII) as starting materials.

3. claims: claims 4, 6-10 (in part), 13-15 (in part), 19, 21, 23-24 (in part), 27, 28-32 (in part), 34

Processes for the preparation of known compounds (III); this problem being solved by using compounds (II) and (XIII) as starting materials. Compounds falling within general formula (III).

4. claims: 3, 6-14 (in part), 16 (in part), 17, 20, 23-24 (in part), 25, 28-32 (in part), 33

Processes for the preparation of known compounds of formula (I) and compounds falling within general formula (I).

5. claims: 5, 6-10 (in part), 13-16 (in part), 18, 26, 28-32 (in part)

Processes for the preparation of known compounds of formula (II) and compounds falling within general formula (II).

6. claims: 22, 23-24 (in part)

Compounds of formula (XVI).

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2006/016019

Patent document cited in search report		Publication date	Patent family* member(s)	Publication date
US 2005043537	A1	24-02-2005	NONE	
US 6002008	A	14-12-1999	NONE	

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/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/US2006/016019

International filing date (day/month/year)
27.04.2006

Priority date (day/month/year)
25.05.2005

International Patent Classification (IPC) or both national classification and IPC
INV. C07C251/50 C07D209/48 C07D213/30 C07D215/54 C07D401/12

Applicant
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 032200 PC
 ATTORNEY SV
 DUE DATE 4/29/07
 DOCKETED WMS 2/1/07

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 2
 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 opinion

see form
PCT/ISA/210

Authorized Officer

Menchaca, Roberto

Telephone No. +31 70 340-9524



**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2006/016019

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:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2006/016019

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. 3, 5, 6-16 (in part), 17-18, 20, 22, 23-24 (in part), 25-26, 28-32 (in part), 33

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. 3, 5, 6-16 (in part), 17-18, 20, 22, 23-24 (in part), 25-26, 28-32 (in part), 33
- ☐ 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 13 *ter*.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/US2006/016019

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. 1-2, 4, 6-16 (in part), 19, 21, 23-24 (in part), 27, 28-32 (in part), 34

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

1. Statement

Novelty (N)	Yes: Claims	4, 7-8, 10-16, 21, 23-24, 27-32, 34
	No: Claims	1-2, 6, 9, 19
Inventive step (IS)	Yes: Claims	13-15, 21, 23-24, 27, 31-32, 34
	No: Claims	1-2, 6-12, 16, 19, 28-30
Industrial applicability (IA)	Yes: Claims	1, 2, 4, 6-16, 19, 21, 23-24, 27, 28-32, 34
	No: Claims	

2. Citations and explanations
 see separate sheet

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

International application No.

PCT/US2006/016019

Re Item IV

Lack of unity of invention

According to Rule 13.1 PCT, "The International application shall relate to one invention only OR to a group of inventions so linked as to form a single general inventive concept".

This is further clarified in Rule 13.2 PCT, which details that "the requirement for unity of invention shall only be fulfilled when there is a technical relationship among those inventions involving one or more of the same corresponding special technical features that defines a contribution which each of the claimed inventions, considered as a whole makes over the prior art".

To decide whether a technical feature is the special technical feature, we must apply the teaching of Rules 13.1 and 13.2 PCT, which stipulate that the technical feature must define a contribution over the prior art to be recognised as the special technical feature (which gives rise to unity).

For the purposes of unity, a single general inventive concept is required. This means that the broadest possible problem to be solved has to be drawn up (i.e. to cover all claimed possibilities). Thus, by definition, the provisos may not be taken into account when determining the presence or lack of unity, since the special technical feature must define a contribution over these provisos as well.

Reference is made to the following documents:

D1: JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 68, August 1946 (1946-08), pages 1246-1250, XP002072256

D2: JOURNAL OF ORGANIC CHEMISTRY, vol. 14, 1949, pages 879-886, XP002396497

D3: RUSSIAN JOURNAL OF ORGANIC CHEMISTRY, vol. 39, no. 8, 2003, pages 1174-1179, XP002396496

D4: JOURNAL OF THE MEDICINAL CHEMISTRY, vol. 43, 2000, pages 1311-1319, XP008065485.

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

International application No.

PCT/US2006/016019

The present application deals with the preparation of compounds of formula (XI) starting from compounds of formula (III) by a reaction with POCl_3 (claim 1). Claim 2 deals with a process for the preparation of compounds of formula (III) by reaction of compounds of formula (I) with compounds of formula (XII). Claim 4 deals with a process for the preparation of compounds of formula (III) by reaction of compounds of formula (II) with compounds of formula (XIII).

D1 discloses (see compounds III and IV, scheme on left-hand column, page 1246) compounds falling within formula (III) in claim 1 of the present application ($\text{R1} = \text{G1} = \text{R4} = \text{H}$, $\text{G2} = \text{Cl}$, $\text{Z} = \text{NH}$, $n = 0$ and $\text{X} = 3\text{-chlorophenyl}$ or a phenyl ring). This disclosure renders claims 1, 2 and 4 non unitary as there is no common technical feature which can act as the special technical feature, i.e. compounds of formula (III) cannot act as the special technical feature. The problems underlying these claims are:

- the provision of an alternative process for the preparation of compounds of formula (XI), (claims 1, 6-10 (in part), 28-29 (in part)).
- the provision of an alternative process for the preparation of known compounds (III). The applicant solves this problem by using compounds (I) and (XII) as starting materials, (claims 2, 6-12 (in part), 16 (in part), 28-30 (in part)).
- the provision of an alternative process for the preparation of known compounds (III). The applicant solves this problem by using compounds (II) and (XIII) as starting materials, (claims 4, 6-10 (in part), 13-15 (in part), 19, 21, 23-24 (in part), 27, 28-32 (in part), 34).

Claim 3 of the present application deals with a process for the preparation of compounds of formula (I) starting from compounds of formula (XIII).

D2 discloses (see paragraph 4, Experimental, page 884) ethyl-ortho (or para)-chloroisoformanilide falling within formula (I) in claim 2 of the present invention ($\text{R1} = \text{G2} = \text{H}$, $\text{G1} = \text{R4} = \text{H}$ or Cl). As these compounds of formula (I) are not novel, they cannot act as the special technical feature linking the process of claims 2 and 3. A further problem underlying the present invention therefore is:

- the provision of an alternative process for the preparation of known compounds of

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

International application No.

PCT/US2006/016019

formula (I), (claims 3, 6-14 (in part), 16 (in part), 17, 20, 23-24 (in part), 25, 28-32 (in part), 33).

Claim 5 of the present application deals with a process for the preparation of compounds of formula (II) starting from compounds of formula (XII).

D3 discloses (see compound IId, scheme on page 1175) a synthetic intermediate falling within formula (II) in claim 4 of the present application ($Z = \text{NH}$, $n = 0$, $X =$ naphthalene). As these compounds are not novel, they cannot act as the special technical feature linking the processes of claims 4 and 5. A further problem underlying the present application is therefore:

- the provision of an alternative process for the preparation of known compounds of formula (II), (claims 5, 6-10 (in part), 13-16 (in part), 18, 26, 28-32 (in part)).

Claim 22 discloses compounds of formula (XVI). These compounds fall within general formula (XIII), which are either used for the preparation of compounds of formula (I), as disclosed in claim 3, or for the preparation of compounds of formula (III), as disclosed in claim 4. D4 has been selected as a representative prior art document disclosing (see compounds 1, 6 and 17, figure 2, page 1313) aniline derivatives falling under the scope of formula (XVI) in claim 22 of the present invention ($R1 = R4 = \text{H}$, $G2 = \text{H}$, Me or Cl , $\text{PA} = \text{phthalimide}$). As these compounds are not novel, they cannot act as the special technical feature linking claims 22, 3 and 4. A further problem underlying the present application is therefore:

- the provision of further compounds falling within formula (XVI), (claim 22, 23-24 (in part)).

In the light of the above, the examiner has identified, a posteriori, six different subjects (see supplemental sheets for details).

Invention 1: (claims: 1, 6-10 (in part), 28-29 (in part)). Processes for the preparation of compounds of formula (XI).

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)

International application No.

PCT/US2006/016019

Invention 2: (claims: 2, 6-12 (in part), 16 (in part), 28-30 (in part)). Processes for the preparation of known compounds (III); this problem being solved by using compounds (I) and (XII) as starting materials.

Invention 3: (claims 4, 6-10 (in part), 13-15 (in part), 19, 21, 23-24 (in part), 27, 28-32 (in part), 34). Processes for the preparation of known compounds (III); this problem being solved by using compounds (II) and (XIII) as starting materials. Compounds falling within general formula (III).

Invention 4: (claims 3, 6-14 (in part), 16 (in part), 17, 20, 23-24 (in part), 25, 28-32 (in part), 33). Processes for the preparation of known compounds of formula (I) and compounds falling within general formula (I).

Invention 5: (claims 5, 6-10 (in part), 13-16 (in part), 18, 26, 28-32 (in part)). Processes for the preparation of known compounds of formula (II) and compounds falling within general formula (II).

Invention 6: (claims: 22, 23-24 (in part)). Compounds of formula (XVI).

The number of subjects of the non-unity is kept to a minimum with due regard for the teaching of **T110/82 (OJ EPO 1983, 274-281)** concerning the balance between :

- a rational procedure up to grant in which interconnected matter should not be needlessly split, nor non-related inventions lumped together for the purpose of saving fees
- and an equitable levying of fees, especially in respect of search, since the expense must be borne by the fees levied for other applications.

This does not mean that were any or all of the further subjects elected for further processing that further non-unities may not be formulated, based on the subsequent prior art retrieved. Moreover, other objections with regard to clarity, support of disclosure and so forth may also be raised, resulting in (an) incomplete search(es).

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

International application No.

PCT/US2006/016019

Since the applicant has paid fees for the first three inventions, the following examination relates only to the subject-matter of claims: 1-2, 4, 6-16 (in part), 19, 21, 23-24 (in part), 27, 28-32 (in part) and 34.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 The following discussion relates to invention 1

1.1 Documents

Reference is made to the following documents:

D1: JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 68, August 1946 (1946-08), pages 1246-1250, XP002072256

D5: US 2005/043537 A1 (2005-02-24)

1.2 Subject-matter

The invention relates to a method for the preparation of 3-cyanoquinolines comprising the step of treating a synthetic intermediate of formula (III) with POCl_3 .

1.3 Novelty

As already stated (see Item IV: "Lack of Unity of Invention"), D1 discloses compounds falling within formula (III), in claim 1 of the present application, which are reacted with POCl_3 to afford the corresponding 3-cyanoquinolines. D5 (see synthetic route 1, bottom-page 4) also anticipates the subject-matter of claim 1. The subject-matter of claim 1 is therefore not novel over D1 and D5 in the sense of Article 33(2) PCT.

Dependent method claims 6 and 9 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty (Article 33(2) PCT).

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

International application No.

PCT/US2006/016019

Dependent claims 7-8, 10 and 28-29 disclose a method for the preparation of 3-cyanoquinolines comprising the use of a synthetic intermediate of formula (III) which is not anticipated by any prior art document (i.e. wherein G1 = protected amino group or a halogen). The subject-matter of dependent claims 7-8, 10 and 28-29 is therefore novel over the prior art in the sense of Article 33(2) PCT.

1.4 Inventive step

The subject-matter of claims 1, 6 and 9, which lacks novelty, does not offer a basis for acknowledging an inventive step in the sense of Article 33(3) PCT.

With regard to the subject-matter of novel claims 7-8, 10 and 28-29, the following is noted concerning inventive step:

D1 is regarded as being the closest prior art to the subject-matter of claims 7-8, 10 and 28-29 and discloses (see novelty section) a method for the preparation of 3-cyanoquinolines comprising the use of synthetic intermediates falling within formula (III) in claim 1 of the present application, which are reacted with POCl_3 .

The subject-matter of claims 7-8, 10 and 28-29 differs from this known D1 in that the synthetic intermediates of formula (III) used thereof possess a protected amino group or a halogen as G1 substituent. In contrast, the intermediates disclosed in D1 possess G1 = H.

The problem to be solved by the present invention may therefore be regarded as the provision of further methods for the preparation of substituted 3-cyanoquinolines. This is achieved in the present invention by reacting the synthetic intermediates of formula (III), wherein G1 = a protected amino group or a halogen, with POCl_3 .

In the absence of a further technical effect associated to the replacement of substituent G1 = H, as in the closest prior art, by either a protected amino group or a halogen, the solution is considered obvious to a person skilled in the art. Said replacement is therefore regarded as merely one of several straightforward possibilities from which the skilled person would select, in accordance with circumstances, without the exercise of inventive skill, in order to solve the problem posed.

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

International application No.

PCT/US2006/016019

The subject-matter of claims 7-8, 10 and 28-29 cannot therefore be considered as involving an inventive step in the sense of Article 33(3) PCT.

1.5 Other remarks

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1 and D5 is not mentioned in the description, nor are these documents identified therein.

2 The following discussion relates to invention 2

2.1 Documents

Reference is made to the following documents:

D1: JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 68, August 1946 (1946-08), pages 1246-1250, XP002072256

D5: US 2005/043537 A1 (2005-02-24)

2.2 Subject-matter

The invention relates to a method for the preparation of compounds of formula (III) from intermediates of formula (I) and (XII), according to claim 2.

2.3 Novelty

D1 discloses (see Item IV: "Lack of Unity of Invention" and scheme on right-hand column, page 1246) the reaction of a substituted aniline derivative with ethyl orthoformate and a compound of formula (XII), according to claim 2 in the present application. The aniline derivative and the ethyl orthoformate react in the reaction media to afford an intermediate of formula (I), according to claim 2 in the present application (this is also acknowledged in claim 3), which further reacts with the compound of formula (XII) to yield the desired compounds of formula (III). D5 also anticipates (see synthetic route 1, bottom-page 4) the subject-matter of claim 2. The subject-matter of claim 2 is therefore not novel over D1 and D5 in the sense of Article 33(2) PCT.

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

International application No.

PCT/US2006/016019

Dependent method claims 6 and 9 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty (Article 33(2) PCT).

Dependent method claims 7-8, 10-12, 16 and 28-30 disclose further features of the method for the preparation of 3-cyanoquinolines comprising the preparation of a synthetic intermediate of formula (III) which are not anticipated by any prior art document. The subject-matter of dependent claims 7-8, 10-12, 16 and 28-30 is therefore novel over the prior art in the sense of Article 33(2) PCT.

2.4 Inventive step

The subject-matter of claims 2, 6 and 9, which lacks novelty, does not offer a basis for acknowledging an inventive step in the sense of Article 33(3) PCT.

With regard to the subject-matter of novel claims 7-8, 10-12, 16 and 28-30, the following is noted concerning inventive step:

D1 is regarded as being the closest prior art to the subject-matter of claims 7-8, 10-12, 16 and 28-30 and discloses (see novelty section) the reaction of a substituted aniline derivative with ethyl orthoformate and a compound of formula (XII), according to claim 2 in the present application.

The subject-matter of claims 7-8, 10-12, 16 and 28-30 mainly differs from this known D1 in that the synthetic intermediate of formula (III) obtained from the compounds of formula (I), either possess a protected amino group or a halogen as G1 substituent. In contrast, the intermediates disclosed in D1 possess G1 = H.

The problem to be solved by the present invention may therefore be regarded as the provision of further methods for the preparation of synthetic intermediate of formula (III), useful for the preparation of substituted 3-cyanoquinolines. This is achieved in the present invention by reacting the synthetic intermediates of formula (I), wherein G1 = a protected amino group or a halogen, with the compounds of formula (XII).

In the absence of a further technical effect associated to the replacement of

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

International application No.

PCT/US2006/016019

substituent G1= H, as in the closest prior art, by either a protected amino group or a halogen, the solution is considered obvious to a person skilled in the art. Said replacement is therefore regarded as merely one of several straightforward possibilities from which the skilled person would select, in accordance with circumstances, without the exercise of inventive skill, in order to solve the problem posed.

The subject-matter of claims 7-8, 10-12, 16 and 28-30 cannot therefore be regarded as involving an inventive step in the sense of Article 33(3) PCT.

2.5 Other remarks

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1 and D5 is not mentioned in the description, nor are these documents identified therein.

3 The following discussion relates to invention 3

3.1 Documents

Reference is made to the following documents:

D1: JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 68, August 1946 (1946-08), pages 1246-1250, XP002072256

D5: US 2005/043537 A1 (2005-02-24)

D6: JOURNAL OF THE INSTITUTION OF CHEMISTS (INDIA), vol. 62, no. 4, July 1990, page 173, XP008068397

3.2 Subject-matter

The invention relates to a method for the preparation of compounds of formula (III) from intermediates of formula (II) and (XIII), according to claim 4.

3.3 Novelty

D1 (see Item IV: "Lack of Unity of Invention"), D5 (see synthetic route 1, bottom-page 4) and D6 (see paragraph 1, page 173) disclose compounds falling within formula (III), according to claim 19 of the present application. The subject-matter of claim 19

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

International application No.

PCT/US2006/016019

is therefore not novel over D1 and D5-D6 in the sense of Article 33(2) PCT.

The subject-matter of method claims 4, 6-10, 13-15, 28-32 and compound claims 21, 23-24, 27, 34 is not anticipated by any prior art document and hence, it is novel (Article 33(2) PCT).

3.4 Inventive step

The subject-matter of claim 19, which lacks novelty, does not offer a basis for acknowledging an inventive step in the sense of Article 33(3) PCT.

With regard to the subject-matter of novel claims 4, 6-10, 13-15, 21, 23-24, 27-32 and 34, the following is noted concerning inventive step:

D1 is regarded as being the closest prior art to the subject-matter of the present invention and discloses the reaction of a substituted aniline derivative with ethyl orthoformate and a compound of formula (XII), according to claim 2 in the present application.

The subject-matter of claims 4, 6-10, 13-15, 21, 23-24, 27-32 and 34 mainly differs from this known D1 in that the synthetic intermediate of formula (III) is obtained upon reaction of an aniline derivative of formula (XIII) and an alfa-cyano-beta-ethoxy acryl derivative of formula (II).

The problem to be solved by the present invention may therefore be regarded as the provision of further methods for the preparation of synthetic intermediate of formula (III), useful for the preparation of substituted 3-cyanoquinolines. This is achieved in the present invention by reacting the synthetic intermediates of formula (XIII) and (II).

The solution proposed cannot be regarded as obvious to a person skilled in the art since the reaction of an aniline derivative of formula (XIII) and an alfa-cyano-beta-ethoxy acryl derivative of formula (II) has neither been disclosed nor hinted at by any prior art document.

The subject-matter of claims 4, 6-10, 13-15, 21, 23-24, 27-32 and 34 can therefore

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

International application No.

PCT/US2006/016019

be regarded as involving an inventive step in the sense of Article 33(3) PCT.

3.5 Other remarks

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1 and D5-D6 is not mentioned in the description, nor are these documents identified therein.

Bitte beachten Sie, dass angeführte Nichtpatentliteratur (wie z. B. wissenschaftliche oder technische Dokumente) je nach geltendem Recht dem Urheberrechtsschutz und/oder anderen Schutzarten für schriftliche Werke unterliegen könnte. Die Vervielfältigung urheberrechtlich geschützter Texte, ihre Verwendung in anderen elektronischen oder gedruckten Publikationen und ihre Weitergabe an Dritte ist ohne ausdrückliche Zustimmung des Rechtsinhabers nicht gestattet.

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XS CPRTENFRDE

PATENT COOPERATION TREATY

From the RECEIVING OFFICE

PCT

To:
RAYMOND R. MANDRA
FITZPATRICK CELLA, HARPER & SCINTO
30 ROCKEFELLER PLAZA
NEW YORK, NEW YORK 10112-3801

INVITATION TO CORRECT DEFECTS IN
THE INTERNATIONAL APPLICATION

(PCT Articles 3(4)(i) and 14(1) and Rule 26)

Date of mailing (day/month/year)	19 Jun 2006
Applicant's or agent's file reference 01997.032200	REPLY DUE within 1 months/days from the above date of mailing
International application No. PCT/US2006/016019	International filing date (day/month/year) 27 Apr 2006
Applicant WYETH	

1. ☒ The applicant is hereby invited, within the time limit indicated above, to correct, in the international application as filed, the defects specified on the attached:
- ☒ Annex A
 - ☐ Annex B1 (text matter of the international application as filed)
 - ☐ Annex C1 (drawings of the international application as filed)
2. ☐ The applicant is hereby invited, within the time limit indicated above, to correct, in the translation of the international application furnished under Rule 12.3 or 12.4, the defects specified on the attached:
- ☐ Annex A
 - ☐ Annex B2 (text matter of the translation of the international application)
 - ☐ Annex C2 (drawings of the translation of the international application)

Additional observations (if necessary):

FILE NO. 01997-032200.R
ATTORNEY DFG
DUE DATE 7/19/06
DOCKETED WMG 6/26/06

HOW TO CORRECT THE DEFECTS?

Correction must be submitted by filing a replacement sheet embodying the correction and a letter accompanying the replacement sheet, which shall draw attention to the difference between the replaced sheet and the replacement sheet. A correction may be stated in a letter only if it is of such a nature that it can be transferred from the letter to the record copy without adversely affecting the clarity and direct reproducibility of the sheet onto which the correction is to be transferred (Rule 26.4).

ATTENTION

Failure to correct the defects will result in the international application being considered withdrawn by this receiving Office (see Rule 26.5 for further details).

A copy of this invitation and any attachments has been sent to the International Bureau

☒ and the International Searching Authority

Name and mailing address of the receiving Office Mail Stop PCT, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 703-305-3230	Authorized officer Theodosia Simpkins Telephone No. 703-308-9290 EX 109
---	---

ANNEX A TO FORM PCT/RO/106

national application No.

PCT/US2006/016019

The receiving Office has found the following defects in the international application as filed:

1. As to signature of the international application (Rules 4.15, 26.2bis(a) and 90.4), the request:

- a. ☐ is not signed* by the applicant or, if there is more than one applicant, by at least one of them
- b. ☐ is not accompanied by the statement referred to in the check list in Box No. IX of the request explaining the lack of the signature of an applicant for the designation of the United States of America
- c. ☐ is signed by what appears to be an agent/common representative but:
 - ☐ the international application is not accompanied by a power of attorney appointing him
 - ☐ the power of attorney accompanying the international application is not signed by all the applicants
- d. ☐ other (specify):

* Although Rule 4.15 requires that all applicants must sign the request (e.g. including all inventors/applicants for the designation of the United States of America), for the purposes of Article 14(1)(a)(i), if there is more than one applicant, it shall be sufficient that the request be signed by one of them (Rule 26.2bis(a)).

However, the applicant's attention is drawn to the fact that the national law applied by each designated Office may require, in connection with the processing of the international application in the national phase, that the applicant furnish the confirmation of the international application by the signature of any applicant for the designated State who has not signed the request (Rule 51bis.1(a)(vi)).

2. As to indications concerning the applicant* who is entitled, according to Rule 19.1, to file the international application with the receiving Office, the request (Rules 4.4, 4.5 and 26.2bis(b)):

- a. ☐ does not properly indicate the applicant's name (specify):
- b. ☐ does not indicate the applicant's address
- c. ☐ does not properly indicate the applicant's address (specify):
- d. ☐ does not indicate the applicant's nationality
- e. ☐ does not indicate the applicant's residence

☐ Further observations about indications concerning other applicants (if applicable):

* Although Rules 4.4 and 4.5 require indications concerning the applicant, or if there are several applicants, of each of them, for the purposes of Article 14(1)(a)(ii), if there is more than one applicant, it shall be sufficient that the indications required under Rule 4.5(a)(ii) and (iii) be provided in respect of one of them who is entitled according to Rule 19.1 to file the international application with the receiving Office (Rule 26.2bis(b)).

However, the applicant's attention is drawn to the fact that the national law applied by each designated Office may require, in connection with the processing of the international application in the national phase, that the applicant furnish any missing indication required under Rule 4.5(a)(ii) and (iii) in respect of any applicant for the designated State (Rule 51bis.1(a)(vii)).

3. As to the language of certain elements of the international application, other than the description and claims (Rules 12.1(c) and 26.3ter(a) and (c)):

- a. ☐ the request is not in a language of publication accepted by this receiving Office; (the) language(s) accepted by this receiving Office is/are:
- b. ☐ the text matter of the drawings is not in the language in which the international application is to be published, which is:
- c. ☐ the abstract is not in the language in which the international application is to be published, which is:

4. The title of the invention:

- a. ☐ is not indicated in Box No. I of the request (Rule 4.1(a))
- b. ☐ is not indicated at the top of the first sheet of the description (Rule 5.1(a))
- c. ☒ as appearing in Box No. I of the request is not identical with the title heading the description (Rule 5.1(a))

5. As to the abstract (Rules 8 and 26.1(b)):

- ☐ the international application does not contain an abstract

01997.032200.PC

INTERNATIONAL APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE AS
RECEIVING OFFICE (RO/US)

In re Application of:	)	
	:	Authorized Officer: Simpkins, T.
Warren Chew et al.	)	
	:	
Application No.: PCT/US2006/016019	)	
	:	
Filed: 27 April 2006	)	
	:	
For: METHOD OF PREPARING	)	
3-CYANO-QUINOLINES	:	
AND INTERMEDIATES	)	
MADE THEREBY	:	July 17, 2006

Commissioner for Patents
BOX PCT
Attn: RO/US
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE TO THE INVITATION TO CORRECT
DEFECTS AND IN THE INTERNATIONAL APPLICATION

Sir:

In reference to the above-identified International Patent Application, this is a response to an Invitation To Correct Defects In The International Application mailed 19 June 2006, having a one month period for response set to expire on 19 July, 2006. Applicant encloses herewith a Substitute sheet of the Request with the correct title recited therein.

The correct title is: METHOD OF PREPARING 3-CYANO-QUINOLINES
AND INTERMEDIATES MADE THEREBY.

If the Authorized Officer has any questions, the Officer is invited to contact Applicant's agent at the telephone number listed below. All correspondence should be directed to the below-listed address.

Respectfully submitted,

R. R. M.
Raymond R. Mandra
Agent for Applicant

FITZPATRICK, CELLA, HARPER & SCINTO
30 Rockefeller Plaza
New York, New York 10112-3801
Facsimile: (212) 218-2200
Telephone: (212) 218-2100

NY_MAIN 579054v1

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office Use Only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference
(if desired) (12 characters maximum) 01997.032200.

Box No. I TITLE OF INVENTION

METHOD OF PREPARING 3-CYANO-QUINOLINES AND INTERMEDIATES MADE THEREBY

Box No. II APPLICANT

☐ This person is also inventor

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

WYETH
Five Giralda Farms
Madison, NJ 07940
US

Telephone No. (973) 660-5000

Facsimile No. (973) 683-2112

Teleprinter No.

Applicant's registration No. with the Office

State (that is, country) of nationality: US

State (that is, country) of residence: US

This person is applicant
for the purposes of:☐all designated
States☒all designated States except
the United States of America☐the United States
of America only☐the States indicated in
the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

CHEW, Warren
751 Querbes Avenue
Outremont QC H2V3W8
Canada

This person is:

☐

applicant only

☒

applicant and inventor

☐inventor only (If this check-box is
marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality: CA

State (that is, country) of residence: CA

This person is applicant
for the purposes of:☐all designated
States☐all designated States except
the United States of America☒the United States
of America only☐the States indicated in
the Supplemental Box☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:

☒

agent

☐

common representative

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

MANDRA, Raymond R.
Fitzpatrick, Cella, Harper & Scinto
30 Rockefeller Plaza
New York, NY 10112-3801
US

Telephone No. (212) 218-2100

Facsimile No. (212) 218-2200

Teleprinter No.

Agent's registration No. with the Office
34,382☐

Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

 Industria y Comercio SUPERINTENDENCIA		SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO DIVISION DE NUEVAS CREACIONES EXTRACTO PARA PUBLICACIÓN SOLICITUD DE PATENTE DE INVENCION PCT	
(21) N° de solicitud:		(51) Int Cl: C07C 251/50, C07D 209/48, C07D 213/30, C07D 215/54, C07D 401/12	
22) Fecha de solicitud:		(71) Solicitante(s) WYETH	
(30) Prioridad	(31) No. 60/684,683	32) Fecha 25/05/05	(33) País US
		(72) Inventor(es) CHEW, Warren y PAPAMICHELAKIS, Maria	
		(74) Apoderado: ALVARO CORREA ORDOÑEZ	
(85) Fecha limite inicio fase nacional: 25/12/07	(86) Datos relativos a la presentación de la solicitud PCT		(87) Publicación internacional
	Fecha de presentación de la solicitud: 27/04/06		Fecha: 30/11/06
	No. de solicitud PCT/US2006/016019		N° publicación: WO/2006/127205
(54) Título: MÉTODO PARA PREPARAR 3-CIANO-QUINOLINAS E INTERMEDIOS HECHOS DE ESTA FORMA			

Reivindicación(es):

1. La presente invención se relaciona con métodos para preparar 3-cianoquinolinas sustituidas e intermedios obtenidos por los métodos de la presente invención. Los métodos de la invención comprenden hacer reaccionar un N-aril-2-propanimida con cloruro de fosforilo para producir las 3-cianoquinolinas sustituidas. Los métodos comprenden hacer reaccionar adicionalmente las arilaminas, ortoformatos y metilenos activos para producir los N-aril-2-propenamida.



No. 07-123653-00000-0000

Fecha: 2007-11-22 16:14:41
Tra. 11 PATENTEIYII
Act. 411 PRESENTACION

Dep. 2020 NUECREACION
Eve: 378 FASENACIONALI
Folios: 238



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 [X]
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud [X]
- ◆ Descripción de la invención [X]
- ◆ Dibujos de ser estos pertinentes []
- ◆ Comprobante de pago de las tasas establecidas [X]

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 []

Charo M. Nava Cortes
Firma Responsable

Fecha _____

Carrera 13 No. 27-00 Piso 5, 7 y 10
Conmutador: 3 82 08 40
Fax: 350 52 20
E-mail: Info@sic.gov.co
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Bogotá, D.C., Colombia

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Folio 240

2020
Bogotá D.C.,

Doctor(a)
CORREA ORDÓÑEZ ALVARO
Apoderado(a) y/o Representante de
WYETH

REFERENCIA	Radicación No.	07 123653
	Solicitud internacional	PCT/US2006/016019
	Fecha inicio fase nacional	25/12/2007
	Trámite	11
	Evento	378
	Actuación	416
	Oficio No.	5288
	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

18 FEB. 2008

ALIX CARMENZA GESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

jfernand