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Delegatura de Propiedad Industrial
División de Nuevas Creaciones

PCT

SOLICITUD DE

**PATENTE DE INVENCION
PCT ENTRADA EN FASE NACIONAL**

09-119104

21 EXPEDIENTE No

54 TITULO DERIVADOS DE 4 AZA INDCI Y SU USO COMO
FUNGICIDAS

50 CLASIFICACION INTERNACIONAL A01N 43/653

71 SOLICITANTE SYNGENTA PARTICIPATIONS AC
SYNGENTA LIMITED

DOMICILIO

Schwarzwaldallee 215, CH-4056 Basilea -
SUIZA
European Regional Centre Priestly Road
Surrey Research Park, Guildford, Surrey GU2
7YH REINO UNIDO

74 APODERADO Dra MARGARITA CASTELLANOS A

22 BOGOTA, D C ,

23 OCT 2009

PD-
26 11 2004



PETITORIO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 09-119107- -00000-0000

Fecha: 2009-10-23 14:20:18 Dep. 2020 NUECREACIONE

Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI

Act. 411 PRESENTACION Folios: 296

al adhesivo de radicación

FORMULARIO DE SOLICITUD DE PATENTES
PCT
ENTRADA EN FASE NACIONAL

SOLICITUD DE:

①

☒ Patente de Invención.	☐ Patente de Modelo de Utilidad.
☒ Capítulo I	☐ Capítulo II

②

SOLICITANTE (71)

Nombre: 1. SYNGENTA PARTICIPATIONS AG
2. SYNGENTA LIMITED
Dirección: 1. Schwarzwaldallee 215,
CH-4058 Basilea - SUIZA
2. European Regional Centre,
Priestley Road, Surrey Research Park
Guildford, Surrey GU2 7YH
REINO UNIDO
Nacionalidad o Domicilio: 1. Basilea - SUIZA
2. Surrey - REINO UNIDO
Lugar de Constitución: SUIZA - REINO UNIDO
Teléfono: Fax:
E-mail:

IDENTIFICACIÓN

C.C.	☐	NIT	☐
C.E.	☐	Otro	☐
Número		Cual	

③

**REPRESENTANTE
O APODERADO**

Nombre: MARGARITA CASTELLANOS A.
Dirección: CALLE 94A No. 7A-09
Teléfono: 756 07 70 Fax: 755 01 58
E-mail: info@castellanosyco.com

IDENTIFICACIÓN

C.C.	☒	NIT	☐
C.E.	☐	Otro	☐
Número		Cual	

④

INVENTOR (ES) (72)

VER ANEXO No. 1

⑤

PCT (86)

Solicitud Internacional No.	<u>PCT/GB2008/001348</u>	Fecha	<u>16/04/2008</u>
Publicación Internacional No.	<u>WO 2008/132434 A2</u>	Fecha	<u>06/11/2008</u>

⑥

Título (54) DERIVADOS DE 4-AZA INDOL Y SU USO COMO FUNGICIDAS

⑦

Clasificación Internacional (51) A01N 43/653 A01N 43/52 A01N 43/42

⑧

Prioridad SI ☒ NO ☐	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
	<u>GB</u>	<u>26/04/2007</u>	<u>0708141.7</u>

⑨

Comprobante de pago No. 09-79,165 y 09-79,167 **Fecha** Octubre 21 de 2009

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

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, junto con la sustitución del mismo a mi favor
- ☐ 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 12x12
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☐ De ser el caso, modificaciones efectuadas a la solicitud internacional.
- ☒ Otros: Tarjeta Propietario, Extracto para la publicación, Forma PCT/IB/306 (NOTIFICACION DE UN CAMBIO)

11 FIGURA CARACTERISTICA:

12 Solicito la concesión de la patente,

NOMBRE:

MARGARITA CASTELLANOS ABONDANO

FIRMA:

Margarita Castellanos Abondano
C.C. No. 39'779.654 Usaquén - TPA 70.819 C.S.J.

23 OCT. 2009

CASTELLANOS & CO LTDA

ABOGADOS
Calle 94 A No. 7 A-09
Bogotá, D.C. – COLOMBIA

**ANEXO # 1
INVENTORES**

1. **PATRICE SELLES**
Syngenta Crop Protection, Inc.
410 Swing Road
Greensboro, NC 27409,
ESTADOS UNIDOS DE AMERICA
2. **FREDRIK CEDERBAUM**
Syngenta Crop Protection AG
Münchwilen AG, Schaffhauserstrasse
CH-4332 Stein
SUIZA
3. **FLORENCE MARIE-EMILIE BONNATERRE**
7 Avenue Georges Clémenceau
FR-93260 Les Lilas
FRANCIA
4. **WILLIAM GUY WHITTINGHAM**
Syngenta Limited
Jealotts Hill International Research Centre
Bracknell, Berkshire RG42 6EY
GRAN BRETAÑA
5. **MAFALDA NINA**
Syngenta Crop Protection AG
Münchwilen AG, Schaffhauserstrasse
CH-4332 Stein
SUIZA
6. **JANE ELIZABETH WIBLEY**
Syngenta Limited
Jealotts Hill International Research Center
Bracknell, Berkshire RG42 6EY
GRAN BRETAÑA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT :

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 09-119107- -00000-0000

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RECIBO OFICIAL DE CAJA : 09 - 79,165
FECHA : OCTUBRE 21 DE 2009

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
ALVARO CASTELLANDS	CONSIGNACION	BANCO DE BOGOTA	062754387	21970410	21/10/2009	8,224,760.00

***** CONCEPTO *****

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

SON: QUINIENTOS CUARENTA MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-

CERTIFICACION DE EXCEDENTE : 09 - 79,167
 FECHA : OCTUBRE 21 DE 2009



***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
ALVARO CASTELLANOS	CONSIGNACION	BANCO DE BOGOTA	062754387	21970410	21/10/2009	8,224,760.00

***** CONCEPTO *****

CANT. RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-09	OTROS SERVICIOS DE PROPIEDAD I	
99	OTROS SERVICIOS ADMINISTRATIVOS	225,000.00
	TOTAL :	\$ 225,000.00

SON: DOSCIENTOS VEINTICINCO MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

ESTA CERTIFICACION DE EXCEDENTE DE PAGO SOLO PODRA SER UTILIZADA
 COMO PARTE DE LA CANCELACION DE UNA TARIFA VIGENTE Y NO PODRA SER
 SUSTITUIDA POR NINGUN RECIBO.

6

CASTELLANOS & CO LTDA
ABOGADOS
Calle 94 A No. 7 A-09
Bogotá, D.C. – COLOMBIA

Señor

Jefe de la División de Nuevas Creaciones

Superintendencia de Industria y Comercio

Ministerio de Comercio, Desarrollo, Industria y Turismo

E.

S.

D.

Ref.: **PODER** conferido por la sociedad **SYNGENTA LIMITED**

Yo, **XIMENA CASTELLANOS ABONDANO**, mayor de edad, identificada y domiciliada como aparece al pie de mi firma, atentamente manifiesto a Uds. que sustituyo en la Dra. **MARGARITA CASTELLANOS ABONDANO**, el poder que me confirió la sociedad **SYNGENTA LIMITED**, con domicilio en **European Regional Centre, Priestly Road, Surrey Research Park, Guildford, Surrey GU2 7YH, REINO UNIDO**, debidamente legalizado por Apostilla, bajo el No. **G201564** el día **4 de Julio de 2003**, con las mismas facultades que me fueron conferidas, para tramitar la solicitud de Patente PCT Entrada en Fase Nacional, en Colombia, para: **"DERIVADOS DE 4-AZA INDOL Y SU USO COMO FUNGICIDAS"**.

Del Señor Jefe,

Acepto


Ximena Castellanos Abondano
C.C. No. **39.773.330** de Usaquén
T.P.A. No. **58.236** del C.S.J.
Calle 94 A No. 7 A-09 – Bogotá, D.C.
Teléfono: 7560770


Margarita Castellanos Abondano
C.C. No. **39.779.654** de Usaquén
T.P.A. No. **70.819** del C.S.J.
Calle 94 A No. 7 A-09 – Bogotá, D.C.
Teléfono: 7560770

Bogotá, D.C.
XCA/MCA/P1834

MEMORIAL SUSTITUCION PODER

NOTARIA 41 DEL CÍRCULO DE BOGOTÁ D.C.
DEPARTAMENTO DE CUNDINAMARCA
REPÚBLICA DE COLOMBIA

El Notario 41 del círculo de Bogotá, da fe de que compareció personalmente: Ximena Castellanos A.
identificada (o) con: 39773330 y tarjeta
profesional de abogado No. 38236 del Consejo
Superior de la Judicatura, quien autentica la firma puesta por ella
(el) mismo en este escrito.
(Art. 84 C. P. C. Decreto. 2282/89 mod. 36)

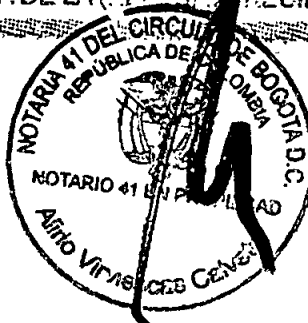
Bogotá D.C. 21 OCT 2009
Ximena Castellanos A.
FIRMA DE LA (EL) COMPARECIENTE



NOTARIA 41 DEL CÍRCULO DE BOGOTÁ D.C.
DEPARTAMENTO DE CUNDINAMARCA
REPÚBLICA DE COLOMBIA

El Notario 41 del círculo de Bogotá, da fe de que compareció personalmente: Margarita Castellanos A.
identificada (o) con: 39779654 y tarjeta
profesional de abogado No. 26019 del Consejo
Superior de la Judicatura, quien autentica la firma puesta por ella
(el) mismo en este escrito.
(Art. 84 C. P. C. Decreto. 2282/89 mod. 36)

Bogotá D.C. 21 OCT 2009
Margarita Castellanos A.
FIRMA DE LA (EL) COMPARECIENTE



COLOMBIA

PODER

El (los) SYNGENTA LIMITED
Domiciliados en Priestly Road, Surrey
Research Park, Guildford, Surrey GU2 7YH
Nombran por el presente a XIMENA CASTELLANOS A. y/o
MARGARITA CASTELLANOS A. abogadas con oficinas en
la Carrera 9 No. 93-09, Bogotá-Colombia para

y para obtener la protección de mi (nuestra) propiedad
Industrial y con este fin autorizamos a dichos apoderados para
que nos representen ante cualesquiera autoridades o
personas de los órdenes administrativo, contencioso -
administrativo y judicial en todo lo relacionado con los
siguientes actos y gestiones:

a) Obtención de patentes de invención, modelos y dibujos
industriales; registro de marcas de fábrica, de servicio,
colectivas o defensivas y de denominaciones de origen,
depósito de nombres y enseñas comerciales; su renovación,
prórroga, inscripción de traspaso y cambio de nombre o
domicilio, cancelación voluntaria y el registro de licencias de
uso de esos derechos; b) Para la obtención de registros
sanitarios; c) Acciones de oposición, observación,
cancelación, nulidad, medidas cautelares y en general los
juicios civiles, penales, administrativos o contencioso -
administrativos que promovamos o se nos promuevan,
pudiendo en todos los actos y gestiones arriba mencionados
sustituir éste mandato, transigir, desistir, recibir, cancelar,
renunciar, aceptar notificaciones y nombrar apoderados
judiciales y extrajudiciales.

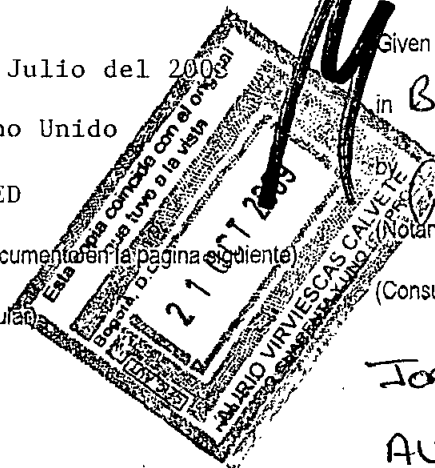
Dado y firmado hoy 2 de Julio del 2003

en Bracknell, Reino Unido

por SYNGENTA LIMITED

(El notario debe suscribir el documento en la página siguiente)

(Se requiere legalización consular)



Given and signed this 2nd JULY 2003

in BRACKNELL, UK

Joanna Chandler

(Notary shall execute on the other side)

(Consular legalization required)

JOANNA CHANDLER.

AUTHORISED SIGNATORY.

ALVARO CASTELLANOS M. & CIA.

ABOGADOS COLOMBIA

Carrera 9 No. 93-09 - P.O. Box 6349 - Bogotá, Colombia
Tels.: (571) 610 74 20 / 60 / 80 - Fax (571) 610 07 06 - e-mail: acastell@imposat.net.co

XC/cm

37367

Registered Office:
SYNGENTA LIMITED
EUROPEAN REGIONAL CENTRE
PRIESTLY ROAD
SURREY RESEARCH PARK
GUILDFORD
SURREY GU2 7YH
UNITED KINGDOM

POWER OF ATTORNEY

I (we) the undersigned SYNGENTA LIMITED
Of

REINO UNIDO

hereby grant(s) Power of Attorney to XIMENA
CASTELLANOS A. and for MARGARITA CASTELLANOS
a. attorneys residing at Carrera 9 No. 93-09, Bogotá-
Colombia, to

and to obtain the protection of my (our) Industrial Property, for
which purpose we authorize the said attorneys to represent
us before any authorities, or persons, specially those,
administrative, contentious and judicial, in all matters
concerning the following:

a) Obtention of patents, models and designs, registration of
trademarks, service, collective and defensive marks, and of
designations of origin; the deposit of trade names and
ensigns; its renewal, extension, recordal of assignments,
change of name or domicile, voluntary cancellation, and the
registration of licenses of use of the above rights; b) For the
obtention of Sanitary registrations; c) Actions of opposition,
cancellation, nullity, infringement, granting of licenses; and in
general the civil, criminal and administrative suits related to
those rights; actions and suits instituted by us or against us;
and that in all the above matters they may substitute this
power of attorney, compromise, desist, cancel, receive,
renounce, accept notifications and appoint attorneys in fact,
in or out of court.

COLOMBIA

CERTIFICADO NOTARIAL (Sociedad)

Hoy 3 de Jul. del año 2003
compareció (eron) personalmente
a quienes conozco como la(s) personas que firma(n) en
representación de la Sociedad (Compañía denominada
Certifico : SYNGENTA LIMITED
a) Que es una sociedad/Compañía legalmente
constituida y existente de acuerdo con las leyes de
b) Que el domicilio de dicha Sociedad/Compañía es
c) Que el objeto u objetos para los cuales se otorga el
presente poder están comprendidos dentro del objeto
social de la mencionada Sociedad /Compañía.
d) Que el Sr. Joanna Chandler
esta autorizado para otorgar el presente poder. Lo anterior
esta probado por medio de los siguientes documentos, que
certifico he visto* Estatutos de constitución

(Ciudad) Egham

(Estado) Surrey

Hoy 3 del Julio del 2003

(Notario Público)

*Los documentos debe identificarse con fecha y origen.

NOTARIAL (Corporation)

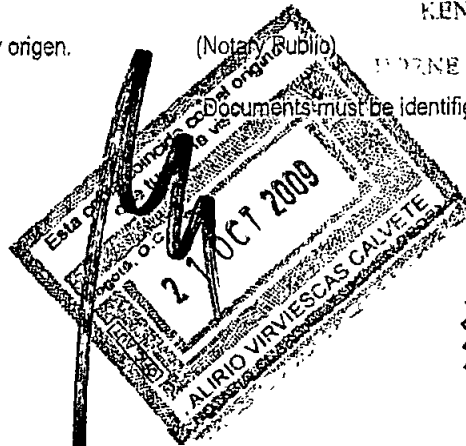
On this 3rd day of July of 2003
personally appeared JOANNA CHANDLER
whom I know to be the person(s) who signed this
document as representative(s) of the Corporation
/Company named SYNGENTA LTD
I certify:

- a) That Syngenta is a corporation (Company legally
constituted and in existence in accordance with the
laws of ENGLAND & WALES
b) That the domicile of said Corporation/Company is GUILDFORD
UK
c) That the purpose or purposes for which the present
Power of Attorney is granted are comprised within
the object set forth in the charter of the mentioned
Corporation/Company.
d) That Mr. M/s JOANNA CHANDLER
is (are) authorized to grant the present Power of Attorney.
The aforementioned was duly proven through the
following documents and I duly certify having seen them*:
Certificate of Incorporation.
(City) Egham

(State) Surrey

EXECUTION
Certified Verified and Authenticated
this 3 day of 7 of the month of July in Surrey
This 3rd Day of July 2003

KENNETH GREENWOOD
NOTARY PUBLIC
BORNE ENGALL AND FREEMAN
Documents must be identified with date and origin



ALVARO CASTELLANOS M. & CIA.

ABOGADOS COLOMBIA

Carrera 9 No. 93-09- P.O.Box 6349 - Bogotá, Colombia
Tels.: (571) 610 74 20 / 60 / 80 - Fax (571) 610 07 06 - e-mail: acastell@impzxc.net.co

XC/cm

APOSTILLE

(Hague Convention of 5 October 1961 / Convention de La Haye du 5 octobre 1961)

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

1. Country: United Kingdom of Great Britain and Northern Ireland
Pays: Royaume-Uni de Grande-Bretagne et d'Irlande du Nord

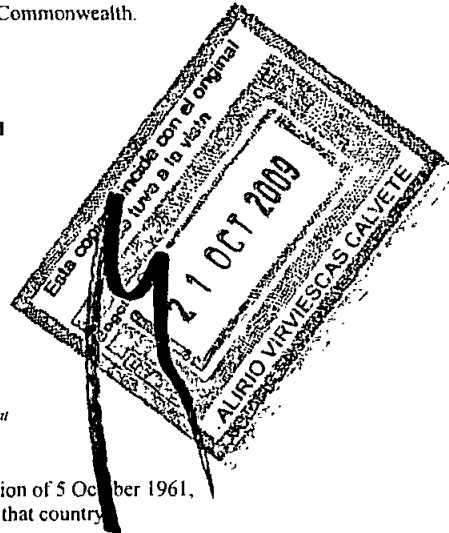
This public document / Le présent acte public

2. Has been signed by **K Greenwood**
a été signé par
3. Acting in the capacity of **Notary Public**
agissant en qualité de
4. Bears the seal/stamp of **The Said Notary Public**
est revêtu du sceau/timbre de

5. at London/à Londres
6. the/le **04 July 2003**
7. by Her Majesty's Principal Secretary of State for Foreign and Commonwealth Affairs /
par le Secrétaire d'Etat Principal de Sa Majesté aux Affaires Etrangères et du Commonwealth.
8. Number/sous No **G201564**
9. Stamp:
timbre:
10. Signature: **J. Ireland**



For the Secretary of State / Pour le Secrétaire d'Etat



If this document is to be used in a country which is not party to the Hague Convention of 5 October 1961,
it should be presented to the consular section of the mission representing that country

-----TRADUCCION OFICIAL No. 03-0718-----

de un documento escrito en INGLES, el cual para su identificación lleva el sello de la Traductora e Intérprete Oficial , según Resoluciones 2755/68 y 01144/97 del Ministerio de Justicia.

(Anexo a un documento de poder de Syngenta Limited)

AUTENTICACIÓN

Certificado, verificado y autenticado en el pueblo de Egham en Surrey

Hoy día 3 de Julio de 2003.

(fdo) ilegible

Kenneth Greenwood – Notario Público

Horne, Engall and Freeman

(Sello en oblea roja)

APOSTILLA

(Convención de La Haya del 5 de octubre de 1961)

1. País: Reino Unido de Gran Bretaña e Irlanda del Norte

Este documento público

2. ha sido firmado por K. Greenwood

3. actuando en su carácter de Notario Público

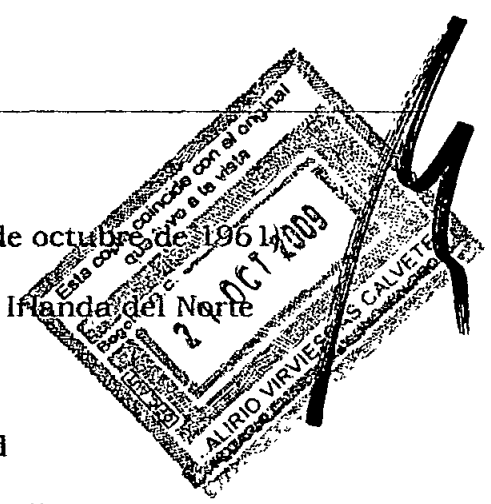
4. lleva el sello de dicho Notario Público

Certificado

5. En Londres

6. el día 4 de Julio de 2003

7. por el Secretario de Estado Principal de Su Majestad para Asuntos Exteriores y de la Comunidad



DORA RUQUE DE BERNAL
TRADUCTORA E INTERPRETE OFICIAL
RES. 02755/68 y 01144/97 - MINISTERIO DE JUSTICIA
B.O. DE ALBUQUERQUE

8 No. G201564

9. Sello

10. Firma: J. Ireland

(fdo) ilegible

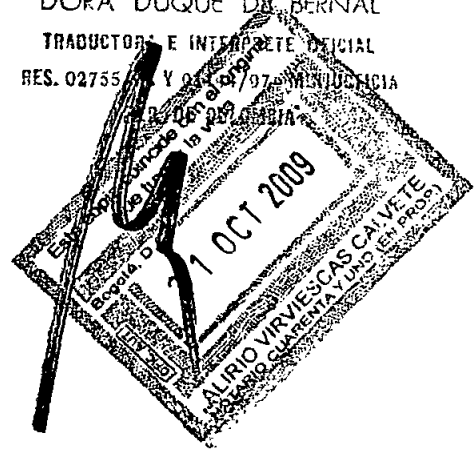
Por el Secretario de Estado

ES TRADUCCION FIEL Y COMPLETA, a la cual me remito,

Bogotá, D. C., Julio 24, 2003

[Handwritten signature]

DORA DUQUE DE BERNAL
TRADUCTORA E INTERPRETE OFICIAL
RES. 02755 Y 0448/97



MINISTERIO DE RELACIONES

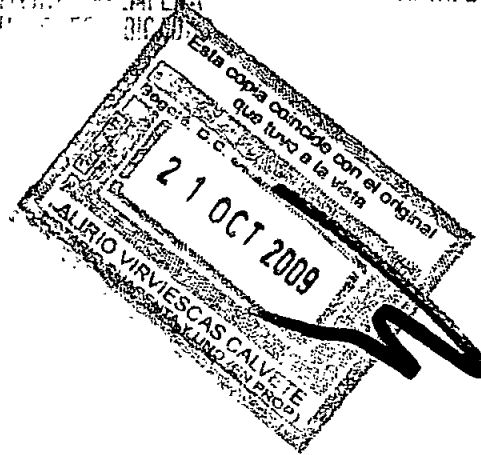
NO SE ASUME
RESPONSABILIDAD DEL TEXTO

Don mave
049710

2003 JUL 25 P 12:02

CUYA FIRMA ACONTECE EN EL
DOCUMENTO DE EMPEÑO
LAS FIRMAS DE DICHO

led
JEFE DE LEGALIZACIONES
SANTAFE DE BOGOTA D.C.



12

CASTELLANOS & CO.
ABOGADOS
Calle 94 A No. 7 A-09
Bogotá, D.C. – COLOMBIA

Señor

Jefe de la División de Nuevas Creaciones

Superintendencia de Industria y Comercio

Ministerio de Comercio, Desarrollo, Industria y Turismo

E. S. D.

Ref.: **PODER** conferido por la sociedad **SYNGENTA PARTICIPATIONS AG**

Yo, **XIMENA CASTELLANOS ABONDANO**, mayor de edad, identificada y domiciliada como aparece al pie de mi firma, atentamente manifiesto a Uds. que sustituyo en la Dra. **MARGARITA CASTELLANOS ABONDANO**, el poder que me confirió la sociedad **SYNGENTA PARTICIPATIONS AG**, con domicilio en **Schwarzwaldalle 215, CH-4058 Basilea, SUIZA**, debidamente legalizado por Apostilla, bajo el No. **8117** el día **1° de Abril de 2004**, con las mismas facultades que me fueron conferidas, para tramitar la solicitud de Patente PCT Entrada en Fase Nacional, en Colombia, para: **"DERIVADOS DE 4-AZA INDOL Y SU USO COMO FUNGICIDAS"**.

Del Señor Jefe,

Acepto


Ximena Castellanos Abondano
C.C. No. **39.773.330** de Usaquén
T.P.A. No. **58.236** del C.S.J.
Calle 94 A No. 7 A-09 – Bogotá, D.C.
Teléfono: 756 07 70


Margarita Castellanos Abondano
C.C. No. **39.779.654** de Usaquén
T.P.A. No. **70.819** del C.S.J.
Calle 94 A No. 7 A-09 – Bogotá, D.C.
Teléfono: 756 07 70

Bogotá, D.C.
XCA/MCA/P1834

NOTARIA 41 DEL CÍRCULO DE BOGOTÁ D.C.
DEPARTAMENTO DE CUNDINAMARCA
REPÚBLICA DE COLOMBIA

El Notario 41 del círculo de Bogotá, da fe de que compareció
personalmente: Ximena Castellanos Abondano
identificada (o) con: 39773330 y tarjeta
profesional de abogado No. 38234 del Consejo
Superior de la Judicatura, quien autentica la firma puesta por ella
(el) mismo en este escrito.

(Art. 84 C. P. C. Decreto. 2282/89 mod. 36)

Bogotá D.C.,

Ximena Castellanos Abondano
FIRMA DE LA (EL)COMPARECIENTE



NOTARIA 41 DEL CÍRCULO DE BOGOTÁ D.C.
DEPARTAMENTO DE CUNDINAMARCA
REPÚBLICA DE COLOMBIA

El Notario 41 del círculo de Bogotá, da fe de que compareció
personalmente: Margaretta Castellanos A
identificada (o) con: 39779654 y tarjeta
profesional de abogado No. 70819 del Consejo
Superior de la Judicatura, quien autentica la firma puesta por ella
(el) mismo en este escrito.

(Art. 84 C. P. C. Decreto. 2282/89 mod. 36)

Bogotá D.C.,

Margaretta Castellanos A
FIRMA DE LA (EL)COMPARECIENTE



PODER

El (los) Gregory W. Warren
SYNGENTA PARTICIPATIONS AG

Nombran por el presente a **XIMENA CASTELLANOS A. y/o MARGARITA CASTELLANOS A.** abogadas con oficinas en la Carrera 9 No. 93-09, Bogotá-Colombia para

y para obtener la protección de mi (nuestra) propiedad Industrial y con este fin autorizamos a dichos apoderados para que nos representen ante cualesquiera autoridades o personas de los órdenes administrativo, contencioso -administrativo y judicial en todo lo relacionado con los siguientes actos y gestiones:

a) Obtención de patentes de invención, modelos y dibujos industriales; registro de marcas de fabrica, de servicio, colectivas o defensivas y de denominaciones de origen, depósito de nombres y enseñas comerciales; su renovación, prórroga, inscripción de traspaso y cambio de nombre o domicilio, cancelación voluntaria y el registro de licencias de uso de esos derechos; b) Para la obtención de registros sanitarios; c) Acciones de oposición, observación, cancelación, nulidad, medidas cautelares y en general los juicios civiles, penales, administrativos o contencioso - administrativos que promovamos o se nos promuevan, pudiendo en todos los actos y gestiones arriba mencionados sustituir éste mandato, transigir, desistir, recibir, cancelar, renunciar, aceptar notificaciones y nombrar apoderados judiciales y extrajudiciales.

Dado y firmado hoy 24 de Marzo de 2004

en Research Triangle Park, Carolina
del Norte 27709
por Gregory W. Warren

(El notario debe suscribir el documento en la pagina siguiente)

(Se requiere legalización consular)

POWER OF ATTORNEY

I (we) the undersigned Gregory W. Warren
Syngenta Participations AG

hereby grant(s) Power of Attorney to **XIMENA CASTELLANOS A. and /or MARGARITA CASTELLANOS A.** attorneys residing at Carrera 9 No. 93-09, Bogota- Colombia, to prosecute

and to obtain the protection of my (our) Industrial Property, for which purpose we authorize the said attorneys to represent us before any authorities, or persons, specially those, administrative, contentious and judicial, in all matters concerning the following:

a) Obtention of patents, models and designs, registration of trademarks, service, collective and defensive marks, and of designations of origin; the deposit of trade names and ensigns; its renewal, extension, recordal of assignments, change of name or domicile, voluntary cancellation, and the registration of licenses of use of the above rights; b) For the obtention of Sanitary registrations; c) Actions of opposition, cancellation, nullity, infringement, granting of licenses; and in general the civil, criminal and administrative suits related to those rights; actions and suits instituted by us or against us; and that in all the above matters they may substitute this power of attorney, compromise, desist, cancel, receive, renounce, accept notifications and appoint attorneys in fact, in or out of court.

Given and signed this 24th March 2004

in Research Triangle Park, North Carolina 27709

by Gregory W. Warren *Gregory W. Warren*

(Notary shall execute on the other side)

(Consular legalization required)

ALVARO CASTELLANOS M. & CIA

ABOGADOS COLOMBIA

Carrera 9 No. 93-09- P.O.Box 6349 - Bogotá, Colombia
Tels.: (571) 610 74 20 / 60 / 80 - Fax (571) 610 07 06 - e-mail: acastell@impsa.net.co



XC/cm

CERTIFICADO NOTARIAL (Sociedad)

Hoy 24 de Marzo del año 2004

compareció (eron) personalmente Gregory W. Warren a quienes conozco como la(s) personas que firma(n) en representación de la Sociedad (Compañía denominada Certifico: Syngenta Participations AG

- a) Que es una sociedad/Compañía legalmente constituida y existente de acuerdo con las leyes de
 b) Que el domicilio de dicha Sociedad/Compañía es Basel, Suiza
 c) Que el objeto u objetos para los cuales se otorga el presente poder están comprendidos dentro del objeto social de la mencionada Sociedad /Compañía.
 d) Que el Sr. Gregory W. Warren esta autorizado para otorgar el presente poder. Lo anterior esta probado por medio de los siguientes documentos, que certifico he visto*

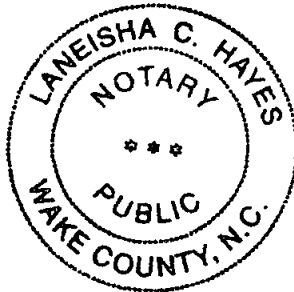
(Ciudad) REsearch Triangle Park

(Estado) Carolina del Norte 27709

Hoy del 24 de Marzo de 2004

(Notario Público) LANEISHA C. HAYES

*Los documentos debe identificarse con fecha y origen.



ALVARO CASTELLANOS M. & CIA.

ABOGADOS COLOMBIA

Carrera 9 No. 93-09- P.O.Box 6349 - Bogotá, Colombia
 Tels.. (571) 610 74 20 / 60 / 80 - Fax (571) 610 07 06 - e-mail acastell@impstat.net.co

NOTARIAL (Corporation)

On this 24th day of March of 2004 personally appeared Gregory W. Warren whom I know to be the person(s) who signed this document as representative(s) of the Corporation /Company named Syngenta Participations AG

I certify:

- a) That Syngenta Participations AG is a corporation (Company legally constituted and in existence in accordance with the laws of Basel, Switzerland
 b) That the domicile of said Corporation/Company is Basel, Switzerland
 c) That the purpose or purposes for which the present Power of Attorney is granted are comprised within the object set forth in the charter of the mentioned Corporation/Company.
 d) That Mr. Gregory W. Warren is (are) authorized to grant the present Power of Attorney. The aforementioned was duly proven through the following documents and I duly certify having seen them*: on the 24th day of March, 2004 in Research Triangle Park, North Carolina 27709.

(City) Research Triangle Park

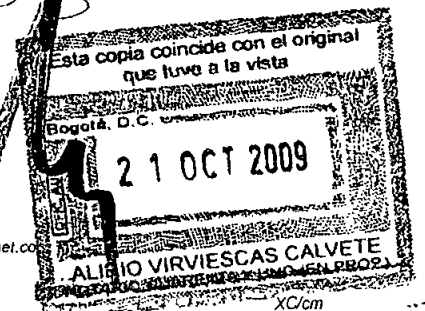
(State) North Carolina, 27709

this 24th day of March of the year 2004

(Notary Public)

*Documents must be identified with date and origin

3/24/04 - Research Triangle Park, North Carolina 27709 - Syngenta Biotech, Inc.





Wake County Register of Deeds
Post Office Box 1897
Raleigh, North Carolina 27602-1897

Laura M. Riddick
Register Of Deeds

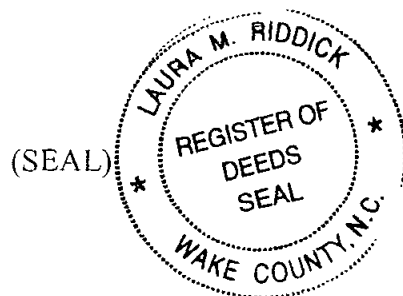
STATE OF NORTH CAROLINA

WAKE COUNTY

CERTIFICATE OF REGISTER OF DEEDS THAT
NOTARY PUBLIC WAS ACTING NOTARY
AT TIME OF SIGNATURE

I, LAURA M. RIDDICK, REGISTER OF DEEDS OF THE AFORESAID COUNTY AND STATE, DO HEREBY CERTIFY THAT Laneisha C. Hayes WAS, AT THE TIME OF SIGNING THE FOREGOING (OR ANNEXED) CERTIFICATE, A DULY COMMISSIONED AND QUALIFIED NOTARY PUBLIC IN AND FOR THE COUNTY OF WAKE, STATE OF NORTH CAROLINA, AND AS SUCH FULL FAITH AND CREDIT IS DUE TO HIS OFFICIAL ACTS; AND, FURTHER, THAT HIS SIGNATURE THERETO IS IN HIS OWN PROPER HANDWRITING.

IN TESTIMONY WHEREOF, I HAVE HEREUNTO SET MY HAND AND SEAL OF OFFICE THIS, THE 30TH DAY OF MARCH, 2004.

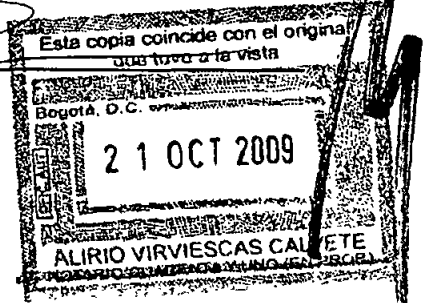


Laura M. Riddick

REGISTER OF DEEDS

Carla

DEPUTY / ASSISTANT



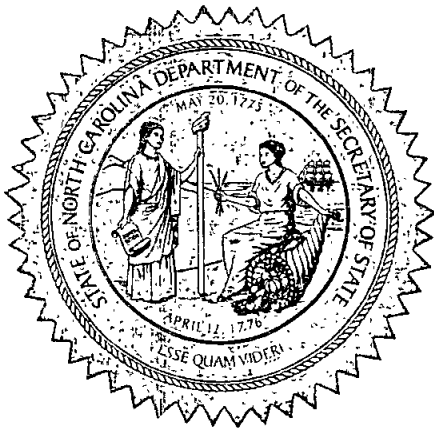
APOSTILLE

(Convention de La Haye 5 octobre 1961)

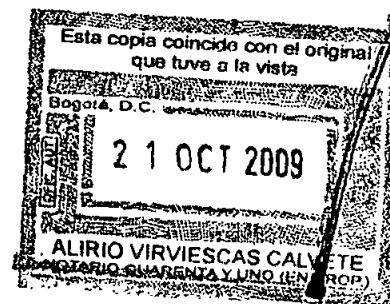
1. COUNTRY: **UNITED STATES OF AMERICA**
2. This Public Document
has been signed by CARLA N. BROWN
3. acting in the capacity of DEPUTY REGISTER OF DEEDS
LAURA M. RIDDICK, REGISTER OF DEEDS
4. bears the seal/stamp of COUNTY OF WAKE, NORTH CAROLINA

CERTIFIED

5. at Raleigh, North Carolina
6. the 1ST DAY OF APRIL, 2004
7. by Deputy Secretary of State, State of North Carolina
8. No. 8117
9. Seal/Stamp:
10. Signature



Roberto S. Morales



-----TRADUCCION OFICIAL No. -040417-----

de un documento escrito en INGLES, el cual para su identificación
lleva el sello de la Traductora e Intérprete oficial, Res. 2755/68 y
01144/97 de Minjusticia, al igual que la presente.-----

------(Anexos a un poder otorgado por Syngenta
Participations AG)

(fdo) ilegible

3/24/04 Research Triangle Park, NC 27709

ESTADO DE CAROLINA DEL NORTE

CONDADO DE WAKE

Yo, Laura M. Riddick, Registrador de Escrituras del condado y estado
antes mencionados, certifico por medio del presente que Laneisha C.
Hayes, al momento de firmar este documento era un Notario Público
debidamente comisionado y habilitado en y para el Condado de Wake,
Estado de Carolina del Norte, y como tal debe dares plena fe y crédito a
sus actos oficiales, y además, que su firma en el mismo es de su propia
letra.

En testimonio de lo cual, he impuesto aquí mi firma y sello de oficio,
hoy día 30 de Marzo de 2004.

Laura M. Riddick, Registrador de Escrituras

Por (fdo) ilegible



DORA SUQUE DE BERNAL
TRADUCTORA E INTERPRETE OFICIAL
RES. DE 2755/68 Y 01144/97 - MINJUSTICIA
RCP. DE COLOMBIA

Delegado

APOSTILLA

(Convención de La Haya de octubre 5, 1961)

1. País: Estados Unidos de América
 2. Este documento público ha sido firmado por CARLA N. BROWN
 3. actuando en su carácter de Delegado del Registrador de Escrituras
 4. lleva el sello de Laura M. Riddick, Registrador de Escrituras
- Condado de Wake, Carolina del Norte

CERTIFICADO

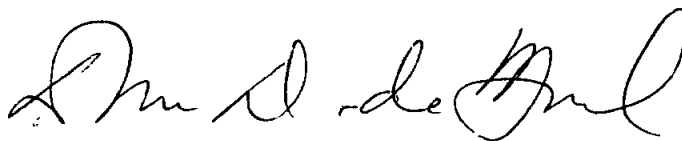
5. En Raleigh. Carolina del Norte
6. el día 1 de Abril de 2004
7. por el Secretario de Estado Delegado, Estado de Carolina del Norte
8. No. 8117
9. Sello: (sello en oblea ocre)

10. Firma

(fdo) Rodney S. Maddox

ES TRADUCCION FIEL Y COMPLETA, a la cual me remito,

Bogotá, Abril 15, 2004



DORA DUQUE DE BERNAL
TRADUCTORA E INTERPRETE OFICIAL
RES. 02755/68 Y 01144/97 - MINJUSTICIA
REP. DE COLOMBIA



2-42
2-42
2-42

Esta copia coincide con el original
que tuvo a la vista
Bogotá, D.C.
21 OCT 2009
ALIRIO VIRVIESCAS CALVE
SECRETARIO DE DEFENSA Y FUERZAS ARMADAS

RECEIVED
Dora Duque
SECRETARIO DE DEFENSA Y FUERZAS ARMADAS

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6EY (GB). NINA, Mafalda [PT/CH]; Syngenta Crop Protection AG, Werk Stein, Schwarzwaldallee 215, CH-4332 Basel (CH). WIBLEY, Jane, Elizabeth [GB/GB]; Syngenta Limited, Jealott's Hill International Research Centre, Bracknell, Berkshire RG42 6EY (GB).

(21) International Application Number:
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(71) Applicants (for all designated States except US): SYNGENTA PARTICIPATIONS AG [CH/CH]; Schwarzwaldallee 215, CH-4058 Basel (CH). SYNGENTA LIMITED [GB/GB]; European Regional Centre, Priestley Road, Surrey Research Park, Guildford, Surrey GU2 7YH (GB).

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(72) Inventors; and

(75) Inventors/Applicants (for US only): SELLES, Patrice [FR/FR]; Syngenta Crop Protection AG, Werk Stein, Schwarzwaldallee 215, CH-4332 Basel (CH). CEDERBAUM, Fredrik [SE/CH]; Syngenta Crop Protection AG, Werk Stein, Schwarzwaldallee 215, CH-4332 Basel (CH). BONNATERRE, Florence, Marie-Emilie [FR/FR]; Syngenta Crop Protection AG, Werk Stein, Schwarzwaldallee 215, CH-4332 Basel (CH). WHITTINGHAM, William, Guy [GB/GB]; Syngenta Limited, Jealott's Hill International Research Centre, Bracknell, Berkshire RG42

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WO 2008/132434 A2

(54) Title: 4-AZA INDOLE DERIVATIVES AND THEIR USE AS FUNGICIDES

(57) Abstract: The present invention relates to a method of preventing and/or controlling fungal infection in plants and/or plant propagation material comprising applying to the plant or plant propagation material a fungicidally effective amount of a compound of formula (I) or a salt of N-oxide thereof. In addition, the present invention also relates to a compound of formula (I).

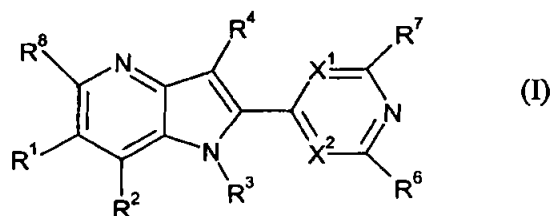
4-AZA INDOLE DERIVATIVES AND THEIR USE AS FUNGICIDES

The present invention relates to novel fungicidally active 4-aza-indoles, compositions comprising these novel compounds and their use in methods for the control and/or prevention of fungal infection in plants. In addition, the invention relates to processes for preparing the novel compounds of the invention.

Certain 4-aza-indoles and their use in the prevention and treatment of human and animal disease, although not that caused by fungi, are described in WO 99/20624. Similar compounds are described in WO 03/06629, WO 2006/014325 and WO 98/22457, the latter also disclosing their use as anti-inflammatory agents.

It has now been found that certain 4-aza-indoles have fungicidal activity and, in particular, activity against plant pathogenic fungi.

Accordingly, the present invention provides a method of preventing and/or controlling fungal infection in plants and/or plant propagation material comprising applying to the plant or plant propagation material a fungicidally effective amount of a compound of formula (I):



wherein:

X¹ is N or CH;

X² is N or CR⁵;

R¹ and R² are, independently,:

(i) hydrogen, halogen, hydroxyl, cyano or nitro,

(ii) optionally substituted alkyl, alkenyl or alkynyl,

- (iii) optionally substituted aryl, heteroaryl, cyclyl or heterocyclyl, or
- (iv) $-C(O)R^{10}$, $-C(O)NR^{10}R^{11}$, $-C(S)NR^{10}R^{11}$, $-C(NOR^{10})R^{11}$, $-C(O)OR^{10}$, $-OR^{10}$, $-SR^{10}$, $-S(O)R^{10}$, $-S(O)NR^{10}R^{11}$, $-S(O)_2NR^{10}R^{11}$, $-S(O)_2R^{10}$, $-NR^{10}R^{11}$, $-P(O)(OR^{10})(OR^{11})$ or $-OP(O)(OR^{10})(OR^{11})$;

5

R^3 is:

- (i) hydrogen, hydroxyl, cyano or nitro,
- (ii) optionally substituted alkyl, alkenyl, allenyl, alkynyl or haloalkyl,
- (iii) optionally substituted aryl, heteroaryl, cyclyl or heterocyclyl or heteroaralkyl or
- 10 (iv) $-C(O)R^{12}$, $-C(O)OR^{12}$, $-OR^{12}$, $-OC(O)R^{12}$, $-S(O)_2R^{12}$ or $-NR^{12}R^{13}$;

R^4 is:

- (i) hydrogen, halogen, hydroxyl, cyano or nitro,
- (ii) optionally substituted alkyl, alkenyl, allenyl, alkynyl or haloalkyl,
- 15 (iii) optionally substituted aryl, heteroaryl, cyclyl or heterocyclyl or
- (iv) $-C(O)R^{14}$, $-C(O)OR^{14}$, $-C(NOR^{14})R^{15}$, $-OR^{14}$, $-SR^{14}$, $-S(O)NR^{14}R^{15}$, $-S(O)_2R^{14}$, or $-NR^{14}R^{15}$;

R^5 is:

- 20 (i) hydrogen, halogen, hydroxyl, cyano or nitro,
- (ii) optionally substituted alkyl, alkenyl or alkynyl,
- (iii) $-C(O)R^{16}$, $-C(O)OR^{16}$, $-OR^{16}$, $-SR^{16}$, $-S(O)R^{16}$, $-S(O)NR^{16}R^{17}$, $-S(O)_2R^{16}$, or $-NR^{16}R^{17}$;

R^6 is hydrogen, halogen, cyano, $-C(O)OR^{18}$, $-SR^{18}$, $-NR^{18}R^{19}$, $-C(O)NR^{18}R^{19}$ or $-N=CR^{20}$, -

- 25 $C(=NR^{18})NR^{19}R^{20}$ or optionally substituted aryl, heteroaryl, cyclyl or heterocyclyl;

R^7 and R^8 are, independently, hydrogen, halogen, hydroxyl, cyano, nitro, $-NR^{21}R^{22}$ or optionally substituted alkyl;

- 30 R^{10} , R^{11} , R^{14} , R^{15} , R^{16} and R^{17} are, independently, hydrogen, halogen, hydroxyl, cyano, nitro, optionally substituted alkyl, alkoxy, alkenyl or alkynyl, or optionally substituted aryl, heteroaryl, cyclyl or heterocyclyl;

R^{12} and R^{13} are, independently, hydrogen, halogen, hydroxyl, cyano, nitro, $-NR^{21}R^{22}$, optionally substituted alkyl, alkoxy, alkenyl or alkynyl, or optionally substituted aryl, heteroaryl, cyclyl or heterocyclyl;

5 R^{18} and R^{19} are, independently,

- (i) hydrogen,
- (ii) optionally substituted alkyl, alkenyl or alkynyl,
- (iii) optionally substituted aryl, heteroaryl, cyclyl or heterocyclyl, or
- (iv) $-C(S)R^{23}-C(O)R^{23}$, $-SO_2R^{23}$, $-C(O)OR^{23}$, $-OR^{23}$ or $C(O)NR^{23}R^{24}$;

10

R^{20} is hydroxyl, optionally substituted alkyl or alkoxy or $-NR^{21}R^{22}$, or $-N=CR^{21}R^{22}$;

R^{21} and R^{22} are, independently, hydrogen, optionally substituted alkyl, alkenyl or alkynyl, optionally substituted cyclyl, heterocyclyl, aryl, or heteroaryl or aralkyl or $-C(O)OR^{25}$;

15

R^{23} and R^{24} are, independently, hydrogen, hydroxyl, optionally substituted alkyl, alkenyl or alkynyl, or optionally substituted aryl, heteroaryl, cyclyl or heterocyclyl or aralkyl; and

R^{25} is optionally substituted alkyl, alkenyl or alkynyl;

20

and/or

independently, (i) R^1 and R^2 , (ii) R^1 and R^3 (iii) R^2 and R^3 , (iv) R^3 and R^5 , (v) R^5 and R^6 , (vi) R^5 and R^{18} , (vii) R^5 and R^{19} , (viii) R^{14} and R^{15} and (ix) R^{18} and R^{19} form an optionally
 25 substituted aryl, heteroaryl, cyclyl or heterocyclyl group containing from 5 to 18 ring atoms;

or a salt of N-oxide thereof.

Unless otherwise stated, the following terms used in the specification and claims
 30 have the meanings given below:

“Alkyl” means a linear saturated monovalent hydrocarbon radical of one to eight carbon atoms or a branched saturated monovalent hydrocarbon radical of three to eight carbon atoms, e.g. methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *tert*-

butyl, *n*-pentyl, *n*-hexyl and the like. Preferably, linear alkyl groups contain one to six carbon atoms, more preferably one to four carbon atoms and most preferably are selected from methyl, ethyl or *n*-propyl. Preferably, branched alkyl groups contain three to six carbon atoms and more preferably are selected from *iso*-propyl, *sec*-butyl, *iso*-butyl or *tert*-butyl.

“Alkenyl” means a linear monovalent saturated hydrocarbon radical of two to eight carbon atoms, or a branched monovalent hydrocarbon radical of three to eight carbon atoms containing at least one double bond, e.g. ethenyl, propenyl and the like. Where appropriate, an alkenyl group can be of either the (*E*)- or (*Z*)-configuration. Preferably, linear alkenyl groups contain two to six carbon atoms and more preferably are selected from ethenyl, prop-1-enyl, prop-2-enyl, prop-1,2-dienyl, but-1-enyl, but-2-enyl, but-3-enyl, but-1,2-dienyl and but-1,3-dienyl. Preferably, branched alkenyl groups contain three to six carbon atoms and more preferably are selected from 1-methylethenyl, 1-methylprop-1-enyl, 1-methylprop-2-enyl, 2-methylprop-1-enyl and 2-methylprop-2-enyl.

“Allenyl” means a linear monovalent saturated hydrocarbon radical of three to eight carbon atoms, or a branched monovalent hydrocarbon radical of three to eight carbon atoms containing at least two double bonds between three contiguous carbon atoms, e.g. propa-1,2-dienyl, penta-1,2-dienyl, penta-2,3-dienyl, hexa-1,2-dienyl and the like. Where appropriate, an alkenyl group can be of either the (*R*)- or (*S*)-configuration. Preferred is propa-1,2-dienyl.

“Alkynyl” means a linear monovalent saturated hydrocarbon radical of two to eight carbon atoms, or a branched monovalent hydrocarbon radical of four to eight carbon atoms, containing at least one triple bond, e.g. ethynyl, propynyl and the like. Preferably, linear alkynyl groups contain two to six carbon atoms and more preferably are selected from ethynyl, prop-1-ynyl, prop-2-ynyl, but-1-ynyl, but-2-ynyl and but-3-ynyl. Preferably, branched alkynyl groups contain four to six carbon atoms and more preferably are selected from 1-methylprop-2-ynyl, 3-methylbut-1-ynyl, 1-methylbut-2-ynyl, 1-methylbut-3-ynyl and 1-methylbut-3-ynyl.

“Alkylene” means a linear saturated divalent hydrocarbon radical of one to six carbon atoms or a branched saturated divalent hydrocarbon radical of three to six carbon atoms, e.g.

methylene, ethylene, propylene, 2-methylpropylene and the like. Preferred alkylene groups are the divalent radicals of the alkyl groups defined above.

5 “Alkenylene” means a linear divalent hydrocarbon radical of two to six carbon atoms or a branched divalent hydrocarbon radical of three to six carbon atoms, containing at least one double bond, e.g. ethenylene, propenylene and the like. Preferred alkenylene groups are the divalent radicals of the alkenyl groups defined above.

10 “Cyclyl” means a monovalent cyclic hydrocarbon radical of three to eight ring carbons, preferably three to six ring carbons, e.g. cyclopropyl, cyclohexyl and the like. Cyclyl groups may be fully saturated or mono- or di-unsaturated. Preferably, cyclyl groups contain three to six ring carbons, more preferably they are selected from cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. Mono-unsaturated cyclyl groups are preferably selected from cyclobutenyl, cyclopentenyl and cyclohexenyl.

15

 “Heterocyclyl” means a cyclyl radical containing one, two or three ring heteroatoms selected from N, O or S(O)_n (where n is an integer from 0 to 2), the remaining ring atoms being carbon where one or two carbon atoms may optionally be replaced by a carbonyl group. Examples of such rings include, but are not limited to, oxirane, oxetane, 20 tetrahydrofuran, tetrahydropyran, 1,3-dioxolane, 1,4-dioxane, aziridine, azetidine, pyrrolidine, piperidine, oxazinane, morpholine, thiomorpholine, imidazolidine, pyrazolidine and piperazine. More preferably, the heterocyclyl group contains three to five ring atoms including one O and/or one N ring atom.

25 “Aryl” means a monovalent monocyclic or bicyclic aromatic hydrocarbon radical of six to ten ring carbons atoms. Suitable aryl groups include phenyl and naphthyl, in particular, phenyl.

 “Heteroaryl” means a monovalent monocyclic or bicyclic aromatic hydrocarbon 30 radical of five to ten ring atoms, preferably five or six ring atoms, containing one, two, three or four ring heteroatoms selected, independently, from N, O or S, the remaining ring atoms being carbon. Examples of heteroaryl groups include, but are not limited to pyridyl, pyrimidinyl, pyrazolyl, thiazolyl, thiophenyl, isoazolyl, and tetrazolyl groups.

“Alkoxy” means a radical -OR, where R is optionally substituted alkyl, alkenyl or alkynyl or an optionally substituted cyclyl, heterocyclyl, aryl or heteroaryl group or an aralkyl or heteroaralkyl group. Preferably, alkoxy groups are selected from methoxy, ethoxy, 1-methylethoxy, propoxy, 1-methylpropoxy and 2-methylpropoxy. More preferably
5 alkoxy means methoxy or ethoxy.

“Halo” or “halogen” means fluoro, chloro, bromo or iodo, preferably chloro or fluoro.

10 “Haloalkyl” means alkyl as defined above substituted with one or more of the same or different halo atoms. Examples of haloalkyl groups include, but are not limited to fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 2-trifluoroethyl, 2-chloro-ethyl, 2-iodoethyl, 3-fluoropropyl, 3-chloropropyl, 2-trifluoro-1-chloroethyl and 1-difluoro-2-difluoro-3-trifluoropropyl.

15 “Haloalkenyl” means alkenyl as defined above substituted with one or more of the same or different halo atoms. Examples of haloalkenyl groups include, but are not limited to 2-dibromoethenyl, 2-fluoro-2-bromoethenyl, 5-bromopent-3-enyl and 3 dichloroprop-2-enyl.

20 “Aralkyl” means a radical -R^aR^b where R^a is an alkylene or alkenylene group and R^b is an aryl group as defined above.

“Heteroaralkyl” means a radical -R^aR^b where R^a is an alkylene or alkenylene group and R^b is a heteroaryl group as defined above.

25 “Acyl” means -C(O)R, wherein R is hydrogen, optionally substituted alkyl, alkenyl or alkynyl or optionally substituted cyclyl, heterocyclyl, aryl or heteroaryl.

30 “Acyloxy” means a radical -OC(O)R where R is hydrogen, optionally substituted alkyl, alkenyl or alkynyl or optionally substituted cyclyl, heterocyclyl, aryl or heteroaryl.

The groups defined above, in particular, alkyl, alkenyl, alkynyl, cyclyl, heterocyclyl, aryl and heteroaryl groups, may be optionally substituted by one or more substituents independently selected from halogen, hydroxyl, cyano, alkyl (optionally substituted by

25
cyano), haloalkyl, alkenyl, haloalkenyl, alkynyl (optionally substituted by -C(O)OR), haloalkynyl, cyclyl (optionally substituted by cyano, halogen, hydroxyl or methyl), heterocyclyl, aryl (optionally substituted by halogen), heteroaryl, alkoxy (optionally substituted by alkoxy or acyl), -C(O)R, -C(O)OR, -SR, -S(O)R, -S(O)₂R, -S(O)NRR',
5 -OS(O)NRR', -P(O)(OR)(OR'), -O(P)(O)(OR)(OR'), -NRR', -NRC(O)OR', -C(O)NRR', -O-N=CRR' or trialkylsilyl, wherein R and R' are, independently, hydrogen or alkyl, alkoxy, haloalkyl, alkenyl, haloalkenyl, alkynyl, cyclyl, heterocyclyl, aryl or heteroaryl. In particular, R and R' are, independently, hydrogen or alkyl (in particular, methyl or ethyl). Preferred optional substituents are alkoxy (in particular, methoxy or ethoxy), hydroxyl,
10 cyano, halogen (in particular, fluoro, chloro or bromo), heterocyclyl (in particular, oxirane or tetrahydrofuran), heteroaryl (in particular, pyridyl), -C(O)OR (wherein R is hydrogen or alkyl (in particular, methyl or ethyl)) and trialkylsilyl (in particular, trimethylsilyl).

The compounds of formula (I) may exist in different geometric or optical isomeric
15 forms or in different tautomeric forms. One or more centres of chirality may be present, in which case compounds of the formula (I) may be present as pure enantiomers, mixtures of enantiomers, pure diastereomers or mixtures of diastereomers. There may be double bonds present in the molecule, such as C=C or C=N bonds, in which case compounds of formula (I) may exist as single isomers or mixtures of isomers. Centres of tautomerisation may be
20 present. This invention covers all such isomers and tautomers and mixtures thereof in all proportions as well as isotopic forms such as deuterated compounds.

Suitable salts of the compounds of formula (I) include acid addition salts such as those with an inorganic acid such as hydrochloric, hydrobromic, sulfuric, nitric or
25 phosphoric acid, or an organic carboxylic acid such as oxalic, tartaric, lactic, butyric, toluic, hexanoic or phthalic acid, or a sulphonic acid such as methane, benzene or toluene sulphonic acid. Other examples of organic carboxylic acids include haloacids such as trifluoroacetic acid.

30 N-oxides are oxidised forms of tertiary amines or oxidised forms of nitrogen containing heteroaromatic compounds. They are described in many books for example in "Heterocyclic N-oxides" by Angelo Albini and Silvio Pietra, CRC Press, Boca Raton, Florida, 1991.

In particularly preferred embodiments of the invention, the preferred groups for X^1 and X^2 and R^1 to R^{25} , in any combination thereof, are as set out below.

Preferably, X^1 is CH.

5

Preferably, X^2 is CR^5 . More preferably, X^2 is CH.

Preferably, R^1 is hydrogen, halogen, cyano, optionally substituted C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl, optionally substituted aryl or $-C(O)R^{10}$, wherein the optional substituents in all cases are as defined above and, more preferably, are selected from hydroxyl, alkoxy, halogen or trialkylsilyl. More preferably, R^1 is hydrogen, halogen, cyano or optionally substituted C_{1-6} alkyl or C_{2-6} alkynyl (in particular, the C_{2-6} alkynyl is 2-trimethylsilyl-ethynyl). Even more preferably, R^1 is hydrogen, chloro, bromo, cyano or methyl. Most preferably, R^1 is hydrogen, chloro or methyl.

15

Preferably, R^2 is hydrogen or C_{1-6} alkyl. More preferably, R^2 is hydrogen or methyl. Most preferably, R^2 is hydrogen.

Preferably, R^3 is hydrogen, hydroxyl, $-C(O)R^{12}$, $-OR^{12}$, $-C(O)OR^{12}$, $-OC(O)R^{12}$, $-S(O)_2R^{12}$, optionally substituted C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} allenyl, C_{2-6} alkynyl or optionally substituted saturated cyclyl, wherein the optional substituents in all cases are as defined above and, more preferably, are selected from cyano, halogen, hydroxyl, C_{1-4} alkyl, C_{2-4} alkenyl, alkoxy (optionally substituted by alkoxy or acyl), cyclyl, heterocyclyl, aryl, heteroaryl, $-NH_2$, trialkylsilyl, $-C(O)R$ or $-C(O)OR$ (wherein R is hydrogen, methyl or ethyl). More preferably, R^3 is hydrogen, $-OR^{12}$ or optionally substituted C_{1-6} alkyl, C_{2-4} alkenyl, C_{3-4} allenyl or C_{2-4} alkynyl. Most preferably, R^3 is hydrogen, cyanomethyl, aminoethyl, aminopropyl, prop-2-enyl, prop-2-ynyl, propa-1,2-dienyl, methoxymethyl, 2-fluoromethyl, $-OCH_2C\equiv CH$, $-OCH_2OCH_3$, $-OCH_2CN$, $-OCH(CH_3)CN$.

30

Preferably, R^4 is hydrogen, halogen, optionally substituted C_{2-6} alkynyl or optionally substituted aryl or heteroaryl, wherein the optional substituents are as defined above and, more preferably, are selected from hydroxyl, halogen (in particular, fluoro or chloro), haloalkyl, acyl or C_{1-4} alkyl (in particular, methyl). More preferably, R^4 is optionally substituted phenyl or optionally substituted heteroaryl. Even more preferably, R^4 is

optionally substituted phenyl. Even more preferably, R⁴ is phenyl, 3-methylphenyl, 3-trifluoromethylphenyl, 4-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,5-difluorophenyl or 3-methyl-4-fluorophenyl. Most preferably, R⁴ is phenyl or 4-fluorophenyl.

5 Preferably R⁵ is hydrogen, halogen, optionally substituted C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl, or forms an optionally substituted aryl, heteraryl, cyclyl or heterocycyl ring with R⁶, wherein the optional substituents in all cases are as defined above and, more preferably, are selected from halogen, cyano, hydroxyl, haloalkyl or C₁₋₄ alkyl. Preferably, the ring formed with R⁶ is a 5 or 6 membered heterocycle. More preferably, R⁵ is hydrogen or
10 halogen. Most preferably, R⁵ is hydrogen.

Preferably R⁶ is hydrogen, chloro, -C(O)OR¹⁸, -NR¹⁸R¹⁹, -N=CR²⁰ or forms an optionally substituted aryl, heteroaryl, cyclyl or heterocycyl ring with R⁵ as defined above. More preferably, R⁶ is hydrogen or -NR¹⁸R¹⁹. More preferably, R⁶ is -NHR¹⁹. More
15 preferably, R⁶ is -NHC(O)R²³.

Preferably R⁷ and R⁸ are, independently, hydrogen, hydroxyl, cyano, -NR²¹R²² or optionally substituted C₁₋₆ alkyl, wherein the optional substituents are as defined above and, more preferably, are selected from halogen, cyano, hydroxyl or haloalkyl. More preferably,
20 R⁷ and R⁸ are, independently hydrogen, hydroxyl or -NR²¹R²². Most preferably, R⁷ and R⁸ are both hydrogen.

Preferably, R¹⁰, R¹¹, R¹⁴, R¹⁵, R¹⁶ and R¹⁷ are, independently, hydrogen or optionally substituted C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl, wherein the optional substituents are as
25 defined above and, more preferably, are hydroxyl, halogen, cyano or alkoxy. More preferably R¹⁰, R¹¹, R¹⁴, R¹⁵, R¹⁶ and R¹⁷ are, independently, hydrogen or optionally substituted C₁₋₃ alkyl. Most preferably, R¹⁰, R¹¹, R¹⁴, R¹⁵, R¹⁶ and R¹⁷ are, independently, hydrogen, methyl or ethyl.

30 Preferably R¹² and R¹³ are, independently, optionally substituted C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl or optionally substituted C₃₋₆ cyclyl, wherein the optional substituents in all cases are as defined above and, more preferably are hydroxyl, halogen, cyano, alkoxy, cyclyl (optionally substituted with hydroxyl or methyl), -C(O)OR, -OS(O)NRR' (wherein R and R' are, independently, hydrogen, alkyl, alkenyl or alkynyl). More preferably, R¹² and

R^{13} are, independently, optionally substituted C_{1-4} alkyl, C_{2-4} alkenyl or C_{2-4} alkynyl. Most preferably, R^{12} and R^{13} are, independently, cyanomethyl, prop-2-enyl or prop-2-ynyl.

Preferably R^{18} is hydrogen, optionally substituted C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl, $-C(O)R^{23}$, $-C(O)OR^{23}$, $-S(O)_2R^{23}$ or $-C(O)NR^{23}R^{24}$ or forms an optionally substituted heterocyclyl ring with R^{19} , wherein the optional substituents in all cases are as defined above and, more preferably are selected from hydroxyl, cyano, halogen or alkoxy. More preferably, R^{18} is hydrogen, C_{1-4} substituted alkyl, C_{2-4} alkenyl, or C_{2-4} alkynyl. Preferably the C_{1-4} alkyl group is ethyl or *iso*-propyl. Preferably, the C_{2-4} alkenyl group is propen-2-enyl. Preferably, the C_{2-4} alkynyl group is prop-2-ynyl or but-2-ynyl. Most preferably, R^{18} is hydrogen.

Preferably R^{19} is hydrogen, $-C(S)R^{23}$, $-C(O)R^{23}$, $-C(O)OR^{23}$, $-S(O)_2R^{23}$ or $-C(O)NR^{23}R^{24}$ optionally substituted C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl, optionally substituted aryl, heteroaryl, cyclyl or heterocyclyl or forms an optionally substituted heterocyclyl ring with R^{18} , wherein the optional substituents in all case are as defined above and, more preferably, are selected from hydroxyl, cyano, halogen, alkoxy, cyclyl or heterocyclyl. More preferably, R^{19} is hydrogen, $-C(S)R^{23}$, $-C(O)R^{23}$ or $-C(O)OR^{23}$ or optionally substituted C_{1-4} alkyl. Preferably, the optionally substituted C_{1-4} alkyl is *iso*-butyl. Most preferably, R^{19} is hydrogen, $-C(O)R^{23}$ or $-C(O)OR^{23}$.

Preferably, R^{20} is $-NR^{21}R^{22}$.

Preferably, R^{21} and R^{22} are, independently, hydrogen, optionally substituted C_{1-4} alkyl or $-C(O)OR^{25}$, wherein the optional substituents are as defined above and, more preferably, are selected from hydroxyl, cyano, halogen, alkoxy, acyl, cyclyl or heterocyclyl. More preferably, R^{21} and R^{22} are, independently, hydrogen or optionally substituted C_{1-4} alkyl. Most preferably, R^{21} and R^{22} are, independently, hydrogen, methyl or ethyl.

Preferably R^{23} and R^{24} are, independently, hydrogen, hydroxyl, optionally substituted C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl or optionally substituted cyclyl or aryl, wherein the optional substituents in all cases are as defined above and, more preferably, are hydroxyl, halogen, cyano, C_{1-4} alkyl, alkoxy, haloalkenyl, cyclyl or $-C(O)OR$ (wherein R is cyclyl). Preferably, the aryl group is optionally substituted phenyl. More preferably, the aryl group is

3-halophenyl or 4-halophenyl. More preferably, R^{23} and R^{24} are, independently, hydrogen, optionally substituted C_{1-6} alkyl or C_{2-6} alkenyl or an optionally substituted saturated or mono-unsaturated cyclyl group. Even more preferably, R^{23} and R^{24} are, independently, optionally substituted C_{1-6} alkyl or an optionally substituted C_{3-6} saturated cyclyl group.

5 Preferably the optionally substituted C_{1-6} alkyl is methyl, ethyl or *iso*-propyl. Preferably, the C_{3-6} saturated cyclyl group is a cyclopropyl or cyclobutyl group, which may be substituted with one or more substituents being selected from cyano, halogen (preferably fluoro), C_{1-4} alkyl (preferably methyl) or haloalkenyl.

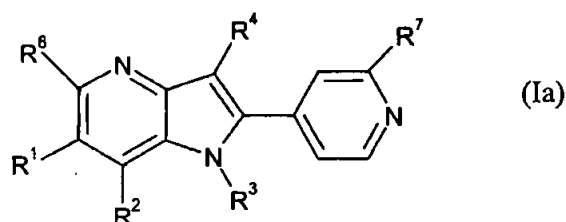
10 Preferably, R^{25} is C_{1-4} alkyl. More preferably, R^{25} is methyl, ethyl, propyl or 2-dimethylethyl.

In a particularly preferred embodiment, when R^3 is hydrogen, R^6 is other than hydrogen. More preferably, R^3 is hydrogen and R^6 is $-NR^{18}R^{19}$. More preferably, R^3 is hydrogen and R^6 is $-NHR^{19}$. More preferably, R^3 is hydrogen and R^6 is $-NHC(O)R^{23}$.

In an alternative preferred embodiment, R^6 is hydrogen and R^3 is other than hydrogen. More preferably, R^6 is hydrogen and R^3 is $-OR^{12}$ or optionally substituted C_{1-6} alkyl, C_{2-4} alkenyl, C_{3-4} allenyl or C_{2-4} alkynyl. Most preferably, R^6 is hydrogen and R^3 is cyanomethyl, aminoethyl, aminopropyl, prop-2-enyl, prop-2-ynyl, propa-1,2-dienyl, methoxymethyl, 2-fluoromethyl, $-OCH_2C\equiv CH$, $-OCH_2OCH_3$, $-OCH_2CN$, $-OCH(CH_3)CN$.

In a particular embodiment, the method of the invention utilises a compound of formula (Ia):

25



wherein R^1 , R^2 , R^3 , R^4 , R^7 and R^8 are as defined above and, preferably:

R^1 is hydrogen, halogen, cyano, optionally substituted C_{1-6} alkyl (in particular, optionally substituted C_{1-4} alkyl and, most particularly, optionally substituted methyl or ethyl, wherein the optional substituent is as defined above and more preferably is hydroxyl, e.g. 1-hydroxyethyl) or $-C(O)R^{10}$ and R^{10} is hydrogen or C_{1-4} alkyl;

R^2 , R^7 and R^8 are, independently, hydrogen, halogen or C_{1-4} alkyl;

R^3 is hydrogen, hydroxyl, cyano, optionally substituted C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} allenyl or C_{2-6} alkynyl, $-NR^{12}R^{13}$, $-OR^{12}$ or $-C(O)R^{12}$, wherein:

(a) the optional substituents on the alkyl, alkenyl and alkynyl groups are as defined above and, more preferably, are independently selected from halo, cyano, hydroxyl, alkoxy (optionally substituted by alkoxy or acyl), C_{1-4} alkyl, C_{2-4} alkenyl, cyclyl, heterocyclyl, heteroaryl, $-C(O)R$, $-C(O)OR$ and $-SR$, wherein R is hydrogen, C_{1-4} alkyl, C_{2-4} alkenyl or C_{2-4} alkynyl, and

(b) R^{12} is optionally substituted alkyl, alkenyl, alkynyl or cyclyl, the optional substituents being as defined above and, more preferably, halo, cyano, hydroxyl, alkoxy, cyclyl, heterocyclyl, $-C(O)R$, $-C(O)OR$ or $-OS(O)NRR'$, wherein R and R' are, independently hydrogen or alkyl,

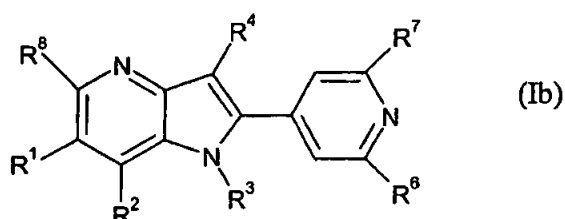
and R^4 is optionally substituted aryl (in particular, phenyl or naphthyl), the optional substituents being as defined above and, more preferably halogen or C_{1-4} alkyl.

More preferably, R^1 is hydrogen, halo or optionally substituted C_{1-4} alkyl, wherein the optional substituent is preferably hydroxyl; R^{10} is methyl or ethyl; R^2 , R^7 and R^8 are, independently, hydrogen, methyl, ethyl or chloro; R^3 is hydrogen, $-OR^{12}$ or optionally substituted C_{1-4} alkyl, C_{2-4} alkenyl or C_{2-4} alkynyl; and R^4 is phenyl, which is optionally substituted by at least one substituent selected from halogen and C_{1-4} alkyl (in particular, methyl).

Even more preferably, R^1 is hydrogen, chloro or methyl; R^2 , R^7 and R^8 are each hydrogen; R^3 is hydrogen, cyanomethyl, prop-2-enyl or prop-2-ynyl; and R^4 is phenyl, 2-

fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 4-chlorophenyl, 3-methylphenyl or 3-methyl-4-fluorophenyl and most preferably is 4-fluorophenyl.

In a particular embodiment, the method of the invention utilises a compound of
5 formula (Ib):



- wherein R^1 , R^2 , R^3 , R^4 , R^6 , R^7 and R^8 are as defined above and, preferably:
- 10 R^1 is hydrogen, halogen, optionally substituted C_{1-6} alkyl or $-C(O)R^{10}$ and R^{10} is hydrogen or C_{1-4} alkyl;
- R^2 is hydrogen or C_{1-4} alkyl;
- 15 R^3 is hydrogen, hydroxyl, optionally substituted C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl, $-C(O)R^{12}$ or $-OR^{12}$ and R^{12} is optionally substituted C_{1-4} alkyl or cyclyl, the optional substituents in all cases being as defined above and, more preferably, halogen, cyano, hydroxyl, alkoxy, cyclyl, heterocyclyl, $-NH_2$, trialkylsilyl or $C(O)OR$, wherein R is
- 20 hydrogen, C_{1-4} alkyl, C_{2-4} alkenyl or C_{2-4} alkynyl;
- R^4 is optionally substituted aryl, the optional substituents being as defined above and, more preferably halogen or C_{1-4} alkyl;
- 25 R^6 is halogen or $-NR^{18}R^{19}$ and
- (i) R^{18} is hydrogen, $-C(O)R^{23}$, $-C(O)OR^{23}$ or optionally substituted C_{1-4} alkyl, C_{2-4} alkenyl or C_{2-4} alkynyl and R^{23} is optionally substituted C_{1-4} alkyl and

- (ii) R^{19} is hydrogen, optionally substituted C_{1-4} alkyl, C_{2-4} alkenyl or C_{2-4} alkynyl, - $C(S)R^{23}$ - $C(O)R^{23}$ or - $C(O)OR^{23}$ and R^{23} is hydrogen, optionally substituted C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl or C_{3-6} cyclyl;

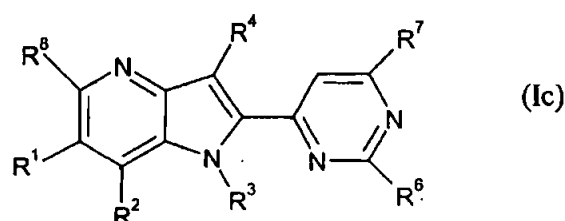
5 R^7 is hydrogen, halogen or C_{1-4} alkyl; and

R^8 is hydrogen, halogen, C_{1-4} alkyl or $NR^{21}R^{22}$ and R^{21} and R^{22} are, independently, hydrogen or C_{1-4} alkyl.

10 More preferably, R^1 is hydrogen, halo or optionally substituted C_{1-4} alkyl; R^2 is hydrogen or methyl; R^3 is hydrogen, optionally substituted C_{1-4} alkyl, C_{2-4} alkenyl or C_{2-4} alkynyl or - OR^{12} ; R^4 is phenyl, which is optionally substituted by at least one substituent selected from halogen and C_{1-4} alkyl; R^6 is halogen or - $NR^{18}R^{19}$ and R^{18} is hydrogen, prop-2-enyl or prop-2-ynyl and R^{19} is - $C(O)R^{23}$ and R^{23} is hydrogen, methyl, ethyl, *iso*-propyl, 1-methylethyl, 1-methylpropyl, 2-dimethylethyl, propyl, 1-methylethenyl, 2-methylprop-1-enyl, but-3-enyl, cyclopropyl, 1-methylcyclopropyl, 1-fluorocyclopropyl or cyclobutyl; R^7 is
15 hydrogen, chloro, fluoro or methyl; and R^8 is hydrogen, chloro, methyl or 2-methoxy-1-ethylamino.

20 Even more preferably, R^1 is hydrogen, chloro or methyl; R^2 hydrogen or methyl; R^3 is hydrogen, cyanomethyl, prop-2-enyl or prop-2-ynyl; R^4 is 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 4-chlorophenyl, 3-methylphenyl or 3-methyl-4-fluorophenyl and most preferably is 4-fluorophenyl; R^6 is - $NR^{18}R^{19}$ and R^{18} is hydrogen and R^{19} is - $C(O)R^{23}$ and R^{23} is methyl, ethyl, *iso*-propyl, cyclopropyl, cyclobutyl or 1-methylcyclopropyl; R^7 hydrogen;
25 and R^8 is hydrogen, chloro or methyl.

In a particular embodiment, the method of the invention utilises a compound of formula (Ic)



wherein R^1 , R^2 , R^3 , R^4 , R^6 , R^7 and R^8 are as defined above and, preferably:

R^1 , R^2 , R^7 and R^8 are, independently, hydrogen, halogen or C_{1-4} alkyl; R^3 is hydrogen or
 5 optionally substituted C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl, the optional substituents being
 as defined above and, more preferably, halogen or alkoxy; R^4 is optionally substituted aryl,
 the optional substituents being as defined above and, more preferably, halogen; and R^6 is
 hydrogen, $-SR^{18}$ or $-NR^{18}R^{19}$ wherein R^{18} is hydrogen or C_{1-4} alkyl and R^{19} is optionally
 substituted alkyl, $-C(S)R^{23}$ or $-C(O)R^{23}$ and R^{23} is hydrogen or C_{1-4} alkyl.

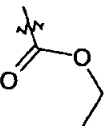
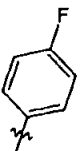
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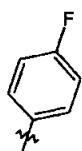
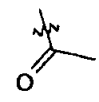
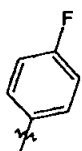
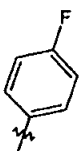
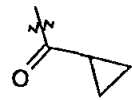
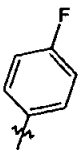
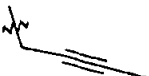
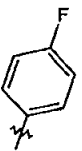
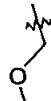
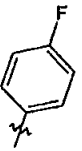
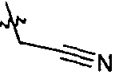
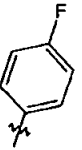
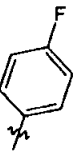
More preferably R^1 , R^2 , R^7 and R^8 are, independently, hydrogen, methyl, ethyl or
 chloro; R^3 is hydrogen, haloalkyl, alkoxyalkyl, alkenyl or alkynyl; R^4 is optionally
 substituted phenyl, the optional substituent being halogen; and R^6 is hydrogen or $-NR^{18}R^{19}$
 wherein R^{18} is hydrogen and R^{19} is 2-methoxy-1-methylethyl, $-C(S)R^{23}$ or $-C(O)R^{23}$ and R^{23}
 15 is C_{1-4} alkyl.

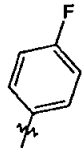
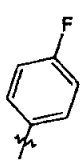
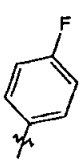
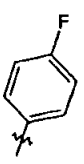
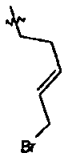
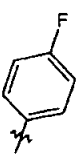
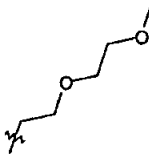
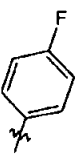
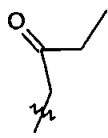
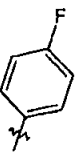
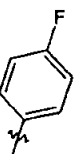
Even more preferably, R^1 , R^2 , R^7 and R^8 are, independently, hydrogen; R^3 is
 hydrogen, 2-fluoroethyl, methoxymethyl, prop-1,2-diene or prop-2-ynyl; R^4 is fluorophenyl
 (in particular, 4-fluorophenyl); and R^6 is $-NR^{18}R^{19}$ wherein R^{18} is hydrogen and R^{19} is -
 20 $C(O)R^{23}$ and R^{23} methyl, ethyl, 1-methylethyl, 1-dimethylethyl or 3-methylpropyl.

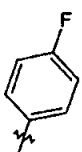
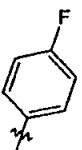
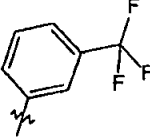
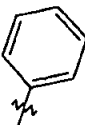
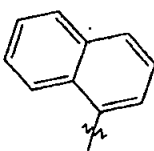
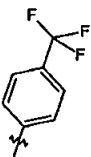
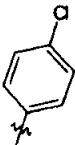
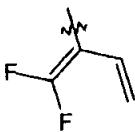
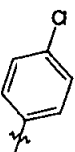
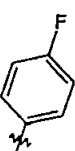
More particularly, compounds for use in the present invention are shown in Table 1
 (compounds of formula (Ia)), Table 2 (compounds of formula (Ib)) and Table 3 (compounds
 of formula (Ic)) below:

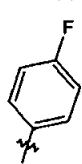
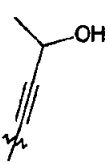
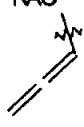
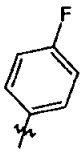
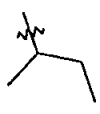
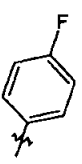
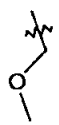
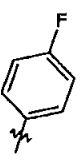
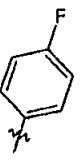
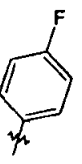
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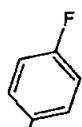
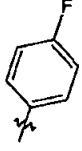
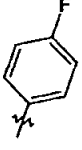
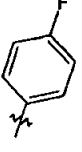
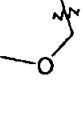
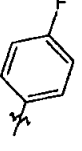
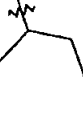
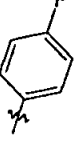
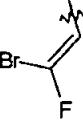
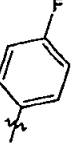
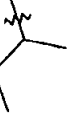
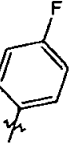
Compound Number	R1	R2	R3	R4	R7	R8	Melting Point	Mass (ES+)
1	H	H			H	H	127.0 - 128.0	

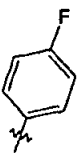
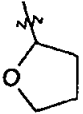
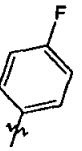
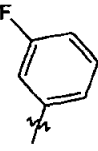
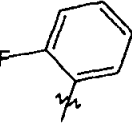
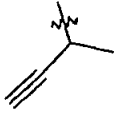
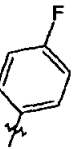
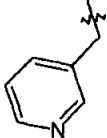
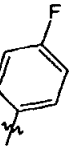
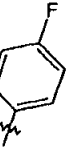
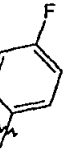
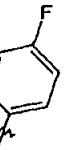
2	H	H	Et		H	H	208.0 – 209.0	
3	H	H			H	H	164.0-165.0	
4	H	H			H	H	175.0 – 176.0	
5	H	H			H	H	169.0 – 170.0	
6	H	H			H	H	165.0-166.0	
7	H	H			H	H	156.0-157.0	
8	H	H			H	H	237.0-238.0	
9	Cl	H	H		H	H	255.0-256.0	

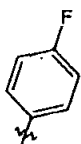
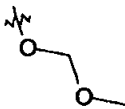
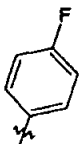
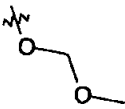
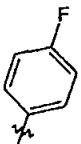
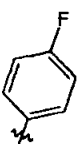
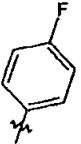
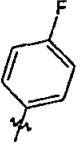
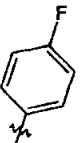
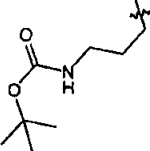
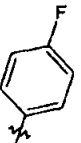
10	H	H			H	H	157.0-158.0	
11	H	H			H	H	169.0-170.0	
12	H	H			H	H	151.0-152.0	
13	H	H			H	H	151.0-152.0	
14	H	H			H	H	-	436/438
15	H	H			H	H	78.0-79.0	
16	H	H			H	H	173.0-174.0	
17	H	H			H	H	181.0-182.0	

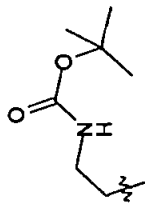
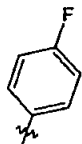
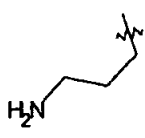
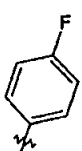
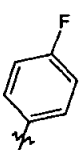
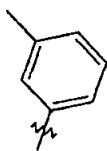
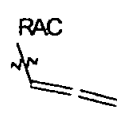
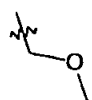
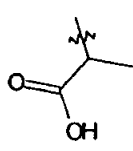
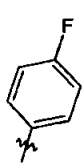
18	H	H			H	H	157.0-158.0	
19	H	H			H	H	124.0-125.0	
20	H	H	Me		H	H	87.0-88.0	
21	H	H	Me		H	H	195.0-196.0	
22	H	H	Me		H	H	200.0-201.0	
23	H	H	Me		H	H	182.0-183.0	
25	H	H	Me		H	H	193.0-194.0	
26	H	H			H	H	-	394
27	H	H	H		H	H	-	290

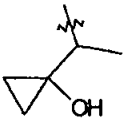
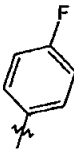
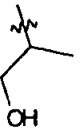
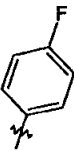
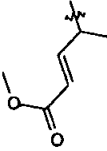
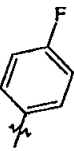
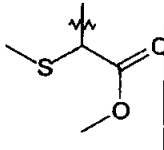
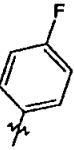
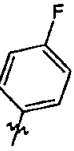
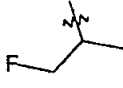
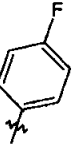
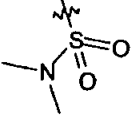
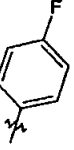
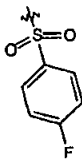
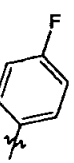
28	H	H	Me		H	H	-	304
29	H	H	Me		H	H	188.0-189.0	
30	H	H	RAC 		H	H	153.0-154.0	
31	H	H	Me		H	H	-	280
32	H	H			H	H	164.0-165.0	
33	Cl	H			H	H	159.0-160.0	
34	Cl	H			H	H	181.0-182.0	
35	Me	H	H		H	H	260.0-261.0	

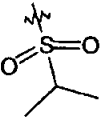
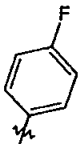
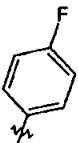
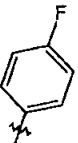
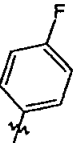
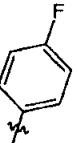
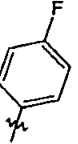
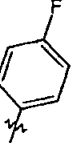
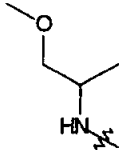
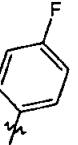
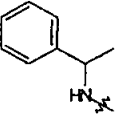
36	Cl	H			H	H	184.0-185.0	
37	Cl	H	RAC 		H	H	175.0-176.0	
38	Me	H			H	H	132.0-133.0	
39	Me	H			H	H	152.0-153.0	
40	Me	H			H	H	140.0-141.0	
41	Me	H			H	H	161.0-162.0	
42	Cl	H	H		H	H	265.0-265.0	
43	H	H			H	H	-	412/414
44	Cl	H			H	H	155.0-156.0	

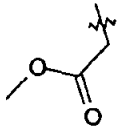
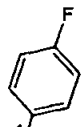
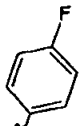
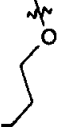
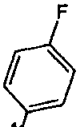
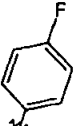
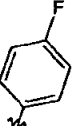
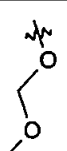
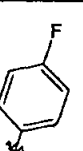
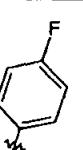
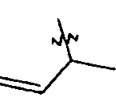
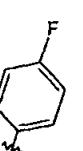
45	Cl	H			H	H	175.0-176.0	
46	Cl	H			H	H	230.0-231.0	
47	H	H	Me		H	H	144.0-145.0	
48	H	H	Me		H	H	134.0-135.0	
49	Cl	H			H	H	209.0-210.0	
50	H	H			H	H	210.0-211.0	
51	H	H	OH		H	H	266.0-267.0	
52	H	H			H	H	128.0-129.0	
53	H	H			H	H	-	346

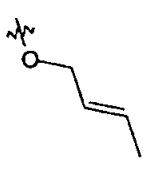
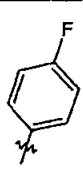
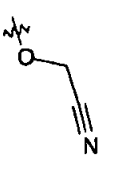
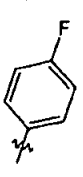
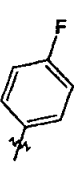
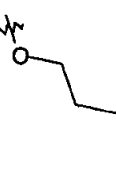
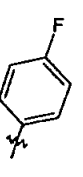
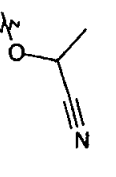
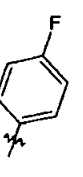
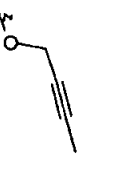
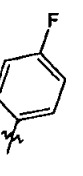
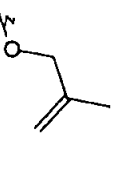
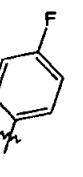
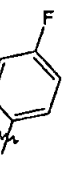
54	H	H			H	H	137.0-138.0	
55	H	H			H	H	150.0-151.0	
55	H	H			H	H	150.0-151.0	
57	H	H			H	H	173.0-174.0	
58	Me	H			H	H	168.0-169.0	
59	H	H			H	H	140.0-141.0	
60	H	H			H	H	174.0-175.0	
61	H	H			H	H	76.0-77.0	

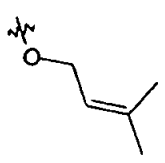
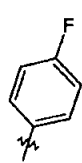
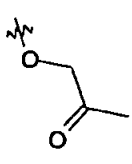
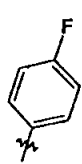
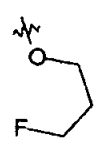
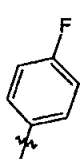
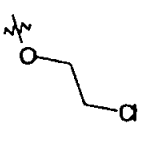
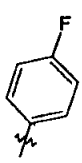
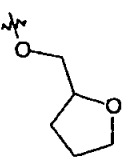
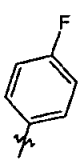
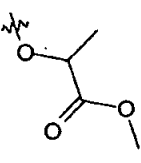
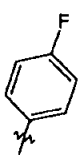
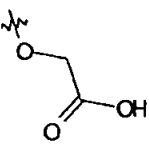
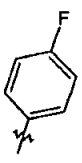
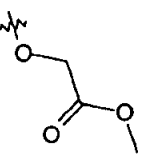
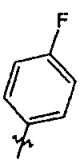
63	H	H			H	H		433
64	H	H			H	H	152.0-153.0	
66	H	H			H	H	149.0-150.0	
67	H	H	Me		H	H	136.0-137.0	
68	H	H		H	H	H	110.0-111.0	
69	H	H		H	H	H	106.0-107.0	
70	H	H		H	H	H	108.0-109.0	
71	H	H		H	H	H	119.0-120.0	
72	H	H			H	H	250.0-250.0	

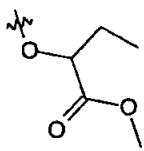
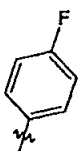
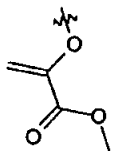
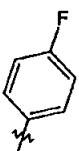
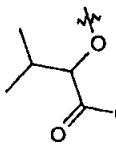
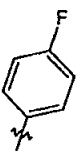
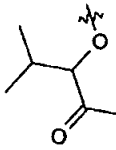
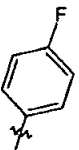
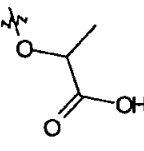
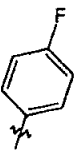
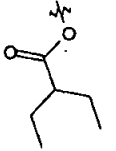
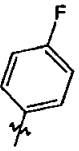
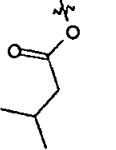
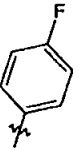
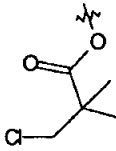
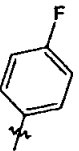
73	H	H			H	H		374
74	H	H			H	H		348
75	H	H			H	H		402
76	H	H			H	H	161.0-162.0	
77	H	H			H	H	133.0-134.0	
78	H	H			H	H	166.0-167.0	
79	H	H			H	H	205.0-206.0	
80	H	H			H	H	189.0-190.0	

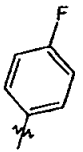
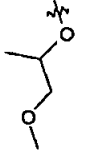
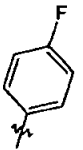
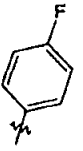
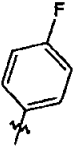
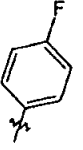
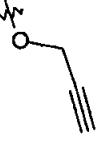
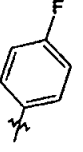
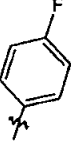
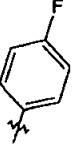
81	H	H			H	H	212.0-212.0	
82	H	H	H		H	Cl	250.0-250.0	
83	H	H			H	Cl	180.0-181.0	
84	H	H			H	Cl	197.0-198.0	
85	H	H			H	Cl	245.0-246.0	
86	H	H			H	Cl	220.0-221.0	
87	H	H			H		159.0-160.0	
88	H	H			H		197.0-198.0	

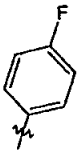
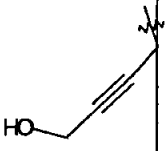
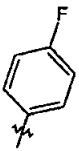
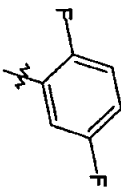
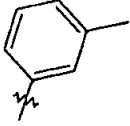
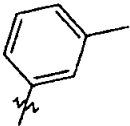
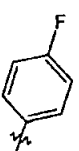
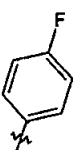
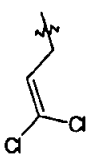
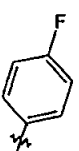
89	H	H			H	H	166.0-167.0	
90	H	H	OH		H	Me	222.0-223.0	
91	H	H			H	Me	165.0-166.0	
92	H	H			H	Me	151.0-152.0	
93	H	H			H	Me		342
94	H	H			H	Me	143.0-144.0	
95	H	H			H	Me	-	374
96	Cl	H			H	H	140.0-142.0	

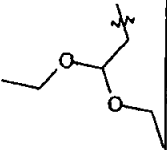
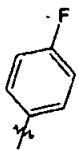
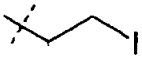
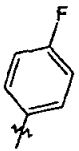
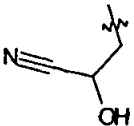
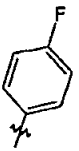
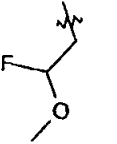
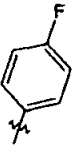
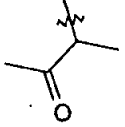
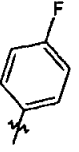
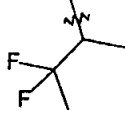
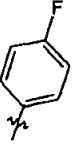
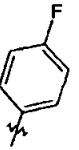
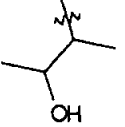
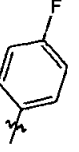
97	H	H			H	H	126.0-127.0	
98	H	H			H	H	154.0-155.0	
99	H	H			H	H	111.0-112.0	
100	H	H			H	H	107.0-108.0	
101	H	H			H	H	155.0-156.0	
102	H	H			H	H	178.0-180.0	
103	H	H			H	H	98.0-99.0	
104	H	H			H	H	163.0-164.0	

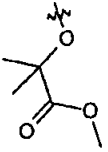
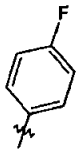
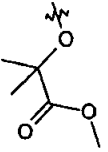
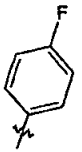
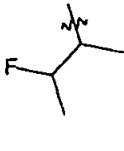
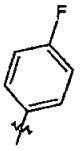
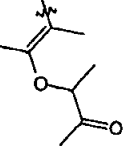
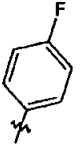
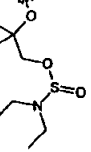
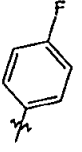
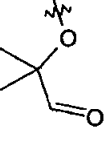
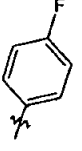
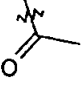
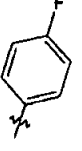
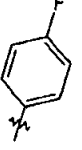
105	H	H			H	H	126.0-127.0	
106	H	H			H	H	-	362
107	H	H			H	H	93.0-94.0	
108	H	H			H	H	150.0-151.0	
109	H	H			H	H	123.0-124.0	
110	H	H			H	H	119.0-120.0	
111	H	H			H	H	192.0-193.0	
112	H	H			H	H	98.0-99.0	

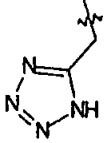
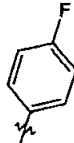
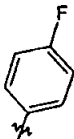
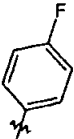
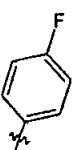
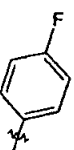
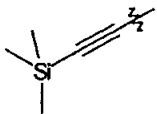
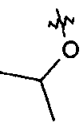
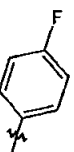
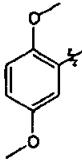
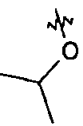
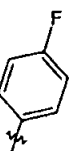
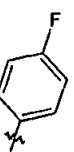
113	H	H			H	H	126.0-127.0	
114	H	H			H	H	148.0-149.0	
115	H	H			H	H	144.0-145.0	
116	H	H			H	H	188.0-189.0	
117	H	H			H	H	197.0-198.0	
118	H	H			H	H	124.0-125.0	
119	H	H			H	H	130.0-131.0	
120	H	H			H	H	146.0-147.0	

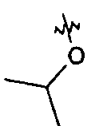
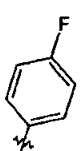
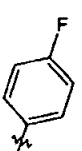
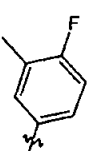
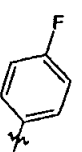
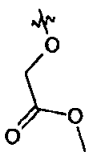
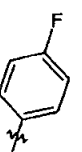
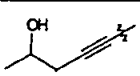
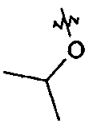
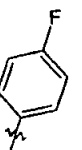
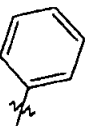
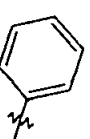
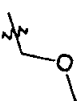
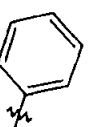
121	H	H			H	H	121.0-121.0	
122	H	H			H	H	121.0-122.0	
123	H	H			H	Me	120.0-121.0	
124	H	Me	OH		H	H	197.0-204.0	
125	H	Me			H	H	167.0-168.0	
126	H	Me			H	H	169.0-170.0	
127	H	Me			H	H	147.0-148.0	
128	H	H			H	H	147.0-148.0	

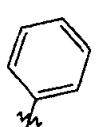
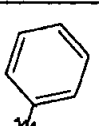
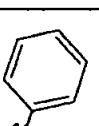
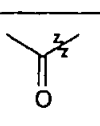
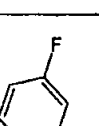
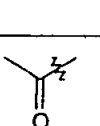
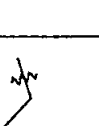
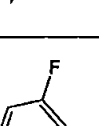
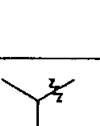
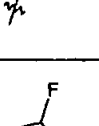
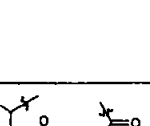
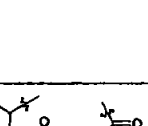
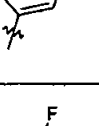
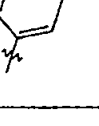
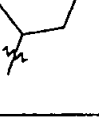
129	H	H			H	H	172.0-173.0	
130	H	H			H	H	124.0-126.0	
131	H	H	H		H	H	130.0-130.0	
132	H	H	H		H	H	250.0-260.0	
133	H	H			H	H	-	332
134	H	H			H	H	220.0-222.0	
135	H	H			H	H	239.0-240.0	
136	H	H			H	H	136.0-137.0	

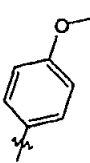
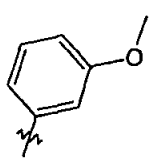
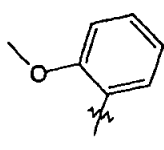
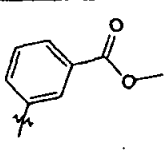
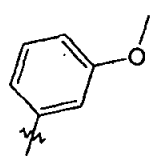
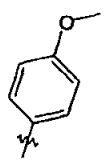
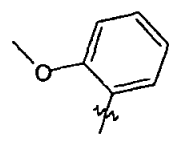
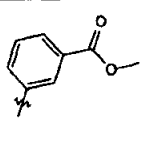
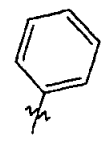
137	H	H			H	H	129.0-130.0	
138	H	H			H	H	164.0-169.0	
139	H	H			H	H	215.0-217.0	
140	H	H			H	H	184.0-185.0	
141	H	H			H	H	215.0-216.0	
142	H	H			H	H	-	382
143	H	H			H	H	-	344
144	H	H			H	H	208.0-209.0	

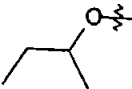
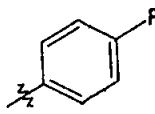
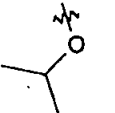
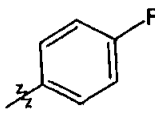
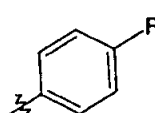
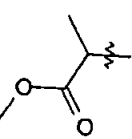
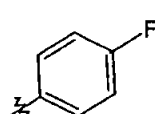
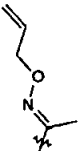
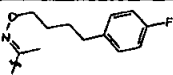
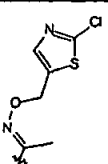
145	H	H			H	H	177.0-178.0	
145	H	H			H	H	177.0-178.0	
146	H	H			H	H		364
147	H	H			H	H	149.0-150.0	
148	H	H			H	H		497
149	H	H			H	H		376
150	Me	H			H	H	148.0-149.0	
151	H	Me	H		H	H	250.0-250.0	

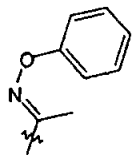
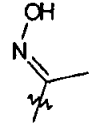
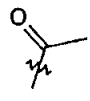
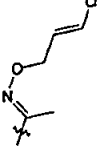
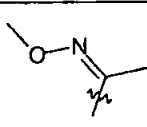
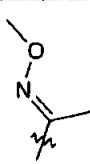
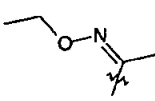
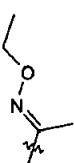
152	H	Me			H	H	225.0-230.0	
153	Br	Me	H	Br	H	H	250.0-999.0	
154	H	Me			H	H	250.0-999.0	
155	H	Me			H	H	132.0-133.0	
155	H	Me			H	H	132.0-133.0	
156	Br	H			H	H	157.0-158.0	
157		H			H	H	181.0-182.0	
158		H			H	H	147.0-148.0	
159	Br	H	H		H	H	263.0-264.0	

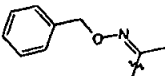
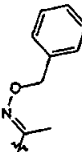
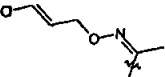
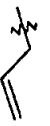
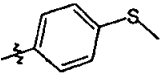
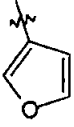
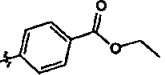
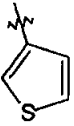
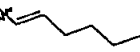
160	-CN	H			H	H	199.0-200.0	
161	-CN	H	H		H	H	265.0-266.0	
162	H	H			H	H		350
163	H	Me			H	H	212.0-213.0	
164	H	Me			H	H	133.0-134.0	
165		H			H	H	-	430
167	H	H			H	H	135.0-136.0	
168	H	H			H	H	151.0-152.0	
169	H	H			H	H	145.0-147.0	

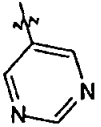
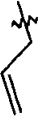
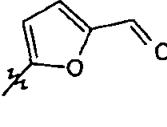
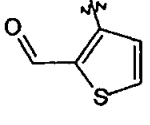
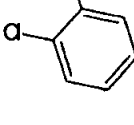
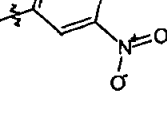
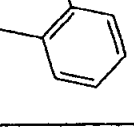
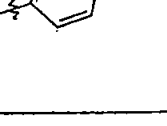
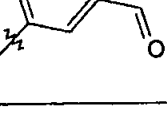
170	H	H			H	H	205.0-206.0	
171	H	H			H	H	174.0-175.0	
172	H	H			H	H	180.0-181.0	
173		H			H	H	185.0-186.0	
174		H			H	H	190.0-191.0	
175		H	H		H	H	217.0-219.0	
176		H			H	H		444
293	H	H			H	H	123.0-124.0	
294	H	H	H		H	H	258.0-259.0	

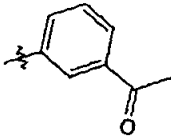
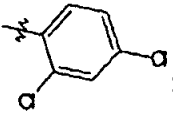
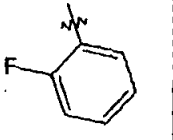
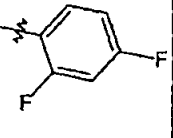
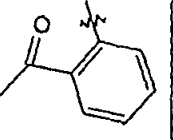
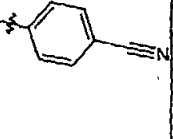
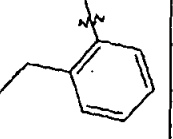
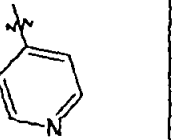
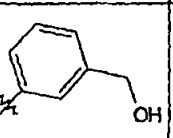
295	H	H			H	H		342
296	H	H	H		H	H	236.0-237.0	
297	H	H	H		H	H	296.0-299.0	
298	H	H	H		H	H	215.0-220.0	
299	H	H			H	H		340
300	H	H			H	H	174.0-175.0	
301	H	H			H	H		340
302	H	H			H	H	134.0-135.0	
303	H	H			H	H	171.0-172.0	

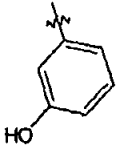
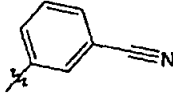
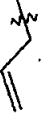
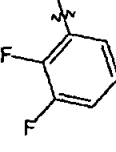
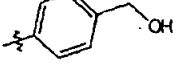
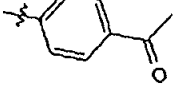
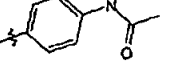
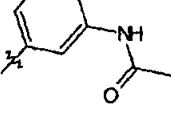
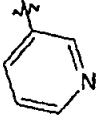
304	H	H			H	H		342
305	H	H	H		H	H	169.0-172.0	
306	H	H			H	H	124.0-125.0	
307	H	H			H	H	139.0-140.0	
308	H	H			H	H	166.0-168.0	
309	H	H			H	H	166.0-167.0	
310	H	H			H	H	-	333
311	H	H			H	H	105.0-110.0	
312	H	H			H	H	141.0-144.0	

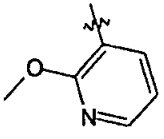
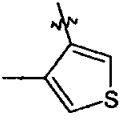
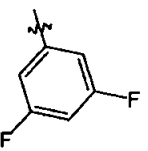
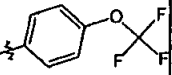
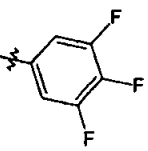
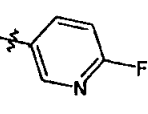
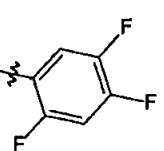
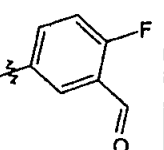
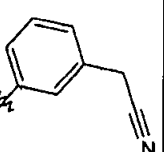
313	H	H			H	H	148.0-151.0	
314	H	H			H	H		293
315	H	H		Br	H	H	148-150	
316	H	H			H	H	-	278
317	H	H			H	H	-	367
318	H	H			H	H	-	307
319	H	H			H	H	-	307
320	H	H			H	H	-	379
321	H	H			H	H	-	379

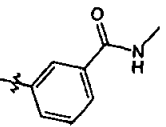
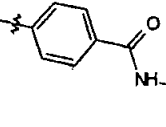
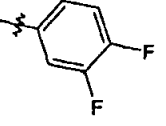
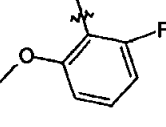
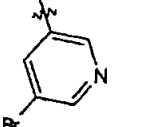
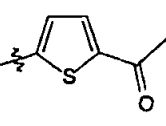
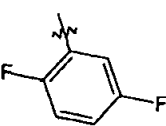
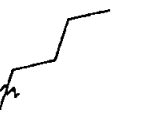
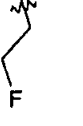
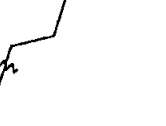
322	H	H			H	H	-	384
323	H	H			H	H	-	384
324	H	H			H	H	-	367
325	H	H			H	H	-	358
326	H	H		Me	H	H	-	250
327	H	H			H	H	-	302
328	H	H			H	H	-	384
329	H	H			H	H	-	318
330	H	H			H	H	-	318

331	H	H			H	H	-	314
332	H	H			H	H	-	330
333	H	H			H	H	-	346
334	H	H			H	H	-	304
335	H	H			H	H	-	346
336	H	H			H	H	-	357
337	H	H			H	H	-	362
338	H	H			H	H	-	340
339	H	H			H	H	-	340

340	H	H			H	H	-	354
341	H	H			H	H	-	380
342	H	H			H	H	-	330
343	H	H			H	H	-	348
344	H	H			H	H	-	354
345	H	H			H	H	-	337
346	H	H			H	H	-	340
347	H	H			H	H	-	313
348	H	H			H	H	-	342

349	H	H			H	H	-	276
350	H	H			H	H	-	328
351	H	H			H	H	-	337
352	H	H			H	H	-	348
353	H	H			H	H	-	342
354	H	H			H	H	-	354
355	H	H			H	H	-	369
356	H	H			H	H	-	369
357	H	H			H	H	-	313

358	H	H			H	H	-	343
359	H	H			H	H	-	332
360	H	H			H	H	-	396
361	H	H			H	H	-	396
362	H	H			H	H	-	366
363	H	H			H	H	-	331
364	H	H			H	H	-	366
365	H	H			H	H	-	358
366	H	H			H	H	-	351

367	H	H			H	H	-	369
368	H	H			H	H	-	369
369	H	H			H	H	-	348
370	H	H			H	H	-	360
371	H	H			H	H	-	391
372	H	H			H	H	-	360
373	H	H			H	H	-	348
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375	H	H			H	H	-	292
376	H	H			H	H	260.0-999.0	

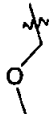
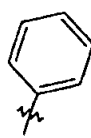
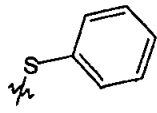
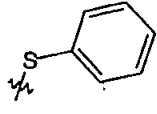
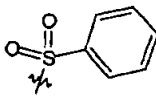
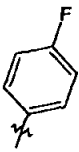
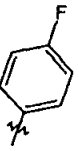
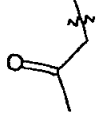
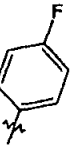
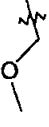
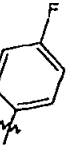
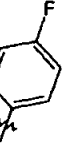
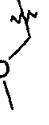
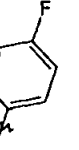
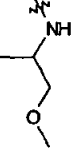
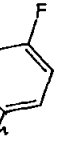
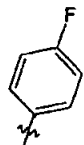
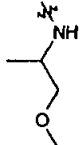
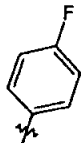
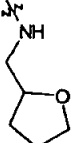
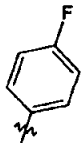
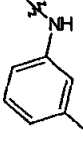
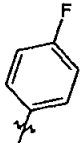
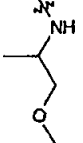
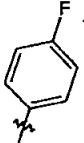
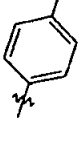
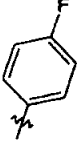
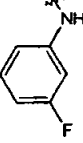
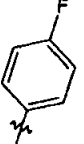
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378	Me	H	H		H	H		286
379	H	H	H		H	H	289-291	
380	H	H			H	H	>260	
381	H	H			H	H		376
382	H	H			H	H		328

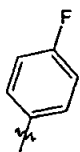
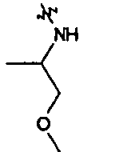
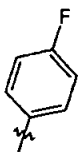
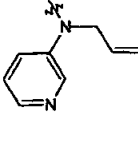
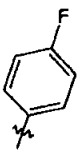
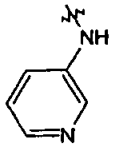
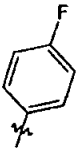
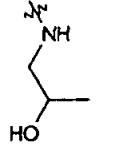
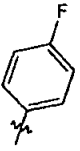
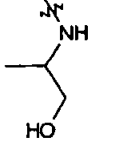
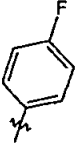
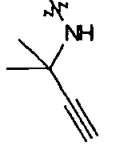
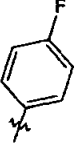
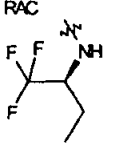
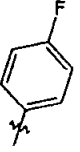
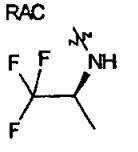
Table 1a – HPLC Retention Times of Certain Compounds of Table 1

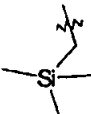
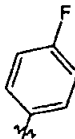
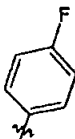
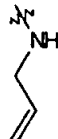
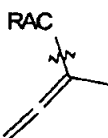
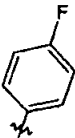
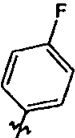
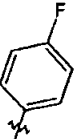
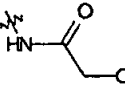
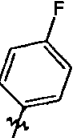
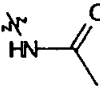
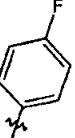
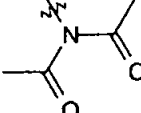
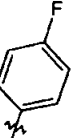
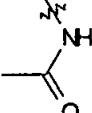
Compound Number	Retention Time (Min)	Method
325	0.93	B
326	0.18	B
327	0.39	B
328	1.08	B
329	0.46	B
330	1.21	B
331	0.28	B
332	0.55	B
333	0.48	B
334	1.01	B
335	0.69	B
336	0.94	B
337	0.58	B
338	0.58	B
339	0.51	B
340	0.6	B
341	1.04	B
342	0.52	B
343	0.73	B
344	0.44	B
345	0.8	B
346	0.84	B
347	0.31	B
348	0.29	B
349	0.26	B
350	0.23	A
351	0.46	A
352	0.34	A
353	0.16	A
354	0.29	A
355	0.17	A
356	0.17	A
357	0.18	A
358	0.17	A
359	0.26	A
360	0.76	A
361	0.98	A
362	0.94	A
363	0.22	A
364	0.57	A
365	0.3	A
366	0.22	A
367	0.17	A
368	0.19	A
369	0.65	A

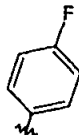
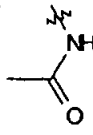
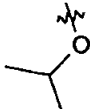
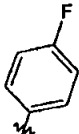
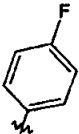
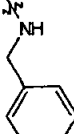
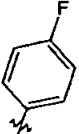
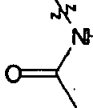
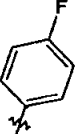
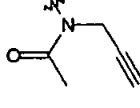
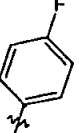
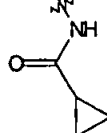
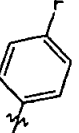
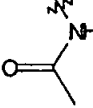
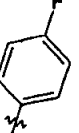
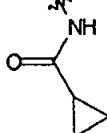
TABLE 2

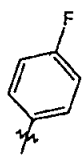
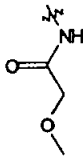
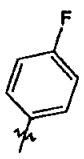
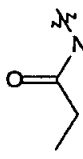
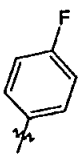
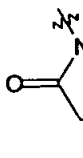
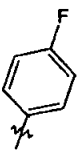
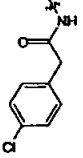
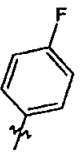
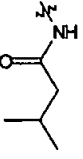
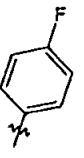
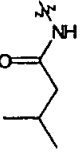
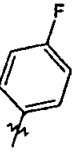
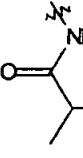
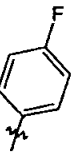
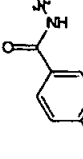
Compound Number	R1	R2	R3	R4	R6	R7	R8	Melting Point °	Mass (ES+)
177	H	H	H		Cl	H	H	260-260	
178	H	H			Cl	H	H	175-176	
179	H	H			Cl	H	H	190-191	
180	H	H			Cl	H	H	166-167	
181	H	H			Cl	H	H	164-165	
182	H	H				H	H		421
183	H	H			Cl	H	H	160-161	

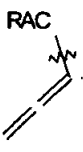
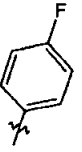
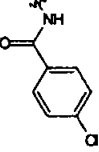
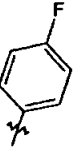
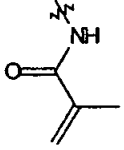
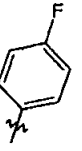
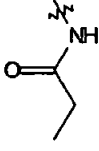
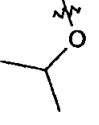
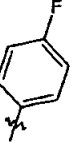
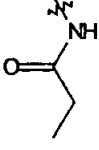
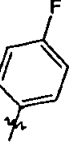
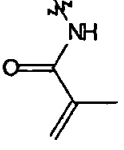
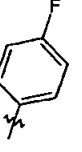
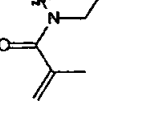
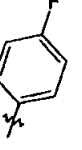
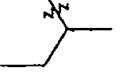
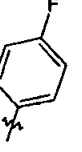
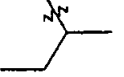
184	H	H				H	H		423
185	H	H				H	H		415
186	H	H				H	H	226-227	
187	H	H				H	H		399
188	Cl	H	H		Cl	H	H	210-211	
189	Cl	H	RAC 		Cl	H	H	184-185	
190	Cl	H				H	H	168-169	
191	H	H			Cl	H	H	143-144	

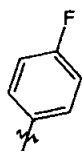
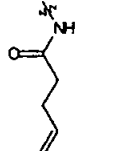
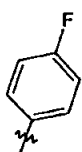
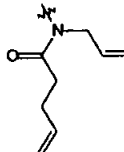
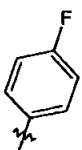
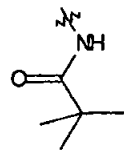
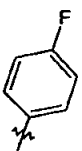
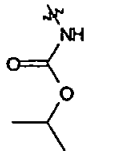
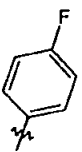
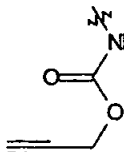
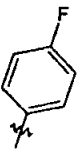
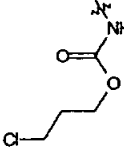
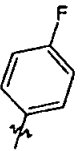
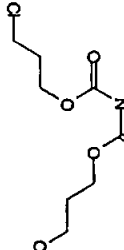
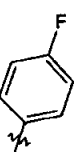
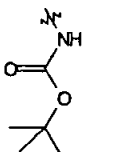
192	Cl	H				H	H		451/ 453
193	Cl	H				H	H		396/ 398
194	Cl	H				H	H	140- 142	
195	Cl	H				H	H	86-90	
196	Cl	H				H	H	-	437/ 439
197	Cl	H				H	H	-	445
198	H	H				H	H	-	461
199	H	H				H	H	89-90	

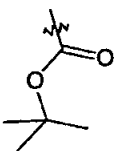
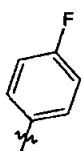
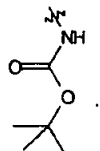
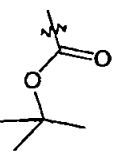
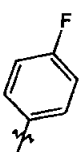
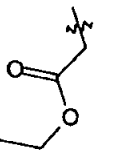
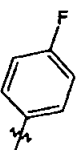
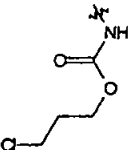
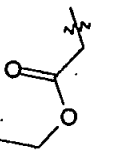
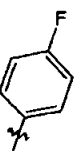
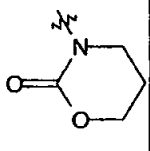
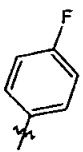
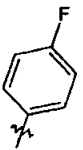
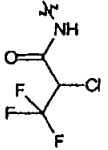
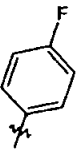
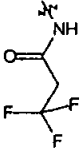
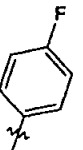
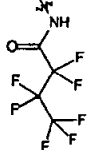
200	H	H			Cl	H	H	89-90	
201	H	H				H	H	150-151	
202	Cl	H			Cl	H	H	146-147	
203	H	H	H		NH ₂	H	H	146-147	
204	H	H	H			H	H	250-250	
205	H	H				H	H	142-143	
206	H	H				H	H	140-141	
207	H	H	H			H	H	210-212	

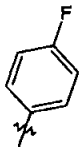
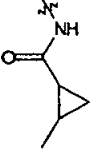
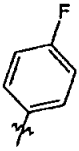
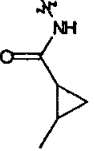
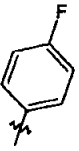
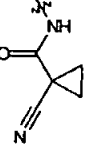
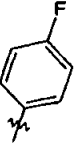
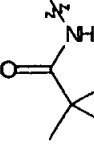
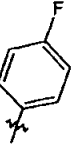
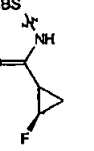
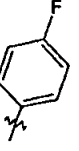
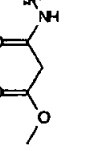
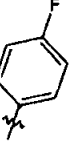
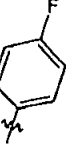
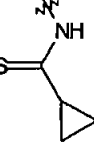
208	H	H				H	H	200-201	
209	Me	H			Cl	H	H	149-150	
210	Me	H	H			H	H	230-231	
211	H	H				H	H	155-156	
212	H	H				H	H	251-252	
213	H	H	H			H	H	244-245	
214	H	H				H	H	-	387
215	H	H				H	H	260-260	

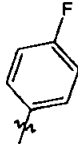
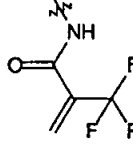
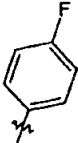
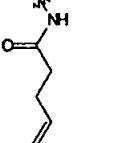
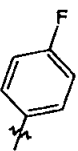
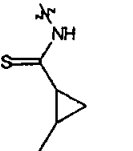
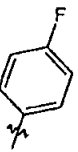
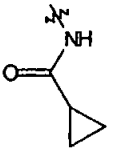
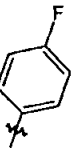
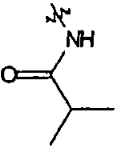
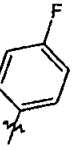
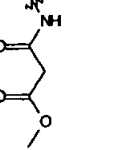
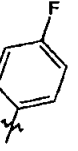
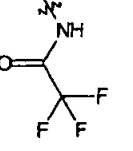
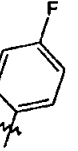
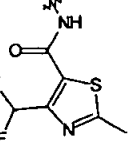
216	H	H	H			H	H	250-251	
217	H	H	H			H	H	198-199	
218	H	H				H	H	195-196	
219	H	H	H			H	H	149-150	
220	H	H	H			H	H	215-216	
221	H	H				H	H	250-250	
222	H	H	H			H	H	250-250	
223	H	H	H			H	H	208-209	

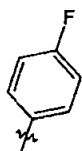
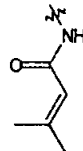
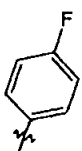
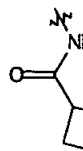
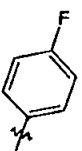
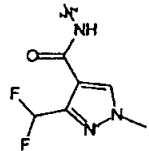
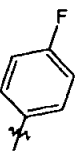
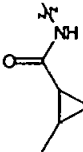
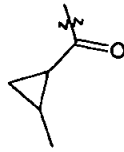
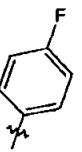
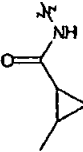
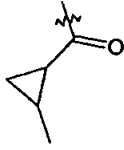
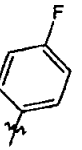
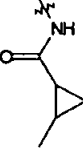
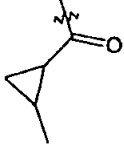
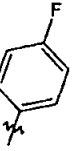
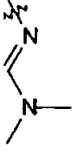
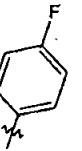
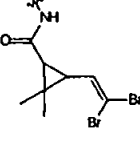
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227	Me	H				H	H	207-208	
228	H	H				H	H	233-234	
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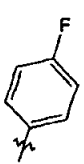
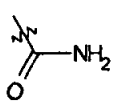
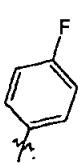
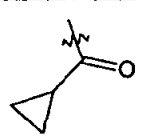
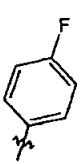
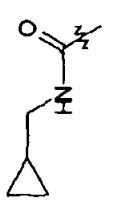
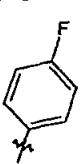
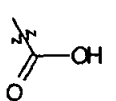
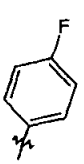
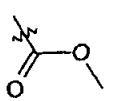
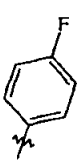
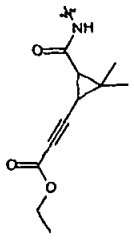
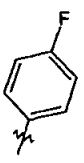
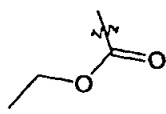
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233	H	H				H	H		467
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235	H	H	H			H	H		391
236	H	H	H			H	H	>250	
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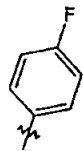
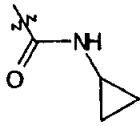
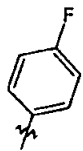
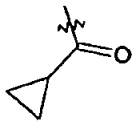
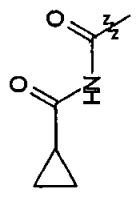
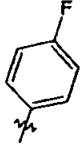
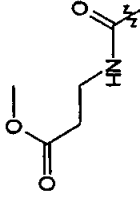
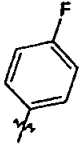
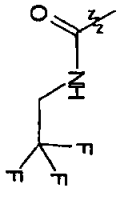
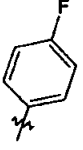
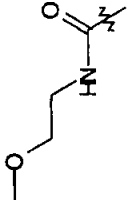
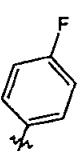
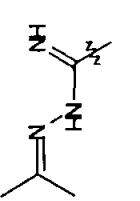
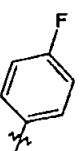
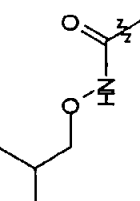
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242	H	H				H	H	181-182	
243	H	H				H	H	250-250	
244	Me	H	H		NH ₂	H	H		319
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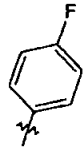
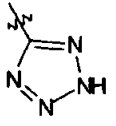
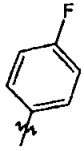
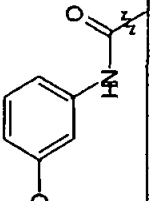
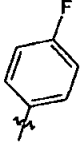
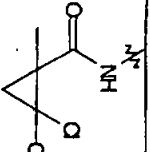
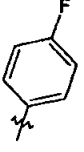
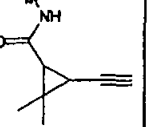
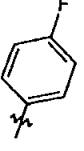
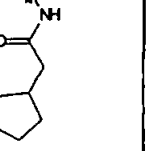
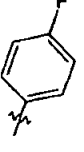
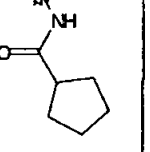
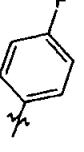
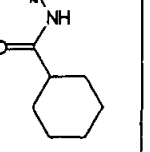
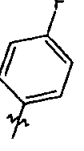
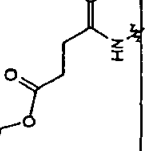
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252	H	H	H			H	H	139	
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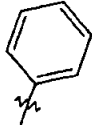
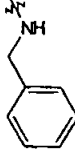
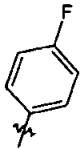
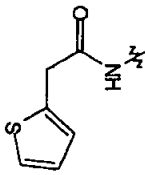
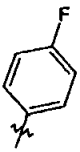
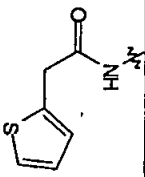
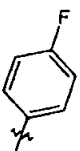
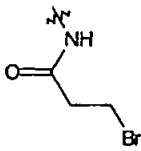
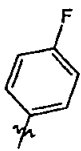
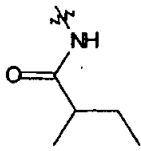
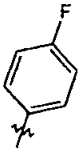
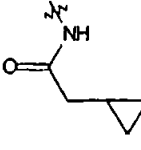
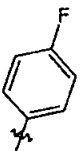
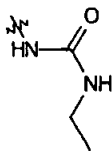
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258	H	H	H			H	H	-	403
259	Me	H	H			H	H	-	387
260	Me	H	H			H	H	-	389
261	Me	H	H			H	H	221-222	
262	H	H	H			H	H	253-254	
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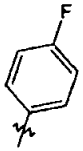
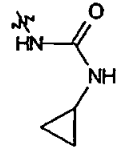
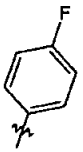
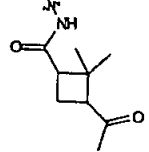
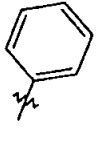
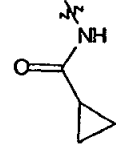
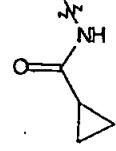
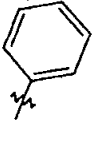
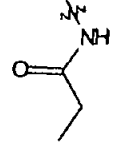
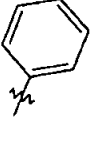
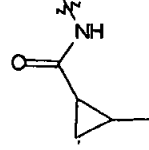
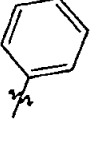
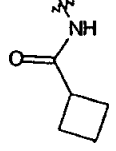
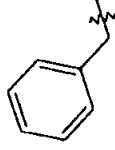
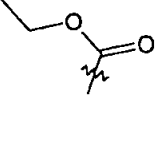
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265	H	H	H			H	H	121-122	
266	H	H	H			H	H	227-230	
267	Me	H	H			H	H	>250	
268	Me	H				H	H	>250	
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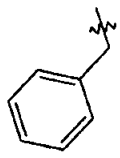
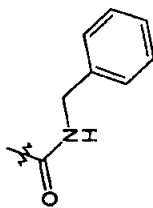
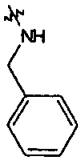
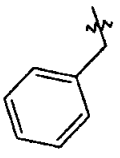
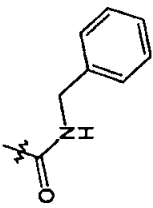
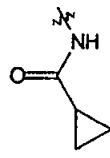
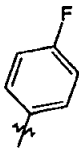
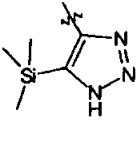
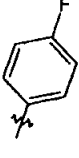
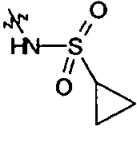
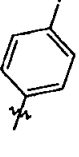
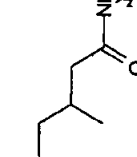
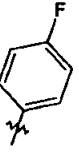
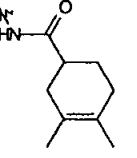
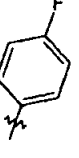
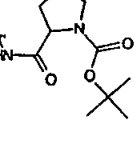
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272	H	H				H	H	123-125	
273	H	H	H			H	H	>260	
274	H	H	H			H	H	242-243	
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383	H	H	H			H	H	175-177	
384	H	H				H	H	240-244	

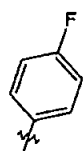
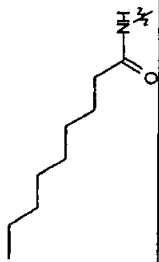
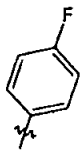
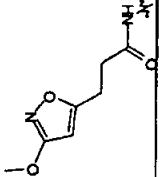
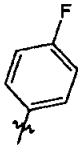
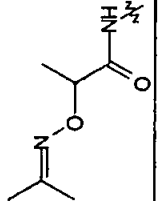
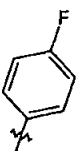
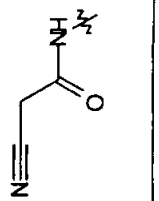
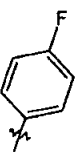
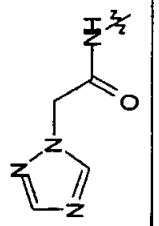
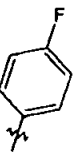
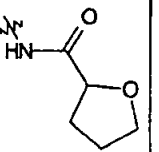
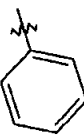
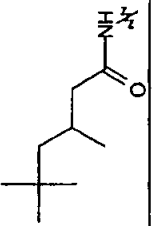
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386	H	H					H	H	-	401
387	H	H	H			H	H	247-250		
388	H	H	H			H	H	184-191		
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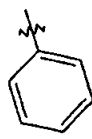
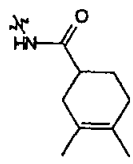
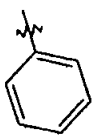
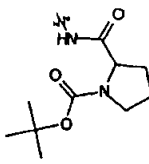
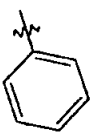
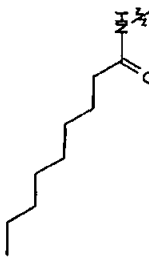
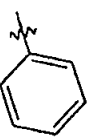
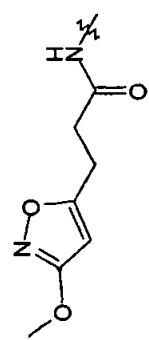
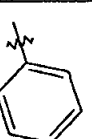
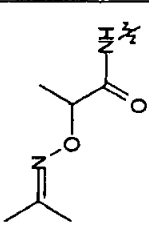
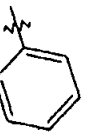
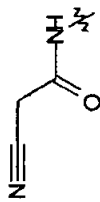
392	H	H	H			H	H	230-236	
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394	H	H	H			H	H	>250	
395	H	H	H			H	H	>250	
396	H	H	H			H	H	>260	
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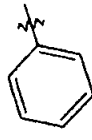
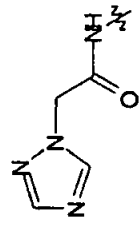
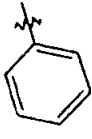
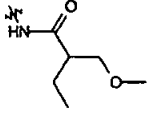
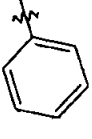
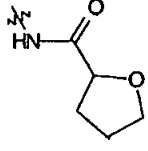
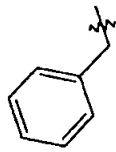
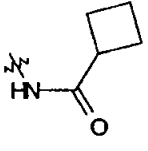
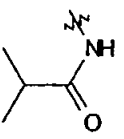
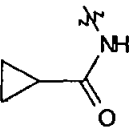
400	H	H	H			H	H	>250	
401	H	H	H			H	H	>250	
401	H	H	H			H	H	>250	
402	H	H	H		Cl	H	H	233-234	
403	H	H	H			H	H	168-169	
404	H	H	H			H	H	242-243	
405	H	H	H			H	H	248-250	
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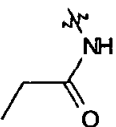
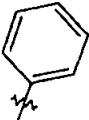
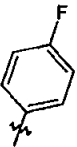
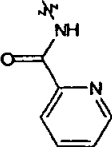
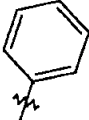
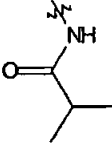
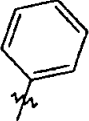
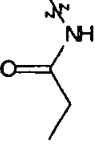
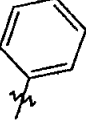
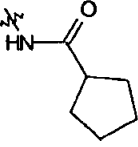
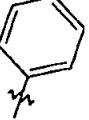
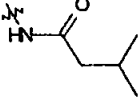
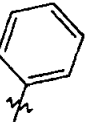
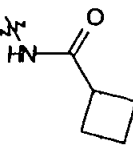
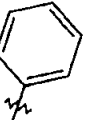
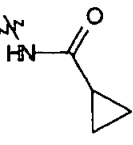
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408	H	H	H			H	H	85-88	
409	H	H	H			H	H	73-76	
410	H	H	H			H	H	94-95	
411	H	H	H			H	H	>250	
412	H	H	H			H	H	259-260	
413	H	H	H			H	H	239-240	
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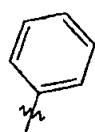
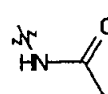
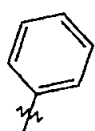
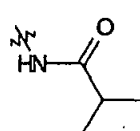
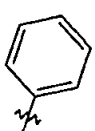
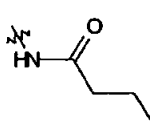
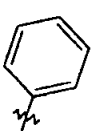
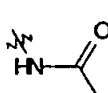
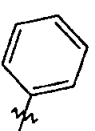
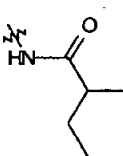
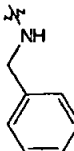
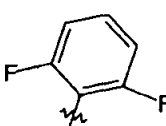
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416	H	H				H	H	201-202	
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418	H	H	H			H	H	237-239	
419	H	H	H			H	H	-	445.2
420	H	H	H			H	H	283-285	
421	H	H	H			H	H	-	502

422	H	H	H			H	H	-	445
423	H	H	H			H	H	-	458
424	H	H	H			H	H	-	432
425	H	H	H			H	H	-	372
426	H	H	H			H	H	-	414
427	H	H	H			H	H	-	403
428	H	H	H			H	H	-	427

429	H	H	H			H	H	-	423
430	H	H	H			H	H	-	484
431	H	H	H			H	H	-	427
432	H	H	H			H	H	-	440
433	H	H	H			H	H	-	414
434	H	H	H			H	H	-	354

435	H	H	H			H	H	-	396
436	H	H	H			H	H	-	401
437	H	H	H			H	H	-	385
438	H	H			F	H	H	-	360
439	H	H	H		NH ₂	H	H	235-240	
440	H	H	H			H	H	-	349
441	H	H	H		F	H	H	235-240	
442	H	H	H			H	H	102-104	
443	H	H	H			H	H	158-160	

444	H	H	H			H	H	102-104	
445	Me	H	H		NH ₂	H	H	149-151	
446	H	H	H			H	H	149-152	
447	Me	H	H			H	H	>260	
448	Me	H	H			H	H	260-999	
449	Me	H	H			H	H	206-207	
450	Me	H	H			H	H	260-999	
451	Me	H	H			H	H	152-153	
452	Me	H	H			H	H	182-183	

453	H	H	H			H	H	168-169	
454	H	H	H			H	H	168-169	
455	H	H	H			H	H	-	357
456	Me	H	H			H	H	-	343
457	H	H	H			H	H	-	371
458	H	H				H	H	178-180	
459	H	H			Cl	H	H	252-253	
460	H	H	H		NH ₂	H	H	>260	323

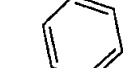
461	H	H	H		NH ₂	H	H	-	410
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Table 2a - HPLC Retention Times of Certain Compounds of Table 2

Compound Number	Retention Time (Min)	Method
419	1.76	A
421	1.49	A
422	1.8	A
423	1.36	A
424	1.45	A
425	1.22	A
426	1.15	A
427	1.33	A
428	1.72	A
429	1.65	A
430	1.46	A
431	1.77	A
432	1.33	A
433	1.41	A
434	1.2	A
435	1.08	A
436	1.4	A
437	1.3	A

Method: see under “Examples” for details of Method A and Method B

TABLE 3

Compound number	R1	R2	R3	R4	R6	R7	R8	Melting point (°C)	Mass Spectrum (ES+)
276								255-260	
277								185-187	
278								122-124	
279								-	317
280								137-138	
281								-	422
282								255-255	
283								-	348

284								235-236	
285								188-189	
286								-	466
287								214-215	
288								221-222	
289								235-236	
290								236-237	
291								245-246	
292								240-241	

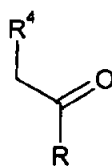
The present invention also provides a compound of formula (I) as defined above with the provisos that (i) when X^1 is CH, X^2 is CR^5 and R^5 and R^6 are both H, R^4 is not 4-fluorophenyl and (ii) the compound of formula (I) is not:

- 3-phenyl-2-pyridin-4-yl-1H-pyrrolo[3,2-b]pyridine
 3-(3-chloro-4-fluoro-phenyl)-2-pyridin-4-yl-1H-pyrrolo[3,2-b]pyridine
 3-(3-chloro-phenyl)-2-pyridin-4-yl-1H-pyrrolo[3,2-b]pyridine
 5 3-(3-trifluoro-phenyl)-2-pyridin-4-yl-1H-pyrrolo[3,2-b]pyridine
 3-(3-methoxy-phenyl)-2-pyridin-4-yl-1H-pyrrolo[3,2-b]pyridine
 3-(2-methylphenyl)-2-pyridin-4-yl-1H-pyrrolo[3,2-b]pyridine
 3-(2-methoxyphenyl)-2-pyridin-4-yl-1H-pyrrolo[3,2-b]pyridine
 1-methyl-2-pyridin-4-yl-3-(3-trifluoromethyl-phenyl)-1H-pyrrolo[3,2-b]pyridine
 10 1-methyl-3-(3-chloro-4-fluoro-phenyl)-2-pyridin-4-yl-1H-pyrrolo[3,2-b]pyridine
 3-(4-fluorophenyl)-2-(2-(2-hydroxyethyl-amino)-pyridin-4-yl)-1H-pyrrolo[3,2-b]pyridine,
 3-(4-fluorophenyl)-2-(2-[HO(CH₂)₂O(CH₂)₂NH]-pyridin-4-yl)-1H-pyrrolo[3,2-b]pyridine,
 3-(4-fluorophenyl)-2-(2-(2-methylamino-ethylamino)-pyridin-4-yl)-1H-pyrrolo[3,2-
 b]pyridine,
 15 3-(4-fluorophenyl)-2-(2-(3-methoxy-propyl-amino)-pyridin-4-yl)-1H-pyrrolo[3,2-b]pyridine,
 3-(4-fluorophenyl)-2-(2-*n*-propylamino-pyridin-4-yl)-1H-pyrrolo[3,2-b]pyridine,
 3-(4-fluorophenyl)-2-(2-(3-hydroxy-propyl-amino)-pyridin-4-yl)-1H-pyrrolo[3,2-b]pyridine,
 3-(4-fluorophenyl)-2-(2-methylamino-pyridin-4-yl)-1H-pyrrolo[3,2-b]pyridine or
 3-(4-fluorophenyl)-2-(2-acetyl-amino pyridin-4-yl)-1H-pyrrolo[3,2-b]pyridine.

20

In a further aspect, the invention relates to a process for the preparation of a compound of formula (I) as claimed in claim 1, comprising:

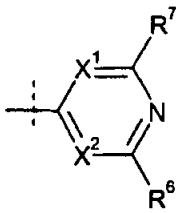
- a) reacting a ketone of formula (D)



25

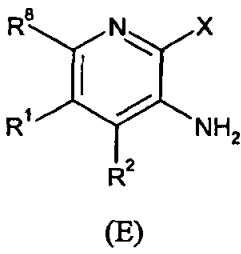
(D)

wherein R⁴ is as defined in claim 1, and R is a group of formula



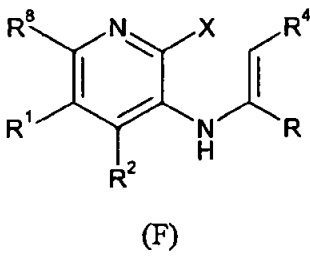
wherein X¹, X², R⁶ and R⁷ are as defined in claim 1, with an aminopyridine of formula (E)

5



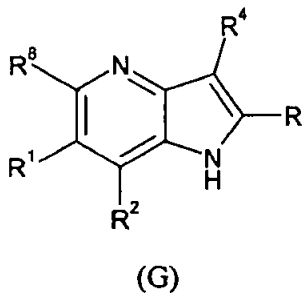
wherein R¹, R² and R⁸ are as defined in claim 1, and X is a halogen, to give an enamine of formula (F),

10



cyclising to give an azaindole of formula (G),

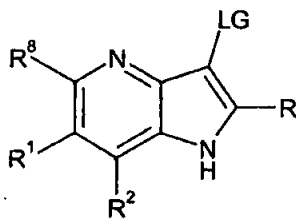
15



and optionally alkylating to give a compound of formula (I) as defined in claim 1; or

20

b) reacting an azaindole of formula (K)

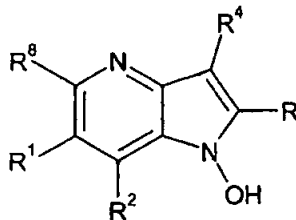


(K)

5 wherein R¹, R² and R⁸ are as defined in claim 1, R is as defined above, and LG is a leaving group with a compound of formula R⁴-B(OH)₂ wherein R⁴ is as defined in claim 1, to give a compound of formula (G) as defined above, and optionally alkylating to give a compound of formula (I) as defined in claim 1;

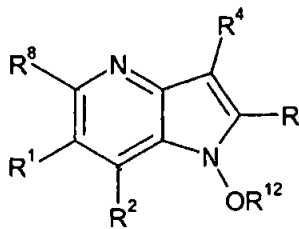
10 c) reacting a compound of formula (G) above with a compound of formula R³-LG wherein LG is a leaving group to give a compound of formula (I) as defined in claim 1;

d) reacting a compound of formula (S)



(S)

15 wherein R¹, R², R⁴, and R⁸ are defined in claim 1, and R is as defined above, with a compound of formula R¹²-LG wherein R¹² is as defined in claim 1 and LG is a leaving group, to give a compound of formula (T)



(T)

20 wherein R¹, R², R⁴, R⁸, and R¹² are defined in claim 1, and R is as defined above, or

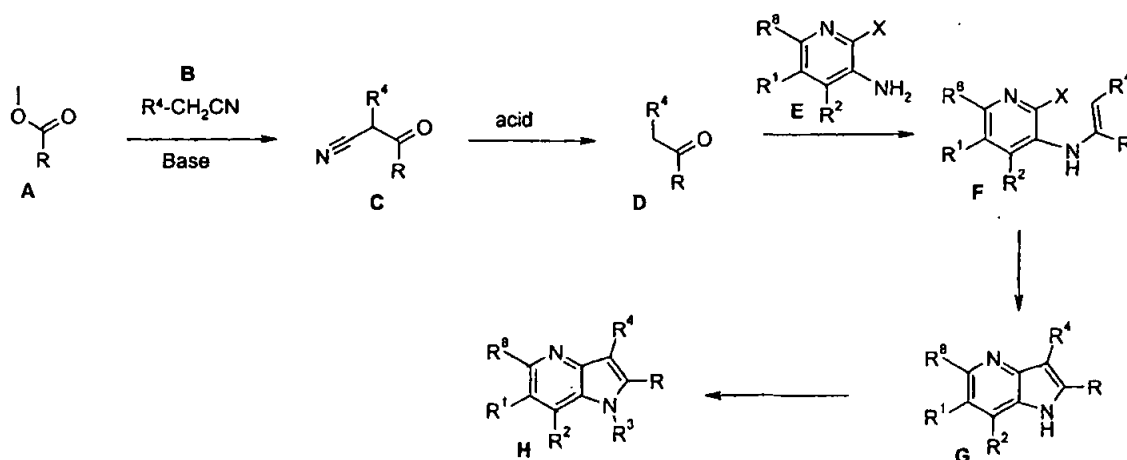
e) converting a compound of formula (I) as defined in claim 1 to a salt of N-oxide thereof. Obviously, the skilled person will appreciate that the compounds of the invention can be made by various other methods.

5 Compounds of the invention and for use in the methods of the invention can be made, for example, by following the reaction scheme and the methods detailed below. The starting materials used for the preparation of the compounds of the invention may be purchased from usual commercial suppliers. The starting materials as well as the intermediates may be purified before use in the next step by state of the art methodologies such as
10 chromatography, crystallization, distillation and filtration.

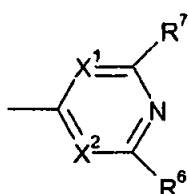
The schemes listed below to exemplify the possible preparation methods for the compounds of general formula I are suggestions that might be modified by those skilled in the art to reach the disclosed compounds. Many of the steps detailed below can be found in 15 *J. Med. Chem.* **2003**, 46, 4702-4713.

Compounds of general formula (I) previously described and listed in the tables above may be prepared following the procedure described in scheme 1:

Scheme 1



wherein R is:



and X¹ and X², R¹ to R⁸ are as defined above and X is halogen.

5 Compounds of formula **C** can be obtained by reaction between an ester of formula **A** and an acetonitrile derivative of formula **B** in the presence of a base such as sodium methoxide or potassium t-butoxide in suitable alcoholic solvent. (see *J. Med. Chem.* **2003**, 46, 4702-4713).

10 Compounds of formula **A** are generally commercially available but might be prepared by state of the art procedures from the corresponding acid, nitrile, or methyl derivative by esterification, hydrolysis or oxidation reactions, respectively.

 Compounds of formula **B**, such as phenyl acetonitrile, 4-fluorophenyl acetonitrile or
15 3-methylphenyl acetonitrile and related compounds are commercially available.

 Acidic treatment of compounds of formula **C** in suitable aqueous acid such as hydrobromic acid results in hydrolysis and decarboxylation leading to compound of formula **D**.

20 Further condensation of **D** with a 3-amino pyridine of formula **E** results in a formation of an enamine of formula **F** where X is a halogen such as bromo, chloro or iodo. The reaction may be performed in an aromatic solvent such as benzene, toluene or xylene in the presence of a catalytic amount of acid such as p-toluene sulfonic acid.

25 Alternatively, compound **F** may exist as its enamine-imine equilibrium; both compounds might be separated under state of the art purification condition such as chromatography.

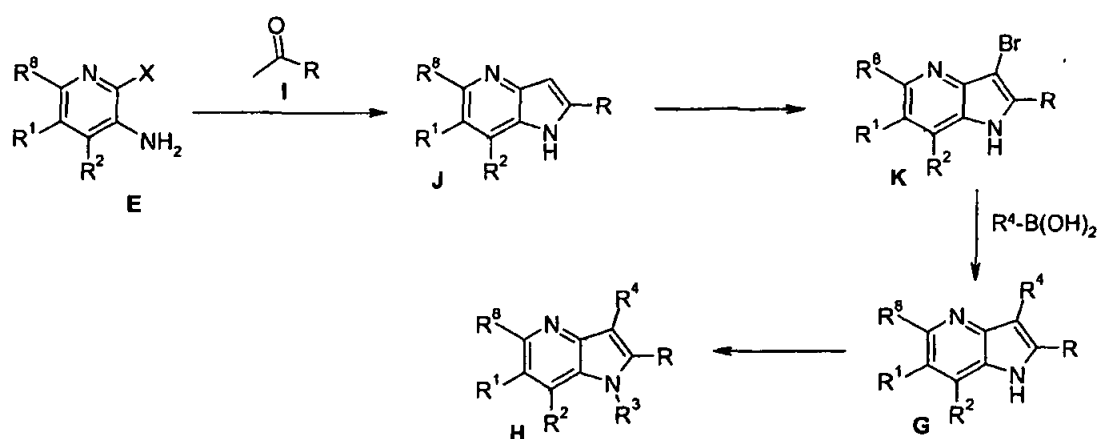
Pyridines of formula **E**, such as 2-chloro-3-amino pyridine, 2-chloro-5-methyl pyridine or 2,5-dichloro-3-amino pyridine, may be commercially available or may be prepared by known methodologies. For example, by reduction of the corresponding nitro derivative (see *J. Chem. Soc.*, 1952, 2042). As a further example, (2,6-Dichloro-3-nitro-
5 pyridin-4-yl)-acetic acid methyl ester can be prepared by vicarious nucleophilic substitution on the parent 2,6-Dichloro-3-nitro-pyridine (see *Liebigs Ann.* 1997, 1805-1816) followed by reduction of the nitro group.

The azaindole (1H-Pyrrolo[3,2-b]pyridine) of formula **G** is obtained by cyclisation of
10 the enamine **F** in the presence of a tertiary amine base such as DABCO and a palladium catalyst such as palladium acetate (II) or dichlorobis(triphenylphosphine) palladium (II) in an inert solvent such as dimethylformamide or dimethylacetamide (see *J. Org. Chem.* 1997, 62, 2676-2677).

15 Compounds of formula **H**, where R^3 is not hydrogen may be obtained by alkylation or acylation of compounds of formula **G**. This alkylation can be realized with an alkylating agent of formula R^3-Y (where Y is a leaving group such as halogen, triflate, mesylate and the like) in the presence of a base such as sodium hydride or lithium hexamethyldisilazane in an aprotic solvent such as dimethylformamide or tetrahydrofuran. Compounds of formula **G**
20 may also be obtained by acylation in the presence of an acylating agent such as R^3COX (where X is a halogen) in the presence of a base such as sodium hydride or lithium hexamethyldisilazane in an aprotic solvent such as dimethylformamide or tetrahydrofuran.

Scheme 2 describes an alternative method for the preparation of compound of
25 formula (I):

Scheme 2



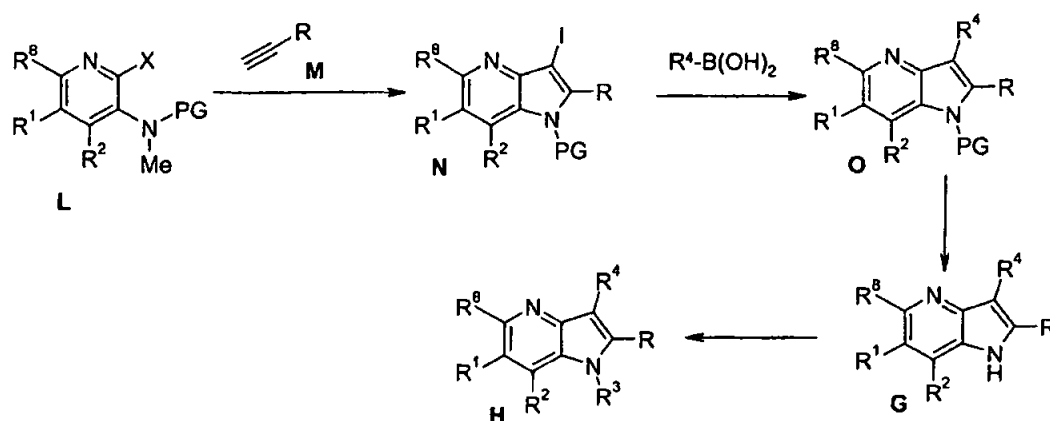
Compounds of formula **J** may be obtained in a single step condensation-cyclisation of a compound of formula **E** and compound of formula **I**. The reaction is carried out in the presence of a base such as potassium phosphate or potassium carbonate, a dehydrating agent such as magnesium or sodium sulphate and a palladium catalyst preferably (di-*t*-butylphosphino) palladium in an inert solvent such as dimethylformamide or dimethylacetamide under an inert atmosphere in a closed vessel. (see: *Angew. Chem. Int. Ed. Eng.* 2004, 4526-4528).

Compounds of formula **J** can regioselectively be brominated in the presence of bromine or *N*-bromosuccinimide in a solvent such as carbon tetrachloride or DMF to give compound of formula **K** (see Synthesis 1982, 1096). Compounds of formula **G** can be obtained by further treatment of **K** in the presence of a boronic acid of formula $R^4B(OH)_2$ (where R^4 is as previously defined) under Suzuki cross coupling conditions (see: *Chem. Comm.*, 1979, 866) under thermal or microwave conditions.

Compounds of type **H** may then be obtained following the procedure described above for scheme 1.

Scheme 3 describes a further alternative method for the preparation of compound of formula (**I**).

Scheme 3



Compounds of formula **L** (where PG is a protective group such as methyl, acetate, benzyl, mesylate, tosylate and the like) may be obtained by sequential protection of the corresponding amino pyridine **E** (see "Protective groups in organic chemistry" Greene and Wuts 4th edition, Wiley Interscience). Compounds of formula **L** can be coupled with compounds of formula **M** under Sonogashira coupling conditions (see: *Synthesis*, **1980** (8) 627-630) and subsequently treated with iodine in an inert solvent such as dichloromethane to undergo direct iodo cyclisation and formation of **N** (see *Org. Letters* **2004**, 6(6)1037-1040).

10

Compounds of formula **M** can be prepared from the parent halogenated compound by reaction under Sonogashira conditions (see: *Synthesis*, **1980** (8) 627-630) with trimethylsilyl acetylene, followed by deprotection under basic conditions of the trimethyl silyl group. Compounds of formula **M** may also be prepared from the parent aldehyde under Corey-Fuchs reaction conditions (see *Tet. Lett.* **1972** (36), 3769).

15

Compounds of formula **O** may be obtained by treatment of **N** under the same conditions as the ones described above for **K** in scheme 2 in the presence of a boronic acid.

Compounds of formula **G** may be obtained by deprotection of compounds of formula **O** under state of the art methods depending on the nature of the protective group. As an example, acetate as protective group can be deprotected under acidic conditions such as HCl or basic conditions such as $LiOH$. It is to be noted that weak protecting groups may be deprotected during the course of reactions to generate compounds of formula **N** or **O**. It is also to be not noticed that PG and R^3 may be the same from the beginning of the preparation thus the sequence of deprotection is not required.

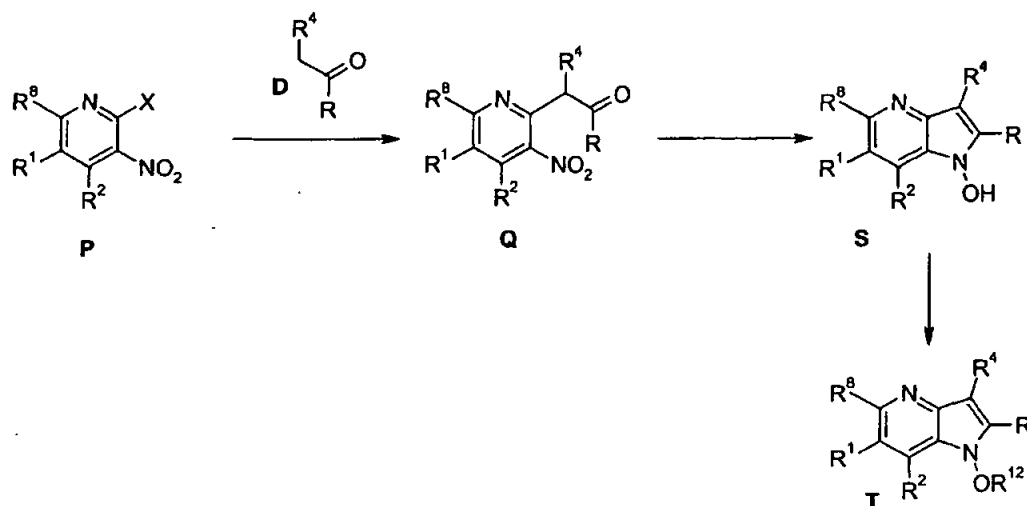
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25

Compounds of formula **H** may be obtained following the procedure described above in scheme 1.

- 5 Scheme 4 describes an alternative method for the preparation of compound of formula (I) where R^3 is OR^{12} as described previously:

Scheme 4



10 Reaction of a ketone of formula **D** (as already described) and a 3-nitropyridine of formula **P** in the presence of a base such as sodium hydride or potassium *t*-butoxide in an aprotic solvent such as dimethylformamide gives a compound of formula **Q** that may also exist as its enol form.

15

Compounds of formula **P**, where X is a halogen such as chlorine or bromine are either commercially available or might be prepared by known methods. Compounds such as 2-chloro-3-nitro-pyridine, 2-bromo-3-chloropyridine, 2-chloro-4-methyl-3-nitropyridine, 2-chloro-5-methyl-3-nitropyridine are commercially available. For the preparation of
20 compounds of formula **P**, the person skilled in the art might like to follow example such as preparation of 2,5-dibromo-3-nitropyridine described in *Tet. Lett.* 59(43) 8555-8570.

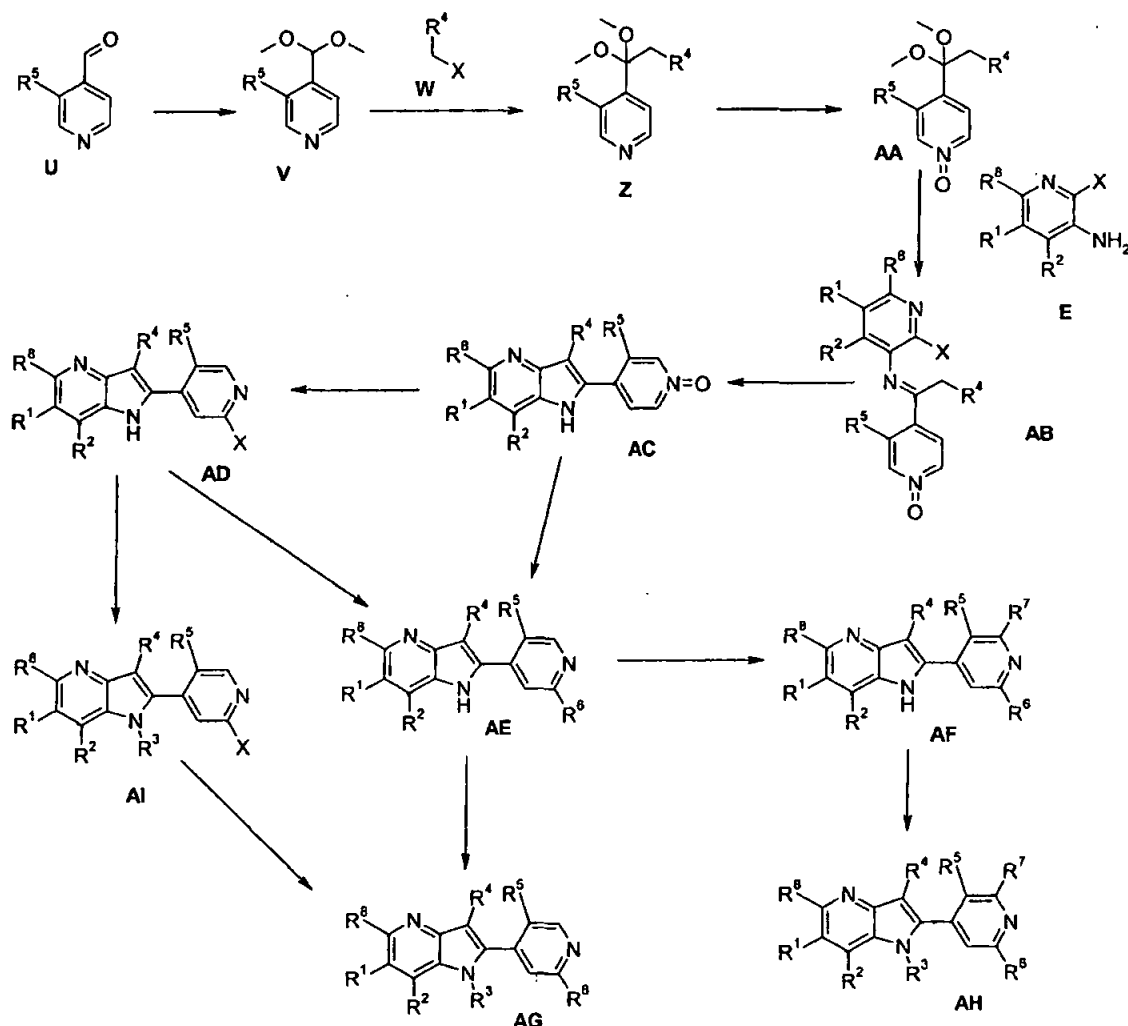
Compounds of formula **Q** can be selectively reduced at the nitro position under different condition to generate the 1-hydroxy-azaindole of formula **S**. For example,

10 compounds of formula **Q** can be treated under Bechamp conditions in the presence of iron in an acidic aqueous media to give compounds of formula **S**. Under these conditions, the complete reduced form of the azaindole might also be formed. Compounds of formula **Q** can also be treated under catalytic hydrogenation condition, in the presence of hydrogen, with or without pressure, with a catalyst such as palladium on charcoal in an alcoholic solvent such as ethanol.

10 Compounds of formula **S** can then be treated under the same conditions as the ones disclosed for **G** in scheme 1 in order to generate compound of formula **T** where R^{12} is as previously described.

Scheme 5 describes an alternative method for the preparation of compound of formula (I) where R^6 is not hydrogen.

Scheme 5



5 For this sequence, a pyridine of formula U where R⁵ is as previously described can be transformed in its acetal V by treating the corresponding aldehyde in methanol or in suitable trialkyl ortho formate such as trimethylorthoformate (for the preparation of the dimethylacetal) in the presence of a catalytic amount of an acid such as sulfuric acid.

10 The compound of formula U may be commercially available for example 4-pyridine carboxaldehyde, 3-nitro isonicotinaldehyde and 3-chloro-4-pyridine carboxaldehyde but may also be prepared by state of the art methodology for example starting from the hydroxymethyl derivative by an oxidation procedure (see *Aus. J. Chem* **1993**, 46(7) 987-993) but also by the reduction of the corresponding ester. The compound of formula U may also
15 be prepared from the halogen or unsubstituted analogue by halogen-metal or hydrogen-metal

exchange followed by treatment with a suitable electrophile such as dimethylformamide (see *Synthesis* 1999, 306-311).

Compounds of formula **Z** can be obtained by treating compounds of formula **V** with a
5 suitable base such as a n-butyl lithium, sodium hydride or lithium hexamethyldisilazane in an
aprotic solvent such as tetrahydrofuran or diethyl ether preferably at low temperature
followed by the treatment of the anion by a compound of formula **W** where **X** is a leaving
group such as halogen (chlorine, bromine or iodide) or a mesylate and R^4 is as previously
described.

10

Compounds of formula **W** are usually commercially available for example 4-
fluorobenzyl chloride, 3-methyl benzyl chloride or benzyl bromide but may also be prepared
by state of the art methodologies.

15 Compounds of formula **Z** can be oxidized to generate compounds of formula **AA**, for
example in the presence of hydrogen peroxide in a solvent such as dichloromethane in the
presence of a catalyst such as methyl trioxorhenium (see *Tet. Lett.* 1996, 37(6), 805-808) or
in the presence of hydrogen peroxide-urea complex in a solvent such as dichloromethane
(see *Chem. Ber.* 1992, 125(8), 1965-1966).

20

Compounds of formula **AA** can be treated by the previously described 3-amino
pyridine of formula **E** under the conditions described for the preparation of **F** in scheme 1 to
generate compound of formula **AB**. Alternatively **AB** can be obtained by reacting **AA** and **E**
together in the absence of solvent at a temperature allowing the distillation of the alcohol
25 formed (see *Synthesis* 1993, 12, 1227-1229).

As previously mentioned, compounds of formula **AB** can exist under its two isomers
imine and enamine that may also be separated for example by chromatography.

30 Cyclisation of **AB** under the conditions described in scheme 1 for the formation of **G**
allows the preparation of the azaindole **AC**.

Compounds of formula **AD** where **X** is halogen such as chlorine or bromine can be
prepared by treating **AC** with $POCl_3$ or $POBr_3$ under conditions used in state of the art

methodology such as chlorination of substituted pyridines in *Chem. and Pharm. Bull.* 1994, 42(9), 1841-1849.

Compounds of formula **AE** can be prepared from **AD** by Buchwald amination or
5 amidation reaction in the presence a primary amide or amine, of a palladium (II) catalyst
such as palladium diacetate, a ligand such as Xantphos®, a base such as potassium or cesium
carbonate in an aprotic solvent such as dioxane or tetrahydrofuran under thermal or
microwave conditions (see *Org. Let.* 2001, 3(21) 3417-3419).

10 Compounds of formula **AE** may also be prepared from **AD** by direct treatment with
an amine such as benzyl amine under thermal or microwave conditions, followed by
treatment with a strong acid such as concentrated sulphuric acid to generate the compound
where R^6 is NH_2 . Such an intermediate can be further treated by an appropriate non
nucleophilic base such as pyridine in a solvent such as dimethylformamide or
15 tetrahydrofuran and an acylating agent such as $R^{20}COX$ where X is chlorine or fluorine and
 R^{20} is as previously described. It can also be treated with an alkylating agent, such as $R^{18}-X$
where X is a leaving group such as halogen or a mesylate, under the same conditions.
Another alkylation or acylation will provide, under the same conditions, compounds where
 R^6 is $NR^{18}R^{19}$, as previously described.

20

Compounds of formula **AE** where R^6 is neither an amine nor an amide can be
prepared directly by treating compounds of formula **AC** with an activating agent followed by
a nucleophile as described in the review from *Science of Synthesis* (2005), 15, 285-387
(Georg Thieme Verlag Publisher). For example, if R^6 is cyanide, compounds of formula **AC**
25 are treated with an activator such as benzoyl chloride in the presence of a cyanide source
such as trimethylsilyl-cyanide in an aprotic solvent such as dimethylformamide or
tetrahydrofuran (See *J. Org. Chem.* 1983, 48, 1375-1377).

Compounds of formula **AE** where R^6 is cyanide can be further modified by state of
30 the art methods to generate all the possible derivatives of the cyanide group: for example,
reduction to the acid or ester, reduction to the amide or reduction to the amine, addition on
cyanide by an alkyl or aryl Grignard to generate the ketone.

Compounds of formula **AI** can be prepared from **AD** following the methodology described in scheme 1 for the preparation of **H** from **G**.

Compounds of formula **AG** can be prepared from **AE** following the methodology used for the preparation of **AI**. Compounds of formula **AG** can also be prepared from **AI** following the methodologies used for the preparation of **AE** from **AD**.

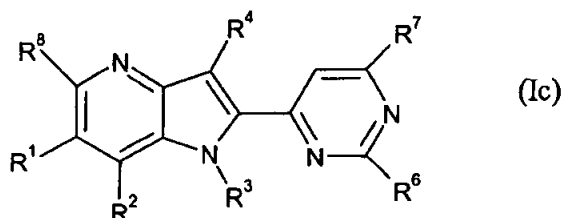
Compounds of formula **AF** can be prepared from **AE** by the following treatment:

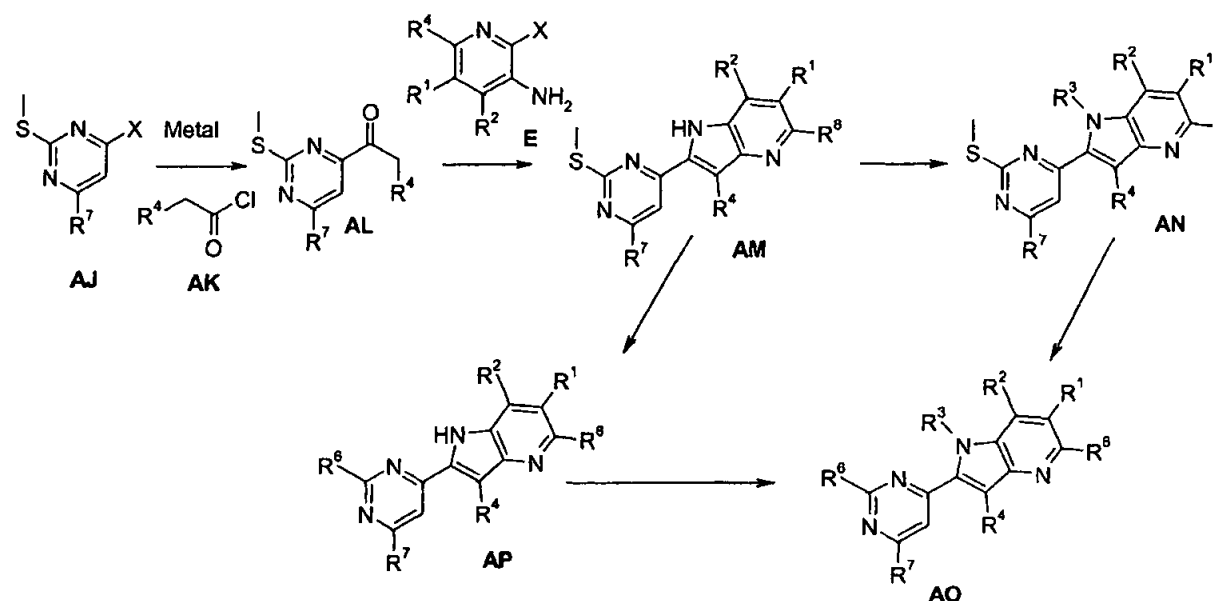
- oxidation of the pyridine following the preparation described for **AA** from **Z**
- direct reaction to introduce R^7 as described for the introduction of R^6 in the preparation of **AE** from **AD**
- R^7 may also be introduced by the methodologies described for the introduction of R^6 in the preparation of **AE** from **AC** via **AD**.

Compounds of formula **AH** may be prepared from compound of formula **AF** following the treatment described for the preparation of **H** in scheme 1.

Further steps may be realized that are not disclosed in the scheme 5 from compound **AC**, **AD**, **AI**, **AE**, **AF**, **AG** and **AH**. These reactions may result in further transformation of R^1 to R^8 , for example, cyclisation between R^6 and R^3 or between R^1 and R^2 .

Scheme 6 describes an alternative method for the preparation of compounds of formula (I) where X^1 is CH and X^2 is N (compounds of formula (Ic), for example, those compounds listed in Table 3).





Scheme 6

Compounds of formula **AL** can be prepared by treatment of pyrimidine of formula **AJ** where X is a halogen such as bromine, chlorine or iodide and R⁷ as previously described in the presence of a suitable base to realize the metal halogen exchange. *n*-butyl lithium, *s*-butyl lithium may be used in an aprotic solvent such as tetrahydrofuran preferably at low temperature. The acyl chloride of formula **AK** can then react with the previously formed anion of the pyrimidine to give compounds of formula **AL**.

Compounds of formula **AJ** may be commercially available such as the 4-iodo-2-methylthio- pyrimidine or obtained by state of the art methods (see for examples *Tet. Lett.* 2001, 42(2), 311-313).

Compounds of formula **AK** are usually commercially available, for example phenylacetyl chloride, *m*-tolylacetyl chloride or 4-fluoro benzeneacetyl chloride but might also be prepared from the corresponding acid.

Compounds of formula **AM** can be prepared from the condensation between compounds of formula **E** and **AL** under the conditions described for the formation of compound **F** in scheme 1, followed by the cyclisation of the imine or enamine obtained under the conditions described in scheme 1 for the formation of compound **G**.

Compound **E** is as previously described.

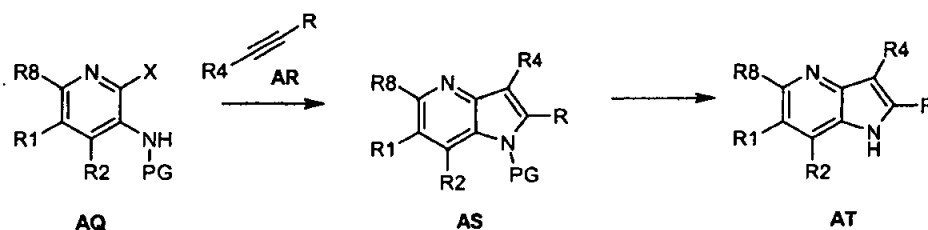
The oxidation of the pyrimidine of compounds of formula **AM** in the presence of an oxidant such as m-chloroperbenzoic acid in a solvent such as dichloromethane results in the formation of the sulfoxide intermediate. Further treatment of this intermediate with an amine such as benzyl amine followed by treatment in concentrated sulphuric acid results in the formation of a compound of formula **AP** where R^6 is NH_2 . Further treatment as previously described for the formation of compound **AE** in scheme 5 results in the formation of **AP** with R^6 as previously described.

Compounds of formula **AN** may be obtained by treatment of compounds of formula **AM** following the same procedure as the one previously described for the formation of compounds of formula **H** from compound of formula **G**.

Compounds of formula **AO** can be prepared from compounds of formula **AN** as previously described for the preparation of compounds of formula **AP** from compounds of formula **AM**.

Compounds of formula **AO** may also be prepared by the direct introduction of R^3 at the indole ring of the compounds of formula **AP** following the procedure previously described for the formation of compounds of formula **H** from compounds of formula **G** in scheme 1.

Scheme 7 describes an alternative method for the preparation of compound of formula (I).



Scheme 7

Compounds of formula AQ (where PG is a protective group such as benzyl, acetate, trifluoroacetate) may be obtained by protection of the corresponding aminopyridine E (see "Protective groups in organic chemistry", Greene and Wuts 4th edition, Wiley Interscience). Compounds of formula AQ can then be coupled with compounds of formula AR (where R⁴ is neither a phenyl nor a 4-fluorophenyl) under palladium-catalyzed indolization conditions (see *Org. Letters* 2004, 6 (22), 4129-4132) to afford compounds AS. The latter can then be deprotected according to known procedures, for instance benzyl groups can be removed by catalytic hydrogenation.

The previously described processes will enable those skilled in the art to understand the general conditions and techniques to be used in this invention. Further modification of groups R¹ to R⁸ to allow the preparation of compounds disclosed in this invention might be necessary to realize for example the formation of cyclic structure between R¹ and R², R¹ and R³, R² and R³, R³ and R⁵ and R⁵ and R⁶. It will be recognized by those skilled in the art that these modifications might be realized by more than one step, involving for example reduction, oxidation, coupling reaction with or without catalyst, nucleophilic substitution, lactonisation, lactamisation and the like.

As indicated above, it has now been found that the compounds of formula I are useful in controlling plant pathogenic fungi when they are applied to a plant or plant propagation material in a fungicidally effective amount.

By 'plant propagation material' is meant generative parts of a plant including seeds of all kinds (fruit, tubers, bulbs, grains etc), roots, rhizomes, cuttings, cut shoots and the like. Plant propagation material may also include plants and young plants which are to be transplanted after germination or after emergence from the soil.

The methods, compounds and compositions of the present invention are, for example, effective against the phytopathogenic fungi of the following classes: Fungi imperfecti (e.g. Botrytis, Pyricularia, Helminthosporium, Fusarium, Septoria, Cercospora and Alternaria), Basidiomycetes (e.g. Rhizoctonia, Hemileia, Puccinia), Ascomycetes (e.g. Venturia and

Erysiphe, Podosphaera, Monilinia, Uncinula and Pyrenophora) and Oomycetes (e.g. Phytophthora, Pythium, Plasmopara). In particular, the methods, compounds and compositions of the present invention are effective against *Botrytis* spp., *Pyricularia* spp., *Fusarium* spp., *Septoria* spp., *Rhizoctonia* spp., *Puccinia* spp., *Erysiphe* spp., *Phytophthora* spp., *Pythium* spp. and *Plasmopara* spp. Most particularly, the methods, compounds and compositions of the present invention are effective against *Botrytis cinerea*, *Pyricularia oryzae*, *Fusarium culmorum*, *Septoria nodurum* and *Septoria tritici*, *Rhizoctonia solani*, *Puccinia recondite*, *Erysiphe graminis*, *Pyrenophora teres*, *Phytophthora infestans*, *Pythium ultimum* and *Plasmopara viticola*.

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The methods, compounds and compositions of the present invention are suitable for controlling such disease on a number of plants and their propagation material including, but not limited to the following target crops: cereals (wheat, barley, rye, oats, maize (including field corn, pop corn and sweet corn), rice, sorghum and related crops); beet (sugar beet and fodder beet); leguminous plants (beans, lentils, peas, soybeans); oil plants (rape, mustard, sunflowers); cucumber plants (marrows, cucumbers, melons); fibre plants (cotton, flax, hemp, jute); vegetables (spinach, lettuce, asparagus, cabbages, carrots, eggplants, onions, pepper, tomatoes, potatoes, paprika, okra); plantation crops (bananas, fruit trees, rubber trees, tree nurseries), ornamentals (flowers, shrubs, broad-leaved trees and evergreens, such as conifers); as well as other plants such as vines, bushberries (such as blueberries), caneberries, cranberries, peppermint, rhubarb, spearmint, sugar cane and turf grasses including, but not limited to, cool-season turf grasses (for example, bluegrasses (*Poa* L.), such as Kentucky bluegrass (*Poa pratensis* L.), rough bluegrass (*Poa trivialis* L.), Canada bluegrass (*Poa compressa* L.) and annual bluegrass (*Poa annua* L.); bentgrasses (*Agrostis* L.), such as creeping bentgrass (*Agrostis palustris* Huds.), colonial bentgrass (*Agrostis tenius* Sibth.), velvet bentgrass (*Agrostis canina* L.) and redtop (*Agrostis alba* L.); fescues (*Festuca* L.), such as tall fescue (*Festuca arundinacea* Schreb.), meadow fescue (*Festuca elatior* L.) and fine fescues such as creeping red fescue (*Festuca rubra* L.), chewings fescue (*Festuca rubra* var. *commutata* Gaud.), sheep fescue (*Festuca ovina* L.) and hard fescue (*Festuca longifolia*); and ryegrasses (*Lolium* L.), such as perennial ryegrass (*Lolium perenne* L.) and annual (Italian) ryegrass (*Lolium multiflorum* Lam.)) and warm-season turf grasses (for example, Bermudagrasses (*Cynodon* L. C. Rich), including hybrid and common Bermudagrass; Zoysiagrasses (*Zoysia* Willd.), St. Augustinegrass (*Stenotaphrum secundatum* (Walt.) Kuntze); and centipedegrass (*Eremochloa ophiuroides* (Munro.) Hack.)).

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In addition 'crops' are to be understood to include those crops that have been made tolerant to pests and pesticides, including herbicides or classes of herbicides, as a result of conventional methods of breeding or genetic engineering. Tolerance to e.g. herbicides
5 means a reduced susceptibility to damage caused by a particular herbicide compared to conventional crop breeds. Crops can be modified or bred so as to be tolerant, for example, to HPPD inhibitors such as mesotrione or EPSPS inhibitors such as glyphosate.

Furthermore, the compounds of formula I find general use as fungicides and may
10 therefore also be used to control pathogenic fungi in related areas, for example in the protection of technical materials, including wood and wood related technical products, in food storage or in hygiene management. As such, the present invention further provides the use of a compound of formula I for controlling fungi.

15 When used in the methods of the invention, the compounds of formula I may be in unmodified form or, preferably, formulated together with carriers and adjuvants conventionally employed in the art of formulation.

The invention therefore also relates to a composition for the control of fungal
20 infection comprising a compound of formula I as defined above and an agriculturally acceptable carrier or diluent.

The agrochemical composition will usually contain from 0.1 to 99% by weight, preferably from 0.1 to 95% by weight, of the compound of formula I, 99.9 to 1% by weight,
25 preferably 99.8 to 5% by weight, of a solid or liquid adjuvant, and from 0 to 25% by weight, preferably from 0.1 to 25% by weight, of a surfactant.

Suitably, the agrochemical compositions and formulations of the present invention are applied prior to disease development. Rates and frequency of use of the formulations are
30 those conventionally used in the art and will depend on the risk of infestation by the fungal pathogen, the developmental stage of the plant and on the location, timing and application method. Advantageous rates of application are normally from 5g to 2kg of active ingredient (a.i.) per hectare (ha), preferably from 10g to 1kg a.i./ha, most preferably from 20g to

600g a.i./ha. When used as seed drenching agent, convenient rates of application are from 10mg to 1g of active substance per kg of seeds.

In practice, as indicated above, the agrochemical compositions comprising compound
5 of formula (I) are applied as a formulation containing the various adjuvants and carriers
known to or used in the industry. They may thus be formulated as granules, as wettable or
soluble powders, as emulsifiable concentrates, as coatable pastes, as dusts, as flowables, as
solutions, as suspensions or emulsions, or as controlled release forms such as microcapsules.
These formulations are described in more detail below and may contain as little as about
10 0.5% to as much as about 95% or more by weight of the active ingredient. The optimum
amount will depend on formulation, application equipment and nature of the plant
pathogenic fungi to be controlled.

Suspension concentrates are aqueous formulations in which finely divided solid
15 particles of the active compound are suspended. Such formulations include anti-settling
agents and dispersing agents and may further include a wetting agent to enhance activity as
well an anti-foam and a crystal growth inhibitor. In use, these concentrates are diluted in
water and normally applied as a spray to the area to be treated. The amount of active
ingredient may range from about 0.5% to about 95% of the concentrate.

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Wettable powders are in the form of finely divided particles which disperse readily in
water or other liquid carriers. The particles contain the active ingredient retained in a solid
matrix. Typical solid matrices include fuller's earth, kaolin clays, silicas and other readily
wet organic or inorganic solids. Wettable powders normally contain about 5% to about 95%
25 of the active ingredient plus a small amount of wetting, dispersing or emulsifying agent.

Emulsifiable concentrates are homogeneous liquid compositions dispersible in water
or other liquid and may consist entirely of the active compound with a liquid or solid
emulsifying agent, or may also contain a liquid carrier, such as xylene, heavy aromatic
30 naphthas, isophorone and other non-volatile organic solvents. In use, these concentrates are
dispersed in water or other liquid and normally applied as a spray to the area to be treated.
The amount of active ingredient may range from about 0.5% to about 95% of the
concentrate.

Granular formulations include both extrudates and relatively coarse particles and are usually applied without dilution to the area in which control of plant pathogenic fungi is required. Typical carriers for granular formulations include sand, fuller's earth, attapulgite clay, bentonite clays, montmorillonite clay, vermiculite, perlite, calcium carbonate, brick, 5 pumice, pyrophyllite, kaolin, dolomite, plaster, wood flour, ground corn cobs, ground peanut hulls, sugars, sodium chloride, sodium sulphate, sodium silicate, sodium borate, magnesia, mica, iron oxide, zinc oxide, titanium oxide, antimony oxide, cryolite, gypsum, diatomaceous earth, calcium sulphate and other organic or inorganic materials which absorb or which can be coated with the active compound. Granular formulations normally contain 10 about 5% to about 25% active ingredients which may include surface-active agents such as heavy aromatic naphthas, kerosene and other petroleum fractions, or vegetable oils; and/or stickers such as dextrans, glue or synthetic resins.

Dusts are free-flowing admixtures of the active ingredient with finely divided solids 15 such as talc, clays, flours and other organic and inorganic solids which act as dispersants and carriers.

Microcapsules are typically droplets or granules of the active ingredient enclosed in an inert porous shell which allows escape of the enclosed material to the surroundings at 20 controlled rates. Encapsulated droplets are typically about 1 to 50 microns in diameter. The enclosed liquid typically constitutes about 50 to 95% of the weight of the capsule and may include solvent in addition to the active compound. Encapsulated granules are generally porous granules with porous membranes sealing the granule pore openings, retaining the active species in liquid form inside the granule pores. Granules typically range from 1 25 millimetre to 1 centimetre and preferably 1 to 2 millimetres in diameter. Granules are formed by extrusion, agglomeration or prilling, or are naturally occurring. Examples of such materials are vermiculite, sintered clay, kaolin, attapulgite clay, sawdust and granular carbon. Shell or membrane materials include natural and synthetic rubbers, cellulosic materials, styrene-butadiene copolymers, polyacrylonitriles, polyacrylates, polyesters, polyamides, 30 polyureas, polyurethanes and starch xanthates.

Other useful formulations for agrochemical applications include simple solutions of the active ingredient in a solvent in which it is completely soluble at the desired concentration, such as acetone, alkylated naphthalenes, xylene and other organic solvents.

Pressurised sprayers, wherein the active ingredient is dispersed in finely-divided form as a result of vaporisation of a low boiling dispersant solvent carrier, may also be used.

Suitable agricultural adjuvants and carriers that are useful in formulating the
 5 compositions of the invention in the formulation types described above are well known to those skilled in the art. Suitable examples of the different classes are found in the non-limiting list below.

Liquid carriers that can be employed include water, toluene, xylene, petroleum
 10 naphtha, crop oil, acetone, methyl ethyl ketone, cyclohexanone, acetic anhydride, acetonitrile, acetophenone, amyl acetate, 2-butanone, chlorobenzene, cyclohexane, cyclohexanol, alkyl acetates, diacetonolcohol, 1,2-dichloropropane, diethanolamine, p-diethylbenzene, diethylene glycol, diethylene glycol abietate, diethylene glycol butyl ether, diethylene glycol ethyl ether, diethylene glycol methyl ether, N,N-dimethyl formamide,
 15 dimethyl sulfoxide, 1,4-dioxane, dipropylene glycol, dipropylene glycol methyl ether, dipropylene glycol dibenzoate, diproxitol, alkyl pyrrolidinone, ethyl acetate, 2-ethyl hexanol, ethylene carbonate, 1,1,1-trichloroethane, 2-heptanone, alpha pinene, d-limonene, ethylene glycol, ethylene glycol butyl ether, ethylene glycol methyl ether, gamma-butyrolactone, glycerol, glycerol diacetate, glycerol monoacetate, glycerol triacetate, hexadecane, hexylene
 20 glycol, isoamyl acetate, isobornyl acetate, isooctane, isophorone, isopropyl benzene, isopropyl myristate, lactic acid, laurylamine, mesityl oxide, methoxy-propanol, methyl isoamyl ketone, methyl isobutyl ketone, methyl laurate, methyl octanoate, methyl oleate, methylene chloride, m-xylene, n-hexane, n-octylamine, octadecanoic acid, octyl amine acetate, oleic acid, oleylamine, o-xylene, phenol, polyethylene glycol (PEG400), propionic
 25 acid, propylene glycol, propylene glycol monomethyl ether, p-xylene, toluene, triethyl phosphate, triethylene glycol, xylene sulfonic acid, paraffin, mineral oil, trichloroethylene, perchloroethylene, ethyl acetate, amyl acetate, butyl acetate, methanol, ethanol, isopropanol, and higher molecular weight alcohols such as amyl alcohol, tetrahydrofurfuryl alcohol, hexanol, octanol, etc. ethylene glycol, propylene glycol, glycerine, N-methyl-2-
 30 pyrrolidinone, and the like. Water is generally the carrier of choice for the dilution of concentrates.

Suitable solid carriers include talc, titanium dioxide, pyrophyllite clay, silica, attapulgite clay, kieselguhr, chalk, diatomaceous earth, lime, calcium carbonate, bentonite

clay, fuller's earth, cotton seed hulls, wheat flour, soybean flour, pumice, wood flour, walnut shell flour, lignin and the like.

A broad range of surface-active agents are advantageously employed in both said
5 liquid and solid compositions, especially those designed to be diluted with carrier before application. These agents, when used, normally comprise from 0.1% to 15% by weight of the formulation. They can be anionic, cationic, non-ionic or polymeric in character and can be employed as emulsifying agents, wetting agents, suspending agents or for other purposes. Typical surface active agents include salts of alkyl sulfates, such as diethanolammonium
10 lauryl sulphate; alkylarylsulfonate salts, such as calcium dodecylbenzenesulfonate; alkylphenol-alkylene oxide addition products, such as nonylphenol-C.sub. 18 ethoxylate; alcohol-alkylene oxide addition products, such as tridecyl alcohol-C.sub. 16 ethoxylate; soaps, such as sodium stearate; alkylnaphthalenesulfonate salts, such as sodium dibutylnaphthalenesulfonate; dialkyl esters of sulfosuccinate salts, such as sodium di(2-
15 ethylhexyl) sulfosuccinate; sorbitol esters, such as sorbitol oleate; quaternary amines, such as lauryl trimethylammonium chloride; polyethylene glycol esters of fatty acids, such as polyethylene glycol stearate; block copolymers of ethylene oxide and propylene oxide; and salts of mono and dialkyl phosphate esters.

20 Other adjuvants commonly utilized in agricultural compositions include crystallisation inhibitors, viscosity modifiers, suspending agents, spray droplet modifiers, pigments, antioxidants, foaming agents, anti-foaming agents, light-blocking agents, compatibilizing agents, antifoam agents, sequestering agents, neutralising agents and buffers, corrosion inhibitors, dyes, odorants, spreading agents, penetration aids, micronutrients,
25 emollients, lubricants, sticking agents, and the like.

In addition, further, other biocidally active ingredients or compositions may be used in the methods of the invention and applied simultaneously or sequentially with the compound of formula (I). When applied simultaneously, these further active ingredients
30 may be formulated together with the compound of the invention or mixed in, for example, the spray tank. These further biocidally active ingredients may be fungicides, herbicides, insecticides, bactericides, acaricides, nematocides and/or plant growth regulators.

Examples of insecticidal compounds for use in the compositions/methods of the present invention include, but are not limited to, pyrethroids (such as permethrin, cypermethrin, fenvalerate, esfenvalerate, deltamethrin, cyhalothrin (in particular, lambda-cyhalothrin), bifenthrin, fenpropathrin, cyfluthrin, tefluthrin, fish safe pyrethroids (for example ethofenprox), natural pyrethrin, tetramethrin, s-bioallethrin, fenfluthrin, prallethrin and 5-benzyl-3-furylmethyl-(E)-(1R,3S)-2,2-dimethyl-3-(2-oxothiolan-3-ylidenemethyl)cyclopropane carboxylate), organophosphates (such as, profenofos, sulprofos, acephate, methyl parathion, azinphos-methyl, demeton-s-methyl, heptenophos, thiometon, fenamiphos, monocrotophos, profenofos, triazophos, methamidophos, dimethoate, phosphamidon, malathion, chlorpyrifos, phosalone, terbufos, fensulfothion, fonofos, phorate, phoxim, pirimiphos-methyl, pirimiphos-ethyl, fenitrothion, fosthiazate and diazinon); carbamates, including aryl carbamates, (such as pirimicarb, triazamate, cloethocarb, carbofuran, furathiocarb, ethiofencarb, aldicarb, thiofurox, carbosulfan, bendiocarb, fenobucarb, propoxur, methomyl and oxamyl), benzoyl ureas (such as diflubenzuron, triflumuron, hexaflumuron, flufenoxuron and chlorfluazuron), organic tin compounds (such as cyhexatin, fenbutatin oxide and azocyclotin), pyrazoles (such as tebufenpyrad and fenpyroximate), macrolides (such as avermectins or milbemycins, for example abamectin, emamectin benzoate, ivermectin, milbemycin, spinosad and azadirachtin), hormones or pheromones, organochlorine compounds (such as endosulfan, benzene hexachloride, DDT, chlordane and dieldrin), amidines (such as chlordimeform and amitraz), fumigant agents (such as chloropicrin, dichloropropane, methyl bromide and metam); chloronicotinyl compounds (such as imidacloprid, thiacloprid, acetamiprid, nitenpyram and thiamethoxam), diacylhydrazines (such as tebufenozide, chromafenozide and methoxyfenozide), diphenyl ethers (such as diofenolan and pyriproxifen), indoxacarb, chlorfenapyr and pymetrozine.

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Examples of herbicidal compounds for use in the compositions/methods of the present invention include, but are not limited to, 2,3,6-TBA, 2,4-D, 2,4-DB, acetochlor, acifluorfen-sodium, aclonifen, acrolein, alachlor, alloxymid, ametryn, amicarbazone, amidosulfuron, aminopyralid, aminotriazol, amitrole, ammonium sulfamate, anilofos, asulam, atrazine, aviglycine, azafenidin, azimsulfuron, BAY FOE 5043, beflubutamid, benazolin, bencarbazone, benfluralin, benfuresate, bensulfuron-methyl, bensulide, bentazone, benzfendizone, benzobicyclon, benzofenap, bialaphos, bifenox, bispyribac-sodium, borax, bromacil, bromobutide, bromophenoxim, bromoxynil, butachlor, butafenacil, butamifos, butralin, butroxydim, butylate, cafenstrole, carbetamide, carfentrazone-ethyl,

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- chloransulam methyl, chlorbromuron, chlorflurenol-methyl, chloridazon, chlorimuron-ethyl, chloroacetic acid, chlorotoluron, chlorpropham, chloresulfuron, chlorthal-dimethyl, cinidon-ethyl, cinmethylin, cinosulfuron, clefoxydim profoxydim, clethodim, clodinafop-propargyl, clomazone, clomeprop, clopyralid, cloransulam, cloransulam-methyl, cumuluron,
- 5 cumyluron, cyanamide, cyanazine, cyclanilide, cycloate, cyclosulfamuron, cycloxydim, cyhalofop, cyhalofop-butyl, cyprosulfamide, daimuron, dalapon, dazomet, desmedipham, desmetryn, dicamba, dichlobenil, dichlorprop, dichlorprop-P, diclofop-methyl, diclosulam, difenzoquat metilsulfate, diflufenican, diflufenzopyr, dimefuron, dimepiperate, dimethachlor, dimethametryn, dimethenamid, dimethenamid-P, dimethipin, dimethylarsinic acid,
- 10 dinitramine, dinoterb, diphenamid, dipropetryn, diquat, ibromide, dithiopyr, diuron, DNOC, DSMA, endothal, EPTC, esprocarb, ethalfluralin, ethametsulfuron-methyl, ethephon, ethofumesate, ethoxyfen-ethyl, ethoxysulfuron, etobenzanid, fencloirid, fenoxaprop-P-ethyl, fentazamide, ferrous sulfate, flamprop, flamprop-M, flazasulfuron, florasulam, fluazifop-butyl, fluazifop-P-butyl, fluazolate, flucarbazone sodium, flucetosulfuron, fluchloralin,
- 15 flufenacet, flufenpyr-thyl, flumetralin, flumetsulam, flumiclorac-pentyl, flumioxazin, flumipropin, fluometuron, fluoroglyphofen-ethyl, fluoxaprop, flupoxam, flupropacil, flupropanate, flupyrsulfuron-methyl-sodium, flurenol, fluridone, flurochloridone, fluroxypyr, flurtamone, fluthiacet-methyl, fluxofenim, fomesafen, foramsulfuron, fosamine, glufosinate-ammonium, glyphosate, halosulfuron-methyl, haloxyfop, haloxyfop-P, HC-252, hexazinone,
- 20 imazamethabenz-methyl, imazamox, imazapic, imazapyr, imazaquin, imazethapyr, imazosulfuron, indanofan, iodosulfuron, iodosulfuron-methyl-sodium, ioxynil, isopropazol, isoproturon, isouron, isoxaben, isoxachlortole, isoxadifen, isoxaflutole, isoxapyrifop, karbutylate, KIH-485, lactofen, lenacil, linuron, MCPA, MCPA-thioethyl, MCPB, mecoprop, mecoprop-P, mefenacet, mefenpyr diethyl, mefluidide, mesosulfuron methyl,
- 25 mesotrione, metam, metamifop (mefluoxafop), metamitron, metazachlor, methabenzthiazuron, methazole, methyl isothiocyanate, methylarsonic acid, methylmymron, metobenzuron, metobromuron, metolachlor, metosulam, metoxuron, metribuzin, metsulfuron-methyl, MK-616, molinate, monolinuron, MSMA, naproanilide, napropamide, naptalam, NDA-402989, neburon, nfenacet, nicosulfuron, nipyraclufen, n-methyl-
- 30 glyphosate, nonanoic acid, norflurazon, oleic acid (fatty acids), orbencarb, orthosulfamuron, oryzalin, oxaciclomefone, oxadiargyl, oxadiazon, oxasulfuron, oxaziclomefone, oxyfluorfen, pebulate, pendimethalin, penoxsulam, pentachlorophenol, pentanochlor, pentoxazone, pethoxamid, petroleum oils, phenmedipham, phenoxaprop-P-ethyl (R), picloram, picolinafen, pinoxaden, piperophos, pretilachlor, primisulfuron, primisulfuron-methyl, procarbazone,

prodiamine, profluazol, profoxydim, prohexcadion calcium, prometon, prometryn,
 propachlor, propanil, propaquizafop, propazine, propham, propisochlor, propoxycarbazone,
 propoxycarbazone-sodium, propyzamide, prosulfocarb, prosulfuron, pyraclostrobin, pyrazogyl,
 pyraflufen-ethyl, pyrasulfotole, pyrazolynate, pyrazosulfuron-ethyl, pyrazoxyfen,
 5 pyribenzoxim, pyributicarb, pyridafol, pyridate, pyrifthalid, pyriminobac-methyl,
 pyrimisulfan, pyriothionac-sodium, quinclorac, quinmerac, quinoclamine, quizalofop,
 quizalofop-P, rimsulfuron, sequestren, sethoxydim, siduron, simazine, simetryn, S-
 metolachlor, sodium chlorate, sulcotrione, sulfentrazon, sulfometuron-methyl, sulfosate,
 sulfosulfuron, sulfuric acid, tar oils, TCA-sodium, tebutam, tebuthiuron, tefluthrin,
 10 tembotrione, tepraloxym, terbacil, terbutozin, terbuthylazine, terbutryn, thenylchlor,
 thiazafuron, thiazimin, thiazopyr, thienocarbazone, thifensulfuron-methyl (thiameturon-
 methyl), thiobencarb, tiocarbazon, topramezone, tralkoxydim, tri-allate, triasulfuron,
 triaziflam, tribenuron-methyl, triclopyr, trietazine, trifluralin, trifloxysulfuron,
 trifloxysulfuron-sodium, trifluralin, triflusulfuron-methyl, trinexapac-ethyl and tritosulfuron.

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Examples of fungicidal compounds for use in the compositions/methods of the
 present invention include, but are not limited to, acibenzolar (CGA245704), ancymidol,
 alanycarb, aldimorph, amisulbrom anilazine, azaconazole, azoxystrobin, benalaxyl,
 benthiavalicarb, benomyl, biloxazol, bitertanol, bixafen blastocidin S, boscalid,
 20 bromuconazole, bupirimate, captan, carbendazim, carbendazim chlorhydrate,
 carboxin, carpropamid, carvone, CGA41396, CGA41397, chinomethionate, chloroneb,
 chlorothalonil, chlorozolinate, clozylacon, copper containing compounds such as copper
 oxychloride, copper oxyquinolate, copper sulphate, copper tallate and Bordeaux mixture,
 cyflufenamid, cymoxanil, cyproconazole, cyprodinil, debacarb, di-2-pyridyl disulphide
 25 1,1'-dioxide, dichlofluanid, diclomezine, dichlozoline, dichlone, dicloran, diclocymet,
 diethofencarb, difenoconazole, difenzoquat, diflometorim, *O,O*-di-*iso*-propyl-*S*-benzyl
 thiophosphate, dimefluazole, dimetconazole, dimethomorph, dimethirimol, dimoxystrobin,
 diniconazole, dinocap, dithianon, dodecyl dimethyl ammonium chloride, dodemorph, dodine,
 doguadine, edifenphos, enestrobin, epoxiconazole, ethaboxam, ethirimol, etridiazole,
 30 famoxadone, fenamidone (RPA407213), fenarimol, fenbuconazole, fenfuram, fenhexamid
 (KBR2738), fenoxanil, fenpiclonil, fenpropidin, fenpropimorph, fentin acetate, fentin
 hydroxide, ferbam, ferimzone, fluazinam, fluopicolide, fludioxonil, fluoxastrobin,
 flumetover, SYP-LI90 (flumorph), fluopyram fluoroimide, fluquinconazole, flusilazole,
 flusulfamide, flutolanil, flutriafol, folpet, fosetyl-aluminium, fuberidazole, furalaxyl,

furametpyr, guazatine, hexaconazole, hydroxyisoxazole, hymexazole, IKF-916
 (Cyazofamid), imazalil, imibenconazole, iminoctadine, iminoctadine triacetate, ipconazole,
 iprobenfos, iprodione, iprovalicarb (SZX0722), isopropanyl butyl carbamate, isoprothiolane,
 kasugamycin, kresoxim-methyl, LY186054, LY211795, LY248908, maneb, mancopper,
 5 mancozeb, mandipropamid, maneb, mfenoxam, mepanipyrim, mepronil, metalaxyl,
 metconazole, methasulfocarb, metiram, metiram-zinc, metominostrobin, metrafenone,
 myclobutanil, myclozoline, neoasozin, nickel dimethyldithiocarbamate, nitrothal-*isopropyl*,
 nuarimol, ofurace, organomercury compounds, orysastrobin, oxadixyl, oxasulfuron, oxine-
 copper, oxolinic acid, oxpoconazole, oxycarboxin, pefurazoate, penconazole, pencycuron,
 10 penthiopyrad, phenazin oxide, phosdiphen, phosphorus acids, phthalide, picoxystrobin
 (ZA1963), polyoxin D, polyram, probenazole, prochloraz, procymidone, propamocarb, prop-
 iconazole, propineb, propionic acid, proquinazid, prothioconazole, pyraclostrobin,
 pyrazophos, Pyribencarb pyrifenoxy, pyrimethanil, pyroquilon, pyroxyfur, pyrrolnitrin,
 quaternary ammonium compounds, quinomethionate, quinoxifen, quintozone, silthiofam
 15 simeconazole, sipconazole (F-155), sodium pentachlorophenate, spiroxamine, streptomycin,
 sulphur, schwefel, tebuconazole, tecloftalam, tecnazene, tetraconazole, thiabendazole,
 thifluzamid, 2-(thiocyanomethylthio)benzothiazole, thiophanate-methyl, thiram, tiadinil
 timibenconazole, tolclofos-methyl, tolylfluanid, triadimefon, triadimenol, triazbutil,
 triazoxide, tricyclazole, tridemorph, trifloxystrobin (CGA279202), triformine, triflumizole,
 20 triticonazole, validamycin A, vapam, valiphenal vinclozolin, zineb, ziram, zoxamide, 3-[5-
 (4-chlorophenyl)-2,3-dimethylisoxazolidin-3-yl]pyridine, 5-chloro-7-(4-methylpiperidine-1-
 yl)-6-(2,4,6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidine and N-(4-chloro-2-nitrophenyl)-
 N-ethyl-4-methyl-benzulfonamide.

25 These formulations of the invention and for use in the methods of the invention can
 be applied to the areas where control is desired by conventional methods such as spraying
 atomising, dusting, scattering, coating or pouring. Dust and liquid compositions, for
 example, can be applied by the use of power-dusters, broom and hand sprayers and spray
 dusters. The formulations can also be applied from airplanes as a dust or a spray or by rope
 30 wick applications. Both solid and liquid formulations may also be applied to the soil in the
 locus of the plant to be treated allowing the active ingredient to penetrate the plant through
 the roots. The formulations of the invention may also be used for dressing applications on
 plant propagation material to provide protection against fungus infections on the plant
 propagation material as well as against phytopathogenic fungi occurring in the soil.

Suitably, the active ingredient may be applied to plant propagation material to be protected by impregnating the plant propagation material, in particular, seeds, either with a liquid formulation of the fungicide or coating it with a solid formulation. In special cases, other types of application are also possible, for example, the specific treatment of plant cuttings or twigs serving propagation.

In addition, the compounds of formula (I) as defined above can be used in the treatment of fungal infections of human and animal subjects. The active compounds as described herein may be combined with a pharmaceutically acceptable carrier and administered or applied to such subjects or infections in an amount effective to treat the infection in accordance with known techniques. Accordingly, therefore, the present invention also provides the use of a compound of formula (I) as defined above in the manufacture of a medicament for the treatment of fungal infection in humans or animals.

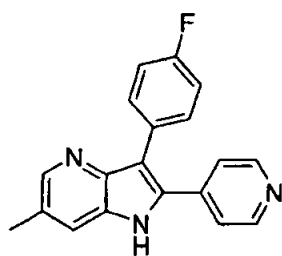
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The present invention will now be described by way of the following non-limiting examples. Those skilled in the art will promptly recognize appropriate variations from the procedures both as to reactants and as to reaction conditions and techniques

20 EXAMPLES

Example 1 - Preparation of 3-(4-Fluoro-phenyl)-6-methyl-2-pyridin-4-yl-1H-pyrrolo[3,2-b]pyridine following procedures described in scheme 1

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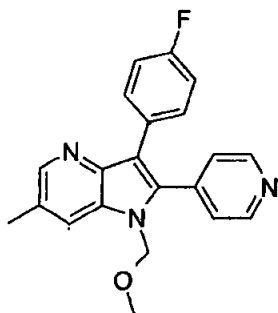
Step 1: 50.6 g of sodium metal (2.1 moles) are dissolved in 1.5 L of absolute ethanol under refluxing conditions. A mixture of 205 g of methyl isonicotinate (1.5 moles) and 202 g of 4-fluorophenyl in 0.5 L of absolute ethanol are added once the temperature has cooled to

30°C. The reaction mixture is refluxed for 4 hours, then cooled and poured into 1.2 L of ice-water. HCl 2N is added to reach pH=3 and the resulting yellow precipitate filtered and dried (271 g). This material is suspended in 1.1 L of 48% HBr solution and heated at 100°C for 8 hours. Once cooled, the reaction mixture is poured into ice-water (1.2L) and the pH is
5 adjusted to 7 with a 25% solution of ammonium hydroxide. After extraction in ethyl acetate, the organic layers are dried over magnesium sulfate and the residue after concentration is purified by chromatography on silica gel (ethylacetate/hexane 2/1) to give 133 g of 2-(4-fluorophenyl)-1-(pyridine-4-yl)ethanone as a yellowish solid.

10 Step 2: A mixture of p-toluenesulfonic acid (500mg), 2-(4-fluorophenyl)-1-(pyridine-4-yl)ethanone (10 g, 46 mmoles) and 5-methyl-3-amino-2-chloropyridine (8.6g, 60 mmoles) in 350 mL of toluene was refluxed overnight with a Dean-Stark removal of water/toluene azeotrope. The reaction mixture was further concentrated, the brown residue suspended in an ethyl acetate / hexane mixture (9/1) and filtered. The solid was solubilised in ethyl acetate
15 and purified by chromatography on silica gel (ethylacetate/hexane 1/1) to give 10 g of (2-Chloro-5-methyl-pyridin-3-yl)-[2-(4-fluoro-phenyl)-1-pyridin-4-yl-ethylidene]-amine as a brown solid.

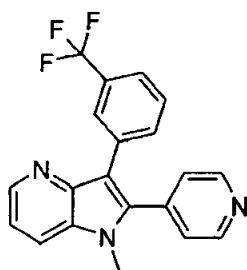
Step 3: 6.15 g (18.1 mmoles) of (2-Chloro-5-methyl-pyridin-3-yl)-[2-(4-fluoro-phenyl)-1-pyridin-4-yl-ethylidene]-amine are dissolved in 100 mL of dimethylformamide under nitrogen. 6.4 g of DABCO (56 mmoles) and 610 mg of
20 bis(triphenylphosphine)palladium dichloride are subsequently added to the reaction mixture which is stirred for 5 hours at 120°C. The cooled reaction mixture is then poured into water and extracted with ethyl acetate. The organic phase is washed with water and dried over
25 magnesium sulfate. The solid residue after concentration is recrystallized into ethyl acetate to afford 5.3 g of 3-(4-Fluoro-phenyl)-6-methyl-2-pyridin-4-yl-1H-pyrrolo[3,2-b]pyridine as a yellowish solid.

Example 2: Preparation of 3-(4-Fluoro-phenyl)-1-methoxymethyl-6-methyl-2-pyridin-4-yl-1H-pyrrolo[3,2-b]pyridine following procedures described in scheme 1
30



Sodium hydride (22 mg, 0.55 mmole 60% in oil) is added to a solution of 150 mg (0.5 mmole) of 3-(4-Fluoro-phenyl)-6-methyl-2-pyridin-4-yl-1H-pyrrolo[3,2-b]pyridine (prepared as described in example 1) in 5 mL of dimethylformamide at room temperature. After 30 min. at room temperature, a solution of 44.5 mg of chloromethyl methyl ether in 0.5 mL of DMF is added to the reaction mixture. After 45 min. at room temperature, the reaction mixture is poured into ammonium chloride solution and extracted with ethyl acetate. The organic phase is washed with water and dried over magnesium sulfate. The solid residue after concentration is recrystallized into ethyl acetate/hexane mixture (1/2) to afford 70 mg of pure 3-(4-Fluoro-phenyl)-1-methoxymethyl-6-methyl-2-pyridin-4-yl-1H-pyrrolo[3,2-b]pyridine as a yellowish solid.

Example 3: Preparation of 1-Methyl-2-pyridin-4-yl-3-(3-trifluoromethyl-phenyl)-1H-pyrrolo[3,2-b]pyridine following scheme 3.



Step 1: 5 g of 3-amino-2-bromopyridine (28.9 mmole) and 15.5 g of formaldehyde in 25 g of formic acid are stirred 6 hours at 100°C. The cooled reaction mixture is poured into water and the pH adjusted to 8-9 by adding sodium hydroxide 2N solution. After extraction in t-butylmethyl ether, the organic layers are washed with water and dried over magnesium

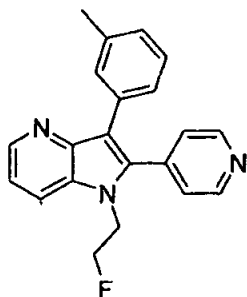
sulfate and the residue after concentration is purified by chromatography on silica gel (ethylacetate/hexane 1/1) to give 3.7 g of (2-Bromo-pyridin-3-yl)-dimethyl-amine as orange oil.

5 Step 2: A mixture of 2 g of (2-Bromo-pyridin-3-yl)-dimethyl-amine (9.95 mmoles), 1.24 g of 4-ethynyl pyridine (12 mmoles) in 120 mL of a 1/1 mixture of triethylamine and dimethylformamide is stirred under argon at room temperature. 750 mg of of bis(triphenylphosphine)palladium dichloride and 400 mg of copper iodide are added to the reaction mixture which is further stirred at room temperature for 3 hours. The reaction
10 mixture is poured into ammonium chloride solution and extracted with ethyl acetate. The organic phase is washed with water and dried over magnesium sulfate. The solid residue after concentration is purified by chromatography on silica gel (ethylacetate/hexane 1/1) to give 1 g of Dimethyl-(2-pyridin-4-ylethynyl-pyridin-3-yl)-amine as orange oil.

15 Step 3: 1 g (4.4 mmoles) of Dimethyl-(2-pyridin-4-ylethynyl-pyridin-3-yl)-amine are dissolved in 60 mL of dichloromethane under argon atmosphere. A solution of 2.27 g of iodine (8.9 mmoles) in 35 mL of dichloromethane is added dropwise in the reaction mixture at 0°C. The reaction mixture is allowed to reach room temperature and further stirred for 4 hours. The reaction mixture is then poured into a solution sodium thiosulfate and extracted
20 with dichloromethane. The organic phase is washed with water and dried over magnesium sulfate. The solid residue after concentration is purified by chromatography on silica gel (ethylacetate) to give 600 mg of 3-Iodo-1-methyl-2-pyridin-4-yl-1H-pyrrolo[3,2-b]pyridine as brown solid.

25 Step 4: To a solution of 130 mg (0.39 mmoles) of 3-Iodo-1-methyl-2-pyridin-4-yl-1H-pyrrolo[3,2-b]pyridine in 5 mL of toluene under nitrogen is added a 1 mL of a 2N solution of sodium carbonate, 78 mg (0.4 mmole) of 3-trifluoromethyl phenylboronic acid and 1 mL of ethanol. To the reaction mixture is finally added 24 mg of tetrakis(triphenylphosphine) palladium before heating at 80°C for 10 hours. The cooled
30 reaction mixture is then poured into ammonium chloride solution and extracted with ethyl acetate. The organic phase is washed with water and dried over magnesium sulfate. The solid residue after concentration is recrystallized into hexane to afford 70 mg of 1-Methyl-2-pyridin-4-yl-3-(3-trifluoromethyl-phenyl)-1H-pyrrolo[3,2-b]pyridine as white crystals.

Example 4: Preparation 1-(2-Fluoro-ethyl)-2-pyridin-4-yl-3-m-tolyl-1H-pyrrolo[3,2-b]pyridine following scheme 2



5

Step 1: Into 12 mL dimethylacetamide are added 240 mg (2 mmoles) of anhydrous magnesium sulfate, 1.3 mL (12 mmoles) of 4-acetyl pyridine, 515 mg (4 mmoles) of 3-amino-2-chloropyridine and 0.3 mL of acetic acid. The resulting suspension is kept under argon. Then 1.1 g (5.2 mmoles) of potassium phosphate and 202 mg (0.4 mmole) of bis-(tri-
10 t-butylphosphine) palladium are added to the reaction mixture which is then sealed in its reaction vessel and stirred at 140°C for 10 hours. The reaction mixture is poured into ammonium chloride solution and extracted with ethyl acetate. The organic phase is washed with water and dried over magnesium sulfate. The solid residue after concentration is purified by chromatography on silica gel (ethylacetate/methanol 9/1) to give 460 mg 2-
15 pyridin-4-yl-1H-pyrrolo[3,2-b]pyridine as brown solid.

Step 2: 800 mg of N-bromosuccinimide (4 mmole) is added to a solution of 720 mg (3.7 mmoles) of 2-pyridin-4-yl-1H-pyrrolo[3,2-b]pyridine in tetrachloromethane. The brown reaction mixture is stirred 5 hours at 50°C and concentrated. The brown residue is purified
20 by chromatography on silica gel (ethylacetate/methanol 9/1) to give 650 mg of 3-Bromo-2-pyridin-4-yl-1H-pyrrolo[3,2-b]pyridine as white crystals.

Step 3: To a solution of 274 mg (1 mmole) of 3-Bromo-2-pyridin-4-yl-1H-pyrrolo[3,2-b]pyridine in 1.8 mL of toluene under nitrogen is added a 0.6 mL of a 2N
25 solution of sodium carbonate, 170 mg (1.25 mmole) of m-tolylboronic acid and 1.2 mL of ethanol. To the reaction mixture is finally added 45 mg of tetrakis(triphenylphosphine) palladium. The reaction mixture is sealed in a microwave vessel and stirred under microwave conditions at 180°C for 2 min. The cooled reaction mixture is then poured into ammonium

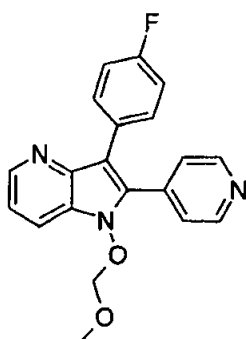
chloride solution and extracted with ethyl acetate. The organic phase is washed with water and dried over magnesium sulfate. The solid residue after concentration is recrystallized into hexane to afford 150 mg of 2-Pyridin-4-yl-3-m-tolyl-1H-pyrrolo[3,2-b]pyridine as white crystals.

5

Step 4: Sodium hydride (34 mg, 0.84 mmole 60% in oil) is added to a solution of 160 mg (0.56 mmole) of 2-Pyridin-4-yl-3-m-tolyl-1H-pyrrolo[3,2-b] in 6 mL of dimethylformamide at room temperature. After 30 min. at room temperature, 107 mg of 1-bromo-2-fluoroethane is added to the reaction mixture. After 20 hours at room temperature, the reaction mixture is poured into ammonium chloride solution and extracted with ethyl acetate. The organic phase is washed with water and dried over magnesium sulfate. The solid residue is purified by chromatography on silica gel (ethylacetate/methanol 9/1) to give 137mg of 1-(2-Fluoro-ethyl)-2-pyridin-4-yl-3-m-tolyl-1H-pyrrolo[3,2-b]pyridine as white crystals.

15

Example 5: Preparation of 3-(4-Fluoro-phenyl)-1-methoxymethoxy-2-pyridin-4-yl-1H-pyrrolo[3,2-b]pyridine following scheme 4



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Step 1: 21.5 g (100 mmoles) of 2-(4-fluorophenyl)-1-(pyridine-4-yl)ethanone (prepared as described in scheme 1) and 34.9 g of 2-chloro-3-nitropyridine are dissolved in 270 mL of dimethylformamide. 8.8 g of sodium hydride (60% in oil (220 mmoles) is slowly added to the reaction mixture which is kept between 0 and 5°C. After stirring for 1 hour at room temperature, the reaction mixture is poured into 1 L of ammonium chloride solution and extracted with ethyl acetate. The organic phase is washed with water and dried over magnesium sulfate. The oily residue is purified by chromatography on silica gel

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(ethylacetate/hexane 1/1) to give 26.7 g of 2-(4-Fluoro-phenyl)-2-(3-nitro-pyridin-2-yl)-1-pyridin-4-yl-ethanone.

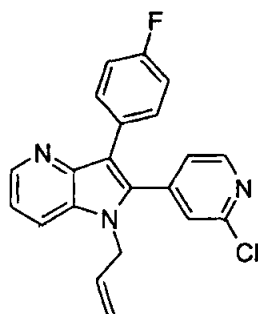
Step 2: 23 g (68.2 mmol) of 2-(4-Fluoro-phenyl)-2-(3-nitro-pyridin-2-yl)-1-pyridin-4-yl-ethanone is dissolved in 700 mL of absolute ethanol. 2.2 g of 10% Palladium on charcoal is added to the solution which is stirred for 6 hours under a hydrogen atmosphere. The reaction mixture is filtered over celite, concentrated and the brown residue is purified by chromatography on silica gel (ethylacetate) to give 7 g of 3-(4-Fluoro-phenyl)-2-pyridin-4-yl-pyrrolo[3,2-b]pyridin-1-ol and 13 g of the starting material is recovered.

10

Step 3: Sodium hydride (30 mg, 0.72 mmol 60% in oil) is added to a solution of 200 mg (0.65 mmol) of 3-(4-Fluoro-phenyl)-2-pyridin-4-yl-pyrrolo[3,2-b]pyridin-1-ol in 6 mL of dimethylformamide at room temperature. After 30 min. at room temperature, 65 mg of chloromethyl methyl ether is added to the reaction mixture. After 1 hour at room temperature, the reaction mixture is poured into ammonium chloride solution and extracted with ethyl acetate. The organic phase is washed with water and dried over magnesium sulfate. The solid residue is purified by chromatography on silica gel (ethylacetate) to give 120 mg of 3-(4-Fluoro-phenyl)-1-methoxymethoxy-2-pyridin-4-yl-1H-pyrrolo[3,2-b]pyridine as white crystals.

20

Example 6: Preparation of 1-Allyl-2-(2-chloro-pyridin-4-yl)-3-(4-fluoro-phenyl)-1H-pyrrolo[3,2-b]pyridine following scheme 5



25

Step 1: 80 g (74.6 mmol) of pyridine-4-carboxaldehyde is dissolved in 150 mL of methanol. 123.5 mL (112 mmol) of trimethyl orthoformate is added to the reaction mixture at room temperature followed by the addition of 33 mL of concentrated sulfuric

acid. The reaction mixture is kept under reflux for 24 hours and once cooled, added to 300 mL of sodium methylate solution. The white suspension obtained is filtered over celite, the filtrate is concentrated under vacuum and 70.3 g of 4-dimethoxymethyl-pyridine is obtained as a yellow oil.

5

Step 2: 315 mL of n-butyllithium 1.6 M solution in hexane is added dropwise to a solution of 70.3 g (0.46 mole) of 4-dimethoxymethyl-pyridine in 1.4 L of tetrahydrofuran under nitrogen at -70°C. After 30 min. at -70°C, 73 g (0.505 mole) of 4-fluorobenzyl chloride in 280 mL of tetrahydrofuran is added dropwise. After 10 more min. at -70°C, the reaction mixture is allowed to reach room temperature and then stirred for 30 further min. The reaction mixture is poured into 2 L ammonium chloride solution and extracted with ethyl acetate. The organic phase is washed with water and dried over magnesium sulfate. After concentration the residue is purified by chromatography on silica gel (ethylacetate/hexane 1/1) to give 114 g of 4-[2-(4-Fluoro-phenyl)-1,1-dimethoxy-ethyl]-pyridine as yellow oil.

15

Step 3: 55 g (0.21 mole) of 4-[2-(4-Fluoro-phenyl)-1,1-dimethoxy-ethyl]-pyridine and 445 mg of methyltrioxorhenium are dissolved in 250 mL of dichloromethane. 112 mL of commercial hydrogen peroxide solution is added to the reaction mixture which is further stirred over night at room temperature. The reaction mixture is then decanted and the organic phase is washed with sodium hydrogen sulfate and water and dried over magnesium sulfate. After concentration, 33 g of 4-[2-(4-Fluoro-phenyl)-1,1-dimethoxy-ethyl]-pyridine 1-oxide is obtained as a green oil.

20

Step 4: 60 g (0.21 mole) of 4-[2-(4-Fluoro-phenyl)-1,1-dimethoxy-ethyl]-pyridine 1-oxide together with 27.9 g (0.21 mole) of 3-amino-2-chloro pyridine are heated under argon at 130°C without solvent for 2 hours. After cooling and before complete crystallisation of the reaction mixture, ethyl acetate is added (150 mL) resulting in the formation of a white precipitate which is filtered to give 32 g of (2-Chloro-pyridin-3-yl)-[2-(4-fluoro-phenyl)-1-(1-oxy-pyridin-4-yl)-ethylidene]-amine.

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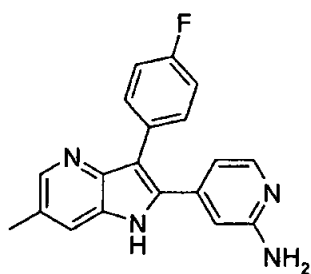
Step 5: 5.8 g (17 mmoles) of (2-Chloro-pyridin-3-yl)-[2-(4-fluoro-phenyl)-1-(1-oxy-pyridin-4-yl)-ethylidene]-amine is dissolved in 100 mL of dimethylformamide under nitrogen. 5.7 g of DABCO (51 mmoles) and 550 mg of bis(triphenylphosphine)palladium

dichloride are subsequently added to the reaction mixture which is stirred for 3 hours at 120°C. The cooled reaction mixture is then poured into water and extracted with ethyl acetate. The organic phase is washed with water and dried over magnesium sulfate. The solid residue after concentration is recrystallized into ethyl acetate to afford 5.2 g of 3-(4-Fluoro-phenyl)-2-(1-oxy-pyridin-4-yl)-1H-pyrrolo[3,2-b]pyridine as a yellowish solid.

Step 6: 12.25 g (40.1 mmoles) of 3-(4-Fluoro-phenyl)-2-(1-oxy-pyridin-4-yl)-1H-pyrrolo[3,2-b]pyridine in 120 mL of phosphoroxychloride are stirred at 120°C for 90 min. The reaction mixture is concentrated under vacuum and the residue treated with methanol and filtered over celite. After concentration of the methanol phase, the solid residue is purified by chromatography on silica gel (ethyl acetate/methanol 9/1) to give 10 g of 2-(2-Chloro-pyridin-4-yl)-3-(4-fluoro-phenyl)-1H-pyrrolo[3,2-b]pyridine as yellow solid.

Step 7: Sodium hydride (120 mg, 3 mmole 60% in oil) is added to a solution of 323.5 mg (1 mmole) of 2-(2-Chloro-pyridin-4-yl)-3-(4-fluoro-phenyl)-1H-pyrrolo[3,2-b]pyridine in 8 mL of dimethylformamide at room temperature. After 30 min. at room temperature, 1.2 g of allyl bromide (10 mmoles) is added to the reaction mixture. After 1 hour at room temperature, the reaction mixture is poured into ammonium chloride solution and extracted with ethyl acetate. The organic phase is washed with water and dried over magnesium sulfate. After concentration the solid residue is purified by chromatography on silica gel (ethyl acetate/hexane 1/1) to give 270 mg of 1-Allyl-2-(2-chloro-pyridin-4-yl)-3-(4-fluoro-phenyl)-1H-pyrrolo[3,2-b]pyridine as white solid.

Example 7: Preparation of 4-[3-(4-Fluoro-phenyl)-6-methyl-1H-pyrrolo[3,2-b]pyridin-2-yl]-pyridin-2-ylamine following scheme 1



Step 1: To a solution of 15 g (0.105 mole) of 5-amino-6-chloro-3-picoline in 100 mL dimethylformamide is added 1 mL of concentrated sulfuric acid. Then a solution of 43.7 g (0.15 mole) of 4-[2-(4-Fluoro-phenyl)-1,1-dimethoxy-ethyl]-pyridine 1-oxide (as previously prepared in example 6) in 80 mL of dimethylformamide is slowly added to the reaction mixture which is subsequently warmed at 80°C for 6 hours. Once cooled, the reaction mixture is poured into ammonium chloride solution and extracted with ethyl acetate. The organic phase is washed with water and dried over magnesium sulfate. After concentration the solid residue is purified by chromatography on silica gel (ethyl acetate/methanol 9/1) to give 16 g of (2-Chloro-5-methyl-pyridin-3-yl)-[2-(4-fluoro-phenyl)-1-(1-oxy-pyridin-4-yl)-ethylidene]-amine as white solid.

Step 2: 34.5 g (97 mmols) of ((2-Chloro-5-methyl-pyridin-3-yl)-[2-(4-fluoro-phenyl)-1-(1-oxy-pyridin-4-yl)-ethylidene]-amine are dissolved in 600 mL of dimethylformamide under nitrogen. 33 g of DABCO (295 mmols) and 3.5 g of bis(triphenylphosphine)palladium dichloride are subsequently added to the reaction mixture which is stirred for 3 hours at 120°C. The cooled reaction mixture is then poured into water and extracted with ethyl acetate. The organic phase is washed with water and dried over magnesium sulfate. The solid residue after concentration is recrystallized in diethyl ether to afford 17 g of 3-(4-Fluoro-phenyl)-6-methyl-2-(1-oxy-pyridin-4-yl)-1H-pyrrolo[3,2-b]pyridine as a yellowish solid.

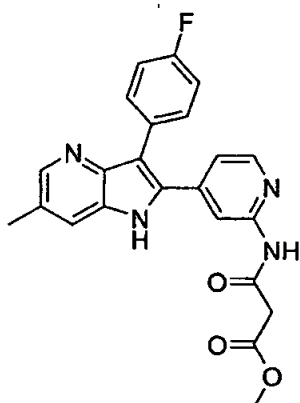
Step 3: 15 g (47 mmols) of 3-(4-Fluoro-phenyl)-6-methyl-2-(1-oxy-pyridin-4-yl)-1H-pyrrolo[3,2-b]pyridine in 150 mL of phosphoroxychloride are stirred at 120°C for 1 hour. The reaction mixture is concentrated under vacuum and the residue treated with methanol and filtered over celite. After concentration of the methanol phase, the solid residue is purified by chromatography on silica gel (ethyl acetate/methanol 9/1) to give 11 g of 2-(2-Chloro-pyridin-4-yl)-3-(4-fluoro-phenyl)-6-methyl-1H-pyrrolo[3,2-b]pyridine as yellow solid.

Step 4: 11 g of 2-(2-Chloro-pyridin-4-yl)-3-(4-fluoro-phenyl)-6-methyl-1H-pyrrolo[3,2-b]pyridine are suspended in 115 ml of benzylamine. The reaction mixture is refluxed at 180°C for 24 hours. After cooling, the reaction mixture is poured into hexane resulting in the formation of a yellow precipitate. After filtration the precipitate is suspended in hot water, filtrated again and washed with hot water resulting in the isolation of 9.55 g of

Benzyl-4-[3-(4-fluoro-phenyl)-6-methyl-1H-pyrrolo[3,2-b]pyridin-2-yl]-pyridin-2-yl-amine as a white solid.

Step 5: 7.8 g (19 mmol) of Benzyl-4-[3-(4-fluoro-phenyl)-6-methyl-1H-pyrrolo[3,2-b]pyridin-2-yl]-pyridin-2-yl-amine is suspended at room temperature in 40 mL of concentrated sulfuric acid. After 1 hour, the reaction is poured into ice (250 g) and kept at 0°C while adding 170 mL of concentrated sodium hydroxide solution to reach pH=10. The resulting precipitate is filtered, suspended again in hot water and stirred at reflux for 1 hour. The reaction mixture is then filtered again and washed with hot water to give 6 g of 4-[3-(4-fluoro-phenyl)-6-methyl-1H-pyrrolo[3,2-b]pyridin-2-yl]-pyridin-2-ylamine as white solid.

Example 8: Preparation N-{4-[3-(4-Fluoro-phenyl)-6-methyl-1H-pyrrolo[3,2-b]pyridin-2-yl]-pyridin-2-yl}-malonamic acid methyl ester following scheme 5

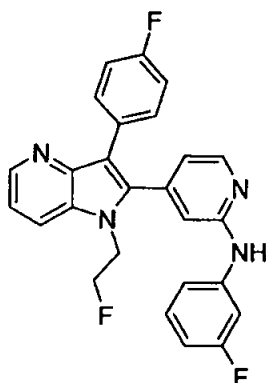


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Chlorocarbonyl-acetic acid methyl ester (129 mg, 0.9 mmol) is added to a solution of 200 mg (0.62 mmol) of 4-[3-(4-Fluoro-phenyl)-6-methyl-1H-pyrrolo[3,2-b]pyridin-2-yl]-pyridin-2-ylamine (prepared following the procedure for example 7) in 3 mL of pyridine at room temperature. After 30 hours at room temperature, Chlorocarbonyl-acetic acid methyl ester (129 mg, 0.9 mmol) is added again to the reaction mixture stirred 12 more hours at room temperature. The reaction mixture is then poured into ammonium chloride solution and extracted with ethyl acetate. The organic phase is washed with water and dried over magnesium sulfate. After concentration the solid residue is purified by chromatography on silica gel (ethyl acetate) to give 40 mg of N-{4-[3-(4-Fluoro-phenyl)-6-methyl-1H-pyrrolo[3,2-b]pyridin-2-yl]-pyridin-2-yl}-malonamic acid methyl ester as white solid.

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Example 9: Preparation of {4-[1-(2-Fluoro-ethyl)-3-(4-fluoro-phenyl)-1H-pyrrolo[3,2-b]pyridin-2-yl]-pyridin-2-yl}-(3-fluoro-phenyl)-amine following scheme 5

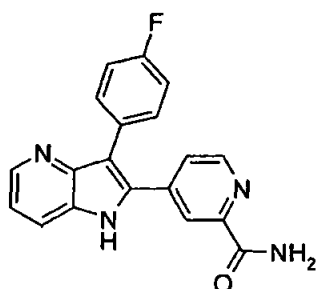


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Step 1: Sodium hydride (371 mg, 9.3 mmoles 60% in oil) is added to a solution of 1 g (3.1 mmoles) of 2-(2-Chloro-pyridin-4-yl)-3-(4-fluoro-phenyl)-1H-pyrrolo[3,2-b]pyridine (prepared following the procedure for example 6) in 20 mL of dimethylformamide at room temperature. After 30 min. at room temperature, 2.75 g of 1-bromo-2-fluoro-ethane (21.6 mmoles) is added to the reaction mixture. After 10 hour at room temperature, the reaction mixture is poured into ammonium chloride solution and extracted with ethyl acetate. The organic phase is washed with water and dried over magnesium sulfate. After concentration the solid residue is purified by chromatography on silica gel (ethyl acetate/hexane 1/1) to give 720 mg of 2-(2-Chloro-pyridin-4-yl)-1-(2-fluoro-ethyl)-3-(4-fluoro-phenyl)-1H-pyrrolo[3,2-b]pyridine as white solid.

Step 2: In a 5 mL microwave vessel (Biotage) are weighted together 185 mg (0.5 mmole) of 2-(2-Chloro-pyridin-4-yl)-1-(2-fluoro-ethyl)-3-(4-fluoro-phenyl)-1H-pyrrolo[3,2-b]pyridine, 67 mg (0.6 mmoles) of 3-fluorophenyl amine, 2 mg of palladium acetate, 7 mg of biphenyl dicyclohexylphosphine and 67 mg (0.7 mmole) of sodium t-butoxide in 2.5 mL of toluene. The reaction mixture is then heated at 180°C for 10 min. under microwave conditions. The reaction mixture is poured into ammonium chloride solution and extracted with ethyl acetate. The organic phase is washed with water and dried over magnesium sulfate. After concentration the solid residue is purified by chromatography on silica gel (ethyl acetate/hexane 1/1) to give 85 mg of {4-[1-(2-Fluoro-ethyl)-3-(4-fluoro-phenyl)-1H-pyrrolo[3,2-b]pyridin-2-yl]-pyridin-2-yl}-(3-fluoro-phenyl)-amine as white solid.

Example 10: Preparation of 4-[3-(4-Fluoro-phenyl)-1H-pyrrolo[3,2-b]pyridin-2-yl]-pyridine-2-carboxylic acid amide following scheme 5



5

Step 1: Trimethylsilyl cyanide (10.3 mL, 82 mmol) is added to a solution of 5.02 g (16.4 mmol) of 3-(4-Fluoro-phenyl)-2-(1-oxy-pyridin-4-yl)-1H-pyrrolo[3,2-b]pyridine (as prepared in example 6) in 35 mL of dimethylformamide. Benzoyl chloride (3.8 mL, 33 mmol) is then slowly added to the reaction mixture. After 8 hours, the reaction mixture is poured into ammonium chloride solution and extracted with ethyl acetate. The organic phase is washed with water and dried over magnesium sulfate. After concentration the solid residue is purified by chromatography on silica gel (ethyl acetate) to give 3.55 g of 4-[3-(4-Fluoro-phenyl)-1H-pyrrolo[3,2-b]pyridin-2-yl]-pyridine-2-carbonitrile as white solid.

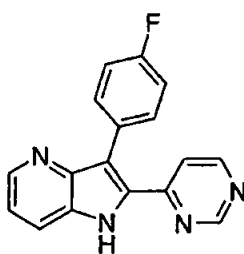
15

Step 2: 1.44 g (4.6 mmol) of 4-[3-(4-Fluoro-phenyl)-1H-pyrrolo[3,2-b]pyridin-2-yl]-pyridine-2-carbonitrile is stirred at room temperature in 8 mL of t-butanol in the presence of 1.03 g (18.3 mmol) of powdered potassium hydroxide. The reaction is stirred at room temperature for 4 hours, concentrated under vacuum and poured into water and ethyl acetate (1/1). Chlorhydric acid 2N is added to the solution to reach pH=5 and the solution is extracted with ethyl acetate. The organic phase is washed with water and dried over magnesium sulfate. After concentration 800 mg of 4-[3-(4-Fluoro-phenyl)-1H-pyrrolo[3,2-b]pyridin-2-yl]-pyridine-2-carboxylic acid amide are obtained as white solid.

20

Example 11: Preparation of 3-(4-Fluoro-phenyl)-2-pyrimidin-4-yl-1H-pyrrolo[3,2-b]pyridine following scheme 1

25



Step 1: 50 g (0.31 mole) of 4-chloro-2-methylthiopyrimidine is solubilised in 300 mL of hydriodic acid at room temperature. The reaction mixture is stirred at room temperature for 8 hours. The reaction mixture is poured into 1.2 L of water and the pH adjusted to 8 with solid sodium bicarbonate. The mixture is extracted with dichloromethane and washed with sodium thiosulfate. After concentration the oily residue gives 74 g of 4-iodo-2-methylthiopyrimidine.

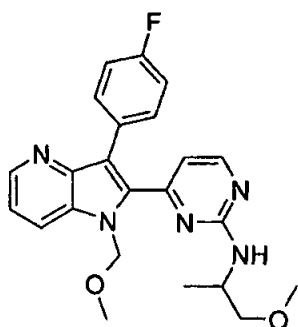
Step 2: 20 g (79 mmole) of 4-iodo-2-methylthiopyrimidine in 165 mL of tetrahydrofuran under argon is cooled to -70°C . 45.5 mL of isopropylmagnesium chloride (2M in THF) is then slowly added to the reaction mixture, keeping the temperature at -70°C . After 30 min., a solution of 4-fluorophenyl acetyl chloride (13.7 g, 79 mmole) in 65 mL tetrahydrofuran is added dropwise to the reaction mixture which is further stirred at -78°C for 1 hour and allowed to reach 0°C . After 30 min. at 0°C , the reaction is poured into ice-water and extracted with ethyl acetate. The organic phase is washed with water and dried over magnesium sulfate. After concentration the oily purified by chromatography on silica gel (ethyl acetate/hexane 4/1) affording 9.5 g of 2-(4-Fluoro-phenyl)-1-(2-methylthio-pyrimidin-4-yl)-ethanone as yellow oil.

Step 3: A mixture of p-toluenesulfonic acid (10mg), 2-(4-Fluoro-phenyl)-1-(2-methylthio-pyrimidin-4-yl)-ethanone (200 mg, 0.76 mmole) and 3-amino-2-chloropyridine (90 mg, 0.7 mmole) in 3 mL of toluene was refluxed overnight with a Dean-Stark removal of water/toluene azeotrope. The reaction mixture was further concentrated, the brown residue suspended in an ethyl acetate / hexane mixture (9/1) and filtered. The solid was solubilised in ethyl acetate and purified by chromatography on silica gel (ethylacetate/hexane 1/1) to give 130 mg of (2-Chloro-pyridin-3-yl)-[2-(4-fluoro-phenyl)-1-(2-methylthio-pyrimidin-4-yl)-ethylidene]-amine as a brown oil.

Step 4: 6.5 g (14.7 mmol) of (2-Chloro-pyridin-3-yl)-[2-(4-fluoro-phenyl)-1-(2-methylthio-pyrimidin-4-yl)-ethylidene]-amine is dissolved in 60 mL of dimethylformamide under nitrogen. 6.2 g of DABCO (52 mmol) and 0.5 g of bis(triphenylphosphine)palladium dichloride are subsequently added to the reaction mixture which is stirred for 4 hours at 120°C. The cooled reaction mixture is then poured into water and extracted with ethyl acetate. The organic phase is washed with water and dried over magnesium sulfate. The solid residue after concentration is recrystallized in diethyl ether to afford 4 g of 3-(4-Fluoro-phenyl)-2-(2-methylthio-pyrimidin-4-yl)-1H-pyrrolo[3,2-b]pyridine as a yellowish solid.

Step 5: 560 mg (1.66 mmol) of 3-(4-Fluoro-phenyl)-2-(2-methylthio-pyrimidin-4-yl)-1H-pyrrolo[3,2-b]pyridine is stirred at room temperature in a mixture of 50 mL of absolute ethanol and 40 mL of ammonia (15% in water). 2 g of Raney nickel (50% in water) is then added to the solution which is further stirred for 3 hours under refluxing conditions. Once cooled, the reaction mixture is filtered over celite and extracted with ethyl acetate. The organic phase is washed with water and dried over magnesium sulfate. The solid residue after concentration is solubilised in ethyl acetate and purified by chromatography on silica gel (ethylacetate/hexane 1/1) to give 250 mg of 3-(4-Fluoro-phenyl)-2-pyrimidin-4-yl-1H-pyrrolo[3,2-b]pyridine as yellowish solid.

Example 12: Preparation of {4-[3-(4-Fluoro-phenyl)-1-methoxymethyl-1H-pyrrolo[3,2-b]pyridin-2-yl]-pyrimidin-2-yl}-(2-methoxy-1-methyl-ethyl)-amine following scheme 1



Step 1: Sodium hydride (130 mg, 2.8 mmol 60% in oil) is added to a solution of 850 mg (2.53 mmol) of 3-(4-Fluoro-phenyl)-2-(2-methylthio-pyrimidin-4-yl)-1H-pyrrolo[3,2-b]pyridine in 30 mL of dimethylformamide at room temperature. After 30 min.

at room temperature, 0.23 mL of chloromethyl methyl ether is added to the reaction mixture. After 1 hour at room temperature, the reaction mixture is poured into ammonium chloride solution and extracted with ethyl acetate. The organic phase is washed with water and dried over magnesium sulfate. The solid residue is purified by chromatography on silica gel (ethyl acetate/hexane 2/1) to give 750 mg of 3-(4-Fluoro-phenyl)-1-methoxymethyl-2-(2-methylthio-pyrimidin-4-yl)-1H-pyrrolo[3,2-b]pyridine as white crystals.

Step 2: 730 mg (1.92 mmoles) of 3-(4-Fluoro-phenyl)-1-methoxymethyl-2-(2-methylthio-pyrimidin-4-yl)-1H-pyrrolo[3,2-b]pyridine in 50 mL of dichloromethane is treated as 0°C with 0.57 g of 3-chloroperbenzoic acid (2.3 mmoles). The reaction mixture is stirred 30 min. at 0°C and poured into ice-water. The mixture is treated with sodium bicarbonate to reach a pH of between 8 and 9 and extracted with dichloromethane to give a yellow wax. 395 mg of this yellow wax is directly solubilised in 3 mL of 2-amino-1-methoxypropane and under microwave conditions heated at 200°C for 20 min. The reaction mixture is poured into ammonium chloride solution and extracted with ethyl acetate. The organic phase is washed with water and dried over magnesium sulfate. The solid residue is purified by chromatography on silica gel (ethyl acetate/hexane 1/5) to give 350 mg of {4-[3-(4-Fluoro-phenyl)-1-methoxymethyl-1H-pyrrolo[3,2-b]pyridin-2-yl]-pyrimidin-2-yl}-(2-methoxy-1-methyl-ethyl)-amine as yellowish wax.

Example 13: Biological activity of the compounds of the invention

The compounds of the invention were tested in a leaf disk assay, as described below to determine their preventative action against a number of fungal species. In all cases, the test compounds were dissolved in DMSO and diluted into water to 200 ppm. The final test solution contained 2% DMSO and 0.025% Tween® 20.

a) *Erysiphe graminis f.sp. hordei* (barley powdery mildew) and *Pyrenophora teres* (barley net blotch): Barley leaf segments were placed on agar in a 24-well plate and sprayed with a solution of the test compound. After allowing the segments to dry completely (24 hours) they were inoculated with a spore suspension of the fungus. After appropriate incubation the activity of a compound was assessed four (*Pyrenophora teres*) or seven (*Erysiphe graminis f.sp. hordei*) days after inoculation as preventive fungicidal activity.

b) *Erysiphe graminis f.sp. tritici* (wheat powdery mildew), *Puccinia recondita f.sp. tritici* (wheat brown rust) and *Septoria nodorum* (wheat glume blotch): Wheat leaf segments were placed on agar in a 24-well plate and sprayed with a solution of the test compound. After allowing the segments to dry completely (24 hours), they were inoculated with a spore suspension of the fungus. After appropriate incubation the activity of a compound was assessed four (*Septoria nodorum*), seven (*Erysiphe graminis f.sp. tritici*) or eight (*Puccinia recondita f.sp. tritici*) days after inoculation as preventive fungicidal activity.

c) *Pyricularia oryzae* (rice blast): Rice leaf segments were placed on agar in a 24-well plate and sprayed with a solution of the test compound. After allowing the segments to dry completely (24 hours), they were inoculated with a spore suspension of the fungus. After appropriate incubation the activity of a compound was assessed five days after inoculation as preventive fungicidal activity.

d) *Botrytis cinerea* (grey mould): Bean leaf disks were placed on agar in a 24-well plate and sprayed with a solution of the test compound. After allowing the disks to dry completely (24 hours), they were inoculated with a spore suspension of the fungus. After appropriate incubation the activity of a compound was assessed three days after inoculation as preventive fungicidal activity.

e) *Phytophthora infestans* (late blight of potato/tomato): Tomato leaf disks were placed on water agar in a 24-well plate and sprayed with a solution of the test compound. After allowing the disks to dry completely (24 hours), they were inoculated with a spore suspension of the fungus. After appropriate incubation the activity of a compound was assessed four days after inoculation as preventive fungicidal activity.

f) *Plasmopara viticola* (downy mildew of grapevine): Grapevine leaf disks were placed on agar in a 24-well plate and sprayed a solution of the test compound. After allowing the disks to dry completely (for between 12 and 24 hours), they were inoculated with a spore suspension of the fungus. After appropriate incubation the activity of a compound was assessed seven days after inoculation as preventive fungicidal activity.

The following compounds (numbering corresponds to Tables 1, 2 and 3 above) gave at least 80% control of the following fungal infection at 200ppm in the leaf disc assays described above:

- 5 *Plasmopara viticola*: 2; 3; 4; 5; 7; 9; 10; 13; 17; 18; 19; 21; 22; 28; 30; 33; 38; 39; 40; 41; 44; 48; 50; 51; 52; 53; 55; 56; 57; 58; 61; 63; 65; 66; 77; 78; 83; 84; 89; 97; 98; 99; 100; 101; 103; 104; 105; 106; 108; 109; 112; 113; 115; 118; 121; 124; 125; 126; 127; 129; 130; 132; 133; 135; 140; 151; 154; 155; 161; 162; 166; 167; 168; 169; 170; 171; 172; 173; 174; 175; 181; 182; 185; 195; 196; 203; 204; 207; 208; 212; 213; 214; 215; 216; 217; 222; 225; 226; 228; 233; 234; 265; 266; 267; 269; 276; 281; 282; 283; 284; 288; 289; 290; 292; 295; 296; 303; 304; 306; 308; 309; 329; 335; 337; 339; 342; 343; 350; 352; 373; 378; 396; 397; 401; 404; 409; 411; 412; 413; 437; 438; 445; 447; 448; 449; 451; 452; 453; 454; 455; 456 and 457.
- 10
- 15 *Phytophthora infestans*: 3; 13; 28; 38; 39; 40; 48; 50; 52; 54; 55; 56; 58; 59; 73; 77; 78; 84; 87; 89; 97; 98; 99; 101; 103; 104; 105; 108; 109; 110; 111; 112; 113; 114; 115; 118; 119; 121; 122; 124; 125; 126; 127; 128; 130; 132; 134; 139; 133; 135; 140; 141; 143; 145; 146; 147; 150; 151; 154; 162; 164; 166; 168; 169; 170; 171; 182; 187; 201; 203; 204; 205; 206; 207; 208; 211; 212; 213; 216; 217; 222; 225; 226; 246; 248; 252; 259; 260; 262; 264; 265; 276; 277; 278; 281; 282; 283; 284; 285; 290; 292; 306; 342; 343; 378; 397; 409; 411; 412; 413; 445; 447; 448; 451; 452; 453; 454; 455 and 456.
- 20
- 25 *Erysiphe graminis f.sp. tritici*: 3; 4; 7; 13; 28; 191; 201; 203; 205; 206; 207; 208; 212; 213; 216; 217; 220; 222; 224; 226; 234; 235; 238; 246; 248; 252; 253; 258; 259; 260; 261; 264; 265; 255; 278; 282; 283; 284; 288; 289; 290; 292; 315; 396; 401; 403; 404; 405; 408; 409; 411; 412; 413; 423; 426; 427; 435; 437; 447; 448; 449; 450; 451; 452; 453; 454; 455; 456 and 457.
- 30
- 30 *Botrytis cinerea*: 4; 6; 30; 56; 66; 93; 97; 98; 100; 101; 104; 105; 119; 123; 127; 133; 135; 139; 140; 143; 151; 166; 167; 173; 207; 211; 212; 213; 216; 222; 225; 228; 255; 258; 260; 262; 263; 265; 266; 269; 292; 306; 398 and 405.

Puccinia recondita f.sp. tritici: 3; 4; 7; 10; 17; 18; 19; 30; 37; 38; 39; 40; 43; 51; 52; 54; 55; 57; 66; 77; 78; 83; 84; 87; 89; 93; 96; 97; 98; 100; 101; 103; 104; 107; 108; 110; 119; 121; 125; 126; 127; 128; 129; 130; 135; 136; 143; 151; 154; 155; 162; 164; 166; 167; 168; 169; 5 170; 171; 172; 173; 174; 175; 204; 205; 206; 207; 208; 211; 212; 213; 215; 216; 217; 219; 220; 222; 225; 226; 228; 234; 235; 238; 244; 245; 246; 248; 252; 253; 255; 258; 259; 260; 261; 262; 263; 264; 265; 267; 277; 278; 282; 283; 288; 289; 294; 295; 303; 319; 337; 342; 343; 369; 373; 378; 395; 396; 401; 403; 404; 405; 408; 409; 411; 412; 413; 423; 424; 427; 432; 433; 437; 448; 449; 450; 451; 452; 453; 454; 455; 456; 457 and 447.

10

In addition, the compounds of the invention were also tested for their ability to inhibit the growth of fungal spores in nutrient broth.

15 a) *Septoria tritici* (wheat leaf blotch), *Botrytis cinerea* (grey mould), *Pyricularia oryzae* (rice blast), *Rhizoctonia solani* (foot rot and damping off), *Fusarium culmorum* (foot rot of cereals): Conidia of the fungus from cryogenic storage were directly mixed into nutrient broth (PDB potato dextrose broth). After placing a (DMSO) solution of the test compounds at 20 ppm into a microtiter plate (96-well format) the nutrient broth containing 20 the fungal spores was added. The test plates were incubated at 24 C and the inhibition of growth was determined photometrically after 72 hrs (*Septoria tritici*, *Botrytis cinerea*, *Pyricularia oryzae*) or 48 hrs (*Rhizoctonia solani*, *Fusarium culmorum*).

b) *Pythium ultimum* (Damping off): Mycelial fragments of the fungus, prepared from 25 a fresh liquid culture, were mixed into potato dextrose broth. A (DMSO) solution of the test compound at 20ppm was then placed into a 96-well microtiter plate and the nutrient broth containing the fungal spores was added. The test plate was incubated at 24°C and the inhibition of growth was determined photometrically after 48 hours.

30 The following compounds (numbering corresponds to Tables 1, 2 and 3 above) gave at least 80% control of the following fungal infection at 20ppm in the liquid culture assays described above:

Septoria tritici: 4; 6; 7; 8; 10; 11; 13; 14; 17; 18; 26; 30; 33; 37; 38; 43; 47; 48; 52; 53; 54; 56; 57; 58; 59; 60; 62; 77; 78; 83; 84; 87; 89; 93; 96; 97; 98; 99; 100; 101; 103; 104; 105; 107; 108; 119; 126; 127; 128; 136; 142; 143; 156; 162; 166; 167; 168; 169; 170; 171; 172; 178; 181; 191; 193; 195; 196; 201; 204; 205; 207; 210; 216; 217; 219; 220; 222; 225; 226;
 5 228; 234; 245; 246; 248; 252; 255; 257; 258; 259; 261; 263; 264; 265; 267; 276; 278; 282; 284; 285; 303; 306; 307; 327; 329; 339; 342; 343; 352; 369; 373; 378; 382; 389; 395; 396; 397; 398; 401; 404; 405; 408; 409; 411; 412; 413; 419; 420; 422; 423; 427; 428; 429; 431; 433; 437; 448; 449; 450; 451; 452; 453; 454; 455; 456; and 457.

10

Pyricularia oryzae: 4; 7; 13; 14; 26; 30; 33; 37; 38; 40; 43; 48; 56; 60; 83; 84; 92; 96; 97; 99; 100; 103; 104; 107; 108; 119; 123; 126; 127; 135; 136; 142; 143; 178; 181; 189; 191; 192; 194; 195; 196; 200; 201; 209; 216; 217; 219; 220; 222; 225; 226; 228; 278; 280; 282 and 306.

15

Pythium ultimum: 4; 6; 7; 8; 10; 13; 16; 17; 18; 27; 30; 38; 40; 43; 48; 50; 52; 53; 54; 55; 57; 58; 59; 62; 73; 76; 77; 78; 89; 91; 93; 97; 98; 99; 100; 101; 103; 104; 105; 106; 107; 108; 109; 110; 111; 112; 113; 115; 117; 119; 121; 123; 124; 125; 126; 127; 129; 130; 132; 133; 134; 135; 136; 139; 141; 143; 145; 146; 147; 148; 149; 150; 151; 152; 154; 155; 162; 166;
 20 167; 168; 169; 170; 171; 172; 175; 195; 196; 197; 201; 203; 204; 205; 206; 207; 208; 210; 212; 216; 217; 219; 220; 222; 224; 225; 226; 234; 244; 245; 248; 251; 255; 256; 257; 258; 259; 260; 261; 262; 263; 264; 265; 266; 267; 269; 276; 278; 282; 283; 284; 288; 289; 307; 308; 329; 337; 339; 342; 343; 348; 352; 369; 373; 378; 394; 396; 397; 398; 400; 401; 404; 405; 408; 409; 411; 412; 413; 420; 427; 429; 432; 433; 435; 436; 437; 445; 448; 449; 450;
 25 451; 452; 453; 454; 455; 456; 457; 395; 399; 402; 403 and 447.

Fusarium culmorum: 4; 6; 7; 10; 13; 38; 40; 43; 84; 97; 104; 128; 133; 162; 166; 168; 169;
 30 216; 217; 220; 222; 234; 248; 255; 259; 264; 265; 278; 397; 398; 409; 413; 404; 405; 411; 412; 449 and 452.

Example 14 – HPLC Methods Used

Method A (Water Alliance 2795 LC) with the following HPLC gradient conditions :

Solvent A: 0.1% formic acid in water/ acetonitrile (9:1)

Solvent B: 0.1% formic acid in acetonitrile)

	Time (minutes)	A (%)	B (%)	Flow rate (ml/min)
5	0	90	10	1.7
	2.5	0	100	1.7
	2.8	0	100	1.7
	2.9	90	10	1.7

10 Type of column: Water atlantis dc18; Column length: 20 mm; Internal diameter of column: 3 mm; Particle Size: 3 micron; Temperature: 40°C.

The characteristic values obtained for each compound were the retention time ("RT", recorded in minutes) and the molecular ion, typically the cation MH^+ as listed in Tables 1, 2 and 3. The HPLC-MS method used is indicated in brackets.

15

Method B (Agilent1100 Series LC) with the following HPLC gradient conditions :

Solvent A: 0.1% formic acid in water / acetonitrile (9:1)

Solvent B: 0.1% formic acid in acetonitrile)

	Time (minutes)	A (%)	B (%)	Flow rate (ml/min)
20	0	90	10	1.7
	2.5	0	100	1.7
	2.8	0	100	1.7
	2.9	90	10	1.7

25 Type of column: Water atlantis dc18; Column length: 20 mm; Internal diameter of column: 3 mm; Particle Size: 3 micron; Temperature: 40°C.

The characteristic values obtained for each compound were the retention time ("RT", recorded in minutes) and the molecular ion, typically the cation MH^+ as listed in Tables 1,2 and 3. The HPLC-MS method used is indicated in brackets.

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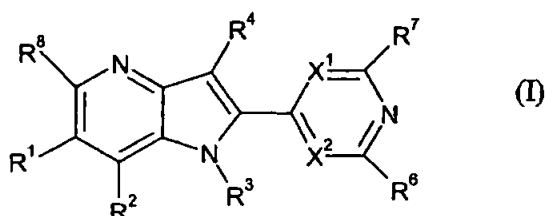
Although the invention has been described with reference to preferred embodiments and examples thereof, the scope of the present invention is not limited only to those

described embodiments. As will be apparent to persons skilled in the art, modifications and adaptations to the above-described invention can be made without departing from the spirit and scope of the invention, which is defined and circumscribed by the appended claims. All publications cited herein are hereby incorporated by reference in their entirety for all

5 purposes to the same extent as if each individual publication were specifically and individually indicated to be so incorporated by reference.

CLAIMS

1. A method of preventing and/or controlling fungal infection in plants and/or plant propagation material comprising applying to the plant or plant propagation material a fungicidally effective amount of a compound of formula (I):



wherein:

10 X^1 is N or CH;

X^2 is N or CR⁵;

R^1 and R^2 are, independently,:

- 15 (i) hydrogen, halogen, hydroxyl, cyano or nitro,
 (ii) optionally substituted alkyl, alkenyl or alkynyl,
 (iii) optionally substituted aryl, heteroaryl, cyclyl or heterocyclyl, or
 (iv) -C(O)R¹⁰, -C(O)NR¹⁰R¹¹, -C(S)NR¹⁰R¹¹, -C(NOR¹⁰)R¹¹, -C(O)OR¹⁰, -OR¹⁰, -SR¹⁰,
 -S(O)R¹⁰, -S(O)NR¹⁰R¹¹, -S(O)₂R¹⁰, -NR¹⁰R¹¹, -P(O)(OR¹⁰)(OR¹¹), or
 20 -OP(O)(OR¹⁰)(OR¹¹);

R^3 is:

- (i) hydrogen, hydroxyl, cyano or nitro,
 (ii) optionally substituted alkyl, alkenyl, allenyl, alkynyl or haloalkyl,
 25 (iii) optionally substituted aryl, heteroaryl, cyclyl or heterocyclyl or heteroaralkyl, or
 (iv) -C(O)R¹², -C(O)OR¹², -OR¹², -OC(O)R¹², -S(O)₂R¹², or -NR¹²R¹³;

R^4 is:

- (i) hydrogen, halogen, hydroxyl, cyano or nitro,
 30 (ii) optionally substituted alkenyl, allenyl, alkynyl or haloalkyl,

(iii) optionally substituted aryl, heteroaryl, cyclyl or heterocyclyl or

(iv) $-C(O)R^{14}$, $-C(O)OR^{14}$, $-C(NOR^{14})R^{15}$, $-OR^{14}$, $-SR^{14}$, $-S(O)NR^{14}R^{15}$, $-S(O)_2R^{14}$, or $-NR^{14}R^{15}$;

5 R^5 is:

(i) hydrogen, halogen, hydroxyl, cyano or nitro,

(ii) optionally substituted alkyl, alkenyl or alkynyl,

(iii) $-C(O)R^{16}$, $-C(O)OR^{16}$, $-OR^{16}$, $-SR^{16}$, $-S(O)R^{16}$, $-S(O)NR^{16}R^{17}$, $-S(O)_2R^{16}$, or $-NR^{16}R^{17}$;

10

R^6 is hydrogen, halogen, cyano, $-C(O)OR^{18}$, $-SR^{18}$, $-NR^{18}R^{19}$, $-C(O)NR^{18}R^{19}$, $-N=CR^{20}$, $-C(=NR^{18})NR^{19}R^{20}$ or optionally substituted aryl, heteroaryl, cyclyl or heterocyclyl;

15

R^7 and R^8 are, independently, hydrogen, halogen, hydroxyl, cyano, nitro, $-NR^{21}R^{22}$ or optionally substituted alkyl;

20

R^{10} , R^{11} , R^{14} , R^{15} , R^{16} and R^{17} are, independently, hydrogen, halogen, hydroxyl, cyano, nitro, optionally substituted alkyl, alkoxy, alkenyl or alkynyl, or optionally substituted aryl, heteroaryl, cyclyl or heterocyclyl;

25

R^{18} and R^{19} are, independently,

(i) hydrogen,

(ii) optionally substituted alkyl, alkenyl or alkynyl,

(iii) optionally substituted aryl, heteroaryl, cyclyl or heterocyclyl, or

(iv) $-C(S)R^{23}$, $-C(O)R^{23}$, $-SO_2R^{23}$, $-C(O)OR^{23}$, $-OR^{23}$ or $C(O)NR^{23}R^{24}$;

30

R^{20} is hydroxyl, optionally substituted alkyl or alkoxy, $-NR^{21}R^{22}$, or $-N=CR^{21}R^{22}$;

144
R²¹ and R²² are, independently, hydrogen, optionally substituted alkyl, alkenyl or alkynyl, optionally substituted cyclyl, heterocyclyl, aryl or heteroaryl or aralkyl or -C(O)OR²⁵;

5 R²³ and R²⁴ are, independently, hydrogen, hydroxyl, optionally substituted alkyl, alkenyl or alkynyl, or optionally substituted aryl, heteroaryl, cyclyl or heterocyclyl or aralkyl; and

R²⁵ is optionally substituted alkyl, alkenyl or alkynyl;

10

and/or

independently, (i) R¹ and R², (ii) R¹ and R³, (iii) R² and R³, (iv) R³ and R⁵, (v) R⁵ and R⁶, (vi) R⁵ and R¹⁸, (vii) R⁵ and R¹⁹, (viii) R¹⁴ and R¹⁵ and (ix) R¹⁸ and R¹⁹ form an
15 optionally substituted aryl, heteroaryl, cyclyl or heterocyclyl group containing from 5 to 18 ring atoms;

or a salt of N-oxide thereof.

20 2. The method of claim 1, wherein X¹ is CH.

3. The method of claim 1 or 2, wherein X² is CH.

4. The method of any one of the preceding claims, wherein R¹ is hydrogen, halogen, cyano, optionally substituted C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl, optionally substituted aryl or -C(O)R¹⁰.
25

5. The method of any one of the preceding claims, wherein R² is hydrogen or C₁₋₆ alkyl.

30 6. The method of any one of the preceding claims, wherein R³ is hydrogen, hydroxyl, -C(O)R¹², -OR¹², -C(O)OR¹², -OC(O)R¹², -S(O)₂R¹², optionally substituted C₁₋₆ alkyl, C₂₋₆ alkenyl, C₃₋₆ allenyl, C₂₋₆ alkynyl or optionally substituted saturated cyclyl.

7. The method of claim 6, wherein R^3 is cyanomethyl, aminoethyl, aminopropyl, prop-2-enyl, prop-2-ynyl, propa-1,2-dienyl, methoxymethyl, 2-fluoromethyl, $-OCH_2C\equiv CH$, $-OCH_2OCH_3$, $-OCH_2CN$, or $-OCH(CH_3)CN$.
- 5 8. The method of claim 6 wherein R^3 is hydrogen.
9. The method of any one of the preceding claims, wherein R^4 is hydrogen, halogen, optionally substituted C_{2-6} alkynyl or optionally substituted aryl or heteroaryl.
- 10 10. The method of claim 9, wherein R^4 is phenyl or 4-fluorophenyl.
11. The method of any preceding claim, wherein R^6 is hydrogen or $-NR^{18}R^{19}$.
12. The method of claim 11, wherein R^6 is $-NHR^{19}$
- 15 13. The method of claim 12, wherein R^{19} is $-C(O)R^{23}$.
14. The method of claim 13 wherein R^{23} is selected from optionally substituted alkyl or cyclyl.
- 20 15. The method of claim 13 wherein R^{23} is selected from hydrogen, methyl, ethyl, *iso*-propyl, 1-methylethyl, 1-methylpropyl, 2-dimethylethyl, propyl, 1-methylethenyl, 2-methylprop-1-enyl, but-3-enyl, cyclopropyl, 1-methylcyclopropyl, 1-fluorocyclopropyl or cyclobutyl.
- 25 16. The method of any one of the preceding claims, wherein R^7 and R^8 are, independently, hydrogen, hydroxyl, cyano, $-NR^{21}R^{22}$ or optionally substituted C_{1-6} alkyl.
- 30 17. The method of claim 1, wherein the compound is one of the compounds set out in Tables 1, 2 or 3.
18. The method of any one of the preceding claims, wherein the fungal infection is a *Botrytis cinerea*, *Pyricularia oryzae*, *Fusarium culmorum*, *Septoria nodurum* and *Septoria tritici*, *Rhizoctonia solani*, *Puccinia recondite*, *Erysiphe graminis*,

Pyrenophora teres, *Phytophthora infestans*, *Pythium ultimum* or *Plasmopara viticola* infection.

19. A compound of formula (I) as defined in any one of claims 1 to 17, with the provisos
 5 that (i) when X^1 is CH, X^2 is CR^5 and R^5 and R^6 are both H, R^4 is not 4-fluorophenyl
 and (ii) the compound of formula (I) is not:

3-phenyl-2-pyridin-4-yl-1H-pyrrolo[3,2-b]pyridine

3-(3-chloro-4-fluoro-phenyl)-2-pyridin-4-yl-1H-pyrrolo[3,2-b]pyridine

10 3-(3-chloro-phenyl)-2-pyridin-4-yl-1H-pyrrolo[3,2-b]pyridine

3-(3-trifluoro-phenyl)-2-pyridin-4-yl-1H-pyrrolo[3,2-b]pyridine

3-(3-methoxy-phenyl)-2-pyridin-4-yl-1H-pyrrolo[3,2-b]pyridine

3-(2-methylphenyl)-2-pyridin-4-yl-1H-pyrrolo[3,2-b]pyridine

3-(2-methoxyphenyl)-2-pyridin-4-yl-1H-pyrrolo[3,2-b]pyridine

15 1-methyl-2-pyridin-4-yl-3-(3-trifluoromethyl-phenyl)-1H-pyrrolo[3,2-b]pyridine

1-methyl-3-(3-chloro-4-fluoro-phenyl)-2-pyridin-4-yl-1H-pyrrolo[3,2-b]pyridine

3-(4-fluorophenyl)-2-(2-(2-hydroxyethyl-amino)-pyridin-4-yl)-1H-pyrrolo[3,2-
 b]pyridine,

3-(4-fluorophenyl)-2-(2-[HO(CH₂)₂O(CH₂)₂NH]-pyridin-4-yl)-1H-pyrrolo[3,2-
 20 b]pyridine,

3-(4-fluorophenyl)-2-(2-(2-methylamino-ethylamino)-pyridin-4-yl)-1H-pyrrolo[3,2-
 b]pyridine,

3-(4-fluorophenyl)-2-(2-(3-methoxy-propyl-amino)-pyridin-4-yl)-1H-pyrrolo[3,2-
 b]pyridine,

25 3-(4-fluorophenyl)-2-(2-*n*-propylamino-pyridin-4-yl)-1H-pyrrolo[3,2-b]pyridine,

3-(4-fluorophenyl)-2-(2-(3-hydroxy-propyl-amino)-pyridin-4-yl)-1H-pyrrolo[3,2-
 b]pyridine,

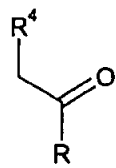
3-(4-fluorophenyl)-2-(2-methylamino-pyridin-4-yl)-1H-pyrrolo[3,2-b]pyridine or

3-(4-fluorophenyl)-2-(2-acetylamino pyridin-4-yl)-1H-pyrrolo[3,2-b]pyridine.

30

20. A process for the preparation of a compound of formula (I) as claimed in claim 1,
 comprising:

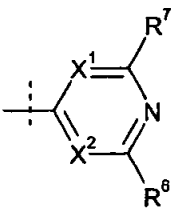
a) reacting a ketone of formula (D)



(D)

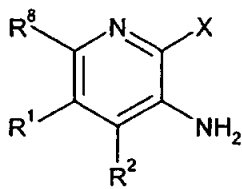
wherein R^4 is as defined in claim 1, and R is a group of formula

5



wherein X^1 , X^2 , R^6 and R^7 are as defined in claim 1, with an aminopyridine of formula (E)

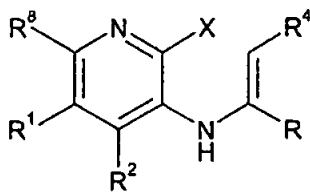
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(E)

wherein R^1 , R^2 and R^8 are as defined in claim 1, and X is a halogen, to give an enamine of formula (F),

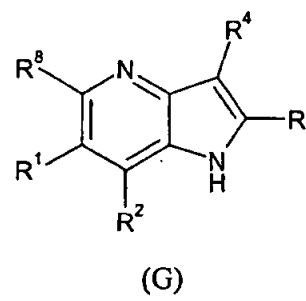
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(F)

cyclising to give an azaindole of formula (G),

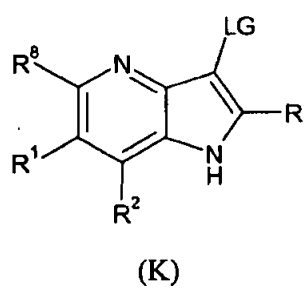
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and optionally alkylating to give a compound of formula (I) as defined in claim 1; or

5

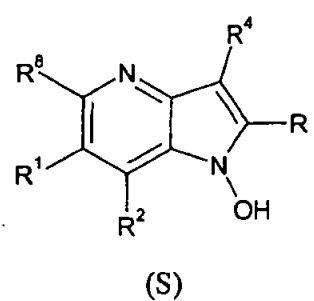
- b) reacting an azaindole of formula (K)



10 wherein R¹, R² and R³ are as defined in claim 1, R is as defined above, and LG is a leaving group with a compound of formula R⁴-B(OH)₂ wherein R⁴ is as defined in claim 1, to give a compound of formula (G) as defined above, and optionally alkylating to give a compound of formula (I) as defined in claim 1;

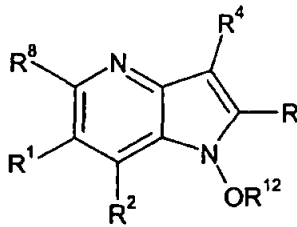
- 15 c) reacting a compound of formula (G) above with a compound of formula R³-LG wherein LG is a leaving group to give a compound of formula (I) as defined in claim 1;

- d) reacting a compound of formula (S)



20

wherein R^1 , R^2 , R^4 , and R^8 are defined in claim 1, and R is as defined above, with a compound of formula R^{12} -LG wherein R^{12} is as defined in claim 1 and LG is a leaving group, to give a compound of formula (T)



(T)

wherein R^1 , R^2 , R^4 , R^8 , and R^{12} are defined in claim 1, and R is as defined above, or

5

- e) converting a compound of formula (I) as defined in claim 1 to a salt of N-oxide thereof.

10

- 21. A composition for the control of fungal infection comprising a compound of formula I as defined in any one of claims 1 to 17 and an agriculturally acceptable carrier or diluent.

15

- 22. A composition for the control of fungal infection comprising a compound of claim 18.

- 23. The composition of claims 21 or 22 which further comprises at least one active ingredient selected from fungicides, herbicides, insecticides, bactericides, acaricides, nematocides and/or plant growth regulators.

20

- 24. A compound of formula (I) as defined in the method of any one of claims 1 to 17 for the treatment of fungal infection in humans or animals.

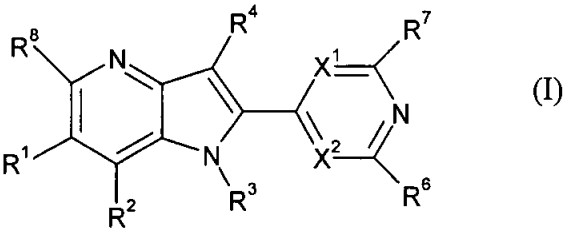
DERIVADOS DE 4-AZA INDOL Y SU USO COMO FUNGICIDAS

La presente invención se refiere a nuevos 4-aza-indoles activos como fungicidas, a composiciones que comprenden estos nuevos compuestos y a su uso en métodos para el control y/o la prevención de infecciones fúngicas en las plantas. Además, la invención se refiere a procesos para preparar los nuevos compuestos de la invención.

Ciertos 4-aza-indoles y su utilización en la prevención y tratamiento de enfermedades humanas y animales, aunque no de aquéllas causadas por hongos, se encuentran descritos en WO 99/20624. Compuestos similares están descritos en WO 03/06629, WO 2006/014325 y WO 98/22457, la última también describe su uso como agentes anti-inflamatorios.

Ahora se ha descubierto que ciertos 4-aza-indoles poseen actividad fungicida y, en particular, actividad frente a hongos patógenos de las plantas.

En consecuencia, la presente invención provee un método de prevención y/o control de la infección fúngica en las plantas y/o material de propagación de plantas que comprende aplicar a las plantas o material de propagación de plantas una cantidad efectiva como fungicida de un compuesto de la fórmula (I):



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donde:
X¹ es N o CH;

X₂ es N o CR⁵;

R^1 y R^2 son, independientemente,:

- (i) hidrógeno, halógeno, hidroxilo, ciano o nitro,
- (ii) alquilo, alquenilo o alquinilo opcionalmente sustituido,
- (iii) arilo, heteroarilo, ciclilo o heterociclilo opcionalmente sustituido, o
- (iv) $-C(O)R^{10}$, $-C(O)NR^{10}R^{11}$, $-C(S)NR^{10}R^{11}$, $-C(NOR^{10})R^{11}$, $-C(O)OR^{10}$, $-OR^{10}$, $-SR^{10}$, $-S(O)R^{10}$, $-S(O)NR^{10}R^{11}$, $-S(O)_2NR^{10}R^{11}$, $-S(O)_2R^{10}$, $-NR^{10}R^{11}$, $-P(O)(OR^{10})(OR^{11})$ u $-OP(O)(OR^{10})(OR^{11})$;

R^3 es:

- (i) hidrógeno, hidroxilo, ciano o nitro,
- (ii) alquilo, alquenilo, alenilo, alquinilo o haloalquilo opcionalmente sustituido,
- (iii) arilo, heteroarilo, ciclilo o heterociclilo o heteroaralquilo opcionalmente sustituido o
- (iv) $-C(O)R^{12}$, $-C(O)OR^{12}$, $-OR^{12}$, $-OC(O)R^{12}$, $-S(O)_2R^{12}$ o $-NR^{12}R^{13}$;

R^4 es:

- (i) hidrógeno, halógeno, hidroxilo, ciano o nitro,
- (ii) alquilo, alquenilo, alenilo, alquinilo o haloalquilo opcionalmente sustituido,
- (iii) arilo, heteroarilo, ciclilo o heterociclilo opcionalmente sustituido o
- (iv) $-C(O)R^{14}$, $-C(O)OR^{14}$, $-C(NOR^{14})R^{15}$, $-OR^{14}$, $-SR^{14}$, $-S(O)NR^{14}R^{15}$, $-S(O)_2R^{14}$, o $-NR^{14}R^{15}$;

R^5 es:

- (i) hidrógeno, halógeno, hidroxilo, ciano o nitro,
- (ii) alquilo, alquenilo o alquinilo opcionalmente sustituido,
- (iii) $-C(O)R^{16}$, $-C(O)OR^{16}$, $-OR^{16}$, $-SR^{16}$, $-S(O)R^{16}$, $-S(O)NR^{16}R^{17}$, $-S(O)_2R^{16}$, o $-NR^{16}R^{17}$;

R^6 es hidrógeno, halógeno, ciano, $-C(O)OR^{18}$, $-SR^{18}$, $-NR^{18}R^{19}$, $-C(O)NR^{18}R^{19}$ o

$-N=CR^{20}$, $-C(=NR^{18})NR^{19}R^{20}$ o arilo, heteroarilo, ciclilo o heterociclilo opcionalmente sustituido;

R^7 y R^8 son, independientemente, hidrógeno, halógeno, hidroxilo, ciano, nitro, $-NR^{21}R^{22}$ o alquilo opcionalmente sustituido;

R^{10} , R^{11} , R^{14} , R^{15} , R^{16} y R^{17} son, independientemente, hidrógeno, halógeno, hidroxilo, ciano, nitro, alquilo, alcoxi, alquenilo o alquinilo opcionalmente sustituido, o arilo, heteroarilo, ciclilo o heterociclilo opcionalmente sustituido;

R^{12} y R^{13} son, independientemente, hidrógeno, halógeno, hidroxilo, ciano, nitro, $-NR^{21}R^{22}$, alquilo, alcoxi, alquenilo o alquinilo opcionalmente sustituido, o arilo, heteroarilo, ciclilo o heterociclilo opcionalmente sustituido;

R^{18} y R^{19} son, independientemente,

- (i) hidrógeno,
- (ii) alquilo, alquenilo o alquinilo opcionalmente sustituido,
- (iii) arilo, heteroarilo, ciclilo o heterociclilo opcionalmente sustituido, o
- (iv) $-C(S)R^{23}$, $-C(O)R^{23}$, $-SO_2R^{23}$, $-C(O)OR^{23}$, $-OR^{23}$ o $C(O)NR^{23}R^{24}$;

R^{20} es hidroxilo, alquilo o alcoxi opcionalmente sustituido o $-NR^{21}R^{22}$, o $-N=CR^{21}R^{22}$;

R^{21} y R^{22} son, independientemente, hidrógeno, alquilo, alquenilo o alquinilo opcionalmente sustituido, ciclilo, heterociclilo, arilo, o heteroarilo o aralquilo opcionalmente sustituido o $-C(O)OR^{25}$;

R^{23} y R^{24} son, independientemente, hidrógeno, hidroxilo, alquilo, alquenilo o alquinilo opcionalmente sustituido, o arilo, heteroarilo, ciclilo o heterociclilo o aralquilo opcionalmente sustituido; y

R²⁵ es alquilo, alquenilo o alquinilo opcionalmente sustituido;

y/o

independientemente, (i) R¹ y R², (ii) R¹ y R³ (iii) R² y R³, (iv) R³ y R⁵, (v) R⁵ y R⁶, (vi) R⁵ y R¹⁸, (vii) R⁵ y R¹⁹, (viii) R¹⁴ y R¹⁵ y (ix) R¹⁸ y R¹⁹ forman un grupo arilo, heteroarilo, ciclilo o heterociclilo opcionalmente sustituido que contiene de 5 a 18 átomos en el anillo;

o una sal de N-óxido del mismo.

A menos que se afirme de otro modo, los siguientes términos utilizados en la memoria descriptiva y en las reivindicaciones poseen los significados que se proporcionan a continuación:

"Alquilo" significa un radical hidrocarburo saturado monovalente lineal de uno a ocho átomos de carbono o un radical hidrocarburo saturado monovalente ramificado de tres a ocho átomos de carbono, por ejemplo metilo, etilo, *n*-propilo, *iso*-propilo, *n*-butilo, *sec*-butilo, *iso*-butilo, *terc*-butilo, *n*-pentilo, *n*-hexilo y similares. Con preferencia, los grupos alquilo lineales contienen uno a seis átomos de carbono, con más preferencia uno a cuatro átomos de carbono y aún con más preferencia están seleccionados de metilo, etilo o *n*-propilo. Con preferencia, los grupos alquilo ramificados contienen tres a seis átomos de carbono y con más preferencia están seleccionados de *iso*-propilo, *sec*-butilo, *iso*-butilo o *terc*-butilo.

"Alquenilo" significa un radical hidrocarburo saturado monovalente lineal de dos a ocho átomos de carbono, o un radical hidrocarburo monovalente ramificado de tres a ocho átomos de carbono que contiene al menos un enlace doble, por ejemplo etenilo, propenilo y similares. Cuando sea apropiado, un grupo alquenilo puede ser o bien de la configuración (E)- o (Z)-. Con preferencia, los grupos alquenilo lineales contienen dos a seis átomos de carbono y con más preferencia

están seleccionados de etenilo, prop-1-enilo, prop-2-enilo, prop-1,2-dienilo, but-1-enilo, but-2-enilo, but-3-enilo, but-1,2-dienilo y but-1,3-dienilo. Con preferencia, los grupos alquenilo ramificados contienen tres a seis átomos de carbono y con más preferencia están seleccionados de 1-metiletlenilo, 1-metilprop-1-enilo, 1-metilprop-2-enilo, 2-metilprop-1-enilo y 2-metilprop-2-enilo.

“Alenilo” significa un radical hidrocarburo saturado monovalente lineal de tres a ocho átomos de carbono, o un radical hidrocarburo monovalente ramificado de tres a ocho átomos de carbono que contiene al menos dos enlaces dobles entre tres átomos de carbono contiguos, por ejemplo propa-1,2 dienilo, penta-1,2 dienilo, penta-2,3 dienilo, hexa-1,2-dienilo y similares. Cuando sea apropiado, un grupo alquenilo puede ser o bien de la configuración (R)- o (S)-. Se prefiere el propa-1,2-dienilo.

“Alquinilo” significa un radical hidrocarburo saturado monovalente lineal de dos a ocho átomos de carbono, o un radical hidrocarburo monovalente ramificado de cuatro a ocho átomos de carbono, que contiene al menos un enlace triple, por ejemplo etinilo, propinilo y similares. Con preferencia, los grupos alquinilo lineales contienen dos a seis átomos de carbono y con más preferencia están seleccionados de etinilo, prop-1-inilo, prop-2-inilo, but-1-inilo, but-2-inilo y but-3-inilo. Con preferencia, los grupos alquinilo ramificados contienen cuatro a seis átomos de carbono y con más preferencia están seleccionados de 1-metilprop-2-inilo, 3-metilbut-1-inilo, 1-metilbut-2-inilo, 1-metilbut-3-inilo y 1-metilbut-3-inilo.

“Alquilenio” significa un radical hidrocarburo saturado divalente lineal de uno a seis átomos de carbono o un radical hidrocarburo saturado divalente ramificado de tres a seis átomos de carbono, por ejemplo metileno, etileno, propileno, 2-metilpropileno y similares. Los grupos alquilenio preferidos son los radicales divalentes de los grupos alquilo definidos precedentemente.

“Alquenileno” significa un radical hidrocarburo divalente lineal de dos a seis átomos de carbono o un radical hidrocarburo divalente ramificado de tres a seis

átomos de carbono, que contiene al menos un enlace doble, por ejemplo etenileno, propenileno y similares. Los grupos alquenileno preferidos son los radicales divalentes de los grupos alqueno definidos precedentemente.

“Ciclilo” significa un radical hidrocarburo cíclico monovalente de tres a ocho carbonos en el anillo, con preferencia tres a seis carbonos en el anillo, por ejemplo ciclopropilo, ciclohexilo y similares. Los grupos ciclilo pueden estar completamente saturados o mono- o di-insaturados. Con preferencia, los grupos ciclilo contienen tres a seis carbonos en el anillo, con más preferencia ellos están seleccionados de ciclopropilo, ciclobutilo, ciclopentilo y ciclohexilo. Los grupos ciclilo mono-insaturados con preferencia están seleccionados de ciclobutenilo, ciclopentenilo y ciclohexenilo.

“Heterociclilo” significa un radical ciclilo que contiene uno, dos o tres heteroátomos en el anillo seleccionados de N, O o $S(O)_n$ (donde n es un entero de 0 a 2), siendo los átomos del anillo restantes carbono donde uno o dos átomos de carbono pueden opcionalmente estar reemplazados con un grupo carbonilo. Los ejemplos de dichos anillos incluyen, pero no se limitan a, oxirano, oxetano, tetrahydrofurano, tetrahydropirano, 1,3-dioxolano, 1,4-dioxano, aziridina, azetidina, pirrolidina, piperidina, oxazinano, morfolina, tiomorfolina, imidazolidina, pirazolidina y piperazina. Con más preferencia, el grupo heterociclilo contiene tres a cinco átomos en el anillo incluyendo un átomo de O y/o uno de N en el anillo.

“Arilo” significa un radical hidrocarburo aromático monocíclico o bicíclico monovalente de seis a diez átomos de carbono en el anillo. Los grupos arilo adecuados incluyen fenilo y naftilo, en particular, fenilo.

“Heteroarilo” significa un radical hidrocarburo aromático monocíclico o bicíclico monovalente de cinco a diez átomos en el anillo, con preferencia cinco o seis átomos en el anillo, que contiene uno, dos, tres o cuatro heteroátomos en el anillo seleccionados, independientemente, de N, O o S, siendo los átomos del

anillo restantes carbono. Los ejemplos de grupos heteroarilo incluyen, pero no se limitan a los grupos piridilo, pirimidinilo, pirazolilo, tiazolilo, tiofenilo, isoazolilo, y tetrazolilo.

“Alcoxi” significa un radical -OR, donde R es alquilo, alquenilo o alquinilo opcionalmente sustituido o un grupo ciclilo, heterociclilo, arilo o heteroarilo opcionalmente sustituido o un grupo aralquilo o heteroaralquilo. Con preferencia, los grupos alcoxi están seleccionados de metoxi, etoxi, 1-metiletoxi, propoxi, 1-metilpropoxi y 2-metilpropoxi. Con más preferencia alcoxi significa metoxi o etoxi.

“Halo” o “halógeno” significa flúor, cloro, bromo o yodo, con preferencia cloro o flúor.

“Haloalquilo” significa alquilo según se definió precedentemente sustituido con uno o más de los mismos o diferentes átomos de halo. Los ejemplos de grupos haloalquilo incluyen, pero no se limitan a fluormetilo, difluormetilo, trifluormetilo, 2-fluoretilo, 2-trifluoretilo, 2-cloro-etilo, 2-yodoetilo, 3-fluorpropilo, 3-cloropropilo, 2-trifluor-1-cloroetilo y 1-difluor-2-difluor-3-trifluorpropilo.

“Haloalquenilo” significa alquenilo según se definió precedentemente sustituido con uno o más de los mismos o diferentes átomos de halo. Los ejemplos de grupos haloalquenilo incluyen, pero no se limitan a 2-dibromoetenilo, 2-fluor-2-bromoetenilo, 5-bromopent-3-enilo y 3 dicloroprop-2-enilo.

“Aralquilo” significa un radical -R^aR^b donde R^a es un grupo alquilenos o alquenileno y R^b es un grupo arilo según se definió precedentemente.

“Heteroaralquilo” significa un radical -R^aR^b donde R^a es un grupo alquilenos o alquenileno y R^b es un grupo heteroarilo según se definió precedentemente.

“Acilo” significa $-C(O)R$, donde R es hidrógeno, alquilo, alquenilo o alquinilo opcionalmente sustituido o ciclilo, heterociclilo, arilo o heteroarilo opcionalmente sustituido.

“Aciloxi” significa un radical $-OC(O)R$ donde R es hidrógeno, alquilo, alquenilo o alquinilo opcionalmente sustituido o ciclilo, heterociclilo, arilo o heteroarilo opcionalmente sustituido.

Los grupos definidos precedentemente, en particular, los grupos alquilo, alquenilo, alquinilo, ciclilo, heterociclilo, arilo y heteroarilo, pueden estar opcionalmente sustituidos con uno o más sustituyentes independientemente seleccionados de halógeno, hidroxilo, ciano, alquilo (opcionalmente sustituido con ciano), haloalquilo, alquenilo, haloalquenilo, alquinilo (opcionalmente sustituido con $-C(O)OR$), haloalquinilo, ciclilo (opcionalmente sustituido con ciano, halógeno, hidroxilo o metilo), heterociclilo, arilo (opcionalmente sustituido con halógeno), heteroarilo, alcoxi (opcionalmente sustituido con alcoxi o acilo), $-C(O)R$, $-C(O)OR$, $-SR$, $-S(O)R$, $-S(O)_2R$, $-S(O)NRR'$, $-OS(O)NRR'$, $-P(O)(OR)(OR')$, $-O(P)(O)(OR)(OR')$, $-NRR'$, $-NRC(O)OR'$, $-C(O)NRR'$, $-O-N=CRR'$ o trialquilsililo, donde R y R' son, independientemente, hidrógeno o alquilo, alcoxi, haloalquilo, alquenilo, haloalquenilo, alquinilo, ciclilo, heterociclilo, arilo o heteroarilo. En particular, R y R' son, independientemente, hidrógeno o alquilo (en particular, metilo o etilo). Los sustituyentes opcionales preferidos son alcoxi (en particular, metoxi o etoxi), hidroxilo, ciano, halógeno (en particular, flúor, cloro o bromo), heterociclilo (en particular, oxirano o tetrahidrofurano), heteroarilo (en particular, piridilo), $-C(O)OR$ (donde R es hidrógeno o alquilo (en particular, metilo o etilo)) y trialquilsililo (en particular, trimetilsililo).

Los compuestos de la fórmula (I) pueden existir en diferentes formas geométricas o isoméricas ópticas o en diferentes formas tautoméricas. Pueden encontrarse presentes uno o más centros de quiralidad, en cuyo caso los compuestos de la fórmula (I) pueden estar presentes como enantiómeros puros,

mezclas de enantiómeros, diastereómeros puros o mezclas de diastereómeros. Puede haber enlaces dobles presentes en la molécula, tales como los enlaces $C=C$ o $C=N$, en cuyo caso los compuestos de la fórmula (I) pueden existir como isómeros únicos de mezclas de isómeros. Pueden encontrarse presentes centros de tautomerización. Esta invención comprende todos dichos isómeros y tautómeros y las mezclas de los mismos en todas las proporciones así como también las formas isotópicas tales como los compuestos deuterados.

Las sales adecuadas de los compuestos de la fórmula (I) incluyen sales de adición de ácidos tales como aquéllas con un ácido inorgánico tal como el ácido clorhídrico, bromhídrico, sulfúrico, nítrico o fosfórico, o un ácido carboxílico orgánico tal como el ácido oxálico, tartárico, láctico, butírico, toluico, hexanoico o ftálico, o un ácido sulfónico tal como el ácido metan, bencen o toluen sulfónico. Otros ejemplos de ácidos carboxílicos orgánicos incluyen haloácidos tales como el ácido trifluoracético.

Los N-óxidos son formas oxidadas de aminas terciarias o formas oxidadas de compuestos heteroaromáticos que contienen nitrógeno. Ellos se describen en muchos libros por ejemplo en "Heterocyclic N-oxides" por Angelo Albini y Silvio Pietra, CRC Press, Boca Raton, Florida, 1991.

En realizaciones particularmente preferidas de la invención, los grupos preferidos para X^1 y X^2 y R^1 a R^{25} , en cualquier combinación de los mismos, son según se establecen a continuación.

Con preferencia, X^1 es CH.

Con preferencia, X^2 es CR^5 . Con más preferencia, X^2 es CH.

Con preferencia, R^1 es hidrógeno, halógeno, ciano, alquilo C_{1-6} , alquenilo C_{2-6} o alquinilo C_{2-6} opcionalmente sustituido, arilo opcionalmente sustituido o

$-C(O)R^{10}$, donde los sustituyentes opcionales en todos los casos son según se definieron precedentemente y, con más preferencia, están seleccionados de hidroxilo, alcoxi, halógeno o trialkilsililo. Con más preferencia, R^1 es hidrógeno, halógeno, ciano o alquilo C_{1-6} o alquinilo C_{2-6} opcionalmente sustituido (en particular, el alquinilo C_{2-6} es 2-trimetilsilil-etinilo). Aún con más preferencia, R^1 es hidrógeno, cloro, bromo, ciano o metilo. Aún con más preferencia, R^1 es hidrógeno, cloro o metilo.

Con preferencia, R^2 es hidrógeno o alquilo C_{1-6} . Con más preferencia, R^2 es hidrógeno o metilo. Aún con más preferencia, R^2 es hidrógeno.

Con preferencia, R^3 es hidrógeno, hidroxilo, $-C(O)R^{12}$, $-OR^{12}$, $-C(O)OR^{12}$, $-OC(O)R^{12}$, $-S(O)_2R^{12}$, alquilo C_{1-6} , alquenilo C_{2-6} , alenilo C_{3-6} , alquinilo C_{2-6} opcionalmente sustituido o ciclilo saturado opcionalmente sustituido, donde los sustituyentes opcionales en todos los casos son según se definieron precedentemente y, con más preferencia, están seleccionados de ciano, halógeno, hidroxilo, alquilo C_{1-4} , alquenilo C_{2-4} , alcoxi (opcionalmente sustituido con alcoxi o acilo), ciclilo, heterociclilo, arilo, heteroarilo, $-NH_2$, trialkilsililo, $-C(O)R$ o $-C(O)OR$ (donde R es hidrógeno, metilo o etilo). Con más preferencia, R^3 es hidrógeno, $-OR^{12}$ o alquilo C_{1-6} , alquenilo C_{2-4} , alenilo C_{3-4} o alquinilo C_{2-4} opcionalmente sustituido. Aún con más preferencia, R^3 es hidrógeno, cianometilo, aminoetilo, aminopropilo, prop-2-enilo, prop-2-inilo, propa-1,2-dienilo, metoximetilo, 2-fluormetilo, $-OCH_2C\equiv CH$, $-OCH_2OCH_3$, $-OCH_2CN$, $-OCH(CH_3)CN$.

Con preferencia, R^4 es hidrógeno, halógeno, alquinilo C_{2-6} opcionalmente sustituido o arilo o heteroarilo opcionalmente sustituido, donde los sustituyentes opcionales son según se definieron precedentemente y, con más preferencia, están seleccionados de hidroxilo, halógeno (en particular, fluor o cloro), haloalquilo, acilo o alquilo C_{1-4} (en particular, metilo). Con más preferencia, R^4 es fenilo opcionalmente sustituido o heteroarilo opcionalmente sustituido. Aún con más preferencia, R^4 es fenilo opcionalmente sustituido. Aún con más preferencia,

R^4 es fenilo, 3-metilfenilo, 3-trifluormetilfenilo, 4-clorofenilo, 2-fluorfenilo, 3-fluorfenilo, 4-fluorfenilo, 2,5-difluorfenilo o 3-metil-4-fluorfenilo. Aún con más preferencia, R^4 es fenilo o 4-fluorfenilo.

Con preferencia R^5 es hidrógeno, halógeno, alquilo C_{1-6} , alquenilo C_{2-6} o alquinilo C_{2-6} opcionalmente sustituido, o forma un anillo arilo, heterarilo, ciclilo o heterocicilo opcionalmente sustituido con R^6 , donde los sustituyentes opcionales en todos los casos son según se definieron precedentemente y, con más preferencia, están seleccionados de halógeno, ciano, hidroxilo, haloalquilo o alquilo C_{1-4} . Con preferencia, el anillo formado con R^6 es un heterociclo de 5 o 6 miembros. Con más preferencia, R^5 es hidrógeno o halógeno. Aún con más preferencia, R^5 es hidrógeno.

Con preferencia R^6 es hidrógeno, cloro, $-C(O)OR^{18}$, $-NR^{18}R^{19}$, $-N=CR^{20}$ o forma un anillo arilo, heteroarilo, ciclilo o heterocicilo opcionalmente sustituido con R^5 según se definió precedentemente. Con más preferencia, R^6 es hidrógeno o $-NR^{18}R^{19}$. Con más preferencia, R^6 es $-NHR^{19}$. Con más preferencia, R^6 es $-NHC(O)R^{23}$.

Con preferencia R^7 y R^8 son, independientemente, hidrógeno, hidroxilo, ciano, $-NR^{21}R^{22}$ o alquilo C_{1-6} opcionalmente sustituido, donde los sustituyentes opcionales son según se definieron precedentemente y, con más preferencia, están seleccionados de halógeno, ciano, hidroxilo o haloalquilo. Con más preferencia, R^7 y R^8 son, independientemente hidrógeno, hidroxilo o $-NR^{21}R^{22}$. Aún con más preferencia, R^7 y R^8 son ambos hidrógeno.

Con preferencia, R^{10} , R^{11} , R^{14} , R^{15} , R^{16} y R^{17} son, independientemente, hidrógeno o alquilo C_{1-6} , alquenilo C_{2-6} o alquinilo C_{2-6} opcionalmente sustituido, donde los sustituyentes opcionales son según se definieron precedentemente y, con más preferencia, son hidroxilo, halógeno, ciano o alcoxi. Con más preferencia R^{10} , R^{11} , R^{14} , R^{15} , R^{16} y R^{17} son, independientemente, hidrógeno o alquilo C_{1-3}

opcionalmente sustituido. Aún con más preferencia, R^{10} , R^{11} , R^{14} , R^{15} , R^{16} y R^{17} son, independientemente, hidrógeno, metilo o etilo.

Con preferencia R^{12} y R^{13} son, independientemente, alquilo C_{1-6} , alquenilo C_{2-6} o alquinilo C_{2-6} opcionalmente sustituido o ciclilo C_{3-6} opcionalmente sustituido, donde los sustituyentes opcionales en todos los casos son según se definieron precedentemente y, con más preferencia son hidroxilo, halógeno, ciano, alcoxi, ciclilo (opcionalmente sustituido con hidroxilo o metilo), $-C(O)OR$, $-OS(O)NRR'$ (donde R y R' son, independientemente, hidrógeno, alquilo, alquenilo o alquinilo). Con más preferencia, R^{12} y R^{13} son, independientemente, alquilo C_{1-4} , alquenilo C_{2-4} o alquinilo C_{2-4} opcionalmente sustituido. Aún con más preferencia, R^{12} y R^{13} son, independientemente, cianometilo, prop-2-enilo o prop-2-inilo.

Con preferencia R^{18} es hidrógeno, alquilo C_{1-6} , alquenilo C_{2-6} o alquinilo C_{2-6} opcionalmente sustituido, $-C(O)R^{23}$, $-C(O)OR^{23}$, $-S(O)_2R^{23}$ o $-C(O)NR^{23}R^{24}$ o forma un anillo heterociclilo opcionalmente sustituido con R^{19} , donde los sustituyentes opcionales en todos los casos son según se definieron precedentemente y, con más preferencia están seleccionados de hidroxilo, ciano, halógeno o alcoxi. Con más preferencia, R^{18} es hidrógeno, alquinilo C_{2-4} , alquenilo C_{2-4} , o alquilo C_{1-4} sustituido. Con preferencia el grupo alquilo C_{1-4} es etilo o *iso*-propilo. Con preferencia, el grupo alquenilo C_{2-4} es propen-2-enilo. Con preferencia, el grupo alquinilo C_{2-4} es prop-2-inilo o but-2-inilo. Aún con más preferencia, R^{18} es hidrógeno.

Con preferencia R^{19} es hidrógeno, $-C(S)R^{23}$, $-C(O)R^{23}$, $-C(O)OR^{23}$, $-S(O)_2R^{23}$ o $-C(O)NR^{23}R^{24}$ alquilo C_{1-6} , alquenilo C_{2-6} o alquinilo C_{2-6} opcionalmente sustituido, arilo, heteroarilo, ciclilo o heterociclilo opcionalmente sustituido o forma un anillo heterociclilo opcionalmente sustituido con R^{18} , donde los sustituyentes opcionales en todos los casos son según se definieron precedentemente y, con más preferencia, están seleccionados de hidroxilo, ciano, halógeno, alcoxi, ciclilo o heterociclilo. Con más preferencia, R^{19} es hidrógeno,

$-C(S)R^{23}$, $-C(O)R^{23}$ o $-C(O)OR^{23}$ o alquilo C_{1-4} opcionalmente sustituido. Con preferencia, el alquilo C_{1-4} opcionalmente sustituido es *iso*-butilo. Aún con más preferencia, R^{19} es hidrógeno, $-C(O)R^{23}$ o $-C(O)OR^{23}$.

Con preferencia, R^{20} es $-NR^{21}R^{22}$.

Con preferencia, R^{21} y R^{22} son, independientemente, hidrógeno, alquilo C_{1-4} opcionalmente sustituido o $-C(O)OR^{25}$, donde los sustituyentes opcionales son según se definieron precedentemente y, con más preferencia, están seleccionados de hidroxilo, ciano, halógeno, alcoxi, acilo, ciclilo o heterociclilo. Con más preferencia, R^{21} y R^{22} son, independientemente, hidrógeno o alquilo C_{1-4} opcionalmente sustituido. Aún con más preferencia, R^{21} y R^{22} son, independientemente, hidrógeno, metilo o etilo.

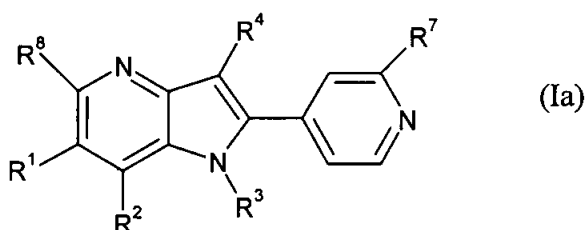
Con preferencia R^{23} y R^{24} son, independientemente, hidrógeno, hidroxilo, alquilo C_{1-6} , alquenilo C_{2-6} o alquinilo C_{2-6} opcionalmente sustituido o ciclilo o arilo opcionalmente sustituido, donde los sustituyentes opcionales en todos los casos son según se definieron precedentemente y, con más preferencia, son hidroxilo, halógeno, ciano, alquilo C_{1-4} , alcoxi, haloalquenilo, ciclilo o $-C(O)OR$ (donde R es ciclilo). Con preferencia, el grupo arilo es fenilo opcionalmente sustituido. Con más preferencia, el grupo arilo es 3-halofenilo o 4-halofenilo. Con más preferencia, R^{23} y R^{24} son, independientemente, hidrógeno, alquilo C_{1-6} o alquenilo C_{2-6} opcionalmente sustituido o un grupo ciclilo saturado o mono-insaturado opcionalmente sustituido. Aún con más preferencia, R^{23} y R^{24} son, independientemente, alquilo C_{1-6} opcionalmente sustituido o un grupo ciclilo C_{3-6} saturado opcionalmente sustituido. Con preferencia el alquilo C_{1-6} opcionalmente sustituido es metilo, etilo o *iso*-propilo. Con preferencia, el grupo ciclilo C_{3-6} saturado es un grupo ciclopropilo o ciclobutilo, el cual puede estar sustituido con uno o más sustituyentes que están seleccionados de ciano, halógeno (con preferencia flúor), alquilo C_{1-4} (con preferencia metilo) o haloalquenilo.

Con preferencia, R^{25} es alquilo C_{1-4} . Con más preferencia, R^{25} es metilo, etilo, propilo o 2-dimetiletilo.

En una realización particularmente preferida, cuando R^3 es hidrógeno, R^6 es distinto a hidrógeno. Con más preferencia, R^3 es hidrógeno y R^6 es $-NR^{18}R^{19}$. Con más preferencia, R^3 es hidrógeno y R^6 es $-NHR^{19}$. Con más preferencia, R^3 es hidrógeno y R^6 es $-NHC(O)R^{23}$.

En una realización preferida alternativa, R^6 es hidrógeno y R^3 es distinto a hidrógeno. Con más preferencia, R^6 es hidrógeno y R^3 es $-OR^{12}$ o alquilo C_{1-6} , alqueno C_{2-4} , alenilo C_{3-4} o alquinilo C_{2-4} opcionalmente sustituido. Aún con más preferencia, R^6 es hidrógeno y R^3 es cianometilo, aminoetilo, aminopropilo, prop-2-enilo, prop-2-inilo, propa-1,2-dienilo, metoximetilo, 2-fluormetilo, $-OCH_2C\equiv CH$, $-OCH_2OCH_3$, $-OCH_2CN$, $-OCH(CH_3)CN$.

En una realización particular, el método de la invención utiliza un compuesto de la fórmula (Ia):



donde R^1 , R^2 , R^3 , R^4 , R^7 y R^8 son según se definieron precedentemente y, con preferencia:

R^1 es hidrógeno, halógeno, ciano, alquilo C_{1-6} opcionalmente sustituido (en particular, alquilo C_{1-4} opcionalmente sustituido y, aún más particularmente, metilo o etilo opcionalmente sustituido, donde el sustituyente opcional es según se

definió precedentemente y con más preferencia es hidroxilo, por ejemplo 1-hidroxiletilo) o $-C(O)R^{10}$ y R^{10} es hidrógeno o alquilo C_{1-4} ;

R^2 , R^7 y R^8 son, independientemente, hidrógeno, halógeno o alquilo C_{1-4} ;

R^3 es hidrógeno, hidroxilo, ciano, alquilo C_{1-6} , alquenilo C_{2-6} , alenilo C_{3-6} o alquinilo C_{2-6} opcionalmente sustituido, $-NR^{12}R^{13}$, $-OR^{12}$ o $-C(O)R^{12}$, donde:

(a) los sustituyentes opcionales sobre los grupos alquilo, alquenilo y alquinilo son según se definieron precedentemente y, con más preferencia, están independientemente seleccionados de halo, ciano, hidroxilo, alcoxi (opcionalmente sustituido con alcoxi o acilo), alquilo C_{1-4} , alquenilo C_{2-4} , ciclilo, heterociclilo, heteroarilo, $-C(O)R$, $-C(O)OR$ y $-SR$, donde R es hidrógeno, alquilo C_{1-4} , alquenilo C_{2-4} o alquinilo C_{2-4} , y

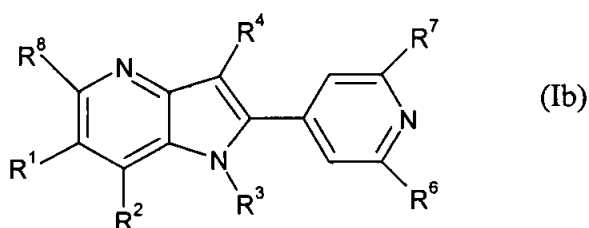
(b) R^{12} es alquilo, alquenilo, alquinilo o ciclilo opcionalmente sustituido, siendo los sustituyentes opcionales según se definieron precedentemente y, con más preferencia, halo, ciano, hidroxilo, alcoxi, ciclilo, heterociclilo, $-C(O)R$, $-C(O)OR$ o $-OS(O)NRR'$, donde R y R' son, independientemente hidrógeno o alquilo,

y R^4 es arilo opcionalmente sustituido (en particular, fenilo o naftilo), siendo los sustituyentes opcionales según se definieron precedentemente y, con más preferencia halógeno o alquilo C_{1-4} .

Con más preferencia, R^1 es hidrógeno, halo o alquilo C_{1-4} opcionalmente sustituido, donde el sustituyente opcional es con preferencia hidroxilo; R^{10} es metilo o etilo; R^2 , R^7 y R^8 son, independientemente, hidrógeno, metilo, etilo o cloro; R^3 es hidrógeno, $-OR^{12}$ o alquilo C_{1-4} , alquenilo C_{2-4} o alquinilo C_{2-4} opcionalmente sustituido; y R^4 es fenilo, el cual está opcionalmente sustituido con al menos un sustituyente seleccionado de halógeno y alquilo C_{1-4} (en particular, metilo).

Aún con más preferencia, R^1 es hidrógeno, cloro o metilo; R^2 , R^7 y R^8 son cada uno hidrógeno; R^3 es hidrógeno, cianometilo, prop-2-enilo o prop-2-inilo; y R^4 es fenilo, 2-fluorfenilo, 3-fluorfenilo, 4-fluorfenilo, 4-clorofenilo, 3-metilfenilo o 3-metil-4-fluorfenilo y aún con más preferencia es 4-fluorfenilo.

En una realización particular, el método de la invención utiliza un compuesto de la fórmula (Ib):



donde R^1 , R^2 , R^3 , R^4 , R^6 , R^7 y R^8 son según se definieron precedentemente y, con preferencia:

R^1 es hidrógeno, halógeno, alquilo C_{1-6} opcionalmente sustituido o $-C(O)R^{10}$ y R^{10} es hidrógeno o alquilo C_{1-4} ;

R^2 es hidrógeno o alquilo C_{1-4} ;

R^3 es hidrógeno, hidroxilo, alquilo C_{1-6} , alqueno C_{2-6} o alquino C_{2-6} opcionalmente sustituido, $-C(O)R^{12}$ o $-OR^{12}$ y R^{12} es ciclilo o alquilo C_{1-4} opcionalmente sustituido, siendo los sustituyentes opcionales en todos los casos según se definieron precedentemente y, con más preferencia, halógeno, ciano, hidroxilo, alcoxi, ciclilo, heterociclilo, $-NH_2$, trialkilsililo o $C(O)OR$, donde R es hidrógeno, alquilo C_{1-4} , alqueno C_{2-4} o alquino C_{2-4} ;

R^4 es arilo opcionalmente sustituido, siendo los sustituyentes opcionales según se definieron precedentemente y, con más preferencia halógeno o alquilo C_{1-4} ;

R^6 es halógeno o $-NR^{18}R^{19}$ y

(i) R^{18} es hidrógeno, $-C(O)R^{23}$, $-C(O)OR^{23}$ o alquilo C_{1-4} , alqueno C_{2-4} o alquino C_{2-4} opcionalmente sustituido y R^{23} es alquilo C_{1-4} opcionalmente sustituido y

(ii) R^{19} es hidrógeno, alquilo C_{1-4} , alqueno C_{2-4} o alquino C_{2-4} opcionalmente sustituido, $-C(S)R^{23}$, $-C(O)R^{23}$ o $-C(O)OR^{23}$ y R^{23} es hidrógeno, alquilo C_{1-4} , alqueno C_{2-4} , alquino C_{2-4} o ciclo C_{3-6} opcionalmente sustituido;

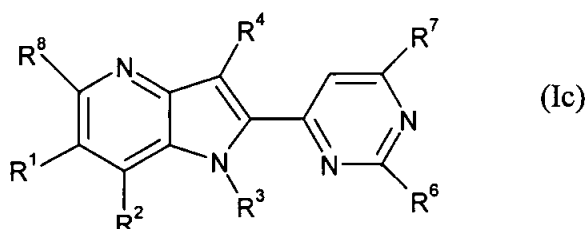
R^7 es hidrógeno, halógeno o alquilo C_{1-4} ; y

R^8 es hidrógeno, halógeno, alquilo C_{1-4} o $NR^{21}R^{22}$ y R^{21} y R^{22} son, independientemente, hidrógeno o alquilo C_{1-4} .

Con más preferencia, R^1 es hidrógeno, halo o alquilo C_{1-4} opcionalmente sustituido; R^2 es hidrógeno o metilo; R^3 es hidrógeno, alquilo C_{1-4} , alqueno C_{2-4} o alquino C_{2-4} opcionalmente sustituido o $-OR^{12}$; R^4 es fenilo, el cual está opcionalmente sustituido con al menos un sustituyente seleccionado de halógeno y alquilo C_{1-4} ; R^6 es halógeno o $-NR^{18}R^{19}$ y R^{18} es hidrógeno, prop-2-enilo o prop-2-inilo y R^{19} es $-C(O)R^{23}$ y R^{23} es hidrógeno, metilo, etilo, *iso*-propilo, 1-metiletilo, 1-metilpropilo, 2-dimetiletilo, propilo, 1-metiletenilo, 2-metilprop-1-enilo, but-3-enilo, ciclopropilo, 1-metilciclopropilo, 1-fluorciclopropilo o ciclobutilo; R^7 es hidrógeno, cloro, flúor o metilo; y R^8 es hidrógeno, cloro, metilo o 2-metoxi-1-etilamino.

Aún con más preferencia, R^1 es hidrógeno, cloro o metilo; R^2 hidrógeno o metilo; R^3 es hidrógeno, cianometilo, prop-2-enilo o prop-2-inilo; R^4 es 2-fluorfenilo, 3-fluorfenilo, 4-fluorfenilo, 4-clorofenilo, 3-metilfenilo o 3-metil-4-fluorfenilo y aún con más preferencia es 4-fluorfenilo; R^6 es $-NR^{18}R^{19}$ y R^{18} es hidrógeno y R^{19} es $-C(O)R^{23}$ y R^{23} es metilo, etilo, *iso*-propilo, ciclopropilo, ciclobutilo o 1-metilciclopropilo; R^7 hidrógeno; y R^8 es hidrógeno, cloro o metilo.

En una realización particular, el método de la invención utiliza un compuesto de la fórmula (Ic)



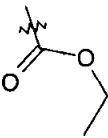
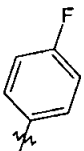
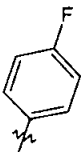
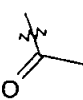
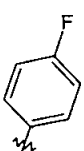
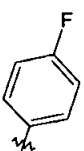
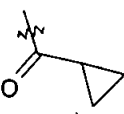
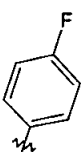
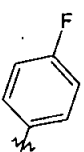
donde R^1 , R^2 , R^3 , R^4 , R^6 , R^7 y R^8 son según se definieron precedentemente y, con preferencia:

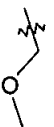
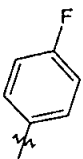
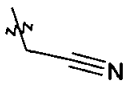
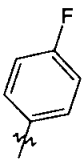
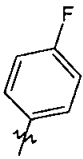
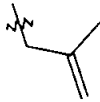
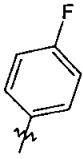
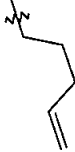
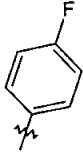
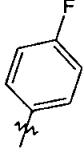
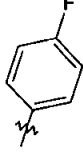
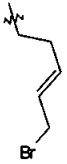
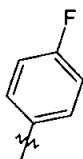
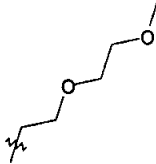
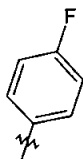
R^1 , R^2 , R^7 y R^8 son, independientemente, hidrógeno, halógeno o alquilo C_{1-4} ; R^3 es hidrógeno o alquilo C_{1-6} , alqueno C_{2-6} o alquino C_{2-6} opcionalmente sustituido, siendo los sustituyentes opcionales según se definieron precedentemente y, con más preferencia, halógeno o alcoxi; R^4 es arilo opcionalmente sustituido, siendo los sustituyentes opcionales según se definieron precedentemente y, con más preferencia, halógeno; y R^6 es hidrógeno, $-SR^{18}$ o $-NR^{18}R^{19}$ donde R^{18} es hidrógeno o alquilo C_{1-4} y R^{19} es alquilo opcionalmente sustituido, $-C(S)R^{23}$ o $-C(O)R^{23}$ y R^{23} es hidrógeno o alquilo C_{1-4} .

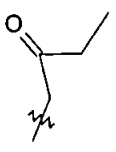
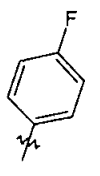
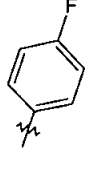
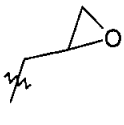
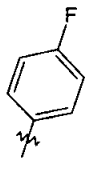
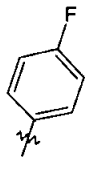
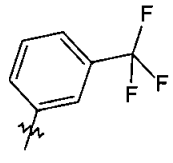
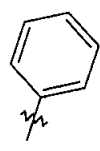
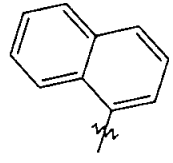
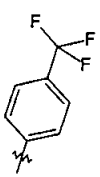
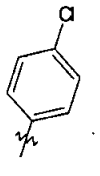
Con más preferencia R^1 , R^2 , R^7 y R^8 son, independientemente, hidrógeno, metilo, etilo o cloro; R^3 es hidrógeno, haloalquilo, alcoxialquilo, alqueno o alquino; R^4 es fenilo opcionalmente sustituido, siendo el sustituyente opcional halógeno; y R^6 es hidrógeno o $-NR^{18}R^{19}$ donde R^{18} es hidrógeno y R^{19} es 2-metoxi-1-metiletilo, $-C(S)R^{23}$ o $-C(O)R^{23}$ y R^{23} es alquilo C_{1-4} .

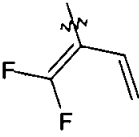
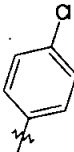
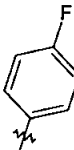
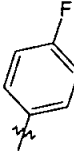
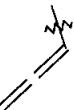
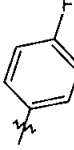
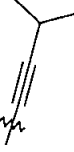
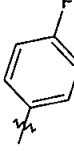
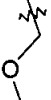
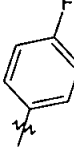
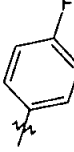
Aún con más preferencia, R^1 , R^2 , R^7 y R^8 son, independientemente, hidrógeno; R^3 es hidrógeno, 2-fluoretilo, metoximetilo, prop-1,2-dieno o prop-2-inilo; R^4 es fluorfenilo (en particular, 4-fluorfenilo); y R^6 es $-NR^{18}R^{19}$ donde R^{18} es hidrógeno y R^{19} es $-C(O)R^{23}$ y R^{23} metilo, etilo, 1-metiletilo, 1-dimetiletilo o 3-metilpropilo.

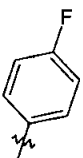
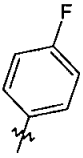
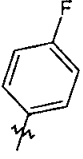
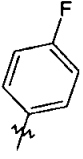
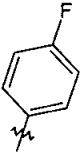
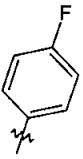
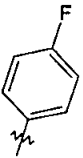
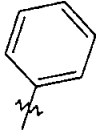
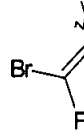
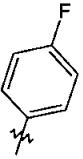
Más particularmente, los compuestos para utilizar en la presente invención se presentan en la Tabla 1 (compuestos de la fórmula (Ia)), en la Tabla 2 (compuestos de la fórmula (Ib)) y en la Tabla 3 (compuestos de la fórmula (Ic)) a continuación:

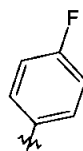
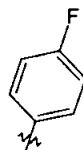
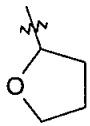
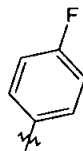
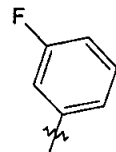
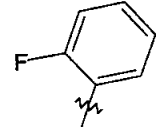
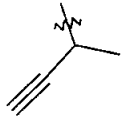
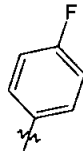
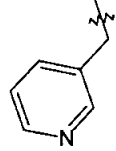
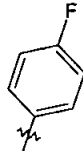
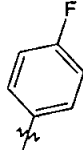
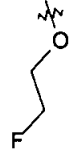
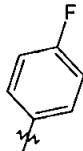
Número de Compuesto	R1	R2	R3	R4	R7	R8	Punto de Fusión °	Masa (ES+)
1	H	H			H	H	127,0 - 128,0	
2	H	H	Et		H	H	208,0- 209,0	
3	H	H			H	H	164,0- 165,0	
4	H	H			H	H	175,0- 176,0	
5	H	H			H	H	169,0- 170,0	
6	H	H			H	H	165,0- 166,0	

7	H	H			H	H	156,0-157,0	
8	H	H			H	H	237,0-238,0	
9	Cl	H	H		H	H	255,0-256,0	
10	H	H			H	H	157,0-158,0	
11	H	H			H	H	169,0-170,0	
12	H	H			H	H	151,0-152,0	
13	H	H			H	H	151,0-152,0	
14	H	H			H	H	-	436/438
15	H	H			H	H	78,0-79,0	

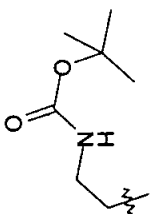
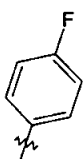
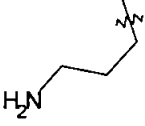
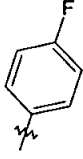
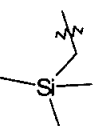
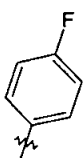
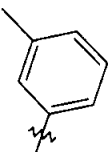
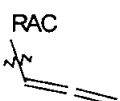
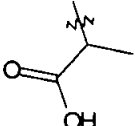
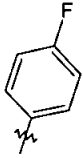
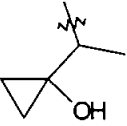
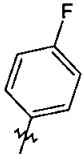
16	H	H			H	H	173,0-174,0	
17	H	H			H	H	181,0-182,0	
18	H	H			H	H	157,0-158,0	
19	H	H			H	H	124,0-125,0	
20	H	H	Me		H	H	87,0-88,0	
21	H	H	Me		H	H	195,0-196,0	
22	H	H	Me		H	H	200,0-201,0	
23	H	H	Me		H	H	182,0-183,0	
25	H	H	Me		H	H	193,0-194,0	

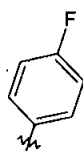
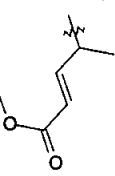
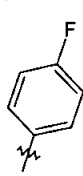
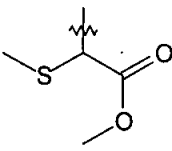
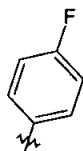
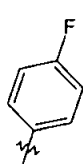
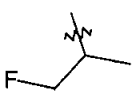
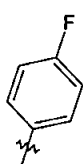
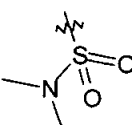
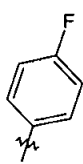
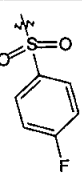
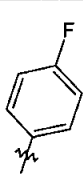
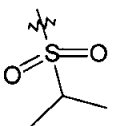
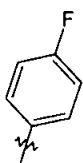
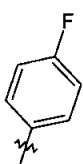
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27	H	H	H		H	H	-	290
28	H	H	Me		H	H	-	304
29	H	H	Me		H	H	188,0-189,0	
30	H	H	RAC 		H	H	153,0-154,0	
31	H	H	Me		H	H	-	280
32	H	H			H	H	164,0-165,0	
33	Cl	H			H	H	159,0-160,0	
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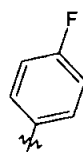
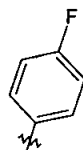
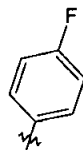
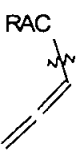
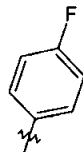
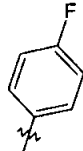
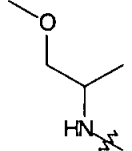
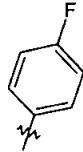
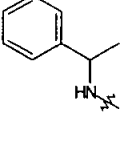
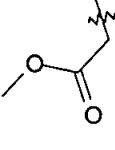
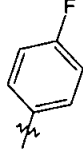
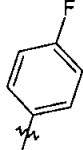
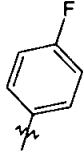
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36	Cl	H			H	H	184,0-185,0	
37	Cl	H			H	H	175,0-176,0	
38	Me	H			H	H	132,0-133,0	
39	Me	H			H	H	152,0-153,0	
40	Me	H			H	H	140,0-141,0	
41	Me	H			H	H	161,0-162,0	
42	Cl	H	H		H	H	265,0-265,0	
43	H	H			H	H	-	412 /414

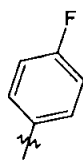
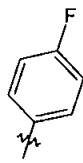
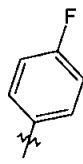
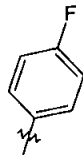
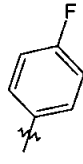
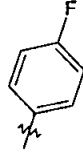
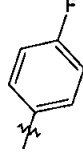
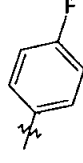
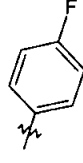
44	Cl	H			H	H	155,0-156,0	
45	Cl	H			H	H	175,0-176,0	
46	Cl	H			H	H	230,0-231,0	
47	H	H	Me		H	H	144,0-145,0	
48	H	H	Me		H	H	134,0-135,0	
49	Cl	H			H	H	209,0-210,0	
50	H	H			H	H	210,0-211,0	
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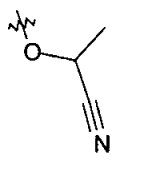
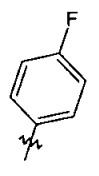
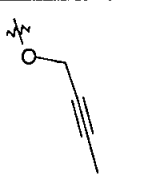
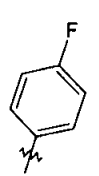
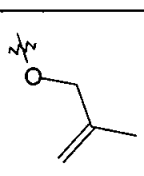
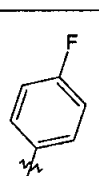
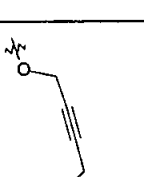
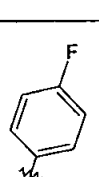
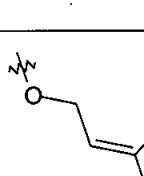
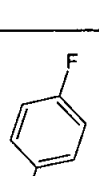
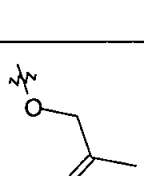
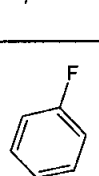
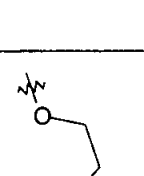
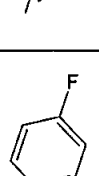
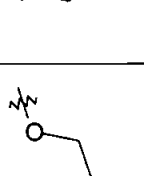
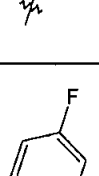
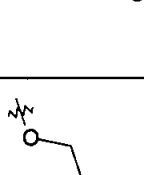
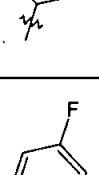
53	H	H			H	H	-	346
54	H	H			H	H	137,0-138,0	
55	H	H			H	H	150,0-151,0	
55	H	H			H	H	150,0-151,0	
57	H	H			H	H	173,0-174,0	
58	Me	H			H	H	168,0-169,0	
59	H	H			H	H	140,0-141,0	
60	H	H			H	H	174,0-175,0	
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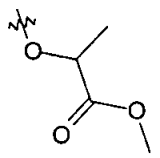
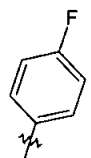
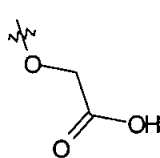
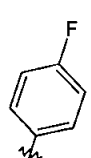
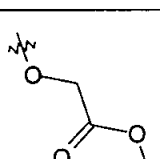
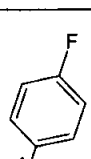
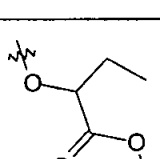
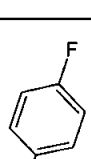
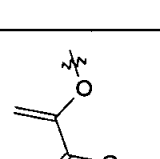
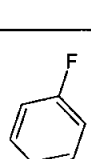
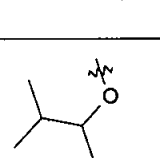
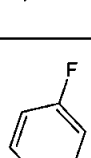
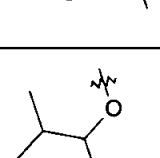
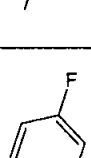
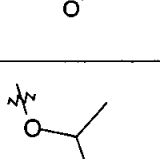
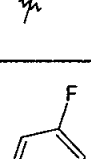
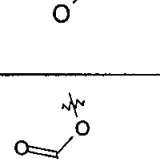
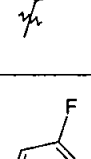
63	H	H			H	H		433
64	H	H			H	H	152,0-153,0	
66	H	H			H	H	149,0-150,0	
67	H	H	Me		H	H	136,0-137,0	
68	H	H		H	H	H	110,0-111,0	
69	H	H		H	H	H	106,0-107,0	
70	H	H		H	H	H	108,0-109,0	
71	H	H		H	H	H	119,0-120,0	
72	H	H			H	H	250,0-250,0	
73	H	H			H	H		374

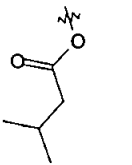
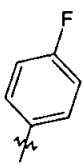
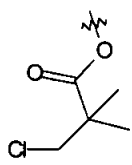
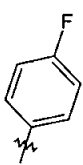
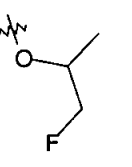
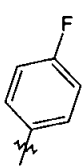
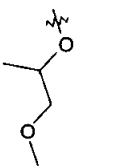
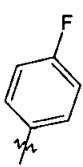
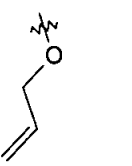
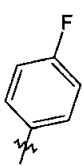
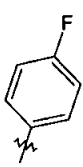
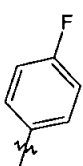
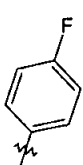
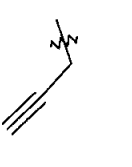
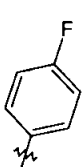
74	H	H			H	H		348
75	H	H			H	H		402
76	H	H			H	H	161,0-162,0	
77	H	H			H	H	133,0-134,0	
78	H	H			H	H	166,0-167,0	
79	H	H			H	H	205,0-206,0	
80	H	H			H	H	189,0-190,0	
81	H	H			H	H	212,0-212,0	
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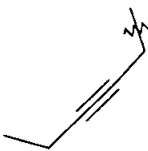
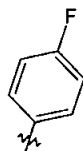
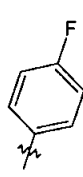
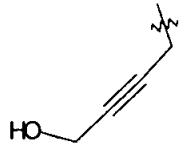
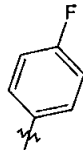
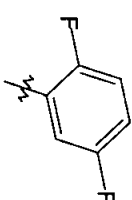
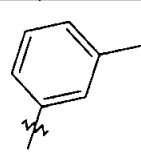
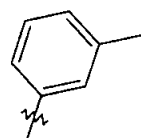
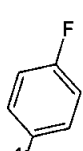
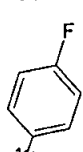
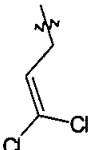
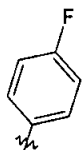
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86	H	H			H	Cl	220,0-221,0	
87	H	H			H		159,0-160,0	
88	H	H			H		197,0-198,0	
89	H	H			H	H	166,0-167,0	
90	H	H	OH		H	Me	222,0-223,0	
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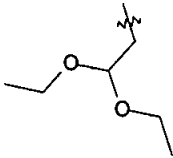
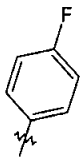
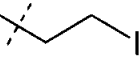
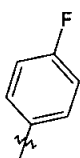
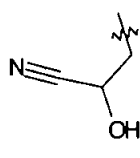
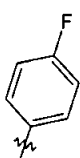
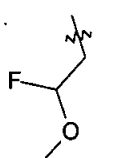
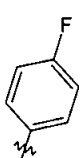
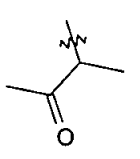
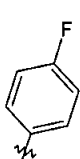
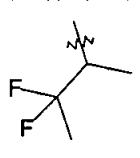
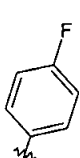
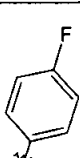
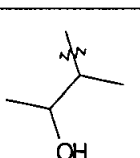
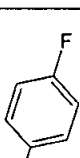
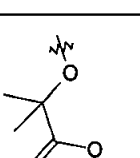
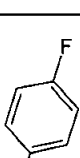
92	H	H			H	Me	151,0-152,0	
93	H	H			H	Me		342
94	H	H			H	Me	143,0-144,0	
95	H	H			H	Me	-	374
96	Cl	H			H	H	140,0-142,0	
97	H	H			H	H	126,0-127,0	
98	H	H			H	H	154,0-155,0	
99	H	H			H	H	111,0-112,0	
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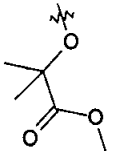
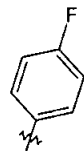
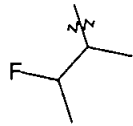
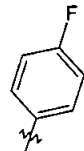
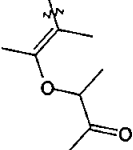
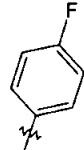
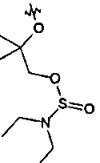
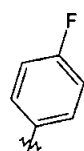
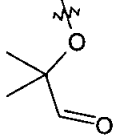
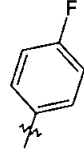
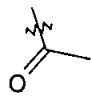
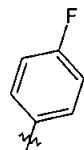
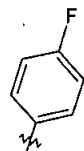
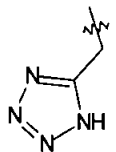
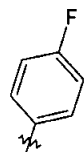
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102	H	H			H	H	178,0-180,0	
103	H	H			H	H	98,0-99,0	
104	H	H			H	H	163,0-164,0	
105	H	H			H	H	126,0-127,0	
106	H	H			H	H	-	362
107	H	H			H	H	93,0-94,0	
108	H	H			H	H	150,0-151,0	
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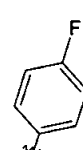
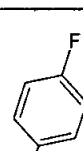
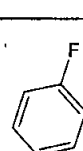
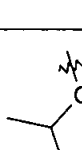
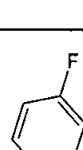
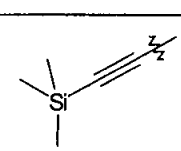
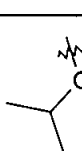
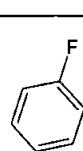
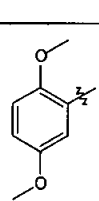
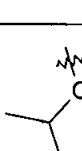
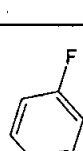
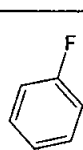
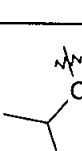
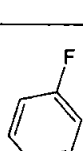
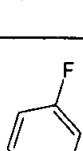
110	H	H			H	H	119,0-120,0	
111	H	H			H	H	192,0-193,0	
112	H	H			H	H	98,0-99,0	
113	H	H			H	H	126,0-127,0	
114	H	H			H	H	148,0-149,0	
115	H	H			H	H	144,0-145,0	
116	H	H			H	H	188,0-189,0	
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118	H	H			H	H	124,0-125,0	

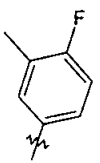
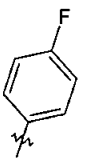
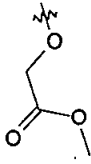
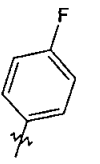
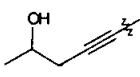
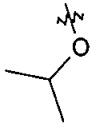
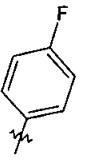
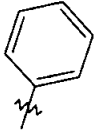
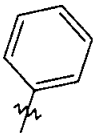
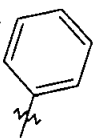
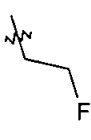
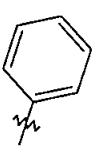
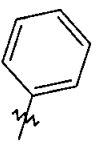
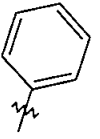
119	H	H			H	H	130,0-131,0	
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121	H	H			H	H	121,0-121,0	
122	H	H			H	H	121,0-122,0	
123	H	H			H	Me	120,0-121,0	
124	H	Me	OH		H	H	197,0-204,0	
125	H	Me			H	H	167,0-168,0	
126	H	Me			H	H	169,0-170,0	
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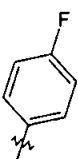
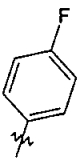
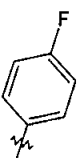
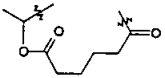
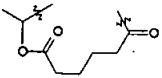
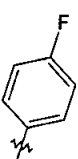
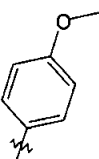
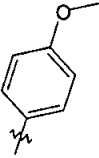
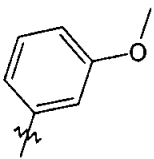
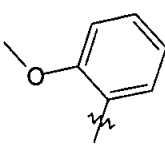
128	H	H			H	H	147,0-148,0	
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130	H	H			H	H	124,0-126,0	
131	H	H	H		H	H	130,0-130,0	
132	H	H	H		H	H	250,0-260,0	
133	H	H			H	H	-	332
134	H	H			H	H	220,0-222,0	
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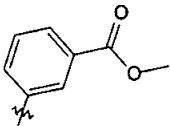
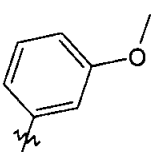
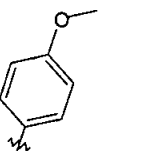
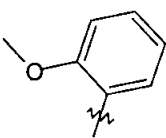
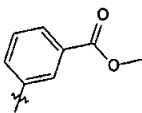
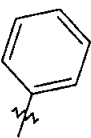
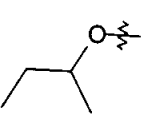
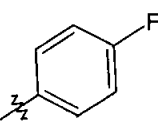
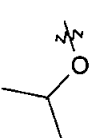
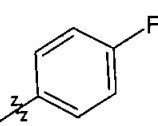
137	H	H			H	H	129,0-130,0	
138	H	H			H	H	164,0-169,0	
139	H	H			H	H	215,0-217,0	
140	H	H			H	H	184,0-185,0	
141	H	H			H	H	215,0-216,0	
142	H	H			H	H	-	382
143	H	H			H	H	-	344
144	H	H			H	H	208,0-209,0	
145	H	H			H	H	177,0-178,0	

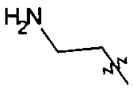
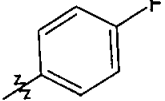
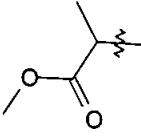
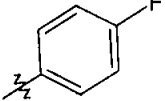
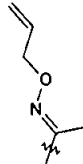
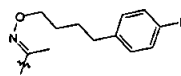
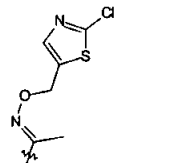
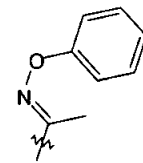
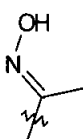
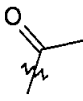
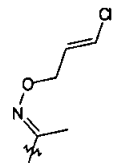
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146	H	H			H	H		364
147	H	H			H	H	149,0-150,0	
148	H	H			H	H		497
149	H	H			H	H		376
150	Me	H			H	H	148,0-149,0	
151	H	Me	H		H	H	250,0-250,0	
152	H	Me			H	H	225,0-230,0	
153	Br	Me	H	Br	H	H	250,0-999,0	

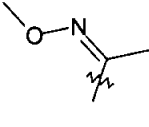
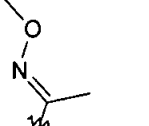
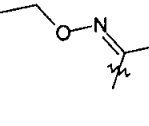
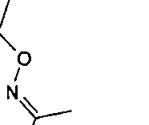
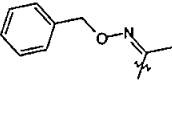
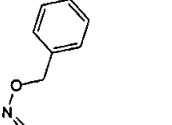
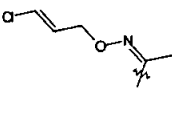
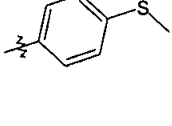
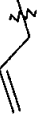
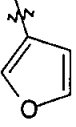
154	H	Me			H	H	250,0-999,0	
155	H	Me			H	H	132,0-133,0	
155	H	Me			H	H	132,0-133,0	
156	Br	H			H	H	157,0-158,0	
157		H			H	H	181,0-182,0	
158		H			H	H	147,0-148,0	
159	Br	H	H		H	H	263,0-264,0	
160	-CN	H			H	H	199,0-200,0	
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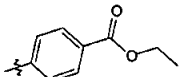
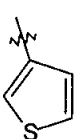
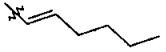
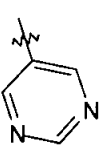
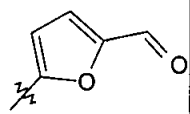
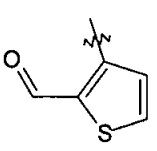
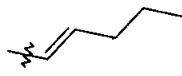
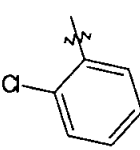
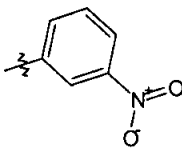
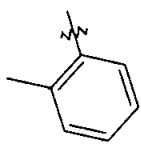
162	H	H			H	H		350
163	H	Me			H	H	212,0-213,0	
164	H	Me			H	H	133,0-134,0	
165		H			H	H	-	430
167	H	H			H	H	135,0-136,0	
168	H	H			H	H	151,0-152,0	
169	H	H			H	H	145,0-147,0	
170	H	H			H	H	205,0-206,0	
171	H	H			H	H	174,0-175,0	
172	H	H			H	H	180,0-181,0	

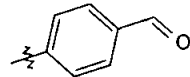
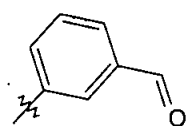
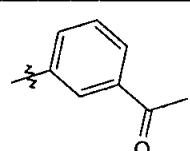
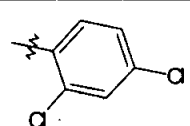
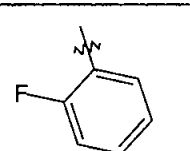
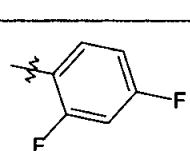
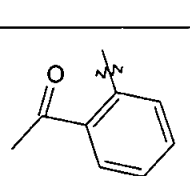
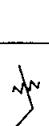
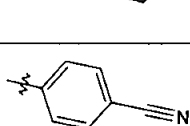
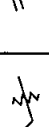
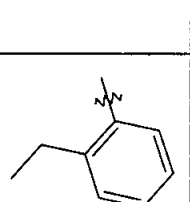
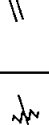
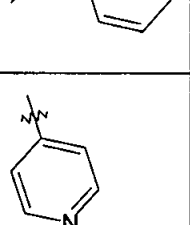
173		H			H	H	185,0-186,0	
174		H			H	H	190,0-191,0	
175		H	H		H	H	217,0-219,0	
176		H			H	H		444
293	H	H			H	H	123,0-124,0	
294	H	H	H		H	H	258,0-259,0	
295	H	H			H	H		342
296	H	H	H		H	H	236,0-237,0	
297	H	H	H		H	H	296,0-299,0	

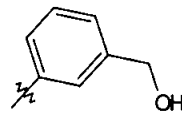
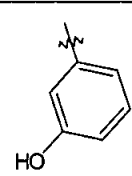
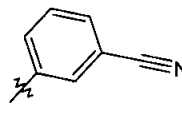
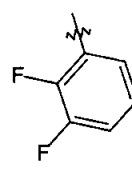
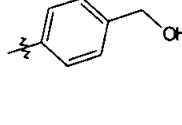
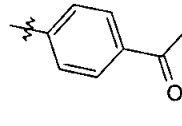
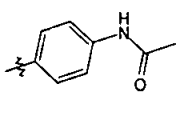
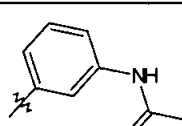
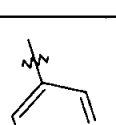
298	H	H	H		H	H	215,0-220,0	
299	H	H			H	H	-	340
300	H	H			H	H	174,0-175,0	
301	H	H			H	H		340
302	H	H			H	H	134,0-135,0	
303	H	H			H	H	171,0-172,0	
304	H	H			H	H		342
305	H	H	H		H	H	169,0-172,0	
306	H	H			H	H	124,0-125,0	
307	H	H			H	H	139,0-140,0	

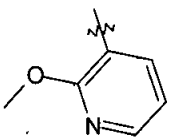
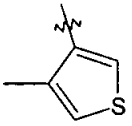
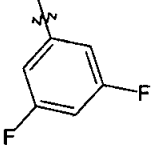
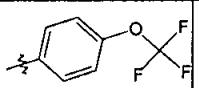
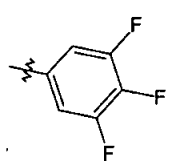
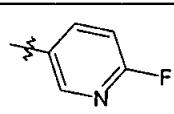
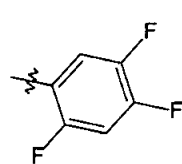
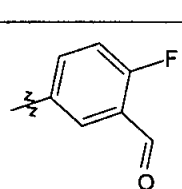
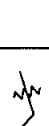
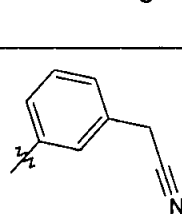
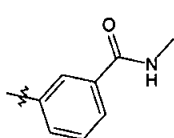
308	H	H			H	H	166,0-168,0	
309	H	H			H	H	166,0-167,0	
310	H	H			H	H	-	333
311	H	H			H	H	105,0-110,0	
312	H	H			H	H	141,0-144,0	
313	H	H			H	H	148,0-151,0	
314	H	H			H	H		293
315	H	H		Br	H	H	148-150	
316	H	H			H	H	-	278
317	H	H			H	H	-	367

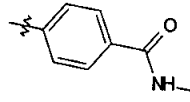
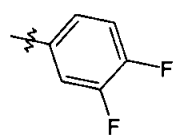
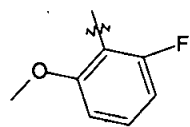
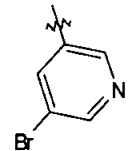
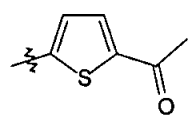
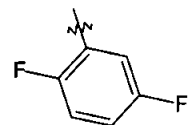
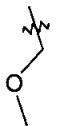
318	H	H			H	H	-	307
319	H	H			H	H	-	307
320	H	H			H	H	-	379
321	H	H			H	H	-	379
322	H	H			H	H	-	384
323	H	H			H	H	-	384
324	H	H			H	H	-	367
325	H	H			H	H	-	358
326	H	H		Me	H	H	-	250
327	H	H			H	H	-	302

328	H	H			H	H	-	384
329	H	H			H	H	-	318
330	H	H			H	H	-	318
331	H	H			H	H	-	314
332	H	H			H	H	-	330
333	H	H			H	H	-	346
334	H	H			H	H	-	304
335	H	H			H	H	-	346
336	H	H			H	H	-	357
337	H	H			H	H	-	362

338	H	H			H	H	-	340
339	H	H			H	H	-	340
340	H	H			H	H	-	354
341	H	H			H	H	-	380
342	H	H			H	H	-	330
343	H	H			H	H	-	348
344	H	H			H	H	-	354
345	H	H			H	H	-	337
346	H	H			H	H	-	340
347	H	H			H	H	-	313

348	H	H			H	H	-	342
349	H	H			H	H	-	276
350	H	H			H	H	-	328
351	H	H			H	H	-	337
352	H	H			H	H	-	348
353	H	H			H	H	-	342
354	H	H			H	H	-	354
355	H	H			H	H	-	369
356	H	H			H	H	-	369
357	H	H			H	H	-	313

358	H	H			H	H	-	343
359	H	H			H	H	-	332
360	H	H			H	H	-	396
361	H	H			H	H	-	396
362	H	H			H	H	-	366
363	H	H			H	H	-	331
364	H	H			H	H	-	366
365	H	H			H	H	-	358
366	H	H			H	H	-	351
367	H	H			H	H	-	369

368	H	H			H	H	-	369
369	H	H			H	H	-	348
370	H	H			H	H	-	360
371	H	H			H	H	-	391
372	H	H			H	H	-	360
373	H	H			H	H	-	348
374	H	H			H	H	-	290
375	H	H			H	H	-	292
376	H	H			H	H	260,0-999,0	
377	H	H			H	H	289,0-291,0	

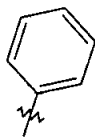
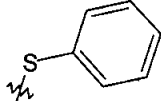
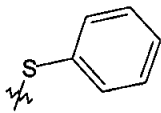
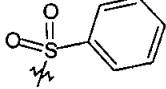
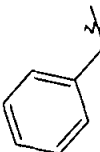
378	Me	H	H		H	H		286
379	H	H	H		H	H	289-291	
380	H	H			H	H	>260	
381	H	H			H	H		376
382	H	H			H	H		328

Tabla 1a – Tiempos de Retención de HPLC de Ciertos Compuestos de la Tabla 1

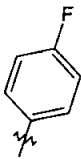
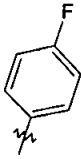
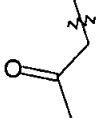
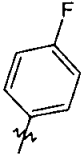
Número de Compuesto	Tiempo de Retención (Min)	Método
325	0,93	B
326	0,18	B
327	0,39	B
328	1,08	B
329	0,46	B
330	1,21	B
331	0,28	B
332	0,55	B

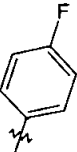
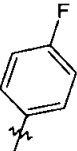
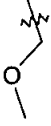
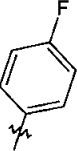
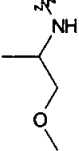
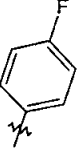
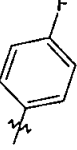
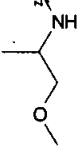
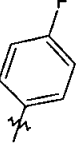
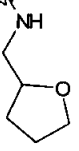
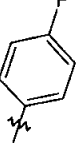
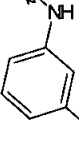
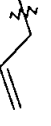
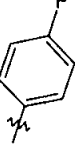
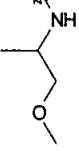
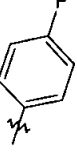
333	0,48	B
334	1,01	B
335	0,69	B
336	0,94	B
337	0,58	B
338	0,58	B
339	0,51	B
340	0,6	B
341	1,04	B
342	0,52	B
343	0,73	B
344	0,44	B
345	0,8	B
346	0,84	B
347	0,31	B
348	0,29	B
349	0,26	B
350	0,23	A
351	0,46	A
352	0,34	A
353	0,16	A
354	0,29	A
355	0,17	A
356	0,17	A
357	0,18	A
358	0,17	A
359	0,26	A
360	0,76	A
361	0,98	A
362	0,94	A

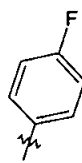
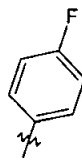
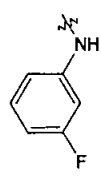
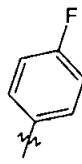
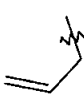
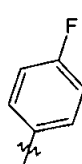
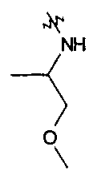
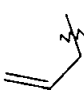
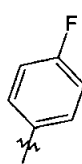
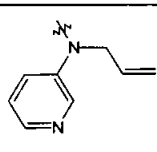
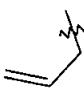
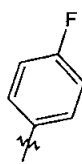
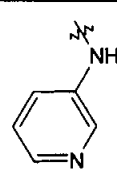
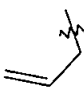
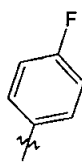
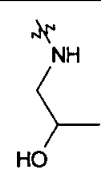
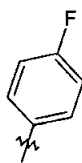
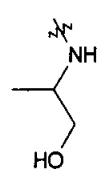
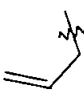
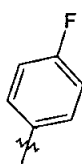
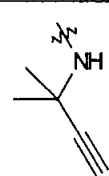
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364	0,57	A
365	0,3	A
366	0,22	A
367	0,17	A
368	0,19	A
369	0,65	A
370	0,25	A
371	0,57	A
372	0,8	A
373	0,34	A

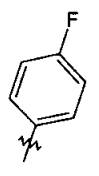
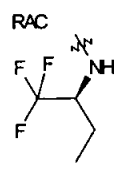
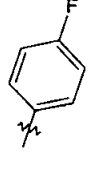
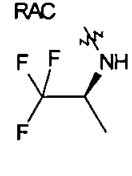
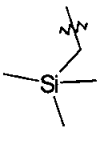
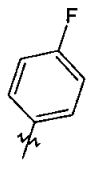
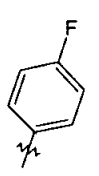
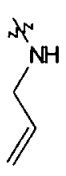
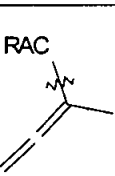
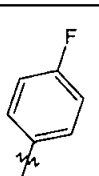
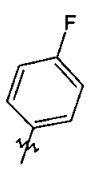
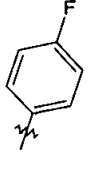
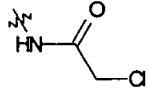
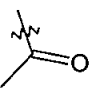
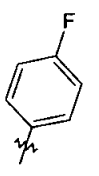
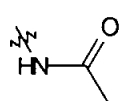
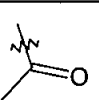
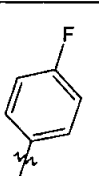
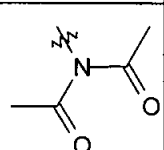
Método: véase bajo los “Ejemplos” para los detalles del Método A y del Método B

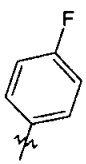
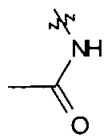
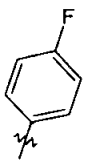
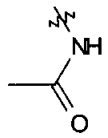
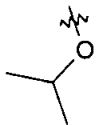
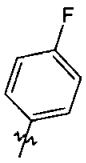
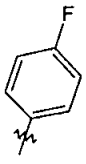
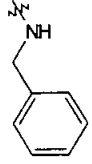
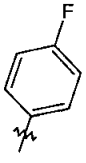
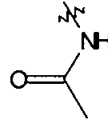
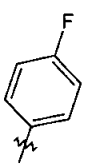
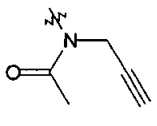
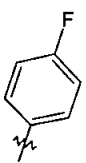
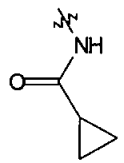
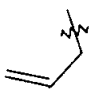
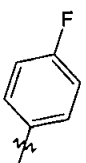
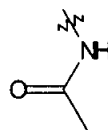
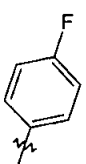
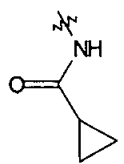
TABLA 2

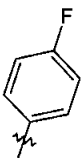
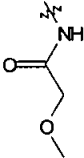
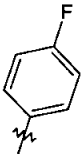
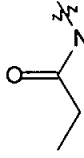
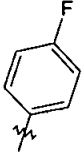
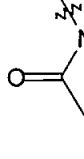
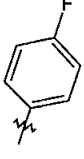
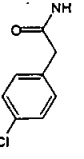
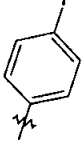
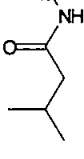
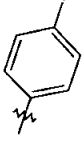
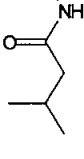
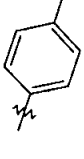
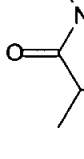
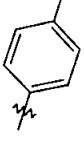
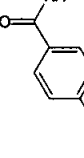
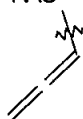
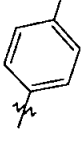
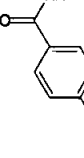
Número de Compuesto	R1	R2	R3	R4	R6	R7	R8	Punto de Fusión °	Masa (ES+ ₋)
177	H	H	H		Cl	H	H	260- 260	
178	H	H			Cl	H	H	175- 176	
179	H	H			Cl	H	H	190- 191	

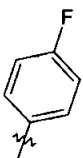
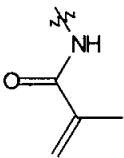
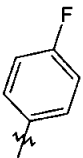
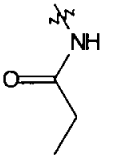
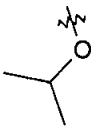
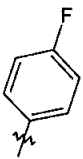
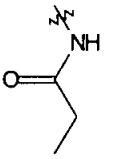
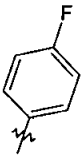
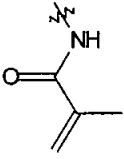
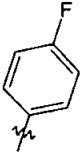
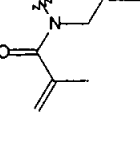
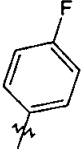
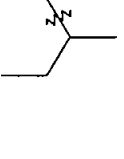
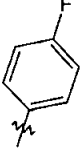
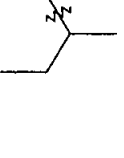
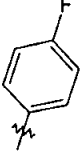
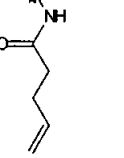
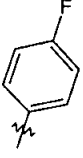
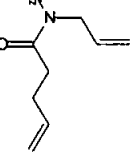
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181	H	H			Cl	H	H	164-165	
182	H	H				H	H		421
183	H	H			Cl	H	H	160-161	
184	H	H				H	H		423
185	H	H				H	H		415
186	H	H				H	H	226-227	
187	H	H				H	H		399
188	Cl	H	H		Cl	H	H	210-211	

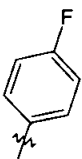
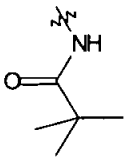
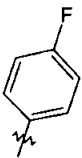
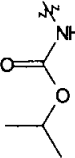
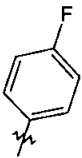
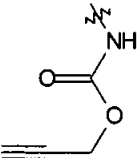
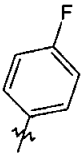
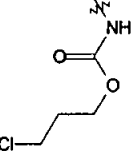
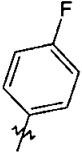
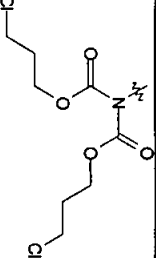
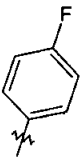
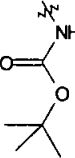
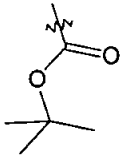
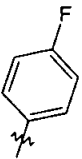
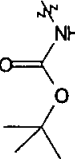
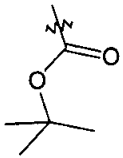
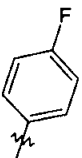
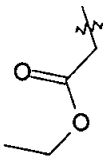
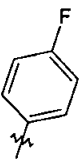
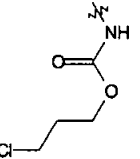
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190	Cl	H				H	H	168-169	
191	H	H			Cl	H	H	143-144	
192	Cl	H				H	H		451/453
193	Cl	H				H	H		396/398
194	Cl	H				H	H	140-142	
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196	Cl	H				H	H	-	437/439
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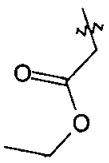
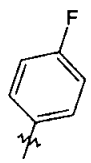
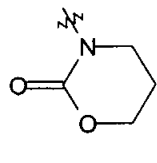
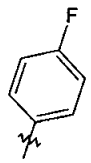
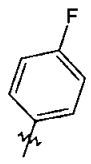
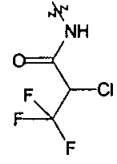
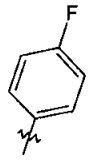
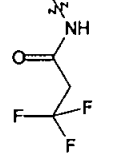
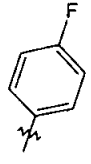
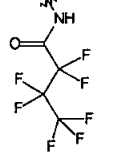
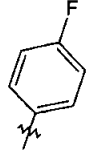
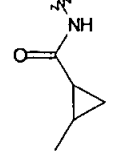
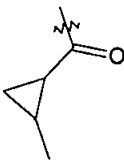
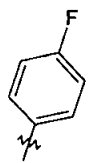
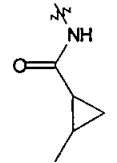
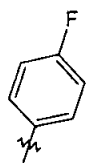
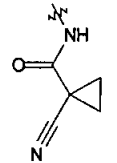
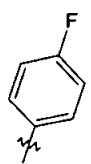
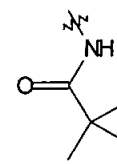
198	H	H				H	H	-	461
199	H	H				H	H	89-90	
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201	H	H				H	H	150-151	
202	Cl	H			Cl	H	H	146-147	
203	H	H	H		NH ₂	H	H	146-147	
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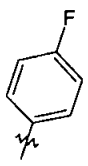
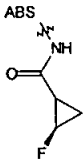
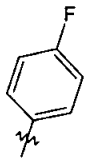
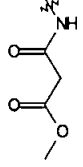
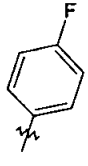
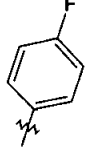
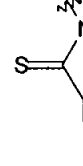
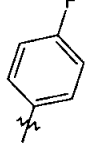
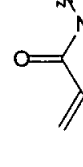
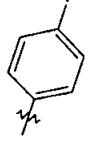
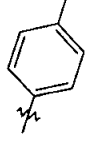
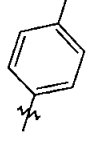
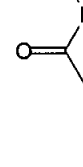
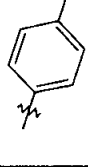
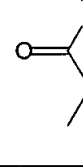
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209	Me	H			Cl	H	H	149-150	
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211	H	H				H	H	155-156	
212	H	H				H	H	251-252	
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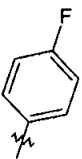
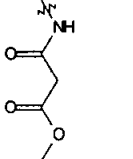
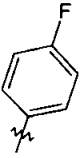
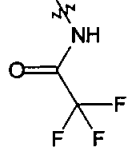
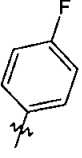
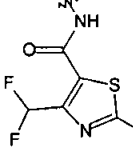
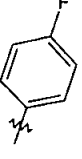
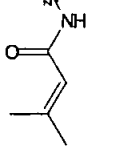
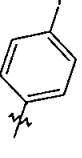
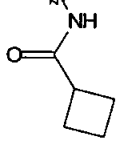
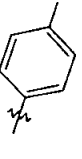
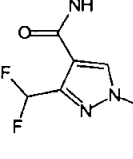
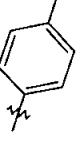
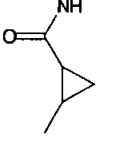
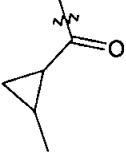
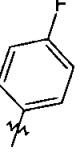
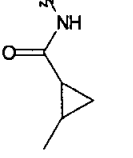
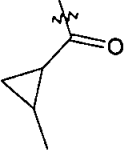
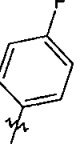
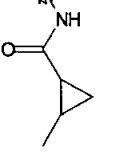
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219	H	H	H			H	H	149-150	
220	H	H	H			H	H	215-216	
221	H	H				H	H	250-250	
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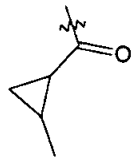
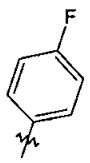
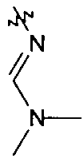
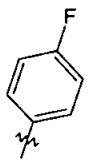
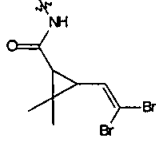
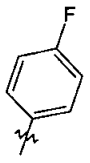
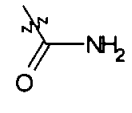
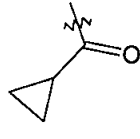
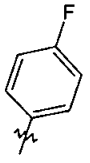
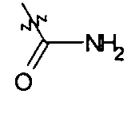
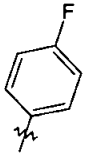
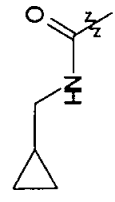
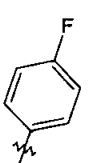
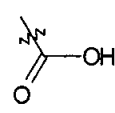
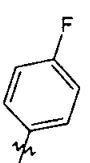
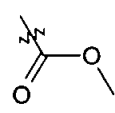
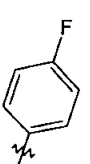
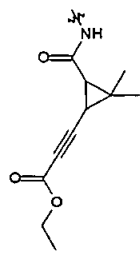
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227	Me	H				H	H	207-208	
228	H	H				H	H	233-234	
229	H	H				H	H	218-219	
230	Me	H	H			H	H	-	360
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232	H	H				H	H	260-260	
233	H	H				H	H		467

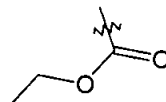
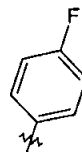
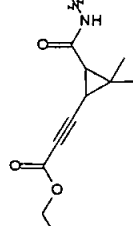
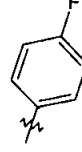
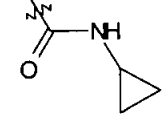
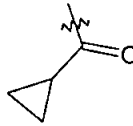
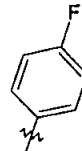
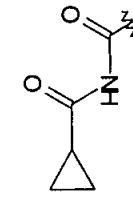
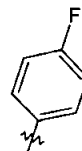
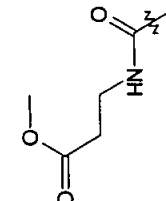
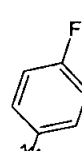
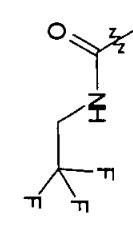
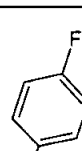
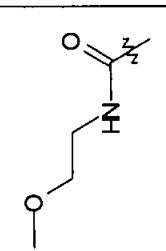
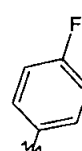
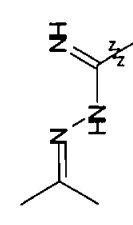
234	H	H	H			H	H	162-163	
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236	H	H	H			H	H	>250	
237	H	H	H			H	H	>250	
238	H	H	H			H	H	233-234	
239	H	H	H			H	H	226-227	
240	H	H				H	H	146-147	
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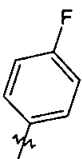
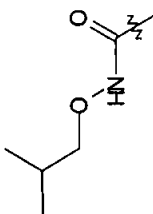
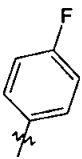
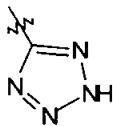
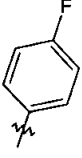
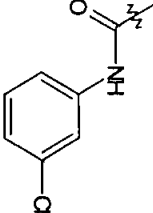
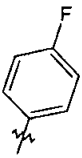
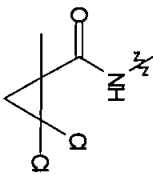
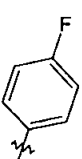
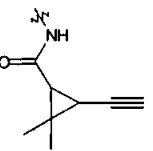
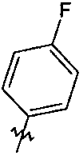
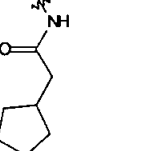
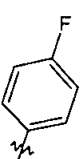
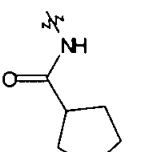
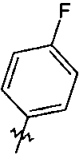
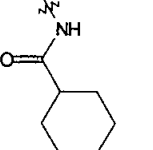
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246	H	H	H			H	H	>250	
247	H	H	H			H	H	210-211	
248	H	H	H			H	H		387
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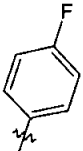
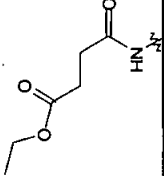
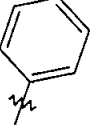
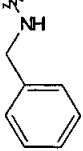
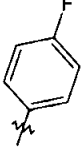
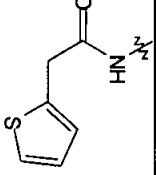
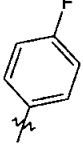
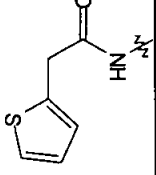
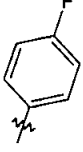
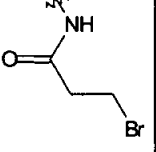
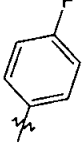
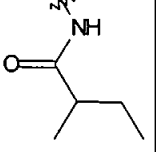
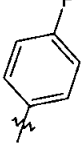
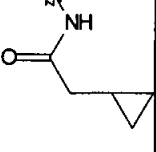
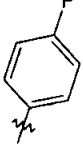
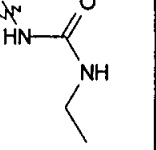
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256	H	H	H			H	H	>260	
257	H	H				H	H	218-220	
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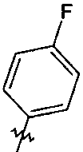
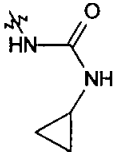
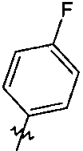
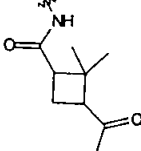
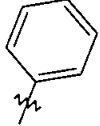
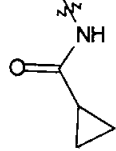
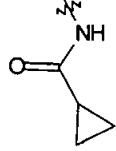
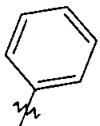
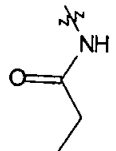
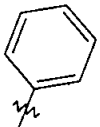
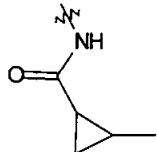
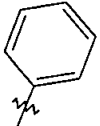
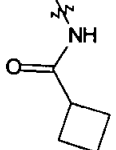
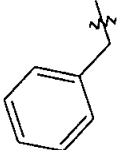
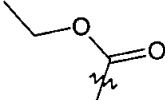
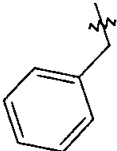
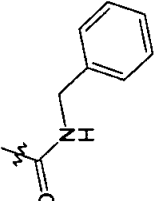
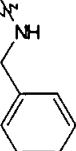
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262	H	H	H			H	H	253-254	
263	H	H	H			H	H	150-152	
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265	H	H	H			H	H	121-122	
266	H	H	H			H	H	227-230	
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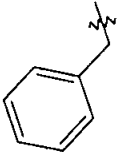
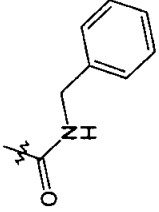
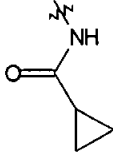
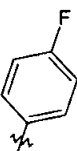
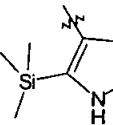
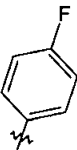
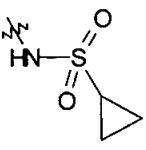
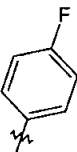
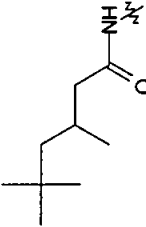
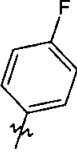
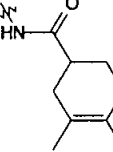
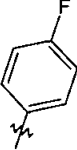
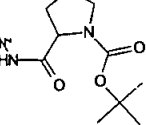
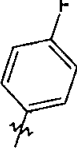
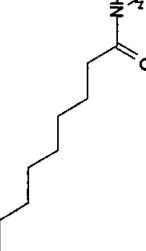
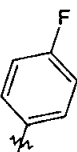
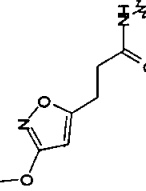
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271	H	H	H			H	H	140-141	
272	H	H				H	H	123-125	
273	H	H	H			H	H	>260	
274	H	H	H			H	H	242-243	
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383	H	H	H			H	H	175-177	

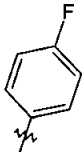
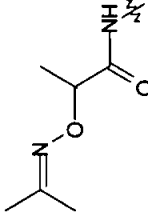
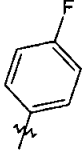
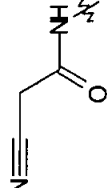
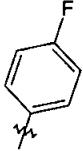
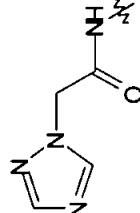
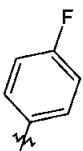
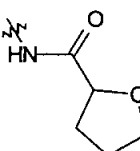
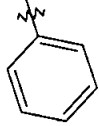
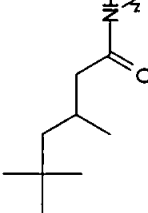
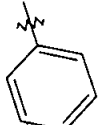
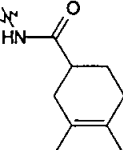
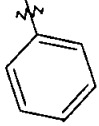
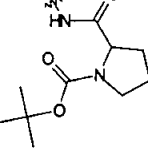
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387	H	H	H			H	H	247-250	
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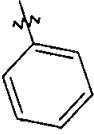
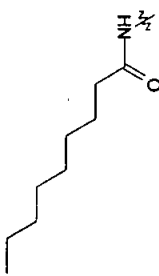
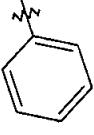
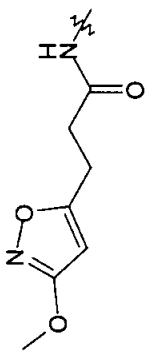
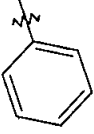
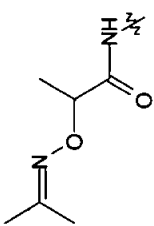
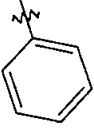
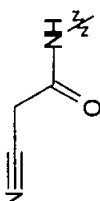
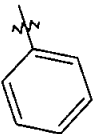
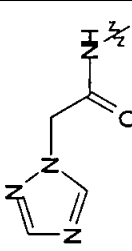
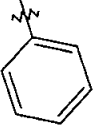
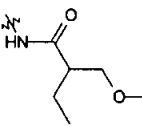
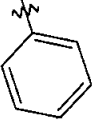
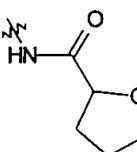
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394	H	H	H			H	H	>250	
395	H	H	H			H	H	>250	
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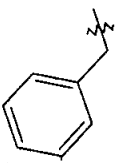
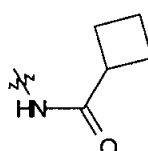
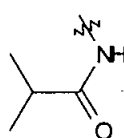
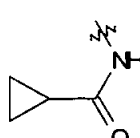
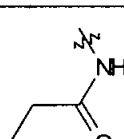
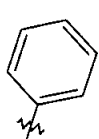
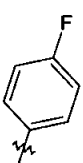
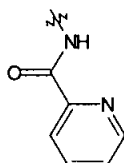
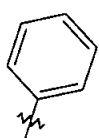
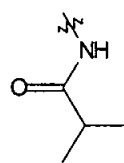
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400	H	H	H			H	H	>250	
401	H	H	H			H	H	>250	
401	H	H	H			H	H	>250	
402	H	H	H		Cl	H	H	233-234	
403	H	H	H			H	H	168-169	
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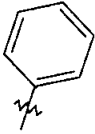
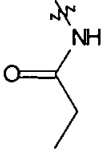
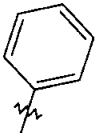
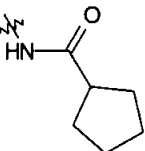
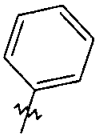
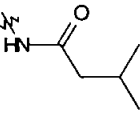
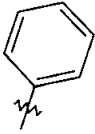
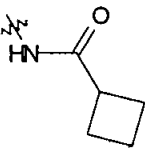
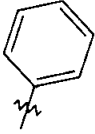
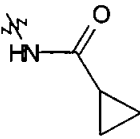
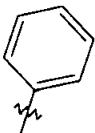
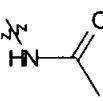
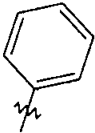
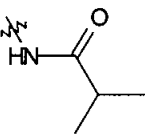
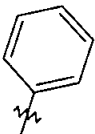
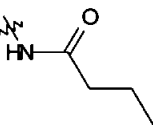
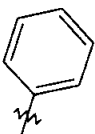
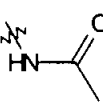
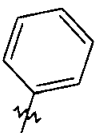
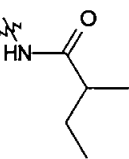
407	H	H	H			H	H	140-150	
408	H	H	H			H	H	85-88	
409	H	H	H			H	H	73-76	
410	H	H	H			H	H	94-95	
411	H	H	H			H	H	>250	
412	H	H	H			H	H	259-260	
413	H	H	H			H	H	239-240	
414	H	H			F	H	H	>260	
415	H	H				H	H	>260	

416	H	H				H	H	201-202	
417	H	H	H			H	H	180-182	
418	H	H	H			H	H	237-239	
419	H	H	H			H	H	-	445,2
420	H	H	H			H	H	283-285	
421	H	H	H			H	H	-	502
422	H	H	H			H	H	-	445
423	H	H	H			H	H	-	458

424	H	H	H			H	H	-	432
425	H	H	H			H	H	-	372
426	H	H	H			H	H	-	414
427	H	H	H			H	H	-	403
428	H	H	H			H	H	-	427
429	H	H	H			H	H	-	423
430	H	H	H			H	H	-	484

431	H	H	H			H	H	-	427
432	H	H	H			H	H	-	440
433	H	H	H			H	H	-	414
434	H	H	H			H	H	-	354
435	H	H	H			H	H	-	396
436	H	H	H			H	H	-	401
437	H	H	H			H	H	-	385

438	H	H			F	H	H	-	360
439	H	H	H		NH ₂	H	H	235-240	
440	H	H	H			H	H	-	349
441	H	H	H		F	H	H	235-240	
442	H	H	H			H	H	102-104	
443	H	H	H			H	H	158-160	
444	H	H	H			H	H	102-104	
445	Me	H	H		NH ₂	H	H	149-151	
446	H	H	H			H	H	149-152	
447	Me	H	H			H	H	>260	

448	Me	H	H			H	H	260-999	
449	Me	H	H			H	H	206-207	
450	Me	H	H			H	H	260-999	
451	Me	H	H			H	H	152-153	
452	Me	H	H			H	H	182-183	
453	H	H	H			H	H	168-169	
454	H	H	H			H	H	168-169	
455	H	H	H			H	H	-	357
456	Me	H	H			H	H	-	343
457	H	H	H			H	H	-	371

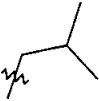
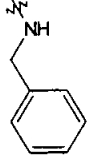
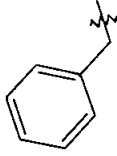
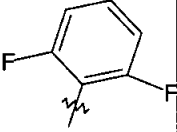
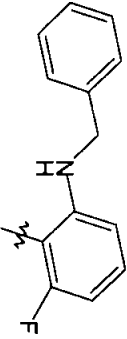
458	H	H				H	H	178-180	
459	H	H			Cl	H	H	252-253	
460	H	H	H		NH ₂	H	H	>260	323
461	H	H	H		NH ₂	H	H	-	410

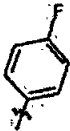
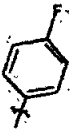
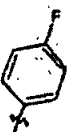
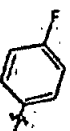
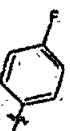
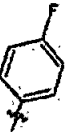
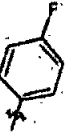
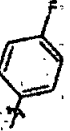
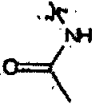
Tabla 2a – Tiempos de Retención de HPLC de Ciertos Compuestos de la Tabla 2

Número de Compuesto	Tiempo de Retención (Min)	Método
419	1,76	A
421	1,49	A
422	1,8	A
423	1,36	A
424	1,45	A
425	1,22	A
426	1,15	A
427	1,33	A
428	1,72	A
429	1,65	A

430	1,46	A
431	1,77	A
432	1,33	A
433	1,41	A
434	1,2	A
435	1,08	A
436	1,4	A
437	1,3	A

Método: véase bajo los “Ejemplos” para los detalles del Método A y del Método B

TABLA 3

Número de Compuesto	R1	R2	R3	R4	R6	R7	R8	Punto de Fusión (°C)	Espectro de Masas (ES+)
276								255-260	
277								185-187	
278								122-124	
279								-	317
280								137-138	
281								-	422
282								255-255	
283								-	348

284								235-236	
285								188-189	
286								-	466
287								214-215	
288								221-222	
289								235-236	
290								236-237	
291								245-246	
292								240-241	

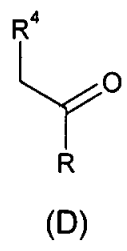
La presente invención también provee un compuesto de la fórmula (I) según se definió precedentemente con las condiciones de que (i) cuando X^1 sea CH , X^2

sea CR⁵ y R⁵ y R⁶ sean ambos H, R⁴ no sea 4-fluorfenilo y (ii) el compuesto de la fórmula (I) no sea:

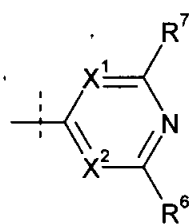
- 3-fenil-2-piridin-4-il-1H-pirrolo[3,2-b]piridina
- 3-(3-cloro-4-fluor-fenil)-2-piridin-4-il-1H-pirrolo[3,2-b]piridina
- 3-(3-cloro-fenil)-2-piridin-4-il-1H-pirrolo[3,2-b]piridina
- 3-(3-trifluor-fenil)-2-piridin-4-il-1H-pirrolo[3,2-b]piridina
- 3-(3-metoxi-fenil)-2-piridin-4-il-1H-pirrolo[3,2-b]piridina
- 3-(2-metilfenil)-2-piridin-4-il-1H-pirrolo[3,2-b]piridina
- 3-(2-metoxifenil)-2-piridin-4-il-1H-pirrolo[3,2-b]piridina
- 1-metil-2-piridin-4-il-3-(3-trifluormetil-fenil)-1H-pirrolo[3,2-b]piridina
- 1-metil-3-(3-cloro-4-fluor-fenil)-2-piridin-4-il-1H-pirrolo[3,2-b]piridina
- 3-(4-fluorfenil)-2-(2-(2-hidroxietil-amino)-piridin-4-il)-1H-pirrolo[3,2-b]piridina,
- 3-(4-fluorfenil)-2-(2-[HO(CH₂)₂O(CH₂)₂NH]-piridin-4-il)-1H-pirrolo[3,2-b]piridina,
- 3-(4-fluorfenil)-2-(2-(2-metilamino-etilamino)-piridin-4-il)-1H-pirrolo[3,2-b]piridina,
- 3-(4-fluorfenil)-2-(2-(3-metoxi-propil-amino)-piridin-4-il)-1H-pirrolo[3,2-b]piridina,
- 3-(4-fluorfenil)-2-(2-*n*-propilamino-piridin-4-il)-1H-pirrolo[3,2-b]piridina,
- 3-(4-fluorfenil)-2-(2-(3-hidroxi-propil-amino)-piridin-4-il)-1H-pirrolo[3,2-b]piridina,
- 3-(4-fluorfenil)-2-(2-metilamino-piridin-4-il)-1H-pirrolo[3,2-b]piridina o
- 3-(4-fluorfenil)-2-(2-acetilamino piridin-4-il)-1H-pirrolo[3,2-b]piridina.

En un aspecto adicional, la invención se refiere a un proceso para la preparación de un compuesto de la fórmula (I) según se reivindica en la reivindicación 1, que comprende:

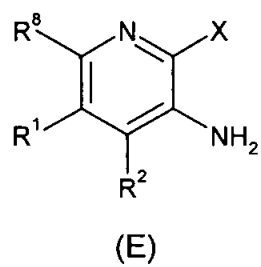
- a) hacer reaccionar una cetona de la fórmula (D)



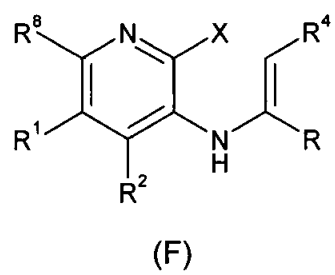
donde R⁴ es según se define en la reivindicación 1, y R es un grupo de la fórmula



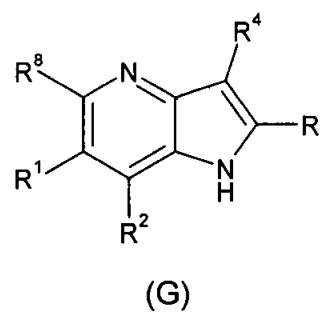
donde X¹, X², R⁶ y R⁷ son según se definen en la reivindicación 1, con una aminopiridina de la fórmula (E)



donde R¹, R² y R⁸ son según se definen en la reivindicación 1, y X es un halógeno, para proporcionar una enamina de la fórmula (F),

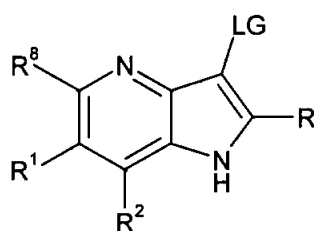


efectuar la ciclación para proporcionar un azaindol de la fórmula (G),



y opcionalmente efectuar la alquilación para proporcionar un compuesto de la fórmula (I) según se define en la reivindicación 1; o

b) hacer reaccionar un azaindol de la fórmula (K)

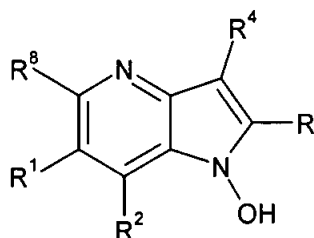


(K)

donde R^1 , R^2 y R^8 son según se definen en la reivindicación 1, R es según se definió precedentemente, y LG es un grupo saliente con un compuesto de la fórmula $R^4-B(OH)_2$ donde R^4 es según se define en la reivindicación 1, para proporcionar un compuesto de la fórmula (G) según se definió precedentemente, y opcionalmente efectuar la alquilación para proporcionar un compuesto de la fórmula (I) según se define en la reivindicación 1;

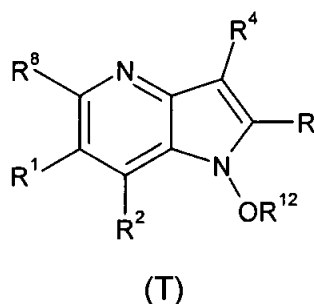
c) hacer reaccionar un compuesto de la fórmula (G) precedente con un compuesto de la fórmula R^3-LG donde LG es un grupo saliente para proporcionar un compuesto de la fórmula (I) según se define en la reivindicación 1;

d) hacer reaccionar un compuesto de la fórmula (S)



(S)

donde R^1 , R^2 , R^4 , y R^8 se definen en la reivindicación 1, y R es según se definió precedentemente, con un compuesto de la fórmula R^{12} -LG donde R^{12} es según se define en la reivindicación 1 y LG es un grupo saliente, para proporcionar un compuesto de la fórmula (T)



donde R^1 , R^2 , R^4 , R^8 , y R^{12} se definen en la reivindicación 1, y R es según se definió precedentemente, o

e) convertir un compuesto de la fórmula (I) según se define en la reivindicación 1 a una sal de N-óxido del mismo. Obviamente, la persona experta apreciará que los compuestos de la invención se pueden elaborar a través de diversos otros métodos.

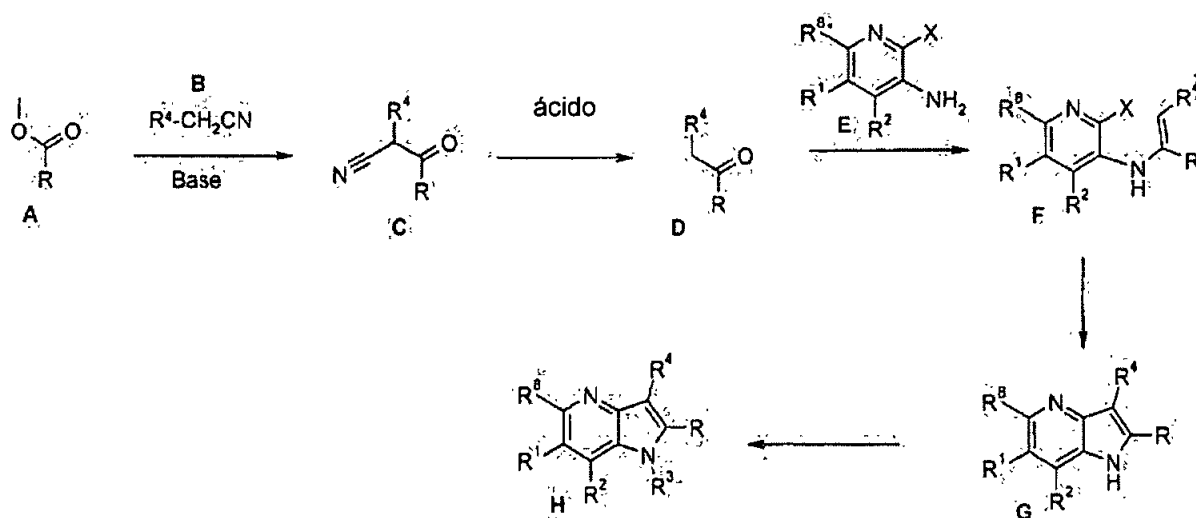
Los compuestos de la invención y para utilizar en los métodos de la invención se pueden elaborar, por ejemplo, siguiendo el esquema de reacción y los métodos que se detallan a continuación. Los materiales de partida utilizados para la preparación de los compuestos de la invención se pueden adquirir de proveedores comerciales usuales. Los materiales de partida así como también los intermediarios se pueden purificar antes del uso en la siguiente etapa a través de metodologías de la técnica tales como cromatografía, cristalización, destilación y filtración.

Los esquemas que se enumeran a continuación para ejemplificar los posibles métodos de preparación para los compuestos de la fórmula general I constituyen sugerencias que podrían ser modificadas por aquéllos expertos en la

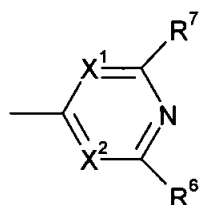
técnica para lograr los compuestos descriptos. Muchas de las etapas detalladas a continuación se pueden encontrar en *J. Med. Chem.* **2003**, 46, 4702-4713.

Los compuestos de la fórmula general (I) previamente descriptos y enumerados en las tablas precedentes se pueden preparar siguiendo el procedimiento descrito en el esquema 1:

Esquema 1



donde R es:



y X^1 y X^2 , R^1 a R^8 son según se definieron precedentemente y X es halógeno.

Los compuestos de la fórmula **C** se pueden obtener mediante la reacción entre un éster de la fórmula **A** y un derivado de acetonitrilo de la fórmula **B** en presencia de una base tal como metóxido de sodio o t-butóxido de potasio en un solvente alcohólico adecuado. (véase *J. Med. Chem.* **2003**, 46, 4702-4713).

Los compuestos de la fórmula **A** generalmente se encuentran disponibles en el comercio pero podrían prepararse a través de los procedimientos de la técnica a partir del correspondiente derivado de ácido, nitrilo, o metilo mediante reacciones de esterificación, hidrólisis u oxidación, respectivamente.

Los compuestos de la fórmula **B**, tales como fenil acetonitrilo, 4-fluorfenil acetonitrilo o 3-metilfenil acetonitrilo y los compuestos relacionados se encuentran disponibles en el comercio.

El tratamiento ácido de los compuestos de la fórmula **C** en un ácido acuoso adecuado tal como el ácido bromhídrico resulta en la hidrólisis y descarboxilación conduciendo al compuesto de la fórmula **D**.

La condensación adicional de **D** con una 3-amino piridina de la fórmula **E** resulta en una formación de una enamina de la fórmula **F** donde X es un halógeno tal como bromo, cloro o yodo. La reacción se puede llevar a cabo en un solvente aromático tal como benceno, tolueno o xileno en presencia de una cantidad catalítica de ácido tal como ácido p-toluen sulfónico.

Alternativamente, el compuesto **F** puede existir como su equilibrio enamina-imina; ambos compuestos se podrían separar a través de la condición de purificación de la técnica tal como cromatografía.

Las piridinas de la fórmula **E**, tales como 2-cloro-3-amino piridina, 2-cloro-5-metil piridina o 2,5-dicloro-3-amino piridina, se pueden encontrar disponibles en el comercio o se pueden preparar a través de metodologías conocidas. Por ejemplo,

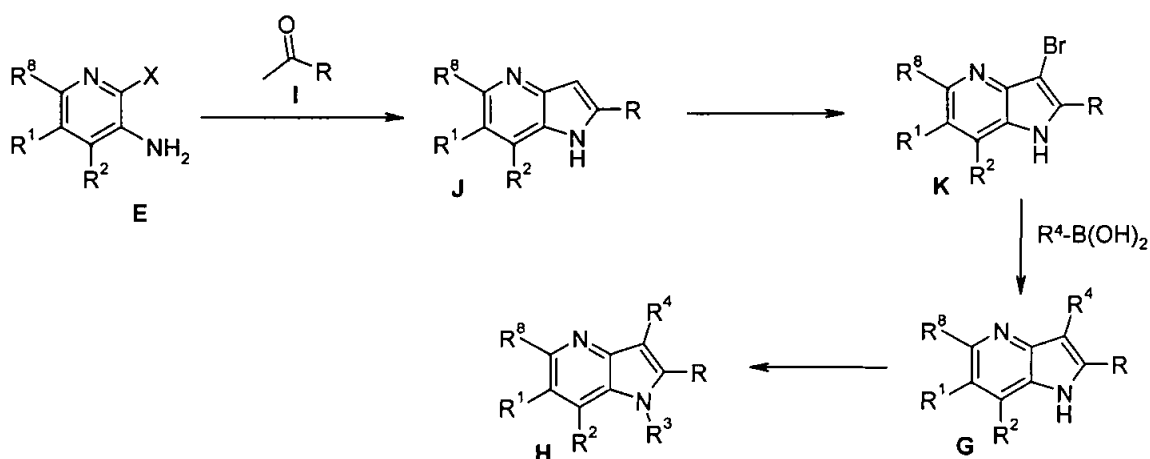
mediante la reducción del correspondiente nitro derivado (véase *J. Chem. Soc.*, **1952**, 2042). Como un ejemplo adicional, se puede preparar metil éster de ácido (2,6-dicloro-3-nitro-piridin-4-il)-acético a través de la sustitución nucleofílica vicaria sobre la 2,6-dicloro-3-nitro-piridina principal (véase *Liebigs Ann.* **1997**, 1805-1816) seguida por la reducción del grupo nitro.

El azaindol (1H-pirrolo[3,2-b]piridina) de la fórmula **G** se obtiene mediante la ciclación de la enamina **F** en presencia de una base de amina terciaria tal como DABCO y un catalizador de paladio tal como acetato de paladio (II) o diclorobis(trifenilfosfin) paladio (II) en un solvente inerte tal como dimetilformamida o dimetilacetamida (véase *J. Org. Chem.* **1997**, 62, 2676-2677).

Los compuestos de la fórmula **H**, donde R^3 no es hidrógeno se pueden obtener mediante la alquilación o acilación de los compuestos de la fórmula **G**. Esta alquilación se puede llevar a cabo con un agente de alquilación de la fórmula R^3-Y (donde Y es un grupo saliente tal como halógeno, triflato, mesilato y similares) en presencia de una base tal como hidruro de sodio o hexametildisilazano de litio en un solvente aprótico tal como dimetilformamida o tetrahidrofurano. Los compuestos de la fórmula **G** también se pueden obtener mediante la acilación en presencia de un agente de acilación tal como R^3COX (donde X es un halógeno) en presencia de una base tal como hidruro de sodio o hexametildisilazano de litio en un solvente aprótico tal como dimetilformamida o tetrahidrofurano.

El esquema 2 describe un método alternativo para la preparación del compuesto de la fórmula (I):

Esquema 2



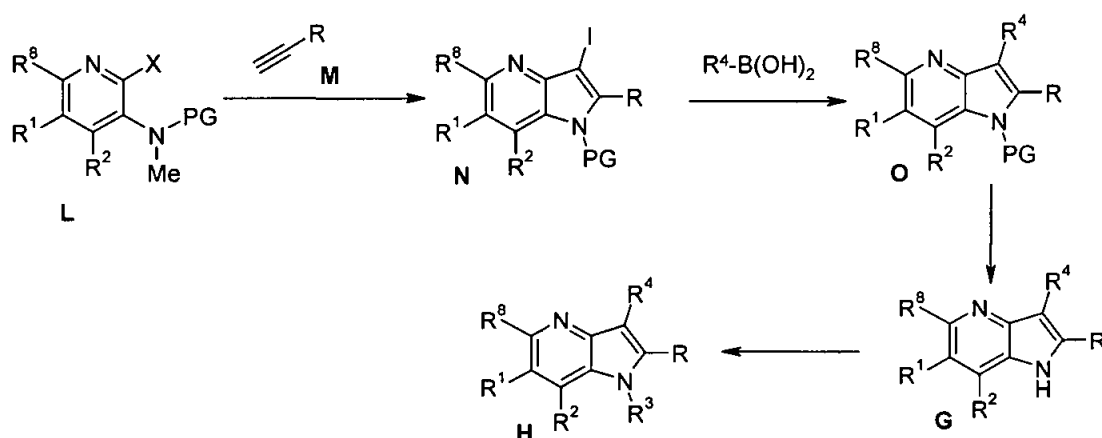
Los compuestos de la fórmula **J** se pueden obtener en una condensación-ciclación de etapa única de un compuesto de la fórmula **E** y un compuesto de la fórmula **I**. La reacción se lleva a cabo en presencia de una base tal como fosfato de potasio o carbonato de potasio, un agente deshidratante tal como sulfato de magnesio o de sodio y un catalizador de paladio con preferencia (di-*t*-butilfosfin) paladio en un solvente inerte tal como dimetilformamida o dimetilacetamida bajo una atmósfera inerte en un recipiente cerrado. (véase: *Angew. Chem. Int. Ed. Eng.* **2004**, 4526-4528).

Los compuestos de la fórmula **J** se pueden bromar regioselectivamente en presencia de bromo o N-bromosuccinimida en un solvente tal como tetracloruro de carbono o DMF para proporcionar el compuesto de la fórmula **K** (véase *Synthesis* 1982, 1096). Los compuestos de la fórmula **G** se pueden obtener mediante el tratamiento adicional de **K** en presencia de un ácido borónico de la fórmula $R^4B(OH)_2$ (donde R^4 es según se definió previamente) bajo condiciones de acoplamiento cruzado de Suzuki (véase: *Chem. Comm.*, **1979**, 866) bajo condiciones térmicas o de microondas.

Los compuestos de tipo **H** luego se pueden obtener siguiendo el procedimiento descrito precedentemente para el esquema 1.

El esquema 3 describe un método alternativo adicional para la preparación del compuesto de la fórmula (I).

Esquema 3



Los compuestos de la fórmula **L** (donde PG es un grupo protector tal como metilo, acetato, bencilo, mesilato, tosilato y similares) se pueden obtener mediante la protección secuencial de la correspondiente amino piridina **E** (véase "Protective groups in organic chemistry" Greene and Wuts 4^{ta} edición, Wiley Interscience). Los compuestos de la fórmula **L** se pueden acoplar con los compuestos de la fórmula **M** bajo condiciones de acoplamiento de Sonogashira (véase: *Synthesis*, **1980** (8) 627-630) y subsiguientemente tratarse con yodo en un solvente inerte tal como diclorometano para experimentar la ciclación directa de yodo y la formación de **N** (véase *Org. Letters* **2004**, 6(6)1037-1040).

Los compuestos de la fórmula **M** se pueden preparar a partir del compuesto halogenado principal a través de la reacción bajo condiciones de Sonogashira (véase: *Synthesis*, **1980** (8) 627-630) con trimetilsilil acetileno, seguido por la desprotección bajo condiciones básicas del grupo trimetil sililo. Los compuestos de la fórmula **M** también se pueden preparar a partir del aldehído principal bajo condiciones de reacción de Corey-Fuchs (véase *Tet. Lett.* **1972** (36), 3769).

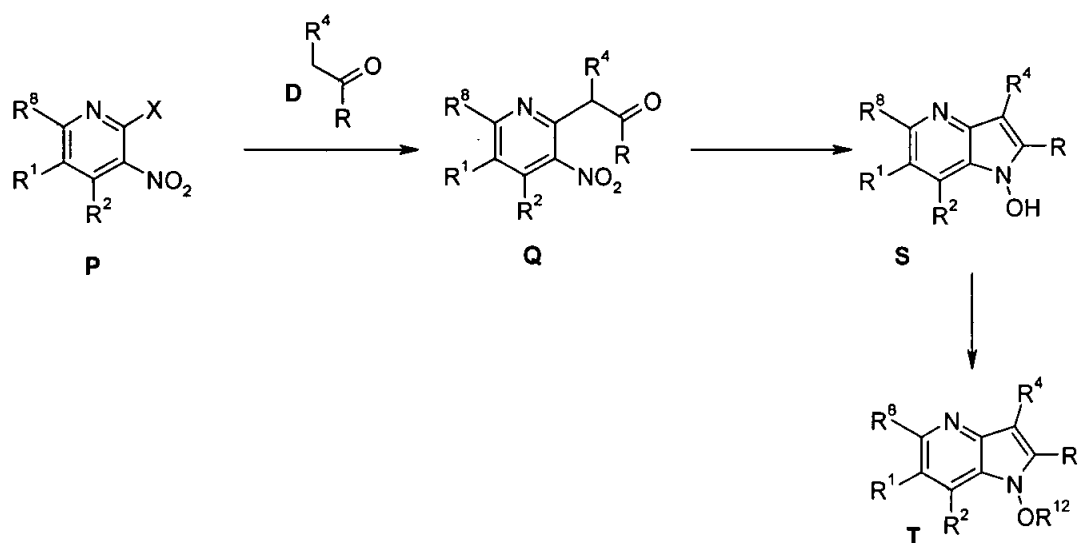
Los compuestos de la fórmula **O** se pueden obtener mediante el tratamiento de **N** bajo las mismas condiciones que las descritas precedentemente para **K** en el esquema 2 en presencia de un ácido borónico.

Los compuestos de la fórmula **G** se pueden obtener mediante la desprotección de los compuestos de la fórmula **O** a través de los métodos de la técnica dependiendo de la naturaleza del grupo protector. Como ejemplo, el acetato como grupo protector puede ser desprotegido bajo condiciones ácidas tales como HCl o condiciones básicas tales como LiOH. Debe notarse que los grupos protectores débiles pueden ser desprotegidos durante el transcurso de las reacciones para generar los compuestos de la fórmula **N** u **O**. También debe notarse que PG y R³ pueden ser los mismos desde el comienzo de la preparación por lo tanto no se requiere la secuencia de desprotección.

Los compuestos de la fórmula **H** se pueden obtener siguiendo el procedimiento descrito precedentemente en el esquema 1.

El esquema 4 describe un método alternativo para la preparación del compuesto de la fórmula (I) donde R³ es OR¹² según se describió previamente:

Esquema 4



La reacción de una cetona de la fórmula **D** (como ya se describió) y una 3-nitropiridina de la fórmula **P** en presencia de una base tal como hidruro de sodio o *t*-butóxido de potasio en un solvente aprótico tal como dimetilformamida proporciona un compuesto de la fórmula **Q** que también puede existir como su forma enol.

Los compuestos de la fórmula **P**, donde X es un halógeno tales como cloro o bromo o bien se encuentran disponibles en el comercio o bien se podrían preparar a través de métodos conocidos. Los compuestos tales como 2-cloro-3-nitro-piridina, 2-bromo-3-cloropiridina, 2-cloro-4-metil-3-nitropiridina, 2-cloro-5-metil-3-nitropiridina se encuentran disponibles en el comercio. Para la preparación de los compuestos de la fórmula **P**, a la persona experta en la técnica podría gustarle seguir un ejemplo tal como la preparación de 2,5-dibromo-3-nitropiridina descrita en *Tet. Lett.* 59(43) 8555-8570.

Los compuestos de la fórmula **Q** se pueden reducir selectivamente en la posición nitro bajo diferentes condiciones para generar el 1-hidroxi-azaindol de la fórmula **S**. Por ejemplo, los compuestos de la fórmula **Q** se pueden tratar bajo condiciones de Bechamp en presencia de hierro en un medio acuoso ácido para proporcionar los compuestos de la fórmula **S**. Bajo estas condiciones, también podría formarse la forma reducida completa del azaindol. Los compuestos de la fórmula **Q** también se pueden tratar bajo condiciones de hidrogenación catalítica, en presencia de hidrógeno, con o sin presión, con un catalizador tal como paladio sobre carbón en un solvente alcohólico tal como etanol.

Los compuestos de la fórmula **S** luego se pueden tratar bajo las mismas condiciones que las descritas para **G** en el esquema 1 con el objeto de producir el compuesto de la fórmula **T** donde R¹² es según se describió previamente.

El compuesto de la fórmula **U** se puede encontrar disponible en el comercio por ejemplo 4-piridin carboxaldehído, 3-nitro isonicotinaldehído y 3-cloro-4-piridin carboxaldehído pero también se puede preparar a través de la metodología de la técnica por ejemplo partiendo del derivado de hidroximetilo a través de un procedimiento de oxidación (véase *Aus. J. Chem* **1993**, 46(7) 987-993) pero también a través de la reducción del éster correspondiente. El compuesto de la fórmula **U** también se puede preparar a partir del halógeno o análogo no sustituido a través del intercambio halógeno-metal o hidrógeno-metal seguido por el tratamiento con un electrófilo adecuado tal como dimetilformamida (véase *Synthesis* **1999**, 306-311).

Los compuestos de la fórmula **Z** se pueden obtener mediante el tratamiento de los compuestos de la fórmula **V** con una base adecuada tal como n-butil litio, hidruro de sodio o hexametildisilazano de litio en un solvente aprótico tal como tetrahidrofurano o dietil éter con preferencia a temperatura baja seguido por el tratamiento del anión a través de un compuesto de la fórmula **W** donde X es un grupo saliente tal como halógeno (cloro, bromo o yoduro) o un mesilato y R⁴ es según se describió previamente.

Los compuestos de la fórmula **W** usualmente se encuentran disponibles en el comercio por ejemplo cloruro de 4-fluorbencilo, cloruro de 3-metil bencilo o bromuro de bencilo pero también se pueden preparar a través de las metodologías de la técnica.

Los compuestos de la fórmula **Z** se pueden oxidar para producir los compuestos de la fórmula **AA**, por ejemplo en presencia de peróxido de hidrógeno en un solvente tal como diclorometano en presencia de un catalizador tal como metil trioxorhenio (véase *Tet. Lett.* **1996**, 37(6), 805-808) o en presencia de un complejo de peróxido de hidrógeno-urea en un solvente tal como diclorometano (véase *Chem. Ber.* **1992**, 125(8), 1965-1966).

Los compuestos de la fórmula **AA** se pueden tratar a través de la 3-amino piridina de la fórmula **E** descrita previamente bajo las condiciones descriptas para la preparación de **F** en el esquema 1 para producir un compuesto de la fórmula **AB**. Alternativamente **AB** se puede obtener haciendo reaccionar **AA** y **E** conjuntamente en ausencia de solvente a una temperatura que permite la destilación del alcohol formado (véase *Synthesis* **1993**, 12, 1227-1229).

Según se mencionó previamente, los compuestos de la fórmula **AB** pueden existir bajo sus dos isómeros imina y enamina que también se pueden separar por ejemplo mediante cromatografía.

La ciclación de **AB** bajo las condiciones descriptas en el esquema 1 para la formación de **G** permite la preparación del azaindol **AC**.

Los compuestos de la fórmula **AD** donde X es halógeno tales como cloro o bromo se pueden preparar mediante el tratamiento de **AC** con POCl₃ o POBr₃ bajo las condiciones utilizadas a través de la metodología de la técnica tales como la cloración de piridinas sustituidas en *Chem. and Pharm. Bull.* **1994**, 42(9), 1841-1849.

Los compuestos de la fórmula **AE** se pueden preparar a partir de **AD** a través de la reacción de amidación o aminación de Buchwald en presencia de una amida o amina primaria, de un catalizador de paladio (II) tal como diacetato de paladio, un ligando tal como Xantphos®, una base tal como carbonato de potasio o de cesio en un solvente aprótico tal como dioxano o tetrahidrofurano bajo condiciones térmicas o de microondas (véase *Org. Let.* **2001**, 3(21) 3417-3419).

Los compuestos de la fórmula **AE** también se pueden preparar a partir de **AD** a través del tratamiento directo con una amina tal como bencil amina bajo condiciones térmicas o de microondas, seguido por el tratamiento con un ácido fuerte tal como ácido sulfúrico concentrado para producir el compuesto donde R⁶

es NH_2 . Dicho intermediario puede tratarse adicionalmente a través de una base no nucleofílica apropiada tal como piridina en un solvente tal como dimetilformamida o tetrahidrofurano y un agente de acilación tal como R^{20}COX donde X es cloro o flúor y R^{20} es según se describió previamente. Éste también puede tratarse con un agente de alquilación, tal como $\text{R}^{18}\text{-X}$ donde X es un grupo saliente tal como halógeno o un mesilato, bajo las mismas condiciones. Otra alquilación o acilación proporcionará, bajo las mismas condiciones, compuestos donde R^6 es $\text{NR}^{18}\text{R}^{19}$, según se describió previamente.

Los compuestos de la fórmula **AE** donde R^6 no es ni una amina ni una amida se pueden preparar directamente mediante el tratamiento de los compuestos de la fórmula **AC** con un agente activador seguido por un nucleófilo según se describió en la reseña de *Science of Synthesis* (2005), 15, 285-387 (Georg Thiem Verlag Publisher). Por ejemplo, si R^6 es cianuro, los compuestos de la fórmula **AC** se tratan con un activador tal como cloruro de benzoilo en presencia de una fuente de cianuro tal como trimetilsilil-cianuro en un solvente aprótico tal como dimetilformamida o tetrahidrofurano (Véase *J. Org. Chem.* **1983**, 48, 1375-1377).

Los compuestos de la fórmula **AE** donde R^6 es cianuro se pueden modificar adicionalmente a través de los métodos de la técnica para producir todos los posibles derivados del grupo cianuro: por ejemplo, reducción al ácido o éster, reducción a la amida o reducción a la amina, adición sobre cianuro a través de un alquil o aril Grignard para producir la cetona.

Los compuestos de la fórmula **AI** se pueden preparar a partir de **AD** siguiendo la metodología descrita en el esquema 1 para la preparación de **H** a partir de **G**.

Los compuestos de la fórmula **AG** se pueden preparar a partir de **AE** siguiendo la metodología utilizada para la preparación de **AI**. Los compuestos de

la fórmula **AG** también se pueden preparar a partir de **AI** siguiendo las metodologías utilizadas para la preparación de **AE** a partir de **AD**.

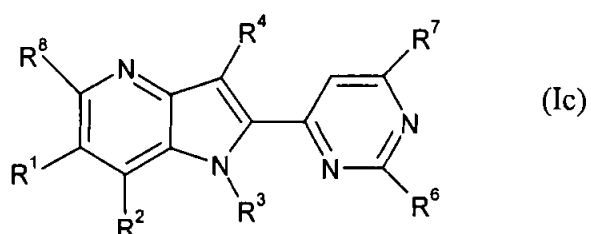
Los compuestos de la fórmula **AF** se pueden preparar a partir de **AE** a través del siguiente tratamiento:

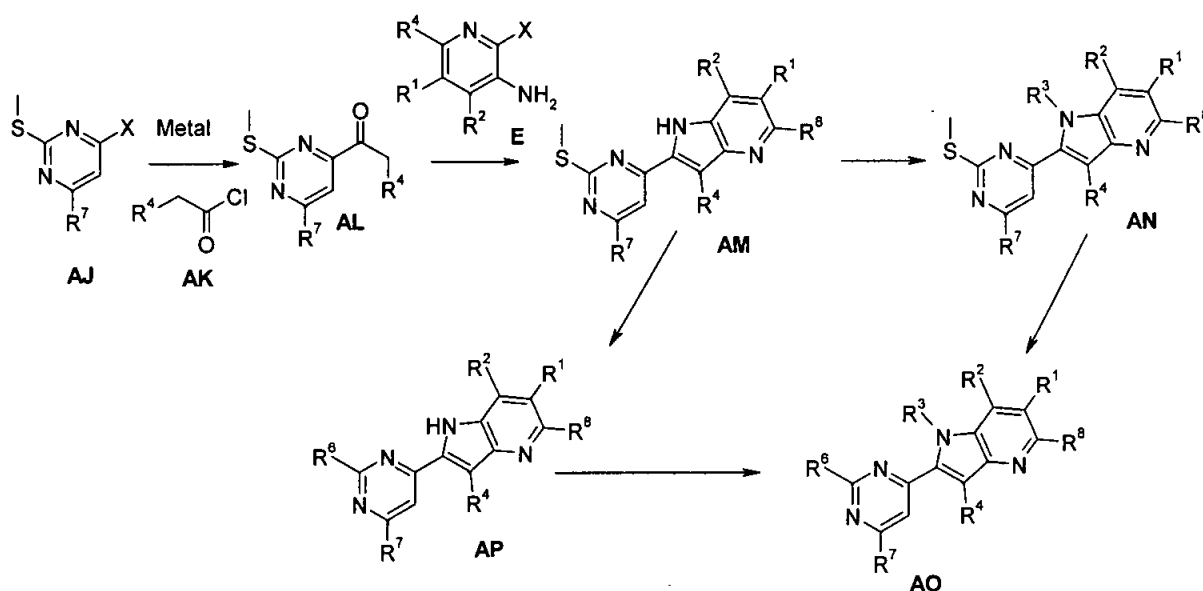
- oxidación de la piridina siguiendo la preparación descrita para **AA** a partir de **Z**
- reacción directa para introducir R^7 según se describió para la introducción de R^6 en la preparación de **AE** a partir de **AD**
- R^7 también puede ser introducido a través de las metodologías descritas para la introducción de R^6 en la preparación de **AE** a partir de **AC** por medio de **AD**.

Los compuestos de la fórmula **AH** se pueden preparar a partir del compuesto de la fórmula **AF** siguiendo el tratamiento descrito para la preparación de **H** en el esquema 1.

Pueden llevarse a cabo etapas adicionales que no se describen en el esquema 5 a partir del compuesto **AC**, **AD**, **AI**, **AE**, **AF**, **AG** y **AH**. Estas reacciones pueden resultar en la transformación adicional de R^1 a R^8 , por ejemplo, la ciclación entre R^6 y R^3 o entre R^1 y R^2 .

El esquema 6 describe un método alternativo para la preparación de los compuestos de la fórmula (I) donde X^1 es CH y X^2 es N (compuestos de la fórmula (Ic), por ejemplo, aquellos compuestos que se enumeran en la Tabla 3).





Esquema 6

Los compuestos de la fórmula **AL** se pueden preparar mediante el tratamiento de la pirimidina de la fórmula **AJ** donde X es un halógeno tal como bromo, cloro o yoduro y R^7 es según se describió previamente en presencia de una base adecuada para llevar a cabo el intercambio metal halógeno. Se pueden utilizar *n*-butil litio, *s*-butil litio en un solvente aprótico tal como tetrahidrofurano con preferencia a temperatura baja. El cloruro de acilo de la fórmula **AK** luego puede reaccionar con el anión de la pirimidina formado previamente para proporcionar los compuestos de la fórmula **AL**.

Los compuestos de la fórmula **AJ** se pueden encontrar disponibles en el comercio tal como la 4-yodo-2-metiltio-pirimidina o se pueden obtener a través de los métodos de la técnica (véase por ejemplo *Tet. Lett.* **2001**, 42(2), 311-313).

Los compuestos de la fórmula **AK** usualmente se encuentran disponibles en el comercio, por ejemplo cloruro de fenilacetilo, cloruro de *m*-tolilacetilo o cloruro de 4-fluorbencenacetilo pero también podrían prepararse a partir del ácido correspondiente.

Los compuestos de la fórmula **AM** se pueden preparar a partir de la condensación entre los compuestos de la fórmula **E** y **AL** bajo las condiciones

descriptas para la formación del compuesto **F** en el esquema 1, seguida por la ciclación de la imina o enamina obtenida bajo las condiciones descriptas en el esquema 1 para la formación del compuesto **G**.

El compuesto **E** es según se describió previamente.

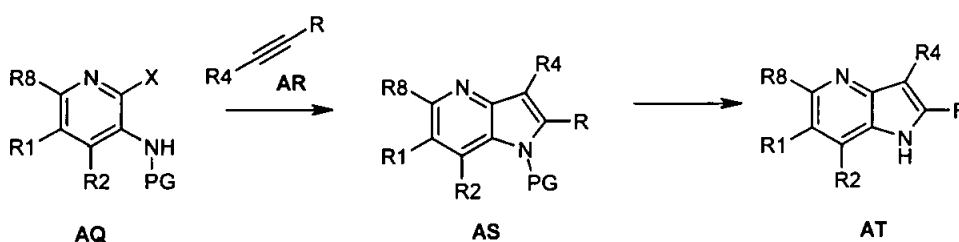
La oxidación de la pirimidina de los compuestos de la fórmula **AM** en presencia de un oxidante tales como el ácido m-cloroperbenzoico en un solvente tal como diclorometano resulta en la formación del intermediario sulfóxido. El tratamiento adicional de este intermediario con una amina tal como bencil amina seguido por el tratamiento en ácido sulfúrico concentrado resulta en la formación de un compuesto de la fórmula **AP** donde R^6 es NH_2 . El tratamiento adicional según se describió previamente para la formación del compuesto **AE** en el esquema 5 resulta en la formación de **AP** con R^6 según se describió previamente.

Los compuestos de la fórmula **AN** se pueden obtener mediante el tratamiento de los compuestos de la fórmula **AM** siguiendo el mismo procedimiento que el descrito previamente para la formación de los compuestos de la fórmula **H** a partir del compuesto de la fórmula **G**.

Los compuestos de la fórmula **AO** se pueden preparar a partir de los compuestos de la fórmula **AN** según se describió previamente para la preparación de los compuestos de la fórmula **AP** a partir de los compuestos de la fórmula **AM**.

Los compuestos de la fórmula **AO** también se pueden preparar a través de la introducción directa de R^3 en el anillo indol de los compuestos de la fórmula **AP** siguiendo el procedimiento descrito previamente para la formación de los compuestos de la fórmula **H** a partir de los compuestos de la fórmula **G** en el esquema 1.

El esquema 7 describe un método alternativo para la preparación del compuesto de la fórmula (I).



Esquema 7

Los compuestos de la fórmula **AQ** (donde PG es un grupo protector tal como bencilo, acetato, trifluoracetato) se pueden obtener mediante la protección de la correspondiente aminopiridina E (véase "Protective groups in organic chemistry", Greene and Wuts 4^{ta} edición, Wiley Interscience). Los compuestos de la fórmula **AQ** luego se pueden acoplar con los compuestos de la fórmula **AR** (donde R⁴ no es ni un fenilo ni un 4-fluorfenilo) bajo condiciones de indolización catalizadas por paladio (véase *Org. Letters* 2004, 6 (22), 4129-4132) para producir los compuestos **AS**. Los últimos luego se pueden desproteger de acuerdo con procedimientos conocidos, por ejemplo los grupos bencilo se pueden remover mediante hidrogenación catalítica.

Los procesos descriptos previamente posibilitarán que aquéllos expertos en la técnica comprendan las técnicas y condiciones generales a utilizarse en esta invención. Las modificaciones adicionales de los grupos R¹ a R⁸ para permitir la preparación de los compuestos descriptos en esta invención podrían ser necesarias para llevar a cabo por ejemplo la formación de una estructura cíclica entre R¹ y R², R¹ y R³, R² y R³, R³ y R⁵ y R⁵ y R⁶. Aquéllos expertos en la técnica reconocerán que estas modificaciones podrían efectuarse en más de una etapa, comprendiendo por ejemplo reacciones de acoplamiento, oxidación, reducción con o sin catalizador, sustitución nucleofílica, lactonización, lactamización y similares.

Según se indicó precedentemente, ahora se ha descubierto que los compuestos de la fórmula I son útiles en el control de hongos patógenos de las plantas cuando ellos se aplican a la planta o material de propagación de plantas en una cantidad efectiva como fungicida.

Por 'material de propagación de plantas' se denota las partes generativas de una planta que incluyen las semillas de todos los tipos (frutos, tubérculos, bulbos, granos etc), raíces, rizomas, recortes, cortes brotes y similares. El material de propagación de plantas también puede incluir a las plantas y a las plantas jóvenes las cuales van a transplantarse luego de la germinación o luego de la emergencia del suelo.

Los métodos, compuestos y composiciones de la presente invención son, por ejemplo, efectivos frente a hongos fitopatógenos de las siguientes clases: Fungi imperfecti (por ejemplo *Botrytis*, *Pyricularia*, *Helminthosporium*, *Fusarium*, *Septoria*, *Cercospora* y *Alternaria*), Basidiomycetes (por ejemplo *Rhizoctonia*, *Hemileia*, *Puccinia*), Ascomycetes (por ejemplo *Venturia* y *Erysiphe*, *Podosphaera*, *Monilinia*, *Uncinula* y *Pyrenophora*) y Oomycetes (por ejemplo *Phytophthora*, *Pythium*, *Plasmopara*). En particular, los métodos, compuestos y composiciones de la presente invención son efectivos frente a *Botrytis* spp., *Pyricularia* spp., *Fusarium* spp., *Septoria* spp., *Rhizoctonia* spp., *Puccinia* spp., *Erysiphe* spp., *Phytophthora* spp., *Pythium* spp. y *Plasmopara* spp. Aún más particularmente, los métodos, compuestos y composiciones de la presente invención son efectivos frente a *Botrytis cinerea*, *Pyricularia oryzae*, *Fusarium culmorum*, *Septoria nodurum* y *Septoria tritici*, *Rhizoctonia solani*, *Puccinia recondite*, *Erysiphe graminis*, *Pyrenophora teres*, *Phytophthora infestans*, *Pythium ultimum* y *Plasmopara viticola*.

Los métodos, compuestos y composiciones de la presente invención son adecuados para controlar dichas enfermedades en una cantidad de plantas y en su material de propagación que incluyen, pero no se limitan a los siguientes

cultivos objetivo: cereales (trigo, cebada, centeno, avena, maíz (incluyendo maíz de campo, maíz explotado y maíz dulce), arroz, sorgo y cultivos relacionados); remolacha (remolacha azucarera y remolacha forrajera); plantas leguminosas (frijoles, lentejas, arvejas, soja); plantas oleaginosas (colza, mostaza, girasoles); plantas cucurbitáceas (calabacines, pepinos, melones); plantas de fibra (algodón, lino, cáñamo, yute); vegetales (espinaca, lechuga, espárrago, repollos, zanahorias, berenjenas, cebollas, pimiento, tomates, papas, pimentón, oca; cultivos de plantación (bananas, árboles frutales, árboles de caucho, almácigos de árboles), ornamentales (florés, arbustos, árboles de hojas anchas y perennes, tales como las coníferas); así como también otras plantas tales como vides, bayas de arbustos (tales como los arándanos), bayas de cañas, arándanos rojos, menta, riubarbo, menta verde, caña de azúcar y gramíneas para céspedes que incluyen, pero no se limitan a, gramíneas para céspedes de temporada fresca (por ejemplo, céspedes azules (*Poa* L.), tales como el césped azul de Kentucky (*Poa pratensis* L.), el césped azul rugoso (*Poa trivialis* L.), el césped azul de Canadá (*Poa compressa* L.) y el césped azul anual (*Poa annua* L.); céspedes bent (*Agrostis* L.), tales como el césped bent rastrero (*Agrostis palustris* Huds.), el césped bent colonial (*Agrostis tenius* Sibth.), el césped bent aterciopelado (*Agrostis canina* L.) y el redtop (*Agrostis alba* L.); festucas (*Festuca* L.), tales como la festuca alta (*Festuca arundinacea* Schreb.), festuca de los prados (*Festuca elatior* L.) y festucas finas tales como la festuca roja rastrera (*Festuca rubra* L.), festuca masticable (*Festuca rubra* var. *commutata* Gaud.), festuca ovina (*Festuca ovina* L.) y festuca dura (*Festuca longifolia*); y raigrás (*Lolium* L.), tal como el raigrás perenne (*Lolium perenne* L.) y el raigrás anual (italiano) (*Lolium multiflorum* Lam.)) y gramíneas para céspedes de temporada cálida (por ejemplo, césped de las Bermudas (*Cynodon* L. C. Rich), que incluye césped de las Bermudas híbrido y común; césped Zoysia (*Zoysia* Willd.), césped St. Augustine (*Stenotaphrum secundatum* (Walt.) Kuntze); y césped ciempiés (*Eremochloa ophiuroides* (Munro.) Hack.)).

Además debe entenderse que 'cultivo' incluye aquellos cultivos que se han tornado tolerantes a las plagas y a los plaguicidas, incluyendo herbicidas o clases de herbicidas, como resultado de los métodos convencionales de reproducción o ingeniería genética. La tolerancia por ejemplo a los herbicidas significa una reducida susceptibilidad al daño causado por un herbicida particular en comparación con las reproducciones de cultivos convencionales. Los cultivos se pueden modificar o reproducir de modo que sean tolerantes, por ejemplo, a los inhibidores de HPPD tales como mesotriona o a los inhibidores de EPSPS tales como glifosato.

Más aún, los compuestos de la fórmula I encuentran un uso general como fungicidas y por consiguiente también pueden utilizarse para controlar hongos patógenos en áreas relacionadas, por ejemplo en la protección de materiales técnicos, que incluyen productos técnicos de madera y relacionados con la madera, en el almacenamiento de alimentos o en la manipulación higiénica. Como tal, la presente invención provee además la utilización de un compuesto de la fórmula I para el control de los hongos.

Cuando se utilizan en los métodos de la invención, los compuestos de la fórmula I se pueden encontrar en forma no modificada o, con preferencia, formulados conjuntamente con portadores y adyuvantes empleados convencionalmente en la técnica de formulación.

Por consiguiente la invención también se refiere a una composición para el control de infecciones fúngicas que comprende un compuesto de la fórmula I según se definió precedentemente y un portador o diluyente aceptable desde el punto de vista agrícola.

La composición agroquímica usualmente contendrá desde 0,1 hasta 99% en peso, con preferencia desde 0,1 hasta 95% en peso, del compuesto de la fórmula I, 99,9 hasta 1% en peso, con preferencia 99,8 hasta 5% en peso, de un

adyuvante sólido o líquido, y desde 0 hasta 25% en peso, con preferencia desde 0,1 hasta 25% en peso, de un surfactante.

De modo adecuado, las formulaciones y composiciones agroquímicas de la presente invención se aplican antes del desarrollo de la enfermedad. Las proporciones y frecuencia de uso de las formulaciones son aquellas que se utilizan convencionalmente en la técnica y dependerán del riesgo de infestación por parte del patógeno fúngico, del estado de desarrollo de la planta y de la ubicación, sincronización y método de aplicación. Las proporciones de aplicación ventajosas son normalmente desde 5 g hasta 2 kg de ingrediente activo (a.i., por sus siglas en inglés) por hectárea (ha), con preferencia desde 10 g hasta 1 kg a.i./ha, aún con más preferencia desde 20 g hasta 600 g a.i./ha. Cuando se utilizan como agente de remojo de semillas, las proporciones de aplicación convenientes son desde 10 mg hasta 1 g de sustancia activa por kg de semillas.

En la práctica, según se indicó precedentemente, las composiciones agroquímicas que comprenden un compuesto de la fórmula (I) se aplican como una formulación que contiene los diversos adyuvantes y portadores conocidos para la industria o utilizados en la industria. De este modo ellas pueden formularse como gránulos, como polvos humectables o solubles, como concentrados emulsionables, como pastas recubiertas, como polvos finos, como floables, como soluciones, como suspensiones o emulsiones, o como formas de liberación controlada tales como microcápsulas. Estas formulaciones se describen en más detalle a continuación y pueden contener tan sólo aproximadamente 0,5% hasta tanto como aproximadamente 95% o más en peso del ingrediente activo. La cantidad óptima dependerá de la formulación, del equipamiento para la aplicación y de la naturaleza de los hongos patógenos de las plantas a ser controlados.

Los concentrados en suspensión son formulaciones acuosas en las cuales se encuentran suspendidas partículas sólidas del compuesto activo finamente divididas. Dichas formulaciones incluyen agentes antiasentamiento y agentes dispersantes y pueden incluir además un agente humectante para mejorar la

actividad así como también un anti-espumante y un inhibidor del crecimiento de cristales. En el uso, estos concentrados se diluyen en agua y normalmente se aplican como un rocío al área a ser tratada. La cantidad de ingrediente activo puede tener un rango desde aproximadamente 0,5% hasta aproximadamente 95% del concentrado.

Los polvos humectables se encuentran en forma de partículas finamente divididas que se dispersan fácilmente en agua o en otros portadores líquidos. Las partículas contienen el ingrediente activo retenido en una matriz sólida. Las matrices sólidas típicas incluyen tierra de fuller, arcillas de caolín, sílices y otros sólidos orgánicos o inorgánicos fácilmente humectables. Los polvos humectables normalmente contienen aproximadamente 5% hasta aproximadamente 95% del ingrediente activo más una pequeña cantidad de agente humectante, dispersante o emulsionante.

Los concentrados emulsionables son composiciones líquidas homogéneas dispersables en agua o en otro líquido y pueden consistir completamente del compuesto activo con un agente emulsionante líquido o sólido, o también pueden contener un portador líquido, tal como xileno, naftas aromáticas pesadas, isoforona y otros solventes orgánicos no volátiles. En el uso, estos concentrados se dispersan en agua o en otro líquido y normalmente se aplican como un rocío al área a ser tratada. La cantidad de ingrediente activo puede tener un rango desde aproximadamente 0,5% hasta aproximadamente 95% del concentrado.

Las formulaciones granulares incluyen tanto a los extrudados como a las partículas relativamente gruesas y usualmente se aplican sin dilución al área en la cual se requiere el control de los hongos patógenos de las plantas. Los portadores típicos para las formulaciones granulares incluyen arena, tierra de fuller, arcilla atapulguita, arcilla bentonita, arcilla montmorillonita, vermiculita, perlita, carbonato de calcio, ladrillo (brick), piedra pómez, pirofilita, caolín, dolomita, yeso (plaster), harina de madera, mazorcas molidas, cáscaras de maní molidas, azúcares,

cloruro de sodio, sulfato de sodio, silicato de sodio, borato de sodio, magnesia, mica, óxido de hierro, óxido de zinc, óxido de titanio, óxido de antimonio, criolita, yeso (gypsum), tierra diatomea, sulfato de calcio y otros materiales orgánicos o inorgánicos que absorben o que se pueden recubrir con el compuesto activo. Las formulaciones granulares normalmente contienen aproximadamente 5% hasta aproximadamente 25% de los ingredientes activos los cuales pueden incluir agentes superficialmente activos tales como naftas aromáticas pesadas, querosén y otras fracciones de petróleo, o aceites vegetales; y/o adhesivos tales como dextrinas, gomas o resinas sintéticas.

Los polvos finos son mezclas de libre fluencia del ingrediente activo con sólidos finamente divididos tales como talco, arcillas, harinas y otros sólidos orgánicos e inorgánicos que actúan como dispersantes y portadores.

Las microcápsulas son típicamente gotas pequeñas o gránulos del ingrediente activo contenidos en un caparazón poroso inerte que permite la salida del material contenido hacia los alrededores a velocidades controladas. Las gotas pequeñas encapsuladas tienen típicamente un diámetro de aproximadamente 1 a 50 micrones. El líquido contenido constituye típicamente aproximadamente 50 a 95% del peso de la cápsula y puede incluir solvente además del compuesto activo. Los gránulos encapsulados son generalmente gránulos porosos con membranas porosas que sellan las aberturas de los poros de los gránulos, reteniendo las especies activas en forma líquida dentro de los poros de los gránulos. Los gránulos tienen típicamente un diámetro en el rango desde 1 milímetro hasta 1 centímetro y con preferencia 1 hasta 2 milímetros. Los gránulos se forman mediante extrusión, aglomeración o perlado, u ocurren naturalmente. Los ejemplos de dichos materiales son vermiculita, arcilla sinterizada, caolín, arcilla atapulguita, aserrín y carbón granular. Los materiales de membrana o de caparazón incluyen cauchos naturales y sintéticos, materiales celulósicos, copolímeros de estireno-butadieno, poliacrilonitrilos, poliacrilatos, poliésteres, poliamidas, poliureas, poliuretanos y xantatos de almidón.

Otras formulaciones útiles para aplicaciones agroquímicas incluyen soluciones simples del ingrediente activo en un solvente en el cual éste es completamente soluble en la concentración deseada, tal como acetona, naftalenos alquilados, xileno y otros solventes orgánicos. También pueden utilizarse rociadores presurizados, donde el ingrediente activo se encuentra disperso en forma finamente dividida como resultado de la vaporización de un portador solvente dispersante de baja ebullición.

Los adyuvantes y portadores agrícolas adecuados que son útiles para formular las composiciones de la invención en los tipos de formulación descriptos precedentemente son muy conocidos por aquéllos expertos en la técnica. Los ejemplos adecuados de las diferentes clases se encuentran en la lista no limitativa a continuación.

Los portadores líquidos que se pueden emplear incluyen agua, tolueno, xileno, éter de petróleo, aceite agrícola, acetona, metil etil cetona, ciclohexanona, anhídrido acético, acetonitrilo, acetofenona, acetato de amilo, 2-butanona, clorobenceno, ciclohexano, ciclohexanol, acetatos de alquilo, diacetonalcohol, 1,2-dicloropropano, dietanolamina, p-dietilbenceno, dietilen glicol, abietato de dietilen glicol, butil éter de dietilen glicol, etil éter de dietilen glicol, metil éter de dietilen glicol, N,N-dimetilformamida, sulfóxido de dimetilo, 1,4-dioxano, dipropilen glicol, metil éter de dipropilen glicol, dibenzoato de dipropilen glicol, diproxitol, alquil pirrolidinona, acetato de etilo, 2-etil hexanol, carbonato de etileno, 1,1,1-tricloroetano, 2-heptanona, alfa-pineno, d-limoneno, etilen glicol, butil éter de etilen glicol, metil éter de etilen glicol, gama butirólactona, glicerol, diacetato de glicerol, monoacetato de glicerol, triacetato de glicerol, hexadecano, hexilen glicol, acetato de isoamilo, acetato de isobornilo, isooctano, isoforona, isopropil benceno, miristato de isopropilo, ácido láctico, laurilamina, óxido de mesitilo, metoxipropanol, metil isoamil cetona, metil isobutil cetona, laurato de metilo, octanoato de metilo, oleato de metilo, cloruro de metileno, m-xileno, n-hexano, n-octilamina,

ácido octadecanoico, acetato de octil amina, ácido oleico, oleilamina, o-xileno, fenol, polietilen glicol (PEG 400), ácido propiónico, propilen glicol, monometil éter de propilen glicol, p-xileno, tolueno, fosfato de trietilo, trietilen glicol, ácido xilen sulfónico, parafina, aceite mineral, tricloroetileno, percloroetileno, acetato de etilo, acetato de amilo, acetato de butilo, metanol, etanol, isopropanol, y alcoholes de peso molecular más alto tales como amil alcohol, tetrahidrofurfuril alcohol, hexanol, octanol, etc. etilen glicol, propilen glicol, glicerina, N-metil-2-pirrolidinona, y similares. Generalmente el portador de elección para la dilución de los concentrados es el agua.

Los portadores sólidos adecuados incluyen talco, dióxido de titanio, arcilla pirofilita, sílice, arcilla atapulgita, kieselguhr, tiza, tierra diatomea, cal, carbonato de calcio, arcilla bentonita, tierra de fuller, cáscaras de semillas de algodón, harina de trigo, harina de soja, piedra pómez, harina de madera, harina de cáscaras de nuez, lignina y similares.

Un amplio rango de agentes superficialmente activos se emplean de modo ventajoso tanto en las composiciones líquidas como sólidas, especialmente aquéllos diseñados para ser diluidos con un portador antes de la aplicación. Estos agentes, cuando se utilizan, normalmente comprenden desde 0,1% hasta 15% en peso de la formulación. Ellos pueden ser de carácter aniónico, catiónico, no iónico o polimérico y se pueden emplear como agentes emulsionantes, agentes humectantes, agentes de suspensión o para otros propósitos. Las sustancias superficialmente activas típicas incluyen sales de sulfatos de alquilo, tales como lauril sulfato de dietanolamonio; sales de alquilarilsulfonato, tales como dodecilbencensulfonato de calcio; productos de adición de alquilfenol-óxido de alquileo, tales como etoxilado de nonilfenol-C.sub. 18; productos de adición de alcohol-óxido de alquileo, tales como etoxilado de tridecil alcohol-C.sub. 16; jabones, tales como estearato de sodio; sales de alquilnaftalensulfonato, tales como dibutilnaftalensulfonato de sodio; dialquil ésteres de sales de sulfosuccinato, tales como di(2-etilhexil)sulfosuccinato de sodio; ésteres de sorbitol, tales como

oleato de sorbitol; aminas cuaternarias, tales como cloruro de lauril trimetilamonio, ésteres de ácidos grasos de polietilen glicol, tales como estearato de polietilen glicol; copolímeros en bloque de óxido de etileno y de óxido de propileno; y sales de ésteres de mono y dialquil fosfato.

Otros adyuvantes comúnmente utilizados en las composiciones agrícolas incluyen inhibidores de la cristalización, modificadores de la viscosidad, agentes de suspensión, modificadores de gotas pequeñas en aerosol, pigmentos, antioxidantes, agentes espumantes, agentes antiespumantes, agentes bloqueadores de luz, agentes compatibilizantes, agentes antiespuma, agentes secuestrantes, agentes neutralizantes y buffers, inhibidores de corrosión, colorantes, fragancias (odorants), agentes dispersantes, auxiliares de penetración, micronutrientes, emolientes, lubricantes, agentes adhesivos, y similares.

Además, adicionalmente, en los métodos de la invención pueden utilizarse otras composiciones o ingredientes activos como biocidas y aplicarse simultáneamente o secuencialmente con el compuesto de la fórmula (I). Cuando se aplican simultáneamente, estos ingredientes activos adicionales se pueden formular conjuntamente con el compuesto de la invención o mezclarse en, por ejemplo, el tanque de rociado. Estos ingredientes activos como biocidas adicionales pueden ser fungicidas, herbicidas, insecticidas, bactericidas, acaricidas, nematocidas y/o reguladores del crecimiento de las plantas.

Los ejemplos de los compuestos insecticidas para utilizar en las composiciones/métodos de la presente invención incluyen, pero no se limitan a, piretroides (tales como permetrina, cipermetrina, fenvalerato, esfenvalerato, deltametrina, cihalotrina (en particular, lambda-cihalotrina), bifentrina, fenpropatrina, ciflutrina, teflutrina, piretroides seguros para los peces (por ejemplo etofenprox), 5-bencil-3-furilmetil-(E)-(1R,3S)-2,2-dimetil-3-(2-oxotiolan-3-ilidenmetil)ciclopropan carboxilato, praletrina, fenflutrina, s-bioaletrina, tetrametrina y piretrina natural), organofosfatos (tales como, profenofos, sulprofos, acefato,

metil paratión, azinfos-metil, demeton-s-metil, heptenofos, tiometon, fenamifos, monocrotofos, profenofos, triazofos, metamidofos, dimetoato, fosfamidon, malation, clorpirifos, fosalona, terbufos, fensulfotion, fonofos, forato, foxim, pirimifos-metil, pirimifos-etil, fenitrothion, fostiazato y diazinon); carbamatos, que incluyen aril carbamatos, (tales como pirimicarb, triazamato, cloetocarb, carbofuran, furatiocarb, etiofencarb, aldicarb, tiofurox, carbosulfan, bendiocarb, fenobucarb, propoxur, metomil y oxamil), benzoil ureas (tales como diflubenzuron, triflumuron, hexaflumuron, flufenoxuron y clorfluazuron), compuestos de estaño orgánico (tales como cihexatina, óxido de fenbutatina y azociclotina), pirazoles (tales como tebufenpirad y fenpiroximato), macrólidos (tales como avermectinas o milbemicinas, por ejemplo abamectina, benzoato de emamectina, ivermectina, milbemicina, spinosad y azadiractina), hormonas o feromonas, compuestos de organocloro (tales como endosulfan, hexacloruro de benceno, DDT, clordano y dieldrina), amidinas (tales como clordimeform y amitraz), agentes fumigantes (tales como cloropicrina, dicloropropano, bromuro de metilo y metam); compuestos de cloronicotinilo (tales como imidacloprid, tiacloprid, acetamiprid, nitenpiram y tiametoxam), diacilhidrazinas (tales como tebufenozida, cromafenozida y metoxifenozida), éteres de difenilo (tales como diofenolan y piriproxifen), indoxacarb, clorfenapir y pimetrozina.

Los ejemplos de los compuestos herbicidas para utilizar en las composiciones/métodos de la presente invención incluyen, pero no se limitan a, 2,3,6-TBA, 2,4-D, 2,4-DB, acetoclor, acifluorfen-sodio, aclonifen, acroleína, alaclor, aloxidim, ametrina, amicarbazona, amidosulfuron, aminopirialid, aminotriazol, amitrol, sulfamato de amonio, anilofos, asulam, atrazina, aviglicina, azafenidina, azimsulfuron, BAY FOE 5043, beflubutamid, benazolina, bencarbazona, benfluralina, benfuresato, bensulfuron-metil, bensulida, bentazona, benzfendizona, benzobiciclon, benzofenap, bialafos, bifenox, bispiribac-sodio, borax, bromacil, bromobutida, bromofenoxim, bromoxinil, butaclor, butafenacil, butamifos, butralina, butroxidim, butilato, cafenstrol, carbetamida, carfentrazona-etil, cloransulam metil, clorbromuron, clorflurenol-metil, cloridazon, clorimuron-etil, ácido cloroacético,

clorotoluron, clorprofam, clorsulfuron, clortal-dimetil, cinidon-etil, cinmetilina, cinosulfuron, clefoxidim profoxidim, cletodim, clodinafop-propargil, clomazona, clomeprop, clopiralid, cloransulam, cloransulam-metil, cumuluron, cumiluron, cianamida, cianazina, ciclanilida, cicloato, ciclosulfamuron, cicloxidim, cihalofof, cihalofof-butil, ciprosulfamida, daimuron, dalapon, dazomet, desmedifam, desmetrina, dicamba, diclobenil, diclorprop, diclorprop-P, diclofof-metil, diclosulam, difenzoquat metilsulfato, diflufenican, diflufenzopir, dimefuron, dimepiperato, dimetaclor, dimetametrina, dimetenamid, dimetenamid-P, dimetipina, ácido dimetilarsínico, dinitramina, dinoterb, difenamid, dipropetrina, diquat, ibromide, ditiopir, diuron, DNOC, DSMA, endotal, EPTC, esprocarb, etalfluralina, etametsulfuron-metil, etefon, etofumesato, etoxifen-etil, etoxisulfuron, etobenzanid, fencloirim, fenoxaprop-P-etil, fentrazamida, sulfato ferroso, flamprop, flamprop-M, flazasulfuron, florasulam, fluazifop-butil, fluazifop-P-butil, fluazolato, flucarbazone sódico, flucetosulfuron, flucloralina, flufenacet, flufenpir-etil, flumetralina, flumetsulam, flumiclorac-pentil, flumioxazin, flumipropin, fluometuron, fluorglicofen-etil, fluoxaprop, flupoxam, flupropacil, flupropanato, flupirsulfuron-metil-sodio, flurenol, fluridona, flurocloridona, fluroxipir, flurtamona, flutiacet-metil, fluxofenim, fomesafen, foramsulfuron, fosamina, glufosinato-amonio, glifosato, halosulfuron-metil, haloxifop, haloxifop-P, HC-252, hexazinona, imazametabenz-metil, imazamox, imazapic, imazapir, imazaquin, imazetapir, imazosulfuron, indanofan, yodosulfuron, yodosulfuron-metil-sodio, ioxinil, isopropazol, isoproturon, isouron, isoxaben, isoxaclortol, isoxadifen, isoxaflutol, isoxapirifop, karbutilato, KIH-485, lactofen, lenacil, linuron, MCPA, MCPA-tioetil, MCPB, mecoprop, mecoprop-P, mefenacet, mefenpir dietil, mefluidida, mesosulfuron metil, mesotriona, metam, metamifop (mefluoxafop), metamitron, metazaclor, metabenzthiazuron, metazol, isotiocianato de metilo, ácido metilarsónico, metildimron, metobenzuron, metobromuron, metolaclor, metosulam, metoxuron, metribuzina, metsulfuron-metil, MK-616, molinato, monolinuron, MSMA, naproanilida, napropamida, naptalam, NDA-402989, neburon, nefenacet, nicosulfuron, nipiraclofen, n-metil-glifosato, ácido nonanoico, norflurazon, ácido oleico (ácidos grasos), orbencarb, ortosulfamuron, orizalina, oxaciclomefone, oxadiargil, oxadiazon, oxasulfuron,

oxaziclomefone, oxifluorfen, pebulato, pendimetalina, penoxsulam, pentaclorofenol, pentanoclor, pentoxazona, petoxamid, aceites de petróleo, fenmedifam, fenoxaprop-P-etil (R), picloram, picolinafen, pinoxaden, piperofos, pretilaclor, primisulfuron, primisulfuron-metil, procarbazona, prodiamina, profluazol, profoxidim, prohexcadion calcio, prometon, prometrina, propaclor, propanil, propaquizafof, propazina, profam, propisoclor, propoxicarbazona, propoxicarbazona-sodio, propizamida, prosulfocarb, prosulfuron, piraclonil, pirazogil, piraflufen-etil, pirasulfotol, pirazolinato, pirazosulfuron-etil, pirazoxifen, piribenzoxim, piributicarb, piridafol, piridato, piriftalid, piriminobac-metil, pirimisulfan, piritiobac-sodio, quinclorac, quinmerac, quinoclamina, quizalofop, quizalofop-P, rimsulfuron, sequestren, setoxidim, siduron, simazina, simetrina, S-metolaclor, clorato de sodio, sulcotriona, sulfentrazona, sulfometuron-metil, sulfosato, sulfosulfuron, ácido sulfúrico, aceites de alquitrán, TCA-sodio, tebutam, tebutiuron, tefuriltriona, tembotriona, tepraloxidim, terbacil, terbumeton, terbutilazina, terbutrina, tenilclor, tiazafluron, tiazimin, tiazopir, tiencarbazona, tifensulfuron-metil (tiameturon-metil), tiobencarb, tiocarbazil, topramezone, tralcoxidim, tri-alato, triasulfuron, triaziflam, tribenuron-metil, triclopir, trietazina, triflosulam, trifloxisulfuron, trifloxisulfuron-sodio, trifluralina, triflusulfuron-metil, trinexapac-etil y tritosulfuron.

Los ejemplos de los compuestos fungicidas para utilizar en las composiciones/métodos de la presente invención incluyen, pero no se limitan a, acibenzolar (CGA245704), ancimidol, alanicarb, aldimorf, amisulbrom, anilazina, azaconazol, azoxistrobina, benalaxil, bentiavalicarb, benomil, biloxazol, bitertanol, bixafen, blasticidin S, boscalid, bromuconazol, bupirinato, captafol, captano, carbendazim, carbendazim clorhidrato, carboxin, carpropamid, carvona, CGA41396, CGA41397, quinometionato, cloroneb, clorotalonil, clorozolinato, clozilacon, compuestos que contienen cobre tales como oxicloruro de cobre, oxiquinolato de cobre, sulfato de cobre, talato de cobre y caldo bordelés, ciflufenamid, cimoxanil, ciproconazol, ciprodinil, debacarb, di-2-piridil disulfuro, 1,1'-dióxido, diclofluanid, diclomezina, diclozolina, diclona, dicloran, diclocimet,

dietofencarb, difenoconazol, difenzoquat, diflumentorim, tiofosfato de O,O-di-*iso*-propil-S-bencilo, dimefluazol, dimetconazol, dimetomorf, dimetirimol, dimoxistrobina, diniconazol, dinocap, ditianon, cloruro de dodecil dimetil amonio, dodemorf, dodina, doguadina, edifenfos, enestrobina, epoxiconazol, etaboxam, etirimol, etridiazol, famoxadona, fenamidona (RPA407213), fenarimol, fenbuconazol, fenfuram, fenhexamid (KBR2738), fenoxanil, fenciclonil, fenpropidin, fenpropimorf, acetato de fentin, hidróxido de fentin, ferbam, ferimzona, fluazinam, fluopicolide, fludioxonil, fluoxastrobina, flumetover, SYP-LI90 (flumorf), fluopiram fluorimida, fluquinconazol, flusilazol, flusulfamida, flutolanil, flutriafol, folpet, fosetil-aluminio, fuberidazol, furalaxil, furametpir, guazatina, hexaconazol, hidroxiisoxazol, himexazol, IKF-916 (Cyazofamid), imazalil, imibenconazol, iminoctadina, iminoctadina triacetato, ipconazol, iprobenfos, iprodiona, iprovalicarb (SZX0722), butil carbamato de isopropanilo, isoprotiolano, kasugamicina, kresoxim-metil, LY186054, LY211795, LY248908, maneb, mancopper, mancozeb, mandipropamid, maneb, mefenoxam, mepanipirim, mepronil, metalaxil, metconazol, metasulfocarb, metiram, metiram-zinc, metominostrobin, metrafenona, miclobutanil, miclozolina, neoasozin, dimetilditiocarbamato de níquel, nitro-*tal-isopropil*, nuarimol, ofurace, compuestos de organomercurio, orisastrobina, oxadixil, oxasulfuron, oxina-cobre, ácido oxolínico, oxpoconazol, oxicarboxina, pefurazoato, penconazol, pencicuron, pentiopirad, óxido de fenazina, fosdifen, ácidos fosforosos, ftalida, picoxistrobina (ZA1963), polioxina D, poliram, probenazol, procloraz, procimidona, propamocarb, propiconazol, propineb, ácido propiónico, proquinazid, protioconazol, piraclostrobina, pirazofos, Piribencarb pirifenox, pirimetanil, piroquilon, piroxifur, pirrolnitrina, compuestos de amonio cuaternario, quinometionato, quinoxifeno, quintozeno, siltiofam simeconazol, sipconazol (F-155), pentaclorofenato de sodio, espiroamina, estreptomycin, azufre, schwefel, tebuconazol, tecloftalam, tecnazeno, tetraconazol, tiabendazol, tifuluzamid, 2-(tiocianometiltio)benzotiazol, tiofanato-metil, tiram, tiadinil timibenconazol, tolclofos-metil, tolilfluandil, triadimefon, triadimenol, triazbutil, triazóxido, triciclazol, tridemorf, trifloxistrobina (CGA279202), triforina, triflumizol, triticonazol, validamicina A, vapam, valifenal vinclozolina, zineb, ziram, zoxamida,

3-[5-(4-clorofenil)-2,3-dimetilisoxazolidin-3-il]piridina, 5-cloro-7-(4-metilpiperidin-1-il)-6-(2,4,6-trifluorfenil)[1,2,4]triazolo[1,5-a]pirimidina y N-(4-cloro-2-nitrofenil)-N-etil-4-metil-benzulfonamida.

Estas formulaciones de la invención y para utilizar en los métodos de la invención se pueden aplicar a las áreas donde se desea el control a través de métodos convencionales tales como rociado, atomización, espolvoreo, dispersión, recubrimiento o vertido. Las composiciones líquidas y en polvo fino, por ejemplo, se pueden aplicar a través de la utilización de espolvoreadores de polvo, espolvoreadores manuales y por barrido y espolvoreadores por rociado. Las formulaciones también se pueden aplicar desde aviones como un polvo o un rocío o a través de aplicaciones con mecha de cuerda. Tanto las formulaciones sólidas como líquidas también se pueden aplicar al suelo en el locus de la planta a ser tratada permitiendo que el ingrediente activo penetre la planta a través de las raíces. Las formulaciones de la invención también se pueden utilizar para aplicaciones de recubrimiento sobre el material de propagación de plantas para proporcionar protección frente a infecciones por hongos en el material de propagación de plantas así como también frente a los hongos fitopatógenos que tienen lugar en el suelo. De modo adecuado, el ingrediente activo se puede aplicar al material de propagación de plantas a ser protegido impregnando el material de propagación de plantas, en particular, las semillas, o bien con una formulación líquida del fungicida o bien recubriéndolo con una formulación sólida. En casos especiales, también son posibles otros tipos de aplicación, por ejemplo, el tratamiento específico de las pequeñas ramas o de los recortes de las plantas que sirven para la propagación.

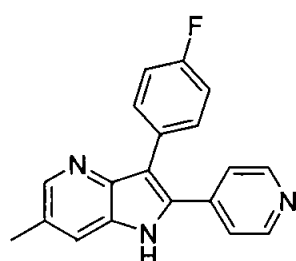
Además, los compuestos de la fórmula (I) según se definieron precedentemente se pueden utilizar en el tratamiento de infecciones fúngicas de sujetos humanos y animales. Los compuestos activos según se describen en la presente se pueden combinar con un portador farmacéuticamente aceptable y administrar o aplicar a dichos sujetos o infecciones en una cantidad efectiva para

tratar la infección de acuerdo con técnicas conocidas. En consecuencia, por lo tanto, la presente invención también provee la utilización de un compuesto de la fórmula (I) según se definió precedentemente en la elaboración de un medicamento para el tratamiento de infecciones fúngicas en humanos o animales.

La presente invención se describirá ahora a través de los siguientes ejemplos no limitativos. Aquéllos expertos en la técnica reconocerán rápidamente las variaciones apropiadas a partir de los procedimientos tanto en lo que se refiere a los reactantes como en lo que se refiere a las técnicas y condiciones de reacción.

EJEMPLOS

Ejemplo 1 - Preparación de 3-(4-fluor-fenil)-6-metil-2-piridin-4-il-1H-pirrol-3,2-b]piridina siguiendo los procedimientos descritos en el esquema 1



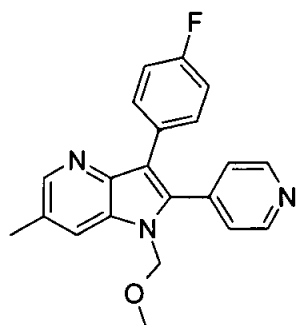
Etapas 1: Se disuelven 50,6 g de metal sodio (2,1 moles) en 1,5 L de etanol absoluto bajo condiciones de reflujo. Una mezcla de 205 g de isonicotinato de metilo (1,5 moles) y 202 g de 4-fluorfenilo en 0,5 L de etanol absoluto se adiciona una vez que la temperatura se ha enfriado hasta 30°C. La mezcla de reacción se refluja durante 4 horas, luego se enfría y se vierte en 1,2 L de hielo-agua. Se adiciona HCl 2 N para lograr un pH=3 y el precipitado amarillo resultante se filtra y se seca (271 g). Este material se suspende en 1,1 L de una solución de HBr 48% y se calienta a 100°C durante 8 horas. Una vez enfriada, la mezcla de reacción se vierte en hielo-agua (1,2 L) y el pH se regula hasta 7 con una solución de hidróxido de amonio 25%. Luego de la extracción en acetato de etilo, las capas orgánicas se

secan sobre sulfato de magnesio y el residuo luego de la concentración se purifica mediante cromatografía sobre gel de sílice (acetato de etilo/hexano 2/1) para proporcionar 133 g de 2-(4-fluorfenil)-1-(piridin-4-il)etanona como un sólido amarillento.

Etapa 2: Una mezcla de ácido p-toluensulfónico (500 mg), 2-(4-fluorfenil)-1-(piridin-4-il)etanona (10 g, 46 mmol) y 5-metil-3-amino-2-cloropiridina (8,6 g, 60 mmol) en 350 mL de tolueno se refluja durante la noche con una extracción Dean-Stark de azeótropo agua/tolueno. La mezcla de reacción se concentró adicionalmente, el residuo marrón se suspendió en una mezcla de acetato de etilo/hexano (9/1) y se filtró. El sólido se solubilizó en acetato de etilo y se purificó mediante cromatografía sobre gel de sílice (acetato de etilo/hexano 1/1) para proporcionar 10 g de (2-cloro-5-metil-piridin-3-il)-[2-(4-fluor-fenil)-1-piridin-4-il-etiliden]-amina como un sólido marrón.

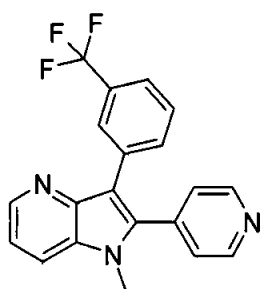
Etapa 3: Se disuelven 6,15 g (18,1 mmol) de (2-cloro-5-metil-piridin-3-il)-[2-(4-fluor-fenil)-1-piridin-4-il-etiliden]-amina en 100 mL de dimetilformamida bajo nitrógeno. Subsiguientemente se adicionan 6,4 g de DABCO (56 mmol) y 610 mg de dicloruro de bis(trifenilfosfin)paladio a la mezcla de reacción la cual se agita durante 5 horas a 120°C. La mezcla de reacción enfriada luego se vierte en agua y se extrae con acetato de etilo. La fase orgánica se lava con agua y se seca sobre sulfato de magnesio. El residuo sólido luego de la concentración se recrystaliza en acetato de etilo para proporcionar 5,3 g de 3-(4-fluor-fenil)-6-metil-2-piridin-4-il-1H-pirrol[3,2-b]piridina como un sólido amarillento.

Ejemplo 2: Preparación de 3-(4-fluor-fenil)-1-metoximetil-6-metil-2-piridin-4-il-1H-pirrol[3,2-b]piridina siguiendo los procedimientos descriptos en el esquema 1



Se adiciona hidruro de sodio (22 mg, 0,55 mmol 60% en aceite) a una solución de 150 mg (0,5 mmol) de 3-(4-fluor-fenil)-6-metil-2-piridin-4-il-1H-pirrólo[3,2-b]piridina (preparada según se describió en el ejemplo 1) en 5 mL de dimetilformamida a temperatura ambiente. Luego de 30 min. a temperatura ambiente, se adiciona a la mezcla de reacción una solución de 44,5 mg de clorometil metil éter en 0,5 mL de DMF. Luego de 45 min. a temperatura ambiente, la mezcla de reacción se vierte en solución de cloruro de amonio y se extrae con acetato de etilo. La fase orgánica se lava con agua y se seca sobre sulfato de magnesio. El residuo sólido luego de la concentración se recristaliza en una mezcla de acetato de etilo/hexano (1/2) para proporcionar 70 mg de 3-(4-fluor-fenil)-1-metoximetil-6-metil-2-piridin-4-il-1H-pirrólo[3,2-b]piridina pura como un sólido amarillento.

Ejemplo 3: Preparación de 1-metil-2-piridin-4-il-3-(3-trifluorometil-fenil)-1H-pirrólo[3,2-b]piridina siguiendo el esquema 3.



Etapla 1: Se agitan 5 g de 3-amino-2-bromopiridina (28,9 mmol) y 15,5 g de formaldehído en 25 g de ácido fórmico 6 horas a 100°C. La mezcla de reacción

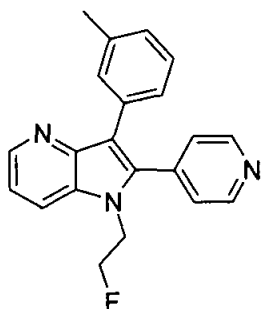
enfriada se vierte en agua y el pH se regula hasta 8-9 mediante la adición de una solución 2 N de hidróxido de sodio. Luego de la extracción en t-butilmetil éter, las capas orgánicas se lavan con agua y se secan sobre sulfato de magnesio y el residuo luego de la concentración se purifica mediante cromatografía sobre gel de sílice (acetato de etilo/hexano 1/1) para proporcionar 3,7 g de (2-bromo-piridin-3-il)-dimetil-amina como un aceite anaranjado.

Etapa 2: Una mezcla de 2 g de (2-bromo-piridin-3-il)-dimetil-amina (9,95 mmol), 1,24 g de 4-etinil piridina (12 mmol) en 120 mL de una mezcla 1/1 de trietilamina y dimetilformamida se agita bajo argón a temperatura ambiente. Se adicionan 750 mg de dicloruro de bis(trifenilfosfin)paladio y 400 mg de yoduro de cobre a la mezcla de reacción la cual se agita adicionalmente a temperatura ambiente durante 3 horas. La mezcla de reacción se vierte en solución de cloruro de amonio y se extrae con acetato de etilo. La fase orgánica se lava con agua y se seca sobre sulfato de magnesio. El residuo sólido luego de la concentración se purifica mediante cromatografía sobre gel de sílice (acetato de etilo/hexano 1/1) para proporcionar 1 g de dimetil-(2-piridin-4-iletinil-piridin-3-il)-amina como un aceite anaranjado.

Etapa 3: Se disuelve 1 g (4,4 mmol) de dimetil-(2-piridin-4-iletinil-piridin-3-il)-amina en 60 mL de diclorometano bajo atmósfera de argón. Una solución de 2,27 g de yodo (8,9 mmol) en 35 mL de diclorometano se adiciona gota a gota en la mezcla de reacción a 0°C. La mezcla de reacción se deja alcanzar temperatura ambiente y se agita adicionalmente durante 4 horas. La mezcla de reacción luego se vierte en una solución de tiosulfato de sodio y se extrae con diclorometano. La fase orgánica se lava con agua y se seca sobre sulfato de magnesio. El residuo sólido luego de la concentración se purifica mediante cromatografía sobre gel de sílice (acetato de etilo) para proporcionar 600 mg de 3-yodo-1-metil-2-piridin-4-il-1H-pirrol[3,2-b]piridina como un sólido marrón.

Etapa 4: A una solución de 130 mg (0,39 mmol) de 3-yodo-1-metil-2-piridin-4-il-1H-pirrolol[3,2-b]piridina en 5 mL de tolueno bajo nitrógeno se le adiciona 1 mL de una solución 2 N de carbonato de sodio, 78 mg (0,4 mmol) de ácido 3-trifluormetil fenilborónico y 1 mL de etanol. Finalmente se adicionan a la mezcla de reacción 24 mg de tetrakis(trifenilfosfin) paladio antes del calentamiento a 80°C durante 10 horas. La mezcla de reacción enfriada luego se vierte en solución de cloruro de amonio y se extrae con acetato de etilo. La fase orgánica se lava con agua y se seca sobre sulfato de magnesio. El residuo sólido luego de la concentración se recrystaliza en hexano para proporcionar 70 mg de 1-metil-2-piridin-4-il-3-(3-trifluormetil-fenil)-1H-pirrolol[3,2-b]piridina como cristales blancos.

Ejemplo 4: Preparación de 1-(2-fluor-etil)-2-piridin-4-il-3-m-tolil-1H-pirrolol[3,2-b]piridina siguiendo el esquema 2



Etapa 1: En 12 mL de dimetilacetamida se adicionan 240 mg (2 mmol) de sulfato de magnesio anhidro, 1,3 mL (12 mmol) de 4-acetil piridina, 515 mg (4 mmol) de 3-amino-2-cloropiridina y 0,3 mL de ácido acético. La suspensión resultante se mantiene bajo argón. Luego se adicionan 1,1 g (5,2 mmol) de fosfato de potasio y 202 mg (0,4 mmol) de bis-(tri-t-butilfosfin) paladio a la mezcla de reacción la cual luego se sella dentro de su recipiente de reacción y se agita a 140°C durante 10 horas. La mezcla de reacción se vierte en solución de cloruro de amonio y se extrae con acetato de etilo. La fase orgánica se lava con agua y se seca sobre sulfato de magnesio. El residuo sólido luego de la concentración se purifica mediante cromatografía sobre gel de sílice (acetato de etilo/metanol 9/1)

para proporcionar 460 mg de 2-piridin-4-il-1H-pirrol[3,2-b]piridina como un sólido marrón.

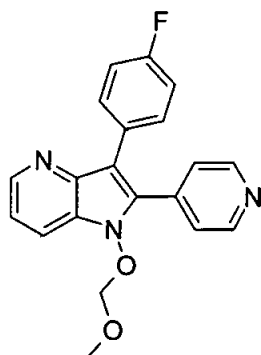
Etapa 2: Se adicionan 800 mg de N-bromosuccinimida (4 mmol) a una solución de 720 mg (3,7 mmol) de 2-piridin-4-il-1H-pirrol[3,2-b]piridina en tetraclorometano. La mezcla de reacción marrón se agita 5 horas a 50°C y se concentra. El residuo marrón se purifica mediante cromatografía sobre gel de sílice (acetato de etilo/metanol 9/1) para proporcionar 650 mg de 3-bromo-2-piridin-4-il-1H-pirrol[3,2-b]piridina como cristales blancos.

Etapa 3: A una solución de 274 mg (1 mmol) de 3-bromo-2-piridin-4-il-1H-pirrol[3,2-b]piridina en 1,8 mL de tolueno bajo nitrógeno se le adicionan 0,6 mL de una solución 2 N de carbonato de sodio, 170 mg (1,25 mmol) de ácido m-tolilborónico y 1,2 mL de etanol. A la mezcla de reacción finalmente se le adicionan 45 mg de tetrakis(trifenilfosfin) paladio. La mezcla de reacción se sella dentro de un recipiente para microondas y se agita bajo condiciones de microondas a 180°C durante 2 min. La mezcla de reacción enfriada luego se vierte en solución de cloruro de amonio y se extrae con acetato de etilo. La fase orgánica se lava con agua y se seca sobre sulfato de magnesio. El residuo sólido luego de la concentración se recrystaliza en hexano para proporcionar 150 mg de 2-piridin-4-il-3-m-tolil-1H-pirrol[3,2-b]piridina como cristales blancos.

Etapa 4: Se adiciona hidruro de sodio (34 mg, 0,84 mmol 60% en aceite) a una solución de 160 mg (0,56 mmol) de 2-piridin-4-il-3-m-tolil-1H-pirrol[3,2-b]piridina en 6 mL de dimetilformamida a temperatura ambiente. Luego de 30 min. a temperatura ambiente, se adicionan a la mezcla de reacción 107 mg de 1-bromo-2-fluoretano. Luego de 20 horas a temperatura ambiente, la mezcla de reacción se vierte en solución de cloruro de amonio y se extrae con acetato de etilo. La fase orgánica se lava con agua y se seca sobre sulfato de magnesio. El residuo sólido se purifica mediante cromatografía sobre gel de sílice (acetato de

etilo/metanol 9/1) para proporcionar 137 mg de 1-(2-fluor-etil)-2-piridin-4-il-3-m-tolil-1H-pirrolo[3,2-b]piridina como cristales blancos.

Ejemplo 5: Preparación de 3-(4-fluor-fenil)-1-metoximetoxi-2-piridin-4-il-1H-pirrolo[3,2-b]piridina siguiendo el esquema 4

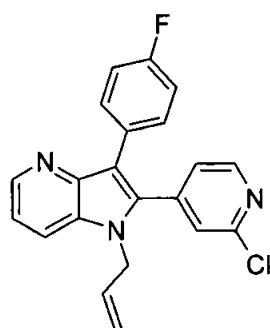


Etapa 1: Se disuelven 21,5 g (100 mmol) de 2-(4-fluorfenil)-1-(piridin-4-il)etanona (preparada según se describió en el esquema 1) y 34,9 g de 2-cloro-3-nitropiridina en 270 mL de dimetilformamida. Se adicionan lentamente 8,8 g de hidruro de sodio (60% en aceite (220 mmol) a la mezcla de reacción la cual se mantiene entre 0 y 5°C. Luego de la agitación durante 1 hora a temperatura ambiente, la mezcla de reacción se vierte en 1 L de solución de cloruro de amonio y se extrae con acetato de etilo. La fase orgánica se lava con agua y se seca sobre sulfato de magnesio. El residuo oleoso se purifica mediante cromatografía sobre gel de sílice (acetato de etilo/hexano 1/1) para proporcionar 26,7 g de 2-(4-fluor-fenil)-2-(3-nitro-piridin-2-il)-1-piridin-4-il-etanona.

Etapa 2: Se disuelven 23 g (68,2 mmol) de 2-(4-fluor-fenil)-2-(3-nitro-piridin-2-il)-1-piridin-4-il-etanona en 700 mL de etanol absoluto. Se adicionan 2,2 g de 10% paladio sobre carbón a la solución la cual se agita durante 6 horas bajo una atmósfera de hidrógeno. La mezcla de reacción se filtra sobre celite, se concentra y el residuo marrón se purifica mediante cromatografía sobre gel de sílice (acetato de etilo) para proporcionar 7 g de 3-(4-fluor-fenil)-2-piridin-4-il-pirrolo[3,2-b]piridin-1-ol y se recuperan 13 g del material de partida.

Etapa 3: Se adiciona hidruro de sodio (30 mg, 0,72 mmol 60% en aceite) a una solución de 200 mg (0,65 mmol) de 3-(4-fluor-fenil)-2-piridin-4-il-pirrolo[3,2-b]piridin-1-ol en 6 mL de dimetilformamida a temperatura ambiente. Luego de 30 min. a temperatura ambiente, se adicionan a la mezcla de reacción 65 mg de clorometil metil éter. Luego de 1 hora a temperatura ambiente, la mezcla de reacción se vierte en solución de cloruro de amonio y se extrae con acetato de etilo. La fase orgánica se lava con agua y se seca sobre sulfato de magnesio. El residuo sólido se purifica mediante cromatografía sobre gel de sílice (acetato de etilo) para proporcionar 120 mg de 3-(4-fluor-fenil)-1-metoximetoxi-2-piridin-4-il-1H-pirrolo[3,2-b]piridina como cristales blancos.

Ejemplo 6: Preparación de 1-alil-2-(2-cloro-piridin-4-il)-3-(4-fluor-fenil)-1H-pirrolo[3,2-b]piridina siguiendo el esquema 5



Etapa 1: Se disuelven 80 g (74,6 mmol) de piridin-4-carboxaldehído en 150 mL de metanol. Se adicionan a la mezcla de reacción 123,5 mL (112 mmol) de ortoformiato de trimetilo a temperatura ambiente seguido por la adición de 33 mL de ácido sulfúrico concentrado. La mezcla de reacción se mantiene bajo reflujo durante 24 horas y una vez enfriada, se adiciona a 300 mL de solución de metilato de sodio. La suspensión blanca obtenida se filtra sobre celite, el filtrado se concentra bajo vacío y se obtienen 70,3 g de 4-dimetoximetil-piridina como un aceite amarillo.

Etapa 2: Se adicionan gota a gota 315 mL de una solución 1,6 M de *n*-butilitio en hexano a una solución de 70,3 g (0,46 mol) de 4-dimetoximetil-piridina en 1,4 L de tetrahidrofurano bajo nitrógeno a -70°C. Luego de 30 min. a -70°C, se adicionan gota a gota 73 g (0,505 mol) de cloruro de 4-fluorobencilo en 280 mL de tetrahidrofurano. Luego de 10 min. más a -70°C, la mezcla de reacción se deja alcanzar temperatura ambiente y luego se agita durante 30 min adicionales. La mezcla de reacción se vierte en una solución de cloruro de amonio 2 L y se extrae con acetato de etilo. La fase orgánica se lava con agua y se seca sobre sulfato de magnesio. Luego de la concentración el residuo se purifica mediante cromatografía sobre gel de sílice (acetato de etilo/hexano 1/1) para proporcionar 114 g de 4-[2-(4-fluor-fenil)-1,1-dimetoxi-etil]-piridina como un aceite amarillo.

Etapa 3: Se disuelven 55 g (0,21 mol) de 4-[2-(4-fluor-fenil)-1,1-dimetoxi-etil]-piridina y 445 mg de metiltrioxorhenio en 250 mL de diclorometano. Se adicionan 112 mL de solución de peróxido de hidrógeno comercial a la mezcla de reacción la cual se agita adicionalmente durante la noche a temperatura ambiente. La mezcla de reacción luego se decanta y la fase orgánica se lava con hidrógeno sulfato de sodio y agua y se seca sobre sulfato de magnesio. Luego de la concentración, se obtienen 33 g de 1-óxido de 4-[2-(4-fluor-fenil)-1,1-dimetoxi-etil]-piridina como un aceite verde.

Etapa 4: Se calientan 60 g (0,21 mol) de 1-óxido de 4-[2-(4-fluor-fenil)-1,1-dimetoxi-etil]-piridina conjuntamente con 27,9 g (0,21 mol) de 3-amino-2-cloro piridina bajo argón a 130°C sin solvente durante 2 horas. Luego del enfriamiento y antes de la cristalización completa de la mezcla de reacción, se adiciona acetato de etilo (150 mL) resultando en la formación de un precipitado blanco el cual se filtra para proporcionar 32 g de (2-cloro-piridin-3-il)-[2-(4-fluor-fenil)-1-(1-oxi-piridin-4-il)-etiliden]-amina.

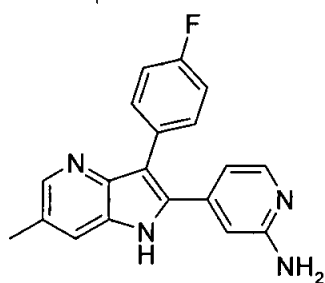
Etapa 5: Se disuelven 5,8 g (17 mmol) de (2-cloro-piridin-3-il)-[2-(4-fluor-fenil)-1-(1-oxi-piridin-4-il)-etiliden]-amina en 100 mL de dimetilformamida bajo

nitrógeno. Subsiguientemente se adicionan 5,7 g de DABCO (51 mmol) y 550 mg de dicloruro de bis(trifenilfosfin)paladio a la mezcla de reacción la cual se agita durante 3 horas a 120°C. La mezcla de reacción enfriada luego se vierte en agua y se extrae con acetato de etilo. La fase orgánica se lava con agua y se seca sobre sulfato de magnesio. El residuo sólido luego de la concentración se recrystaliza en acetato de etilo para proporcionar 5,2 g de 3-(4-fluor-fenil)-2-(1-oxi-piridin-4-il)-1H-pirrolo[3,2-b]piridina como un sólido amarillento.

Etapa 6: Se agitan 12,25 g (40,1 mmol) de 3-(4-fluor-fenil)-2-(1-oxi-piridin-4-il)-1H-pirrolo[3,2-b]piridina en 120 mL de fosforoxiclورو a 120°C durante 90 min. La mezcla de reacción se concentra bajo vacío y el residuo se trata con metanol y se filtra sobre celite. Luego de la concentración de la fase metanol, el residuo sólido se purifica mediante cromatografía sobre gel de sílice (acetato de etilo/metanol 9/1) para proporcionar 10 g de 2-(2-cloro-piridin-4-il)-3-(4-fluor-fenil)-1H-pirrolo[3,2-b]piridina como un sólido amarillo.

Etapa 7: Se adiciona hidruro de sodio (120 mg, 3 mmol 60% en aceite) a una solución de 323,5 mg (1 mmol) de 2-(2-cloro-piridin-4-il)-3-(4-fluor-fenil)-1H-pirrolo[3,2-b]piridina en 8 mL de dimetilformamida a temperatura ambiente. Luego de 30 min. a temperatura ambiente, se adiciona a la mezcla de reacción 1,2 g de bromuro de alilo (10 mmol). Luego de 1 hora a temperatura ambiente, la mezcla de reacción se vierte en solución de cloruro de amonio y se extrae con acetato de etilo. La fase orgánica se lava con agua y se seca sobre sulfato de magnesio. Luego de la concentración el residuo sólido se purifica mediante cromatografía sobre gel de sílice (acetato de etilo/hexano 1/1) para proporcionar 270 mg de 1-alil-2-(2-cloro-piridin-4-il)-3-(4-fluor-fenil)-1H-pirrolo[3,2-b]piridina como un sólido blanco.

Ejemplo 7: Preparación de 4-[3-(4-fluor-fenil)-6-metil-1H-pirrolo[3,2-b]piridin-2-il]-piridin-2-ilamina siguiendo el esquema 1



Etapa 1: A una solución de 15 g (0,105 mol) de 5-amino-6-cloro-3-picolina en 100 mL de dimetilformamida se le adiciona 1 mL de ácido sulfúrico concentrado. Luego se adiciona lentamente una solución de 43,7 g (0,15 mol) de 1-óxido de 4-[2-(4-fluor-fenil)-1,1-dimetoxi-etil]-piridina (según se preparó previamente en el ejemplo 6) en 80 mL de dimetilformamida a la mezcla de reacción la cual subsiguientemente se entibia a 80°C durante 6 horas. Una vez enfriada, la mezcla de reacción se vierte en solución de cloruro de amonio y se extrae con acetato de etilo. La fase orgánica se lava con agua y se seca sobre sulfato de magnesio. Luego de la concentración el residuo sólido se purifica mediante cromatografía sobre gel de sílice (acetato de etilo/metanol 9/1) para proporcionar 16 g de (2-cloro-5-metil-piridin-3-il)-[2-(4-fluor-fenil)-1-(1-oxi-piridin-4-il)-etiliden]-amina como un sólido blanco.

Etapa 2: Se disuelven 34,5 g (97 mmol) de (2-cloro-5-metil-piridin-3-il)-[2-(4-fluor-fenil)-1-(1-oxi-piridin-4-il)-etiliden]-amina en 600 mL de dimetilformamida bajo nitrógeno. Subsiguientemente se adicionan 33 g de DABCO (295 mmol) y 3,5 g de dicloruro de bis(trifenilfosfin)paladio a la mezcla de reacción la cual se agita durante 3 horas a 120°C. La mezcla de reacción enfriada luego se vierte en agua y se extrae con acetato de etilo. La fase orgánica se lava con agua y se seca sobre sulfato de magnesio. El residuo sólido luego de la concentración se recrystaliza en dietil éter para proporcionar 17 g de 3-(4-fluor-fenil)-6-metil-2-(1-oxi-piridin-4-il)-1H-pirrol[3,2-b]piridina como un sólido amarillento.

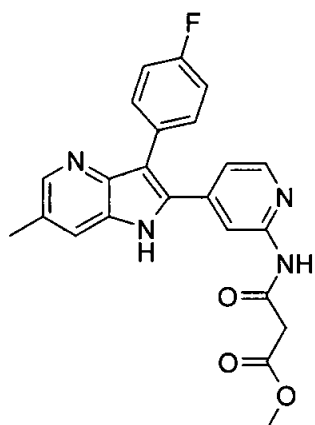
Etapa 3: Se agitan 15 g (47 mmol) de 3-(4-fluor-fenil)-6-metil-2-(1-oxi-piridin-4-il)-1H-pirrol[3,2-b]piridina en 150 mL de fosforoxicloruro a 120°C durante 1

hora. La mezcla de reacción se concentra bajo vacío y el residuo se trata con metanol y se filtra sobre celite. Luego de la concentración de la fase metanol, el residuo sólido se purifica mediante cromatografía sobre gel de sílice (acetato de etilo/metanol 9/1) para proporcionar 11 g de 2-(2-cloro-piridin-4-il)-3-(4-fluor-fenil)-6-metil-1H-pirrolo[3,2-b]piridina como un sólido amarillo.

Etapa 4: Se suspenden 11 g de 2-(2-cloro-piridin-4-il)-3-(4-fluor-fenil)-6-metil-1H-pirrolo[3,2-b]piridina en 115 ml de bencilamina. La mezcla de reacción se refluja a 180°C durante 24 horas. Luego del enfriamiento, la mezcla de reacción se vierte en hexano resultando en la formación de un precipitado amarilló. Luego de la filtración el precipitado se suspende en agua caliente, se filtra nuevamente y se lava con agua caliente resultando en el aislamiento de 9,55 g de bencil-{4-[3-(4-fluor-fenil)-6-metil-1H-pirrolo[3,2-b]piridin-2-il]-piridin-2-il}-amina como un sólido blanco.

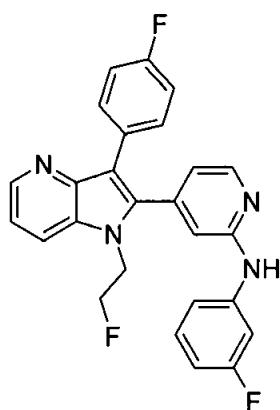
Etapa 5: Se suspenden 7,8 g (19 mmol) de bencil-{4-[3-(4-fluor-fenil)-6-metil-1H-pirrolo[3,2-b]piridin-2-il]-piridin-2-il}-amina a temperatura ambiente en 40 mL de ácido sulfúrico concentrado. Luego de 1 hora, la reacción se vierte en hielo (250 g) y se mantiene a 0°C mientras se adicionan 170 mL de solución de hidróxido de sodio concentrado para lograr un pH=10. El precipitado resultante se filtra, se suspende nuevamente en agua caliente y se agita a reflujo durante 1 hora. La mezcla de reacción luego se filtra nuevamente y se lava con agua caliente para proporcionar 6 g de 4-[3-(4-fluor-fenil)-6-metil-1H-pirrolo[3,2-b]piridin-2-il]-piridin-2-ilamina como un sólido blanco.

Ejemplo 8: Preparación de metil éster de ácido N-{4-[3-(4-fluor-fenil)-6-metil-1H-pirrolo[3,2-b]piridin-2-il]-piridin-2-il}-malonámico siguiendo el esquema 5



Se adiciona metil éster de ácido clorocarbonil-acético (129 mg, 0,9 mmol) a una solución de 200 mg (0,62 mmol) de 4-[3-(4-fluor-fenil)-6-metil-1H-pirrólo[3,2-b]piridin-2-il]-piridin-2-ilamina (preparada siguiendo el procedimiento para el ejemplo 7) en 3 mL de piridina a temperatura ambiente. Luego de 30 horas a temperatura ambiente, se adiciona nuevamente a la mezcla de reacción metil éster de ácido clorocarbonil-acético (129 mg, 0,9 mmol) se agita 12 horas más a temperatura ambiente. La mezcla de reacción luego se vierte en solución de cloruro de amonio y se extrae con acetato de etilo. La fase orgánica se lava con agua y se seca sobre sulfato de magnesio. Luego de la concentración el residuo sólido se purifica mediante cromatografía sobre gel de sílice (acetato de etilo) para proporcionar 40 mg de metil éster de ácido N-{4-[3-(4-fluor-fenil)-6-metil-1H-pirrólo[3,2-b]piridin-2-il]-piridin-2-il}-malonámico como un sólido blanco.

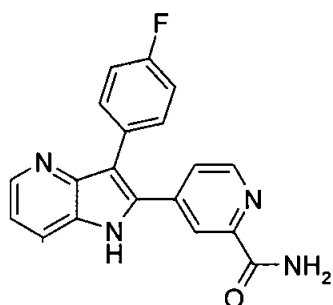
Ejemplo 9: Preparación de {4-[1-(2-fluor-etil)-3-(4-fluor-fenil)-1H-pirrólo[3,2-b]piridin-2-il]-piridin-2-il}-(3-fluor-fenil)-amina siguiendo el esquema 5



Etapa 1: Se adiciona hidruro de sodio (371 mg, 9,3 mmol 60% en aceite) a una solución de 1 g (3,1 mmol) de 2-(2-cloro-piridin-4-il)-3-(4-fluor-fenil)-1H-pirrolo[3,2-b]piridina (preparada siguiendo el procedimiento para el ejemplo 6) en 20 mL de dimetilformamida a temperatura ambiente. Luego de 30 min. a temperatura ambiente, se adicionan a la mezcla de reacción 2,75 g de 1-bromo-2-fluor-etano (21,6 mmol). Luego de 10 horas a temperatura ambiente, la mezcla de reacción se vierte en solución de cloruro de amonio y se extrae con acetato de etilo. La fase orgánica se lava con agua y se seca sobre sulfato de magnesio. Luego de la concentración el residuo sólido se purifica mediante cromatografía sobre gel de sílice (acetato de etilo/hexano 1/1) para proporcionar 720 mg de 2-(2-cloro-piridin-4-il)-1-(2-fluor-etil)-3-(4-fluor-fenil)-1H-pirrolo[3,2-b]piridina como un sólido blanco.

Etapa 2: En un recipiente para microondas de 5 mL (Biotage) se pesan conjuntamente 185 mg (0,5 mmol) de 2-(2-cloro-piridin-4-il)-1-(2-fluor-etil)-3-(4-fluor-fenil)-1H-pirrolo[3,2-b]piridina, 67 mg (0,6 mmol) de 3-fluorfenil amina, 2 mg de acetato de paladio, 7 mg de bifenilil dicitclohexilfosfina y 67 mg (0,7 mmol) de t-butóxido de sodio en 2,5 mL de tolueno. La mezcla de reacción luego se calienta a 180°C durante 10 min. bajo condiciones de microondas. La mezcla de reacción se vierte en solución de cloruro de amonio y se extrae con acetato de etilo. La fase orgánica se lava con agua y se seca sobre sulfato de magnesio. Luego de la concentración el residuo sólido se purifica mediante cromatografía sobre gel de sílice (acetato de etilo/hexano 1/1) para proporcionar 85 mg de {4-[1-(2-fluor-etil)-3-(4-fluor-fenil)-1H-pirrolo[3,2-b]piridin-2-il]-piridin-2-il}-(3-fluor-fenil)-amina como un sólido blanco.

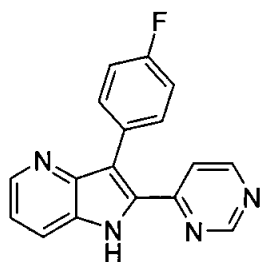
Ejemplo 10: Preparación de amida de ácido 4-[3-(4-fluor-fenil)-1H-pirrolo[3,2-b]piridin-2-il]-piridin-2-carboxílico siguiendo el esquema 5



Etapa 1: Se adiciona cianuro de trimetilsililo (10,3 mL, 82 mmol) a una solución de 5,02 g (16,4 mmol) de 3-(4-fluor-fenil)-2-(1-oxi-piridin-4-il)-1H-pirrollo[3,2-b]piridina (según se preparó en el ejemplo 6) en 35 mL de dimetilformamida. Luego se adiciona lentamente a la mezcla de reacción cloruro de benzoilo (3,8 mL, 33 mmol). Luego de 8 horas, la mezcla de reacción se vierte en solución de cloruro de amonio y se extrae con acetato de etilo. La fase orgánica se lava con agua y se seca sobre sulfato de magnesio. Luego de la concentración el residuo sólido se purifica mediante cromatografía sobre gel de sílice (acetato de etilo) para proporcionar 3,55 g de 4-[3-(4-fluor-fenil)-1H-pirrollo[3,2-b]piridin-2-il]-piridin-2-carbonitrilo como un sólido blanco.

Etapa 2: Se agita 1,44 g (4,6 mmol) de 4-[3-(4-fluor-fenil)-1H-pirrollo[3,2-b]piridin-2-il]-piridin-2-carbonitrilo a temperatura ambiente en 8 mL de t-butanol en presencia de 1,03 g (18,3 mmol) de hidróxido de potasio en polvo. La reacción se agita a temperatura ambiente durante 4 horas, se concentra bajo vacío y se vierte en agua y acetato de etilo (1/1). Se adiciona a la solución ácido clorhídrico 2 N para lograr un pH=5 y la solución se extrae con acetato de etilo. La fase orgánica se lava con agua y se seca sobre sulfato de magnesio. Luego de la concentración se obtienen 800 mg de amida de ácido 4-[3-(4-fluor-fenil)-1H-pirrollo[3,2-b]piridin-2-il]-piridin-2-carboxílico como un sólido blanco.

Ejemplo 11: Preparación de 3-(4-fluor-fenil)-2-pirimidin-4-il-1H-pirrollo[3,2-b]piridina siguiendo el esquema 1



Etapa 1: Se solubilizan 50 g (0,31 mol) de 4-cloro-2-metiltiopirimidina en 300 mL de ácido yodhídrico a temperatura ambiente. La mezcla de reacción se agita a temperatura ambiente durante 8 horas. La mezcla de reacción se vierte en 1,2 L de agua y el pH se regula hasta 8 con bicarbonato de sodio sólido. La mezcla se extrae con diclorometano y se lava con tiosulfato de sodio. Luego de la concentración el residuo oleoso proporciona 74 g de 4-yodo-2-metiltiopirimidina.

Etapa 2: Se enfrían 20 g (79 mmol) de 4-yodo-2-metiltiopirimidina en 165 mL de tetrahidrofurano bajo argón hasta -70°C . Luego se adicionan lentamente a la mezcla de reacción 45,5 mL de cloruro de isopropilmagnesio (2 M en THF), manteniendo la temperatura a -70°C . Luego de 30 min., se adiciona gota a gota una solución de cloruro de 4-fluorfenil acetilo (13,7 g, 79 mmol) en 65 mL de tetrahidrofurano a la mezcla de reacción la cual se agita adicionalmente a -78°C durante 1 hora y se deja llegar a 0°C . Luego de 30 min. a 0°C , la reacción se vierte en hielo-agua y se extrae con acetato de etilo. La fase orgánica se lava con agua y se seca sobre sulfato de magnesio. Luego de la concentración la fase oleosa se purificó mediante cromatografía sobre gel de sílice (acetato de etilo/hexano 4/1) proporcionando 9,5 g de 2-(4-fluor-fenil)-1-(2-metiltio-pirimidin-4-il)-etanona como un aceite amarillo.

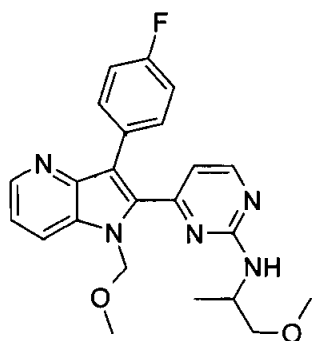
Etapa 3: Una mezcla de ácido p-toluensulfónico (10 mg), 2-(4-fluor-fenil)-1-(2-metiltio-pirimidin-4-il)-etanona (200 mg, 0,76 mmol) y 3-amino-2-cloropiridina (90 mg, 0,7 mmol) en 3 mL de tolueno se reflujoó durante la noche con una extracción Dean-Stark de azeótropo agua/tolueno. La mezcla de reacción se concentró adicionalmente, el residuo marrón se suspendió en una mezcla de acetato de etilo/hexano (9/1) y se filtró. El sólido se solubilizó en acetato de etilo y

se purificó mediante cromatografía sobre gel de sílice (acetato de etilo/hexano 1/1) para proporcionar 130 mg de (2-cloro-piridin-3-il)-[2-(4-fluor-fenil)-1-(2-metiltio-pirimidin-4-il)-etiliden]-amina como un aceite marrón.

Etapas 4: Se disuelven 6,5 g (14,7 mmol) de (2-cloro-piridin-3-il)-[2-(4-fluor-fenil)-1-(2-metiltio-pirimidin-4-il)-etiliden]-amina en 60 mL de dimetilformamida bajo nitrógeno. Subsiguientemente se adicionan 6,2 g de DABCO (52 mmol) y 0,5 g de dicloruro de bis(trifenilfosfin)paladio a la mezcla de reacción la cual se agita durante 4 horas a 120°C. La mezcla de reacción enfriada luego se vierte en agua y se extrae con acetato de etilo. La fase orgánica se lava con agua y se seca sobre sulfato de magnesio. El residuo sólido luego de la concentración se recrystaliza en dietil éter para proporcionar 4 g of 3-(4-fluor-fenil)-2-(2-metiltio-pirimidin-4-il)-1H-pirrol[3,2-b]piridina como un sólido amarillento.

Etapas 5: Se agitan 560 mg (1,66 mmol) de 3-(4-fluor-fenil)-2-(2-metiltio-pirimidin-4-il)-1H-pirrol[3,2-b]piridina a temperatura ambiente en una mezcla de 50 mL de etanol absoluto y 40 mL de amoníaco (15% en agua). Luego se adicionan 2 g de níquel Raney (50% en agua) a la solución la cual se agita adicionalmente durante 3 horas bajo condiciones de reflujo. Una vez enfriada, la mezcla de reacción se filtra sobre celite y se extrae con acetato de etilo. La fase orgánica se lava con agua y se seca sobre sulfato de magnesio. El residuo sólido luego de la concentración se solubiliza en acetato de etilo y se purifica mediante cromatografía sobre gel de sílice (acetato de etilo/hexano 1/1) para proporcionar 250 mg de 3-(4-fluor-fenil)-2-pirimidin-4-il-1H-pirrol[3,2-b]piridina como un sólido amarillento.

Ejemplo 12: Preparación de {4-[3-(4-fluor-fenil)-1-metoximetil-1H-pirrol[3,2-b]piridin-2-il]-pirimidin-2-il}-(2-metoxi-1-metil-etil)-amina siguiendo el esquema 1



Etapa 1: Se adiciona hidruro de sodio (130 mg, 2,8 mmol 60% en aceite) a una solución de 850 mg (2,53 mmol) de 3-(4-fluor-fenil)-2-(2-metiltio-pirimidin-4-il)-1H-pirrol[3,2-b]piridina en 30 mL de dimetilformamida a temperatura ambiente. Luego de 30 min. a temperatura ambiente, se adiciona a la mezcla de reacción 0,23 mL de clorometil metil éter. Luego de 1 hora a temperatura ambiente, la mezcla de reacción se vierte en solución de cloruro de amonio y se extrae con acetato de etilo. La fase orgánica se lava con agua y se seca sobre sulfato de magnesio. El residuo sólido se purifica mediante cromatografía sobre gel de sílice (acetato de etilo/hexano 2/1) para proporcionar 750 mg de 3-(4-fluor-fenil)-1-metoximetil-2-(2-metiltio-pirimidin-4-il)-1H-pirrol[3,2-b]piridina como cristales blancos.

Etapa 2: Se tratan 730 mg (1,92 mmol) de 3-(4-fluor-fenil)-1-metoximetil-2-(2-metiltio-pirimidin-4-il)-1H-pirrol[3,2-b]piridina en 50 mL de diclorometano a 0°C con 0,57 g de ácido 3-cloroperbenzoico (2,3 mmol). La mezcla de reacción se agita 30 min. a 0°C y se vierte en hielo-agua. La mezcla se trata con bicarbonato de sodio para lograr un pH de entre 8 y 9 y se extrae con diclorometano para proporcionar una cera amarilla. Se solubilizan 395 mg de esta cera amarilla directamente en 3 mL de 2-amino-1-metoxipropano y bajo condiciones de microondas se calientan a 200°C durante 20 min. La mezcla de reacción se vierte en solución de cloruro de amonio y se extrae con acetato de etilo. La fase orgánica se lava con agua y se seca sobre sulfato de magnesio. El residuo sólido se purifica mediante cromatografía sobre gel de sílice (acetato de etilo/hexano 1/5) para

proporcionar 350 mg de {4-[3-(4-fluor-fenil)-1-metoximetil-1H-pirrol[3,2-b]piridin-2-il]-pirimidin-2-il}-(2-metoxi-1-metil-etil)-amina como una cera amarillenta.

Ejemplo 13: Actividad biológica de los compuestos de la invención

Los compuestos de la invención se evaluaron en un ensayo de disco de hoja, según se describe a continuación para determinar su acción preventiva frente a una cantidad de especies fúngicas. En todos los casos, los compuestos de ensayo se disolvieron en DMSO y se diluyeron en agua hasta 200 ppm. La solución de ensayo final contenía 2% DMSO y 0,025% Tween® 20.

a) *Erysiphe graminis f.sp. hordei* (moho en polvo de la cebada) y *Pyrenophora teres* (mancha reticulada de la cebada): Se colocaron segmentos de hojas de cebada sobre agar en una placa de 24 pocillos y se rociaron con una solución del compuesto de ensayo. Luego de permitir que los segmentos se secaran por completo (24 horas) ellos se inocularon con una suspensión de esporas del hongo. Después de la incubación apropiada la actividad de un compuesto se evaluó cuatro (*Pyrenophora teres*) o siete (*Erysiphe graminis f.sp. hordei*) días luego de la inoculación como actividad fungicida preventiva.

b) *Erysiphe graminis f.sp. tritici* (moho en polvo del trigo), *Puccinia recondita f.sp. tritici* (roya marrón del trigo) y *Septoria nodorum* (mancha de la gluma del trigo): Se colocaron segmentos de hojas de trigo sobre agar en una placa de 24 pocillos y se rociaron con una solución del compuesto de ensayo. Luego de permitir que los segmentos se secaran por completo (24 horas), ellos se inocularon con una suspensión de esporas del hongo. Después de la incubación apropiada la actividad de un compuesto se evaluó cuatro (*Septoria nodorum*), siete (*Erysiphe graminis f.sp. tritici*) u ocho (*Puccinia recondita f.sp. tritici*) días luego de la inoculación como actividad fungicida preventiva.

c) *Pyricularia oryzae* (piriculariosis del arroz): Se colocaron segmentos de hojas de arroz sobre agar en una placa de 24 pocillos y se rociaron con una solución del compuesto de ensayo. Luego de permitir que los segmentos se secaran por completo (24 horas), ellos se inocularon con una suspensión de esporas del hongo. Después de la incubación apropiada la actividad de un compuesto se evaluó cinco días luego de la inoculación como actividad fungicida preventiva.

d) *Botrytis cinerea* (moho gris): Se colocaron discos de hojas de frijol sobre agar en una placa de 24 pocillos y se rociaron con una solución del compuesto de ensayo. Luego de permitir que los discos se secaran por completo (24 horas), ellos se inocularon con una suspensión de esporas del hongo. Después de la incubación apropiada la actividad de un compuesto se evaluó tres días luego de la inoculación como actividad fungicida preventiva.

e) *Phytophthora infestans* (tizón tardío de la papa/tomate): Se colocaron discos de hojas de tomate sobre agua agar en una placa de 24 pocillos y se rociaron con una solución del compuesto de ensayo. Luego de permitir que los discos se secaran por completo (24 horas), ellos se inocularon con una suspensión de esporas del hongo. Después de la incubación apropiada la actividad de un compuesto se evaluó cuatro días luego de la inoculación como actividad fungicida preventiva.

f) *Plasmopara viticola* (mildiu vellosa de la vid): Se colocaron discos de hojas de vid sobre agar en una placa de 24 pocillos y se rociaron con una solución del compuesto de ensayo. Luego de permitir que los discos se secaran por completo (entre 12 y 24 horas), ellos se inocularon con una suspensión de esporas del hongo. Después de la incubación apropiada la actividad de un compuesto se evaluó siete días luego de la inoculación como actividad fungicida preventiva.

Los siguientes compuestos (la numeración corresponde a las Tablas 1, 2 y 3 precedentes) proporcionaron al menos 80% de control de las siguientes infecciones fúngicas a 200 ppm en los ensayos de discos de hojas descriptos precedentemente:

Plasmopara viticola: 2; 3; 4; 5; 7; 9; 10; 13; 17; 18; 19; 21; 22; 28; 30; 33; 38; 39; 40; 41; 44; 48; 50; 51; 52; 53; 55; 56; 57; 58; 61; 63; 65; 66; 77; 78; 83; 84; 89; 97; 98; 99; 100; 101; 103; 104; 105; 106; 108; 109; 112; 113; 115; 118; 121; 124; 125; 126; 127; 129; 130; 132; 133; 135; 140; 151; 154; 155; 161; 162; 166; 167; 168; 169; 170; 171; 172; 173; 174; 175; 181; 182; 185; 195; 196; 203; 204; 207; 208; 212; 213; 214; 215; 216; 217; 222; 225; 226; 228; 233; 234; 265; 266; 267; 269; 276; 281; 282; 283; 284; 288; 289; 290; 292; 295; 296; 303; 304; 306; 308; 309; 329; 335; 337; 339; 342; 343; 350; 352; 373; 378; 396; 397; 401; 404; 409; 411; 412; 413; 437; 438; 445; 447; 448; 449; 451; 452; 453; 454; 455; 456 y 457.

Phytophthora infestans: 3; 13; 28; 38; 39; 40; 48; 50; 52; 54; 55; 56; 58; 59; 73; 77; 78; 84; 87; 89; 97; 98; 99; 101; 103; 104; 105; 108; 109; 110; 111; 112; 113; 114; 115; 118; 119; 121; 122; 124; 125; 126; 127; 128; 130; 132; 134; 139; 133; 135; 140; 141; 143; 145; 146; 147; 150; 151; 154; 162; 164; 166; 168; 169; 170; 171; 182; 187; 201; 203; 204; 205; 206; 207; 208; 211; 212; 213; 216; 217; 222; 225; 226; 246; 248; 252; 259; 260; 262; 264; 265; 276; 277; 278; 281; 282; 283; 284; 285; 290; 292; 306; 342; 343; 378; 397; 409; 411; 412; 413; 445; 447; 448; 451; 452; 453; 454; 455 y 456.

Erysiphe graminis f.sp. tritici: 3; 4; 7; 13; 28; 191; 201; 203; 205; 206; 207; 208; 212; 213; 216; 217; 220; 222; 224; 226; 234; 235; 238; 246; 248; 252; 253; 258; 259; 260; 261; 264; 265; 255; 278; 282; 283; 284; 288; 289; 290; 292; 315; 396; 401; 403; 404; 405; 408; 409; 411; 412; 413; 423; 426; 427; 435; 437; 447; 448; 449; 450; 451; 452; 453; 454; 455; 456 y 457.

Botrytis cinerea: 4; 6; 30; 56; 66; 93; 97; 98; 100; 101; 104; 105; 119; 123; 127; 133; 135; 139; 140; 143; 151; 166; 167; 173; 207; 211; 212; 213; 216; 222; 225; 228; 255; 258; 260; 262; 263; 265; 266; 269; 292; 306; 398 y 405.

Puccinia recondita f.sp. tritici: 3; 4; 7; 10; 17; 18; 19; 30; 37; 38; 39; 40; 43; 51; 52; 54; 55; 57; 66; 77; 78; 83; 84; 87; 89; 93; 96; 97; 98; 100; 101; 103; 104; 107; 108; 110; 119; 121; 125; 126; 127; 128; 129; 130; 135; 136; 143; 151; 154; 155; 162; 164; 166; 167; 168; 169; 170; 171; 172; 173; 174; 175; 204; 205; 206; 207; 208; 211; 212; 213; 215; 216; 217; 219; 220; 222; 225; 226; 228; 234; 235; 238; 244; 245; 246; 248; 252; 253; 255; 258; 259; 260; 261; 262; 263; 264; 265; 267; 277; 278; 282; 283; 288; 289; 294; 295; 303; 319; 337; 342; 343; 369; 373; 378; 395; 396; 401; 403; 404; 405; 408; 409; 411; 412; 413; 423; 424; 427; 432; 433; 437; 448; 449; 450; 451; 452; 453; 454; 455; 456; 457 y 447.

Además, los compuestos de la invención también se evaluaron en cuanto a su capacidad para inhibir el crecimiento de esporas fúngicas en caldo nutriente.

a) *Septoria tritici* (mancha de la hoja de trigo), *Botrytis cinerea* (moho gris), *Pyricularia oryzae* (piriculariasis del arroz), *Rhizoctonia solani* (podredumbre de la raíz y marchitamiento fúngico), *Fusarium culmorum* (podredumbre de la raíz de los cereales): Se mezclaron conidios del hongo de almacenamiento criogénico directamente dentro de caldo nutriente (PDB caldo de dextrosa de papa, por sus siglas en inglés). Luego de colocar una solución (DMSO) de los compuestos de ensayo a 20 ppm dentro de una placa de microtitulación (formato de 96 pocillos) se adicionó el caldo nutriente que contenía las esporas fúngicas. Las placas de ensayo se incubaron a 24°C y se determinó fotométricamente la inhibición del crecimiento luego de 72 hs (*Septoria tritici*, *Botrytis cinerea*, *Pyricularia oryzae*) o de 48 hs (*Rhizoctonia solani*, *Fusarium culmorum*).

b) *Pythium ultimum* (marchitamiento fúngico): Se mezclaron fragmentos miceliales del hongo, preparados a partir de un cultivo de líquido reciente,

directamente dentro de caldo de dextrosa de papa. Luego se colocó una solución (DMSO) del compuesto de ensayo a 20 ppm dentro de una placa de microtitulación de 96 pocillos y se adicionó el caldo nutriente que contenía las esporas fúngicas. La placa de ensayo se incubó a 24°C y se determinó fotométricamente la inhibición del crecimiento luego de 48 hs.

Los siguientes compuestos (la numeración corresponde a las Tablas 1, 2 y 3 precedentes) proporcionaron al menos 80% de control de las siguientes infecciones fúngicas a 200 ppm en los ensayos de cultivo de líquidos descriptos precedentemente:

Septoria tritici: 4; 6; 7; 8; 10; 11; 13; 14; 17; 18; 26; 30; 33; 37; 38; 43; 47; 48; 52; 53; 54; 56; 57; 58; 59; 60; 62; 77; 78; 83; 84; 87; 89; 93; 96; 97; 98; 99; 100; 101; 103; 104; 105; 107; 108; 119; 126; 127; 128; 136; 142; 143; 156; 162; 166; 167; 168; 169; 170; 171; 172; 178; 181; 191; 193; 195; 196; 201; 204; 205; 207; 210; 216; 217; 219; 220; 222; 225; 226; 228; 234; 245; 246; 248; 252; 255; 257; 258; 259; 261; 263; 264; 265; 267; 276; 278; 282; 284; 285; 303; 306; 307; 327; 329; 339; 342; 343; 352; 369; 373; 378; 382; 389; 395; 396; 397; 398; 401; 404; 405; 408; 409; 411; 412; 413; 419; 420; 422; 423; 427; 428; 429; 431; 433; 437; 448; 449; 450; 451; 452; 453; 454; 455; 456; y 457.

Pyricularia oryzae: 4; 7; 13; 14; 26; 30; 33; 37; 38; 40; 43; 48; 56; 60; 83; 84; 92; 96; 97; 99; 100; 103; 104; 107; 108; 119; 123; 126; 127; 135; 136; 142; 143; 178; 181; 189; 191; 192; 194; 195; 196; 200; 201; 209; 216; 217; 219; 220; 222; 225; 226; 228; 278; 280; 282 y 306.

Pythium ultimum: 4; 6; 7; 8; 10; 13; 16; 17; 18; 27; 30; 38; 40; 43; 48; 50; 52; 53; 54; 55; 57; 58; 59; 62; 73; 76; 77; 78; 89; 91; 93; 97; 98; 99; 100; 101; 103; 104; 105; 106; 107; 108; 109; 110; 111; 112; 113; 115; 117; 119; 121; 123; 124; 125; 126; 127; 129; 130; 132; 133; 134; 135; 136; 139; 141; 143; 145; 146; 147; 148; 149; 150; 151; 152; 154; 155; 162; 166; 167; 168; 169; 170; 171; 172; 175; 195;

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Fusarium culmorum: 4; 6; 7; 10; 13; 38; 40; 43; 84; 97; 104; 128; 133; 162; 166; 168; 169; 216; 217; 220; 222; 234; 248; 255; 259; 264; 265; 278; 397; 398; 409; 413; 404; 405; 411; 412; 449 y 452.

Ejemplo 14 – Métodos de HPLC Utilizados

Método A (Water Alliance 2795 LC) con las siguientes condiciones de gradiente HPLC:

Solvente A: 0,1% ácido fórmico en agua/acetonitrilo (9:1)

Solvente B: 0,1% ácido fórmico en acetonitrilo)

Tiempo (minutos)	A (%)	B (%)	Velocidad de flujo (ml/min)
0	90	10	1,7
2,5	0	100	1,7
2,8	0	100	1,7
2,9	90	10	1,7

Tipo de columna: Water atlantis dc18; Longitud de columna: 20 mm; Diámetro interno de columna: 3 mm; Tamaño de Partícula: 3 micrones; Temperatura: 40°C.

Los valores característicos obtenidos para cada compuesto fueron el tiempo de retención (“TR”, registrado en minutos) y el ión molecular, típicamente el catión MH⁺ según se enumera en las Tablas 1, 2 y 3. El método de HPLC-MS utilizado se indica entre paréntesis.

Método B (Agilent 1100 Series LC) con las siguientes condiciones de gradiente HPLC:

Solvente A: 0,1% ácido fórmico en agua/acetonitrilo (9:1)

Solvente B: 0,1% ácido fórmico en acetonitrilo)

Tiempo (minutos)	A (%)	B (%)	Velocidad de flujo (ml/min)
0	90	10	1,7
2,5	0	100	1,7
2,8	0	100	1,7
2,9	90	10	1,7

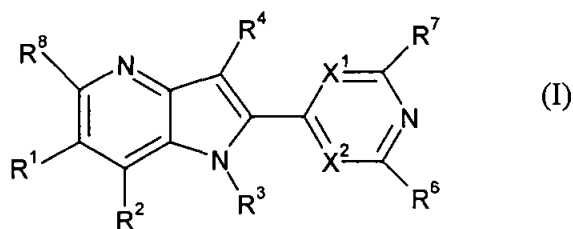
Tipo de columna: Water atlantis dc18; Longitud de columna: 20 mm; Diámetro interno de columna: 3 mm; Tamaño de Partícula: 3 micrones; Temperatura: 40°C.

Los valores característicos obtenidos para cada compuesto fueron el tiempo de retención ("TR", registrado en minutos) y el ión molecular, típicamente el catión MH^+ según se enumera en las Tablas 1, 2 y 3. El método de HPLC-MS utilizado se indica entre paréntesis.

Aunque la invención se ha descripto con referencia a las realizaciones preferidas y a los ejemplos de las mismas, el alcance de la presente invención no se limita solamente a aquellas realizaciones descriptas. Como será evidente para las personas expertas en la técnica, se pueden efectuar modificaciones y adaptaciones a la invención descripta precedentemente sin apartarse del espíritu y alcance de la invención, la cual se encuentra definida y circunscripta por las reivindicaciones anexas. Todas las publicaciones citadas en la presente se incorporan por la presente como referencia en su totalidad para todos los propósitos en la misma medida en que si cada publicación individual se encontrara indicada específicamente e individualmente para incorporarse de tal modo como referencia.

REIVINDICACIONES

1. Un método de prevención y/o control de la infección fúngica en las plantas y/o material de propagación de plantas que comprende aplicar a las plantas o material de propagación de plantas una cantidad efectiva como fungicida de un compuesto de la fórmula (I):



donde:

X^1 es N o CH;

X_2 es N o CR^5 ;

R^1 y R^2 son independientemente, :

- (i) hidrógeno, halógeno, hidroxilo, ciano o nitro,
- (ii) alquilo, alquenilo o alquinilo opcionalmente sustituido,
- (iii) arilo, heteroarilo, ciclilo o heterociclilo opcionalmente sustituido, o
- (iv) $-C(O)R^{10}$, $-C(O)NR^{10}R^{11}$, $-C(S)NR^{10}R^{11}$, $-C(NOR^{10})R^{11}$, $-C(O)OR^{10}$, $-OR^{10}$, $-SR^{10}$, $-S(O)R^{10}$, $-S(O)NR^{10}R^{11}$, $-S(O)_2R^{10}$, $-NR^{10}R^{11}$, $-P(O)(OR^{10})(OR^{11})$ u $-OP(O)(OR^{10})(OR^{11})$;

R^3 es:

- (i) hidrógeno, hidroxilo, ciano o nitro,
- (ii) alquilo, alquenilo, alenilo, alquinilo o haloalquilo opcionalmente sustituido,
- (iii) arilo, heteroarilo, ciclilo o heterociclilo o heteroaralquilo opcionalmente sustituido, o
- (iv) $-C(O)R^{12}$, $-C(O)OR^{12}$, $-OR^{12}$, $-OC(O)R^{12}$, $-S(O)_2R^{12}$ o $-NR^{12}R^{13}$;

R^4 es:

- (i) hidrógeno, halógeno, hidroxilo, ciano o nitro,
- (ii) alqueno, aleno, alquino o haloalquilo opcionalmente sustituido,
- (iii) arilo, heteroarilo, ciclilo o heterociclilo opcionalmente sustituido o
- (iv) $-C(O)R^{14}$, $-C(O)OR^{14}$, $-C(NOR^{14})R^{15}$, $-OR^{14}$, $-SR^{14}$, $-S(O)NR^{14}R^{15}$, $-S(O)_2R^{14}$ o $-NR^{14}R^{15}$;

R^5 es:

- (i) hidrógeno, halógeno, hidroxilo, ciano o nitro,
- (ii) alquilo, alqueno o alquino opcionalmente sustituido,
- (iii) $-C(O)R^{16}$, $-C(O)OR^{16}$, $-OR^{16}$, $-SR^{16}$, $-S(O)R^{16}$, $-S(O)NR^{16}R^{17}$, $-S(O)_2R^{16}$ o $-NR^{16}R^{17}$;

R^6 es hidrógeno, halógeno, ciano, $-C(O)OR^{18}$, $-SR^{18}$, $-NR^{18}R^{19}$, $-C(O)NR^{18}R^{19}$, $-N=CR^{20}$, $-C(=NR^{18})NR^{19}R^{20}$ o arilo, heteroarilo, ciclilo o heterociclilo opcionalmente sustituido;

R^7 y R^8 son, independientemente, hidrógeno, halógeno, hidroxilo, ciano, nitro, $-NR^{21}R^{22}$ o alquilo opcionalmente sustituido;

R^{10} , R^{11} , R^{14} , R^{15} , R^{16} y R^{17} son, independientemente, hidrógeno, halógeno, hidroxilo, ciano, nitro, alquilo, alcoxi, alqueno o alquino opcionalmente sustituido, o arilo, heteroarilo, ciclilo o heterociclilo opcionalmente sustituido;

R^{12} y R^{13} son, independientemente, hidrógeno, halógeno, hidroxilo, ciano, nitro, $-NR^{21}R^{22}$, alquilo, alcoxi, alqueno o alquino opcionalmente sustituido, o arilo, heteroarilo, ciclilo o heterociclilo opcionalmente sustituido;

R^{18} y R^{19} son independientemente,

- (i) hidrógeno,
- (ii) alquilo, alquenilo o alquinilo opcionalmente sustituido,
- (iii) arilo, heteroarilo, ciclilo o heterociclilo opcionalmente sustituido, o
- (iv) $-C(S)R^{23}$, $-C(O)R^{23}$, $-SO_2R^{23}$, $-C(O)OR^{23}$, $-OR^{23}$ o $C(O)NR^{23}R^{24}$,

R^{20} es hidroxilo, alquilo o alcoxi opcionalmente sustituido, $-NR^{21}R^{22}$ o $-N=CR^{21}R^{22}$;

R^{21} y R^{22} son, independientemente, hidrógeno, alquilo, alquenilo o alquinilo opcionalmente sustituido, ciclilo, heterociclilo, arilo o heteroarilo o aralquilo opcionalmente sustituido o $-C(O)OR^{25}$;

R^{23} y R^{24} son, independientemente, hidrógeno, hidroxilo, alquilo, alquenilo o alquinilo opcionalmente sustituido, o arilo, heteroarilo, ciclilo o heterociclilo o aralquilo opcionalmente sustituido; y

R^{25} es alquilo, alquenilo o alquinilo opcionalmente sustituido;

y/o

independientemente, (i) R^1 y R^2 , (ii) R^1 y R^3 (iii) R^2 y R^3 , (iv) R^3 y R^5 , (v) R^5 y R^6 , (vi) R^5 y R^{18} , (vii) R^5 y R^{19} , (viii) R^{14} y R^{15} y (ix) R^{18} y R^{19} forman un grupo arilo, heteroarilo, ciclilo o heterociclilo opcionalmente sustituido que contiene de 5 a 18 átomos en el anillo;

o una sal de N-óxido del mismo.

2. El método de la reivindicación 1, donde X^1 es CH.

3. El método de la reivindicación 1 o 2, donde X^2 es CH.

4. El método de cualquiera de las reivindicaciones precedentes, donde R^1 es hidrógeno, halógeno, ciano, alquilo C_{1-6} , alquenilo C_{2-6} o alquinilo C_{2-6} opcionalmente sustituido, arilo opcionalmente sustituido o $-C(O)R^{10}$.
5. El método de cualquiera de las reivindicaciones precedentes, donde R^2 es hidrógeno o alquilo C_{1-6} .
6. El método de cualquiera de las reivindicaciones precedentes, donde R^3 es hidrógeno, hidroxilo, $-C(O)R^{12}$, $-OR^{12}$, $-C(O)OR^{12}$, $-OC(O)R^{12}$, $-S(O)_2R^{12}$, alquilo C_{1-6} , alquenilo C_{2-6} , alenilo C_{3-6} , alquinilo C_{2-6} opcionalmente sustituido o ciclilo saturado opcionalmente sustituido.
7. El método de la reivindicación 6, donde R^3 es cianometilo, aminoetilo, aminopropilo, prop-2-enilo, prop-2-inilo, propa-1,2-dienilo, metoximetilo, 2-fluormetilo, $-OCH_2C\equiv CH$, $-OCH_2OCH_3$, $-OCH_2CN$, o $-OCH(CH_3)CN$.
8. El método de la reivindicación 6, donde R^3 es hidrógeno.
9. El método de cualquiera de las reivindicaciones precedentes, donde R^4 es hidrógeno, halógeno, alquinilo C_{2-6} opcionalmente sustituido o arilo o heteroarilo opcionalmente sustituido.
10. El método de la reivindicación 9, donde R^4 es fenilo o 4-fluorfenilo.
11. El método de cualquier reivindicación precedente, donde R^6 es hidrógeno o $-NR^{18}R^{19}$.
12. El método de la reivindicación 11, donde R^6 es $-NHR^{19}$.
13. El método de la reivindicación 12, donde R^{19} es $-C(O)R^{23}$.

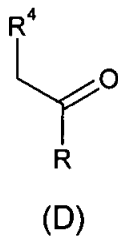
14. El método de la reivindicación 13, donde R^{23} está seleccionado de alquilo o ciclilo opcionalmente sustituido.
15. El método de la reivindicación 13, donde R^{23} está seleccionado de hidrógeno, metilo, etilo, *iso*-propilo, 1-metiletilo, 1-metilpropilo, 2-dimetiletilo, propilo, 1-metiletenilo, 2-metilprop-1-enilo, but-3-enilo, ciclopropilo, 1-metilciclopropilo, 1-fluorciclopropilo o ciclobutilo.
16. El método de cualquiera de las reivindicaciones precedentes, donde R^7 y R^8 son, independientemente, hidrógeno, hidroxilo, ciano, $-NR^{21}R^{22}$ o alquilo C_{1-6} opcionalmente sustituido.
17. El método de la reivindicación 1, donde el compuesto es uno de los compuestos que se establecen en las Tablas 1, 2 o 3.
18. El método de cualquiera de las reivindicaciones precedentes, donde la infección fúngica consiste en una infección por *Botrytis cinerea*, *Pyricularia oryzae*, *Fusarium culmorum*, *Septoria nodurum* y *Septoria tritici*, *Rhizoctonia solani*, *Puccinia recondite*, *Erysiphe graminis*, *Pyrenophora teres*, *Phytophthora infestans*, *Pythium ultimum* o *Plasmopara viticola*.
19. Un compuesto de la fórmula (I) según se definió en cualquiera de las reivindicaciones 1 a 17, con las condiciones de que (i) cuando X^1 sea CH, X^2 sea CR^5 y R^5 y R^6 sean ambos H, R^4 no sea 4-fluorfenilo y (ii) el compuesto de la fórmula (I) no sea:

- 3-fenil-2-piridin-4-il-1H-pirrolo[3,2-b]piridina
- 3-(3-cloro-4-fluor-fenil)-2-piridin-4-il-1H-pirrolo[3,2-b]piridina
- 3-(3-cloro-fenil)-2-piridin-4-il-1H-pirrolo[3,2-b]piridina
- 3-(3-trifluor-fenil)-2-piridin-4-il-1H-pirrolo[3,2-b]piridina
- 3-(3-metoxi-fenil)-2-piridin-4-il-1H-pirrolo[3,2-b]piridina

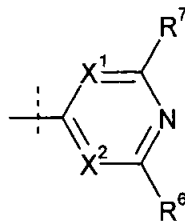
3-(2-metilfenil)-2-piridin-4-il-1H-pirrolo[3,2-b]piridina
 3-(2-metoxifenil)-2-piridin-4-il-1H-pirrolo[3,2-b]piridina
 1-metil-2-piridin-4-il-3-(3-trifluormetil-fenil)-1H-pirrolo[3,2-b]piridina
 1-metil-3-(3-cloro-4-fluor-fenil)-2-piridin-4-il-1H-pirrolo[3,2-b]piridina
 3-(4-fluorfenil)-2-(2-(2-hidroxietil-amino)-piridin-4-il)-1H-pirrolo[3,2-b]piridina,
 3-(4-fluorfenil)-2-(2-[HO(CH₂)₂O(CH₂)₂NH]-piridin-4-il)-1H-pirrolo[3,2-b]piridina,
 3-(4-fluorfenil)-2-(2-(2-metilamino-etilamino)-piridin-4-il)-1H-pirrolo[3,2-b]piridina,
 3-(4-fluorfenil)-2-(2-(3-metoxi-propil-amino)-piridin-4-il)-1H-pirrolo[3,2-b]piridina,
 3-(4-fluorfenil)-2-(2-*n*-propilamino-piridin-4-il)-1H-pirrolo[3,2-b]piridina,
 3-(4-fluorfenil)-2-(2-(3-hidroxi-propil-amino)-piridin-4-il)-1H-pirrolo[3,2-b]piridina,
 3-(4-fluorfenil)-2-(2-metilamino-piridin-4-il)-1H-pirrolo[3,2-b]piridina o
 3-(4-fluorfenil)-2-(2-acetilamino piridin-4-il)-1H-pirrolo[3,2-b]piridina.

20. Un proceso para la preparación de un compuesto de la fórmula (I) según se reivindicó en la reivindicación 1, que comprende:

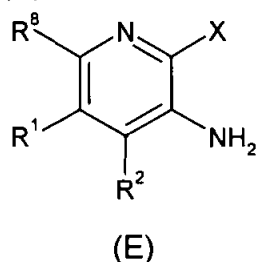
a) hacer reaccionar una cetona de la fórmula (D)



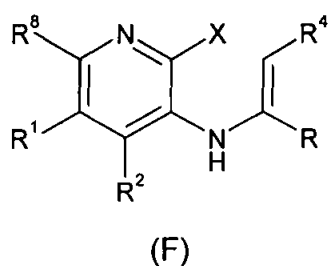
donde R⁴ es según se definió en la reivindicación 1, y R es un grupo de la fórmula



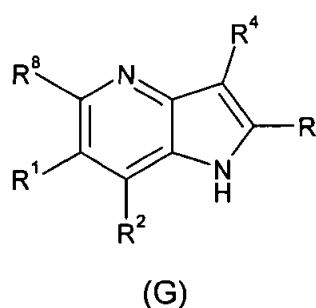
donde X^1 , X^2 , R^6 y R^7 son según se definieron en la reivindicación 1, con una aminopiridina de la fórmula (E)



donde R^1 , R^2 y R^8 son según se definieron en la reivindicación 1, y X es un halógeno, para proporcionar una enamina de la fórmula (F),

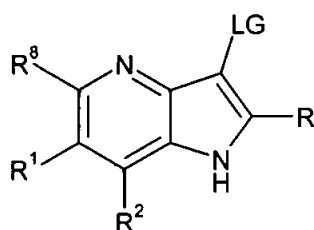


efectuar la ciclación para proporcionar un azaindol de la fórmula (G),



y opcionalmente efectuar la alquilación para proporcionar un compuesto de la fórmula (I) según se definió en la reivindicación 1; o

b) hacer reaccionar un azaindol de la fórmula (K)

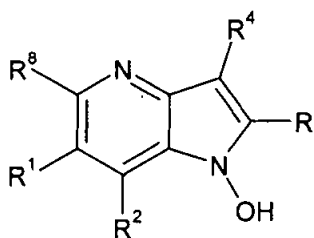


(K)

donde R^1 , R^2 y R^8 son según se definieron en la reivindicación 1, R es según se definió precedentemente, y LG es un grupo saliente con un compuesto de la fórmula $R^4-B(OH)_2$, donde R^4 es según se definió en la reivindicación 1, para proporcionar un compuesto de la fórmula (G) según se definió precedentemente, y opcionalmente efectuar la alquilación para proporcionar un compuesto de la fórmula (I) según se definió en la reivindicación 1;

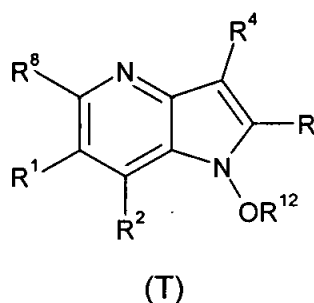
c) hacer reaccionar un compuesto de la fórmula (G) precedente con un compuesto de la fórmula R^3-LG donde LG es un grupo saliente para proporcionar un compuesto de la fórmula (I) según se definió en la reivindicación 1;

d) hacer reaccionar un compuesto de la fórmula (S)



(S)

donde R^1 , R^2 , R^4 , y R^8 se definen en la reivindicación 1, y R es según se definió precedentemente, con un compuesto de la fórmula $R^{12}-LG$ donde R^{12} es según se definió en la reivindicación 1 y LG es un grupo saliente, para proporcionar un compuesto de la fórmula (T)



donde R¹, R², R⁴, R⁸, y R¹² se definen en la reivindicación 1, y R es según se definió precedentemente, o

e) convertir un compuesto de la fórmula (I) según se definió en la reivindicación 1 a una sal de N-óxido del mismo.

21. Una composición para el control de la infección fúngica que comprende un compuesto de la fórmula I según se definió en cualquiera de las reivindicaciones 1 a 17 y un portador o diluyente aceptable desde el punto de vista agrícola.

22. Una composición para el control de la infección fúngica que comprende un compuesto de la reivindicación 18.

23. La composición de las reivindicaciones 21 o 22 que comprende además al menos un ingrediente activo seleccionado de fungicidas, herbicidas, insecticidas, bactericidas, acaricidas, nematocidas y/o reguladores del crecimiento de las plantas.

24. Un compuesto de la fórmula (I) según se definió en el método de cualquiera de las reivindicaciones 1 a 17 para el tratamiento de la infección fúngica en humanos o animales.

RESUMEN**DERIVADOS DE 4-AZA INDOL Y SU USO COMO FUNGICIDAS**

La presente invención se refiere a un método de prevención y/o control de la infección fúngica en las plantas y/o material de propagación de plantas que comprende aplicar a las plantas o material de propagación de plantas una cantidad efectiva como fungicida de un compuesto de la fórmula (I) o una sal de N-óxido del mismo. Además, la presente invención también se refiere a un compuesto de la fórmula (I).



Industria y Comercio

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

TARJETA ARCHIVO PROPIETARIOS

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(21) N° de solicitud:

(22) Fecha de solicitud:

(51) Clasificación Internacional :

(71) Solicitante(s) **SYNGENTA PARTICIPATIONS AG, SYNGENTA LIMITED**

(72) Inventor(es) **PATRICE SELLES, FREDRIK CEDERBAUM, FLORENCE MARIE-EMILIE BONNATERRE, WILLIAM GUY WHITTINGHAM, MAFALDA NINA, JANE ELIZABETH WIBLEY**

(74) Apoderado: **DRA. MARGARITA CASTELLANOS ABONDANO**

(30) Prioridad

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(84) Título: **DERIVADOS DE 4-AZA INDOL Y SU USO COMO FUNGICIDAS**

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING
OF A CHANGE

(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

To:

INTELLECTUAL PROPERTY DEPARTMENT
Syngenta Limited
PO Box 3538
Jealott's Hill Research Centre
Bracknell RG42 6YA
ROYAUME-UNI

Date of mailing (day/month/year) 22 September 2009 (22.09.2009)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference PPD 71569/WO	
International application No. PCT/GB2008/001348	International filing date (day/month/year) 16 April 2008 (16.04.2008)

1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

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	Facsimile No.	
	E-mail address	

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☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

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	Facsimile No.	
	E-mail address ☐ Notifications by e-mail authorized	

3. Further observations, if necessary:

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☐ the receiving Office	☐ the International Preliminary Examining Authority
☐ the International Searching Authority	☒ the designated Offices concerned
☐ the Authority(ies) specified for supplementary search	☐ the elected Offices concerned
	☐ other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Doherty Fiona
Facsimile No. +41 22 338 87 40	e-mail pt01.pct@wipo.int Telephone No. +41 22 338 74 01

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 ☐ the agent

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	Facsimile No.	
	E-mail address ☐ Notifications by e-mail authorized	

3. Further observations, if necessary:

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| ☐ the International Searching Authority | ☒ the designated Offices concerned |
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	Facsimile No.	
	E-mail address	

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	Facsimile No.	
	E-mail address ☐ Notifications by e-mail authorized	

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	Facsimile No.	
	E-mail address	
2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:		
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Name and Address NINA, Mafalda Syngenta Crop Protection AG Münchwilen AG, Schaffhauserstrasse CH-4332 Stein Switzerland	State of Nationality PT	State of Residence CH
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