Diana Narvaez

CSA674109

Organizacion y Digitalizacion CSA Ltda

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENTARIO

Industria y Comercio

SUPERINTENDENCIA

PCT

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIVISIÓN DE NUEVAS CREACIONES

09-139231

SOLICITUD DE PATENTE DE INVENCIÓN

TITULO: DERIVADOS POLICÍCLICOS DE INDAZOL Y SU USO COMO INHIBIDORES DE ERK PARA EL TRATAMIENTO DEL CANCER.

SOLICITANTE: SCHERING CORPORATION

DIRECCIÓN: 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 E.U.A.

APODERADO: CARLOS R. OLARTE

BOGOTÁ 04 de Diciembre de 2009

Titulo Cumple, No pago Examen
Fr. 05-01-2010

P2009/000200

1/4

OLARTE RAISBECK

OLARTE RAISBECK MOUF

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-139231- -00000-0000
Fecha: 2009-12-04 16:59:34 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 928

PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2009/000200**

SOLICITUD DE:

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

[X] Capítulo I. [ ] Capítulo II.

(2) **SOLICITANTE (71)**

Nombre: SCHERING CORPORATION
Dirección: 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 E.U.A.
Nacionalidad o Domicilio: Estadounidense
Lugar de Constitución: Estados Unidos
Teléfono: _____ **Fax:** _____
E-mail: _____

IDENTIFICACIÓN
C.C. [ ] **NIT** [ ]
C.E. [ ] **Otro** [ ]
Cual _____
Número _____

REPRESENTANTE O APODERADO

Nombre: CARLOS R. OLARTE
Dirección: World Trade Center, Torre A, Calle 100 No. 8A-37 Piso 10.
Teléfono: 601-7700 **Fax:** 601-7799
E-mail: office@olarteraisbeck.com

IDENTIFICACIÓN
C.C. [x] **NIT** [ ]
C.E. [ ] **Otro** [ ]
Cual _____
Número 79.782.747 Btá
TP 74.295

INVENTOR (ES) (72)

Nombre: VER PAGINA ADJUNTA
Dirección: VER PAGINA ADJUNTA
Nacionalidad o Domicilio: VER PAGINA ADJUNTA

(5) **PCT (86)**

Solicitud Internacional No. PCT/US2008/006979 Fecha Junio 4, 2008

Publicación Internacional No. WO 2008/153858 Fecha Diciembre 18, 2008

(6) **Título (54)** **NOVEDOSOS COMPUESTOS QUE SON INHIBIDORES DE ERK**
(f 933)

Clasificación Internacional (51) C07D 401/14, C07D 403/14, C07D 407/14, C07D 409/14, C07D 413/14, C07D 417/14, C07D 491/056, A61K 31/4245, A61K 31/444, A61K 31/506, A61P 35/00

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

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Junio 5, 2007	11/810,282

(9) **Comprobante de pago No.** 0990,781 **Fecha** Diciembre 02 de 2009

(10) **ANEXOS**

- [X] Comprobante de pago de la tasa de presentación de la solicitud.
- [X] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [X] Poderes, si fuere el caso. Adjunto copia simple ver expediente No. 07-132.393.
- [ ] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones.
- [X] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos).
- [X] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos).
- [ ] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
- [ ] Traducción del examen preliminar internacional efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [ ] Arte final 12 x 12.
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [X] Otros. Búsqueda Internacional.

(11) **FIGURA CARACTERÍSTICA:**

(12) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE FIRMA

C.C. 79.782.747 Btá T.P. 74.295

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

3

P2009/200
Schering Corp.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 09-139231- -00000-0000

Fecha: 2009-12-04 16:59:34 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 928

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 09 - 90,781
FECHA : DICIEMBRE 2 DE 2009

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBE&	CONSIGNACION	BANCO DE BOGOTA	062754307	130524634	02/12/2009	5,523,000.00

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

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

SON: QUINIENTOS CUARENTA MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

Traducción oficial del Inglés por Marlén Neira Castro, resolución 2117 del Ministerio de Justicia de Colombia

APOSTILLA EN PODER DE REPRESENTACIÓN DE

SCHERING CORPORATION

APOSTILLA

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

1. País: Estados Unidos de América
   - Este documento Público
2. ha sido firmado por Marguerite La Corte
3. Quien ejerce funciones de Notario público de Nueva Jersey
4. Lleva el sello de Marguertie La Corte Notario

CERTIFICADO

5. En Trenton, Nueva Jersey
6. El 29 de agosto 2003
7. Por John E. McCormac Contador Publico- Tesorero de Nueva Jersey 8. No. A 180345
9. Gran Sello del Estado de Nueva Jersey
10. Firma legible de John M.

PODER DE REPRESENTACIÓN

Bilingüe inglés- español otorgado en Kenilworth, Nueva Jersey, Estados Unidos, el 7 de agosto de 2003 y firmado por Edward H. Mazer - Director Juridico senior.

CERTIFICADO NOTARIAL

Bilingüe inglés- español, fechado el 7 de agosto, 2003 certificando las funciones de Edward H. Mazer - Director Juridico senior, de Schering Corporation.

Las certificaciones anteriores se basan en el Poder de representación fechado el 4 noviembre de 2002.

Sello: Marguerite La Corte- Notario público,
Estado de Nueva Jersey
Su comisión vence el 7 de octubre de 2003.
Sello en alto relieve del Notario Público

Es traducción fiel del inglés, con copia archivo, para confrontación. Bogotá 5 septiembre, 2003.

MARLEN NEIRA CASTRO
Traductor e Intérprete Oficial
Inglés - Español - Inglés
Resolución No. 2117 del 7 Oct 1987

APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA

2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
MARGUERITE LA CORTE

3. ACTING IN THE CAPACITY OF:
NOTARY PUBLIC OF NEW JERSEY

4. BEARS THE SEAL/STAMP OF:
MARGUERITE LA CORTE, NOTARY

CERTIFIED

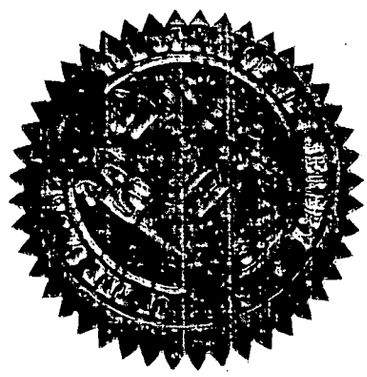
5. AT TRENTON, NEW JERSEY

6. THE 29TH DAY OF AUGUST 2003

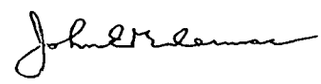
7. BY: John E McCormac, CPA, NEW JERSEY TREASURER

8. NO. A180345

9. SEAL/STAMP:



10. SIGNATURE



OLARTERAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

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Power of Attorney

The undersigned,
SCHERING CORPORATION

domiciled in
2000 Galloping Hill Road, Kenilworth, New Jersey 07033–0532, U.S.A.

by means of these presents hereby grants to **Carlos R. Olarte and/or Ana María Frieri** full and sufficient Power of Attorney to file, prosecute, obtain, defend and enforce any and all of the company's **Patents, Utility Models and Industrial Designs** in the Republic of Colombia, to which end it empowers them to take all steps necessary before any administrative or judicial authority of any class for the objects stated, to file petitions, appeals, replies and oppositions, pay taxes and annuities, request testimonies, receive documents and securities, abandon applications and collect refunds. Sufficient power is hereby granted to receive notifications on behalf of the Company, to confer powers on those who are to represent the company judicially and extrajudicially, to answer in court in the matter of all claims and demands that may be presented in connection with the objects stated, giving them likewise power to substitute these presents and revoke such substitutions.

Poder

El suscrito,

domiciliado en
2000 Galloping Hill Road, Kenilworth, New Jersey 07033–0532, U.S.A.

por medio del presente otorga a **Carlos R. Olarte y/o Ana María Frieri** poder especial, amplio y suficiente para presentar, tramitar, obtener, defender y hacer respetar todas y cualquiera de **Patentes, Modelos de Utilidad y Diseños Industriales** de la compañía en la República de Colombia, a cuyo efecto los faculta para dar todos los pasos necesarios ante cualquier autoridad administrativa o judicial de cualquier jerarquía para cumplir con lo encomendado, elevar solicitudes, apelaciones, respuestas y oposiciones, pagar impuestos y anualidades, solicitar testimonios, recibir documentos y valores, desistir y percibir. Se concede poder bastante para recibir notificaciones a nombre de la compañía, otorgar poderes a quienes vayan a representar a la compañía judicial y extrajudicialmente, responder en juicio a todas las reclamaciones o demandas que por motivo de lo encomendado se presentaren, dándoles asimismo facultad para sustituir el presente y revocar dichas sustituciones.

Signature/Firma: _____
Edward H. Mazer, Senior Legal Director

Date/Fecha: August 7, 2003

City,Country/Ciudad,Pais: Kenilworth, New Jersey, U.S.A.

OLARTERAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

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Fax: +57-1 638-6201

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Notarial Certification

On this date, August 7, 2003

The undersigned Notary Public certifies:

1. That Edward H. Mazer

of legal age and domiciled in 119 Greenwood Drive, Millburn, New Jersey 07041, U.S.A. signed the foregoing document.

2. That the grantor has executed the foregoing document as Senior Legal Director of SCHERING CORPORATION

3. That SCHERING CORPORATION having its principal place of business located in 2000 Galloping Hill Road, Kenilworth, New Jersey 07033-0530, U.SA. is duly incorporated, is currently in existence, and that the purposes for which the Power of Attorney is granted are within the scope of its corporate purposes.

4. That the grantor has the authority to execute the Power of Attorney and that his/her representation is legal.

5. The foundation for my certifications contained in points 2, 3 and 4 was the exhibition of the following authentic document(s):

Power of Attorney, dated November 4, 2002.

Certificación Notarial

En esta fecha,

el Notario Público suscrito certifica:

1. Que

mayor de edad, domiciliado

suscribió el documento que antecede.

2. Que el otorgante ha suscrito el referido documento en su carácter de

de

4. Que

con sede principal ubicada en

está legalmente constituida, que tiene existencia legal vigente y que los propósitos para los cuales se otorga el poder se encuentra dentro de los que comprenden su objeto social.

4. Que el otorgante tiene la representación para suscribir el poder, y que ésta es legítima.

5. El fundamento de mis certificaciones contenidas en los puntos 2, 3 y 4 fue la exhibición de los (del) siguiente(s) documento(s) auténtico(s):

BLIC (Signature):

Marguerite La Corte

Marguerite La Corte
Notary Public of New Jersey
My Commission Expires October 7, 2003

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

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C07D 407/14 (2006.01) *A61K 31/444* (2006.01)
C07D 409/14 (2006.01) *A61K 31/506* (2006.01)
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11/810,282 5 June 2007 (05.06.2007) US

(71) Applicant *(for all designated States except US)*: **SCHERING CORPORATION** [US/US]; 2000 Galloping Hill Road, Kenilworth, New Jersey 07033-0530 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **COOPER, Alan** [US/US]; 23 Natalie Drive, West Caldwell, New Jersey 07006 (US). **DENG, Yongqi** [CN/US]; 55 Ellison Road, Newton, Massachusetts 02459 (US). **SHIPPS, Gerald, W., Jr.** [US/US]; 5 Daniel Drive, Stoneham, Massachusetts 02180 (US). **SHIH, Neng-Yang** [US/US]; 2 Tyler Road, Lexington, Massachusetts 02420 (US). **ZHU, Hugh** [CN/US]; 29 Deerwood Trail W, Warren, New Jersey 07059 (US). **KELLY, Joseph** [IE/US]; 112 Princeton Road, Parlin, New Jersey 08859 (US). **DOLL, Ronald** [US/US]; 8 Concord Lane, Convent Station, New Jersey 07960 (US). **NAN, Yang** [US/US]; 163 Linden Avenue, Malden, Massachusetts 02148 (US). **DESAI, Jagdish** [US/US]; 3 Forest Park Terrace, Monroe Township, New Jersey 08831 (US). **WANG, James** [US/US]; 47 Unami Terrace, Westfield, New Jersey 07090 (US). **PALIWAL, Sunil** [IN/US]; 5 Golf View Court, Monroe Township, New Jersey 08831 (US). **TSUI, Hon-Chung** [CN/US]; 41 Cortland Drive, East Brunswick, New Jersey 08816 (US). **BOGA, Sobhana, Babu** [IN/US]; 79 Country Club Lane, Scotch Plains, New Jersey 07076 (US). **ALHASSAN, Abdul-Basit** [GH/US]; 1 Country Club Lane, Scotch Plains, New Jersey 07076 (US). **GAO, Xiaolei** [CN/US]; 111 Timothy Place, Bridgewater, New Jersey 08807 (US). **ZHU, Liang** [CN/US]; 17 Charlesbank Way, Waltham, Massachusetts 02473 (US). **PATEL, Mehul** [US/US]; 4 Chester Avenue, Apt. 4, Waltham, Massachusetts 02453 (US).

(74) Agent: **JEANETTE, Henry, C.**; Schering-Plough Corporation, Patent Department, K-6-1 1990, 2000 Galloping Hill Road, Kenilworth, New Jersey 07033-0530 (US).

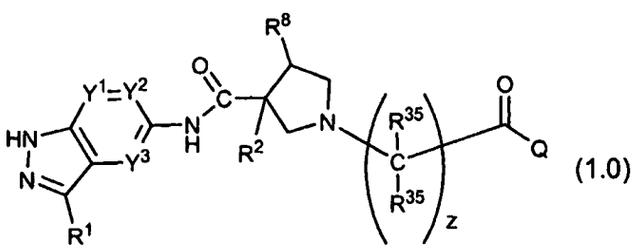
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM,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

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

[Continued on next page]

(54) Title: POLYCYCLIC INDAZOLE DERIVATIVES AND THEIR USE AS ERK INHIBITORS FOR THE TREATMENT OF CANCER



(1.0)

(57) Abstract: Disclosed are the ERK inhibitors of formula 1.0: (Chemical formula should be inserted here as it appears on abstract in paper form) and the pharmaceutically acceptable salts, esters and solvates thereof. Q is a piperidine or piperazine ring that can have a bridge or a fused ring. The piperidine ring can have a double bond in the ring. All other substitutents are as defined herein. Also disclosed are methods of treating cancer using the compounds of formula 1.0.

WO 2008/153858 A1

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

POLYCYCLIC INDAZOLE DERIVATIVES AND THEIR USE AS ERK INHIBITORS FOR THE TREATMENT OF CANCER

BACKGROUND

The processes involved in tumor growth, progression, and metastasis are mediated by signaling pathways that are activated in cancer cells. The ERK pathway plays a central role in regulating mammalian cell growth by relaying extracellular signals from ligand-bound cell surface tyrosine kinase receptors such as erbB family, PDGF, FGF, and VEGF receptor tyrosine kinase. Activation of the ERK pathway is via a cascade of phosphorylation events that begins with activation of Ras. Activation of Ras leads to the recruitment and activation of Raf, a serine-threonine kinase. Activated Raf then phosphorylates and activates MEK1/2, which then phosphorylates and activates ERK1/2. When activated, ERK1/2 phosphorylates several downstream targets involved in a multitude of cellular events including cytoskeletal changes and transcriptional activation. The ERK/MAPK pathway is one of the most important for cell proliferation, and it is believed that the ERK/MAPK pathway is frequently activated in many tumors. Ras genes, which are upstream of ERK1/2, are mutated in several cancers including colorectal, melanoma, breast and pancreatic tumors. The high Ras activity is accompanied by elevated ERK activity in many human tumors. In addition, mutations of BRAF, a serine-threonine kinase of the Raf family, are associated with increased kinase activity. Mutations in BRAF have been identified in melanomas (60%), thyroid cancers (greater than 40%) and colorectal cancers. These observations indicate that the ERK1/2 signalling pathway is an attractive pathway for anticancer therapies in a broad spectrum of human tumours.

Therefore, a welcome contribution to the art would be small-molecules (i.e., compounds) that inhibit ERK activity (i.e., ERK1 and ERK2 activity), which small-molecules would be useful for treating a broad spectrum of cancers, such as, for example, melanoma, pancreatic cancer, thryroid cancer, colorectal cancer, lung

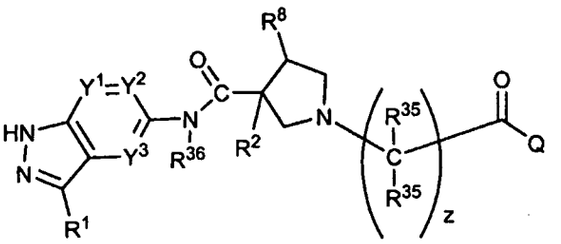
cancer, breast cancer, and ovarian cancer. Such a contribution is provided by this invention.

SUMMARY OF THE INVENTION

This invention provides compounds that inhibit the activity of ERK1 and/or the activity of ERK2.

The compounds of this invention also inhibit the phosphorylation of ERK1 and ERK2.

Thus, this invention provides compounds that are ERK inhibitors (i.e., ERK1 inhibitors and/or ERK2 inhibitors), said compounds being of the formula 1.0:



(1.0)

or the pharmaceutically acceptable salts, esters and solvates thereof, wherein:

Y^1, Y^2, and Y^3 are each independently selected from the group consisting of: C, N and substituted carbon;

Q is selected from the group consisting of: piperidinyl, piperazinyl, tetrahydropyridinyl (e.g., 1,2,3,6-tetrahydopyridinyl), bridged piperazinyl, bridged piperidinyl, bridged tetrahydropyridinyl, substituted piperidinyl, substituted piperazinyl, substituted tetrahydropyridinyl (e.g., a substituted 1,2,3,6-tetrahydo-pyridinyl), bridged substituted piperazinyl, bridged substituted piperidinyl, and bridged substituted tetrahydropyridinyl;

z is 1 to 3 (and preferably 1); and

R^1, R^2, R^8, R^{35} and R^{36} are as defined below.

This invention provides compounds of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 165) in pure or isolated form.

This invention provides compounds of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 165) in pure form.

This invention provides compounds of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 165) in isolated form.

This invention provides compounds of formula 1.0.

This invention provides pharmaceutically acceptable salts of the compounds of formula 1.0.

This invention provides pharmaceutically acceptable esters of the compounds of formula 1.0.

This invention provides solvates of the compounds of formula 1.0.

This invention provides the final compounds of Examples 1 to 827.

This invention also provides a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) and a pharmaceutically acceptable carrier.

This invention also provides a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) and an effective amount of at least one other (e.g., 1, 2 or 3, 1 or 2, and usually 1) pharmaceutically active ingredient (such as, for example, a chemotherapeutic agent), and a pharmaceutically acceptable carrier.

This invention also provides a method of inhibiting ERK (i.e., inhibiting the activity of ERK) in a patient in need of such treatment comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143).

This invention also provides a method of inhibiting ERK1 (i.e., inhibiting the activity of ERK1) in a patient in need of such treatment comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143).

This invention also provides a method of inhibiting ERK2 (i.e., inhibiting the activity of ERK2) in a patient in need of such treatment comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143).

This invention also provides a method of inhibiting ERK1 and ERK2 (i.e., inhibiting the activity of ERK1 and ERK2) in a patient in need of such treatment comprising administering to said patient an effective amount of at least one (e.g., 1, 2

or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143).

This invention also provides a method for treating cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143).

This invention also provides a method for treating cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143).

This invention also provides a method for treating cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method of treating cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) in combination with at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) signal transduction inhibitor.

This invention also provides a method of treating cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) in combination with at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) signal transduction inhibitor.

This invention also provides a method for treating lung cancer, pancreatic cancer, colon cancer (e.g., colorectal cancer), myeloid leukemias (e.g., AML, CML, and CMML), thyroid cancer, myelodysplastic syndrome (MDS), bladder carcinoma, epidermal carcinoma, melanoma, breast cancer, prostate cancer, head and neck cancers (e.g., squamous cell cancer of the head and neck), ovarian cancer, brain cancers (e.g., gliomas, such as glioma blastoma multiforme), cancers of mesenchymal origin (e.g., fibrosarcomas and rhabdomyosarcomas), sarcomas, tetracarcinomas, nuroblastomas, kidney carcinomas, hepatomas, non-Hodgkin's lymphoma, multiple myeloma, or anaplastic thyroid carcinoma, in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143).

This invention also provides a method for treating lung cancer, pancreatic cancer, colon cancer (e.g., colorectal cancer), myeloid leukemias (e.g., AML, CML, and CMML), thyroid cancer, myelodysplastic syndrome (MDS), bladder carcinoma, epidermal carcinoma, melanoma, breast cancer, prostate cancer, head and neck cancers (e.g., squamous cell cancer of the head and neck), ovarian cancer, brain cancers (e.g., gliomas, such as glioma blastoma multiforme), cancers of mesenchymal origin (e.g., fibrosarcomas and rhabdomyosarcomas), sarcomas, tetracarcinomas, nuroblastomas, kidney carcinomas, hepatomas, non-Hodgkin's lymphoma, multiple myeloma, or anaplastic thyroid carcinoma in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating lung cancer, pancreatic cancer, colon cancer (e.g., colorectal cancer), myeloid leukemias (e.g., AML, CML, and CMML), thyroid cancer, myelodysplastic syndrome (MDS), bladder carcinoma, epidermal carcinoma, melanoma, breast cancer, prostate cancer, head and neck cancers (e.g., squamous cell cancer of the head and neck), ovarian cancer, brain cancers (e.g., gliomas, such as glioma blastoma multiforme), cancers of mesenchymal origin (e.g., fibrosarcomas and rhabdomyosarcomas), sarcomas, tetracarcinomas, nuroblastomas, kidney carcinomas, hepatomas, non-Hodgkin's

lymphoma, multiple myeloma, or anaplastic thyroid carcinoma in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143).

This invention also provides a method for treating lung cancer, pancreatic cancer, colon cancer (e.g., colorectal cancer), myeloid leukemias (e.g., AML, CML, and CMML), thyroid cancer, myelodysplastic syndrome (MDS), bladder carcinoma, epidermal carcinoma, melanoma, breast cancer, prostate cancer, head and neck cancers (e.g., squamous cell cancer of the head and neck), ovarian cancer, brain cancers (e.g., gliomas, such as glioma blastoma multiforme), cancers of mesenchymal origin (e.g., fibrosarcomas and rhabdomyosarcomas), sarcomas, tetracarcinomas, nuroblastomas, kidney carcinomas, hepatomas, non-Hodgkin's lymphoma, multiple myeloma, or anaplastic thyroid carcinoma in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), wherein said cancer is selected from the group consisting of: melanoma, pancreatic cancer, thryroid cancer, colorectal cancer, lung cancer, breast cancer, and ovarian cancer.

This invention also provides a method for treating cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent wherein said cancer is selected from the group consisting of: melanoma, pancreatic cancer, thryroid cancer, colorectal cancer, lung cancer, breast cancer, and ovarian cancer.

This invention also provides a method for treating cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), wherein said cancer is selected from the group consisting of: melanoma, pancreatic cancer, thryroid cancer, colorectal cancer, lung cancer, breast cancer, and ovarian cancer.

This invention also provides a method for treating cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent wherein said cancer is selected from the group consisting of: melanoma, pancreatic cancer, thryroid cancer, colorectal cancer, lung cancer, breast cancer, and ovarian cancer.

This invention also provides a method for treating melanoma in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143).

This invention also provides a method for treating melanoma in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating melanoma in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143).

This invention also provides a method for treating melanoma in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for

example, as described in any one of Embodiment Nos. 1 to 143), in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating pancreatic cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143).

This invention also provides a method for treating pancreatic cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating pancreatic cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143).

This invention also provides a method for treating pancreatic cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating thyroid cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143).

This invention also provides a method for treating thyroid cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 1431), in

combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating thyroid cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143).

This invention also provides a method for treating thyroid cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating colorectal cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143).

This invention also provides a method for treating colorectal cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating colorectal cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143).

This invention also provides a method for treating colorectal cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), in combination with

an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating lung cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143).

This invention also provides a method for treating lung cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating lung cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143).

This invention also provides a method for treating lung cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating breast cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143).

This invention also provides a method for treating breast cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating breast cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143).

This invention also provides a method for treating breast cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating ovarian cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143).

This invention also provides a method for treating ovarian cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating ovarian cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143).

This invention also provides a method for treating ovarian cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides methods of treating breast cancer (i.e., post-menopausal and premenopausal breast cancer, e.g., hormone-dependent breast cancer) in a patient in need of such treatment, said treatment comprising the administration of an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) in combination with hormonal therapies (i.e., antihormonal agents).

This invention also provides methods of treating breast cancer (i.e., post-menopausal and premenopausal breast cancer, e.g., hormone-dependent breast cancer) in a patient in need of such treatment, said treatment comprising the administration of an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) in combination with hormonal therapies (i.e., antihormonal agents).

This invention also provides methods of treating breast cancer (i.e., post-menopausal and premenopausal breast cancer, e.g., hormone-dependent breast cancer) in a patient in need of such treatment, said treatment comprising the administration of an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) in combination with hormonal therapies (i.e., antihormonal agents), and in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides methods of treating breast cancer (i.e., post-menopausal and premenopausal breast cancer, e.g., hormone-dependent breast cancer) in a patient in need of such treatment, said treatment comprising the administration of an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) in combination with hormonal therapies (i.e., antihormonal agents), and in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

The methods of treating breast cancer described herein include the treatment of hormone-dependent metastatic and advanced breast cancer, adjuvant therapy for

hormone-dependent primary and early breast cancer, the treatment of ductal carcinoma in situ, and the treatment of inflammatory breast cancer in situ.

The methods of treating hormone-dependent breast cancer can also be used to prevent breast cancer in patients having a high risk of developing breast cancer.

Thus, this invention also provides methods of preventing breast cancer (i.e., post-menopausal and premenopausal breast cancer, e.g., hormone-dependent breast cancer) in a patient in need of such treatment, said treatment comprising the administration of an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) in combination with hormonal therapies (i.e., antihormonal agents).

This invention also provides methods of preventing breast cancer (i.e., post-menopausal and premenopausal breast cancer, e.g., hormone-dependent breast cancer) in a patient in need of such treatment, said treatment comprising the administration of an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) in combination with hormonal therapies (i.e., antihormonal agents).

This invention also provides methods of preventing breast cancer (i.e., post-menopausal and premenopausal breast cancer, e.g., hormone-dependent breast cancer) in a patient in need of such treatment, said treatment comprising the administration of an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) in combination with hormonal therapies (i.e., antihormonal agents), and in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides methods of preventing breast cancer (i.e., post-menopausal and premenopausal breast cancer, e.g., hormone-dependent breast cancer) in a patient in need of such treatment, said treatment comprising the administration of an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) in combination with hormonal therapies (i.e., antihormonal agents), and in combination

with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating brain cancer (e.g., glioma, such as glioma blastoma multiforme) in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143).

This invention also provides a method for treating brain cancer (e.g., glioma, such as glioma blastoma multiforme) in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating brain cancer (e.g., glioma, such as glioma blastoma multiforme) a in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143).

This invention also provides a method for treating brain cancer (e.g., glioma, such as glioma blastoma multiforme) in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating brain cancer (e.g., glioma, such as glioma blastoma multiforme) in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), in combination with an effective amount of a chemotherapeutic agent wherein said chemotherapeutic agent is temozolomide.

This invention also provides a method for treating brain cancer (e.g., glioma, such as glioma blastoma multiforme) in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), in combination with an effective amount of a chemotherapeutic agent, wherein said chemotherapeutic agent is temozolomide.

This invention also provides a method for treating prostate cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143).

This invention also provides a method for treating prostate cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating prostate cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143).

This invention also provides a method for treating prostate cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating myelodysplastic syndrome in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143).

This invention also provides a method for treating myelodysplastic syndrome in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating myelodysplastic syndrome in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143).

This invention also provides a method for treating myelodysplastic syndrome in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating myeloid leukemias in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143).

This invention also provides a method for treating myeloid leukemias in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating myeloid leukemias in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143).

This invention also provides a method for treating myeloid leukemias in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating acute myelogenous leukemia (AML) in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143).

This invention also provides a method for treating acute myelogenous leukemia (AML) in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating acute myelogenous leukemia (AML)in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143).

This invention also provides a method for treating acute myelogenous leukemia (AML)in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating chronic myelomonocytic leukemia (CMML) in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2,

and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143).

This invention also provides a method for treating chronic myelomonocytic leukemia (CMML) in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating chronic myelomonocytic leukemia (CMML) in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143).

This invention also provides a method for treating chronic myelomonocytic leukemia (CMML) in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating chronic myelogenous leukemia (chronic myeloid leukemia, CML) in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143).

This invention also provides a method for treating chronic myelogenous leukemia (chronic myeloid leukemia, CML) in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating chronic myelogenous leukemia (chronic myeloid leukemia, CML) in a patient in need of such treatment, said

method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143).

This invention also provides a method for treating chronic myelogenous leukemia (chronic myeloid leukemia, CML) in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating myeloid leukemias in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143).

This invention also provides a method for treating myeloid leukemias in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating myeloid leukemias in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143).

This invention also provides a method for treating myeloid leukemias in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating bladder cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143).

This invention also provides a method for treating bladder cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating bladder cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example; as described in any one of Embodiment Nos. 1 to 143).

This invention also provides a method for treating bladder cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating non-Hodgkin's lymphoma in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143).

This invention also provides a method for treating non-Hodgkin's lymphoma in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating non-Hodgkin's lymphoma in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143).

This invention also provides a method for treating non-Hodgkin's lymphoma in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating multiple myeloma in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143).

This invention also provides a method for treating multiple myeloma in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating multiple myeloma in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143).

This invention also provides a method for treating multiple myeloma in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

In the methods of this invention the compounds of this invention can be administered concurrently or sequentially (i.e., consecutively) with the chemotherapeutic agents or the signal transduction inhibitor.

The methods of treating cancers described herein can optionally include the administration of an effective amount of radiation (i.e., the methods of treating cancers described herein optionally include the administration of radiation therapy).

DETAILED DESCRIPTION OF THE INVENTION

As described herein, unless otherwise indicated, the use of a drug or compound in a specified period is per treatment cycle. For example, once a day means once per day of each day of the treatment cycle. Twice a day means twice per day each day of the treatment cycle. Once a week means one time per week during the treatment cycle. Once every three weeks means once per three weeks during the treatment cycle.

The following abbreviations have the following meanings unless defined otherwise:

ACN	Acetonitrile
AcOH	Acetic acid
DAST	(diethylamino)sulfur trifluoride
DCC	Dicyclohexylcarbodiimide
DCU	Dicyclohexylurea
DCM	Dichloromethane
DI	Deionized water
DIAD	Diisopropylazodicarboxylate
DIEA	Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DME	Dimethoxyethane
DMF	Dimethylformamide
DMFDMA	N,N-Dimethylformamide dimethylacetal
DMSO	Dimethyl sulfoxide
DTT	Dithiothreitol
EDCI	1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride
EtOAc	Ethyl acetate
EtOH	Ethanol
HATU	N,N,N',N'-Tetramethyl-O-(7-Azabenzotriazol-1-yl)Uronium

	hexafluorophosphate
Hex	hexanes
HOBt	1-Hydroxylbenzotriazole
HPLC	High pressure liquid chromatography
LCMS	Liquid chromatography mass spectrometry
LDA	Lithium diisopropylamide
mCPBA	*meta*-Chloroperoxybenzoic acid
MeOH	Methanol
MTT	(3-[4,5-dimethyl-thiazol-2-yl]-2,5-diphenyltetrazolium bromide, Thiazolyl blue)
NMR	Nuclear magnetic resonance
PFP	Pentafluorophenol
PMB	p-methoxybenzyl
Pyr	Pyridine
Rb	Round bottom flask
Rbt	Round bottom flask
RT	Room temperature
SEMCl	2-(Trimethylsily)ethoxy methyl chloride
TEA	Triethylamine
Tr	Triphenyl methane
Trt	Triphenyl methane
TrCl	Triphenyl methane chloride
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl

As used herein, unless otherwise specified, the following terms have the following meanings:

"anti-cancer agent" means a drug (medicament or pharmaceutically active ingredient) for treating cancer;

"antineoplastic agent" means a drug (medicament or pharmaceutically active ingredient) for treating cancer (i.e., a chemotherapeutic agent);

"at least one", as used in reference to the number of compounds of this invention means for example 1-6, generally 1-4, more generally 1, 2 or 3, and usually one or two, and more usually one;

"at least one", as used in reference to the number of chemotherapeutic agents used, means for example 1-6, generally 1-4, more generally 1, 2 or 3, and usually one or two, or one;

"chemotherapeutic agent" means a drug (medicament or pharmaceutically active ingredient) for treating cancer (i.e., and antineeoplastic agent);

"compound" with reference to the antineoplastic agents, includes the agents that are antibodies;

"concurrently" means (1) simultaneously in time (e.g., at the same time); or (2) at different times during the course of a common treatment schedule;

"consecutively" means one following the other;

"different" as used in the phrase "different antineoplastic agents" means that the agents are not the same compound or structure; preferably, "different" as used in the phrase "different antineoplastic agents" means not from the same class of antineoplastic agents; for example, one antineoplastic agent is a taxane, and another antineoplastic agent is a platinum coordinator compound;

"effective amount" or "therapeutically effective amount" is meant to describe an amount of compound or a composition of the present invention, or an amount of radiation, effective in treating or inhibiting the diseases or conditions described herein, and thus producing the desired therapeutic, ameliorative, inhibitory or preventative effect; thus, for example, in the methods of treating cancer described herein "effective amount" (or "therapeutically effective amount") means, for example, the amount of the compound (or drug), or radiation, that results in: (a) the reduction, alleviation or disappearance of one or more symptoms caused by the cancer, (b) the reduction of tumor size, (c) the elimination of the tumor, and/or (d) long-term disease stabilization (growth arrest) of the tumor; for example, in the treatment of lung cancer (e.g., non small cell lung cancer) a therapeutically effective amount is that amount that alleviates or eliminates cough, shortness of breath and/or pain; also, for example, an effective amount, or a therapeutically effective amount of the ERK inhibitor (i.e., a compound of this invention) is that amount which results in the reduction in ERK (ERK1 and/or ERK2) activity and phosphorylation; the reduction in ERK activity may be determined by the analysis of pharmacodynamic markers such as phosphorylated RSK1,2 and phosphorylated ERK1,2, using techniques well known in the art;

"Ex" in the tables represents "Example";

"one or more" has the same meaning as "at least one";

"patient" means an animal, such as a mammal (e.g., a human being, and preferably a human being);

"prodrug" means compounds that are rapidly transformed, for example, by hydrolysis in blood, in vivo to the parent compound, i.e., to the compounds of formula 1.0 or to a salt and/or to a solvate thereof; a thorough discussion is provided in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series, and in Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference; the scope of this invention includes Prodrugs of the novel compounds of this invention;

sequentially-represents (1) administration of one component of the method ((a) compound of the invention, or (b) chemotherapeutic agent, signal transduction inhibitor and/or radiation therapy) followed by administration of the other component or components; after adminsitration of one component, the next component can be administered substantially immediately after the first component, or the next component can be administered after an effective time period after the first component; the effective time period is the amount of time given for realization of maximum benefit from the administration of the first component; and

"solvate" means a physical association of a compound of this invention with one or more solvent molecules; this physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding; in certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid; "solvate" encompasses both solution-phase and isolatable solvates; non-limiting examples of suitable solvates include ethanolates, methanolates, and the like; "hydrate" is a solvate wherein the solvent molecule is H_2O.

As used herein, unless otherwise specified, the following terms have the following meanings, and unless otherwise specified, the definitions of each term (i.e., moiety or substituent) apply when that term is used individually or as a component of another term (e.g., the definition of aryl is the same for aryl and for the aryl portion of arylalkyl, alkylaryl, arylalkynyl, and the like):

"acyl" means an H-C(O)-, alkyl-C(O)-, alkenyl-C(O)-, Alkynyl-C(O)-, cycloalkyl-C(O)-, cycloalkenyl-C(O)-, or cycloalkynyl-C(O)- group in which the various groups are as defined below (and as defined below, the alkyl, alkenyl, alkynyl,

cycloalkyl, cycloalkenyl and cycloalkynyl moieties can be substituted); the bond to the parent moiety is through the carbonyl; preferred acyls contain a lower alkyl; Non-limiting examples of suitable acyl groups include formyl, acetyl, propanoyl, 2-methylpropanoyl, butanoyl and cyclohexanoyl;

"alkenyl" means an aliphatic hydrocarbon group (chain) comprising at least one carbon to carbon double bond, wherein the chain can be straight or branched, and wherein said group comprises about 2 to about 15 carbon atoms; Preferred alkenyl groups comprise about 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 6 carbon atoms in the chain; branched means that one or more lower alkyl groups, such as methyl, ethyl or propyl, or alkenyl groups are attached to a linear alkenyl chain; "lower alkenyl" means an alkenyl group comprising about 2 to about 6 carbon atoms in the chain, and the chain can be straight or branched; the term "substituted alkenyl" means that the alkenyl group is substituted by one or more independently selected substituents, and each substituent is independently selected from the group consisting of: halo, alkyl; aryl, cycloalkyl, cyano, alkoxy and –S(alkyl); non-limiting examples of suitable alkenyl groups include ethenyl, propenyl, n-butenyl, 3-methylbut-2-enyl, n-pentenyl, octenyl and decenyl;

"alkoxy" means an alkyl-O- group (i.e., the bond to the parent moiety is through the ether oxygen) in which the alkyl group is unsubstituted or substituted as described below; non-limiting examples of suitable alkoxy groups include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy and heptoxy;

"alkoxycarbonyl" means an alkyl-O-CO- group (i.e., the bond to the parent moiety is through the carbonyl) wherein the alkyl group is unsubstituted or substituted as previously defined; non-limiting examples of suitable alkoxycarbonyl groups include methoxycarbonyl and ethoxycarbonyl;

"alkyl" (including the alkyl portions of other moieties, such as trifluoroalkyl and alkyloxy) means an aliphatic hydrocarbon group (chain) that can be straight or branched wherein said group comprises about 1 to about 20 carbon atoms in the chain; preferred alkyl groups comprise about 1 to about 12 carbon atoms in the chain; more preferred alkyl groups comprise about 1 to about 6 carbon atoms in the chain; branched means that one or more lower alkyl groups, such as methyl, ethyl or propyl, are attached to a linear alkyl chain; "lower alkyl" means a group comprising about 1 to about 6 carbon atoms in the chain, and said chain can be straight or branched; the term "substituted alkyl" means that the alkyl group is substituted by one or more

independently selected substituents, and wherein each substituent is independently selected from the group consisting of: halo, aryl, cycloalkyl, cyano, hydroxy, alkoxy, alkylthio, amino, -NH(alkyl), -NH(cycloalkyl), -N(alkyl)$_2$, carboxy, –C(O)O-alkyl and –S(alkyl); non-limiting examples of suitable alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, n-pentyl, heptyl, nonyl, decyl, fluoromethyl, trifluoromethyl and cyclopropylmethyl;

"alkylaryl" (or alkaryl) means an alkyl-aryl- group (i.e., the bond to the parent moiety is through the aryl group) wherein the alkyl group is unsubstituted or substituted as defined above, and the aryl group is unsubstituted or substituted as defined below; preferred alkylaryls comprise a lower alkyl group; non-limiting examples of suitable alkylaryl groups include o-tolyl, p-tolyl and xylyl;

"alkylheteroaryl" means an alkyl-heteroaryl- group (i.e., the bond to the parent moiety is through the heteroaryl group) wherein the alkyl is unsubstituted or substituted as defined above and the heteroaryl group is unsubstituted or substituted as defined below;

"alkylsulfinyl" means an alkyl-S(O)- group (i.e., the bond to the parent moiety is through the sulfinyl) wherein the alkyl group is unsubstituted or substituted as previously defined; preferred groups are those in which the alkyl group is lower alkyl;

"alkylsulfonyl" means an alkyl-S(O_2)- group (i.e., the bond to the parent moiety is through the sulfonyl) wherein the alkyl group is unsubstituted or substituted as previously defined; preferred groups are those in which the alkyl group is lower alkyl;

"alkylthio" means an alkyl-S- group (i.e., the bond to the parent moiety is through the sulfur) wherein the alkyl group is unsubstituted or substituted as previously described; non-limiting examples of suitable alkylthio groups include methylthio, ethylthio, i-propylthio and heptylthio;

"alkynyl" means an aliphatic hydrocarbon group (chain) comprising at least one carbon to carbon triple bond, wherein the chain can be straight or branched, and wherein the group comprises about 2 to about 15 carbon atoms in the; preferred alkynyl groups comprise about 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 4 carbon atoms in the chain; Branched means that one or more lower alkyl groups, such as methyl, ethyl or propyl, are attached to a linear alkynyl chain; "lower alkynyl" means an alkynyl group comprising about 2 to about 6

carbon atoms in the chain, and the chain can be straight or branched; non-limiting examples of suitable alkynyl groups include ethynyl, propynyl, 2-butynyl, 3-methylbutynyl, n-pentynyl, and decynyl; the term "substituted alkynyl" means that the alkynyl group is substituted by one or more independently selected, and each substituent is independently selected from the group consisting of alkyl; aryl and cycloalkyl;

"amino means a $-NH_2$ group;

"aralkenyl" (or arylalkenyl) means an aryl-alkenyl- group (i.e., the bond to the parent moiety is through the alkenyl group) wherein the aryl group is unsubstituted or substituted as defined below, and the alkenyl group is unsubstituted or substituted as defined above; preferred aralkenyls contain a lower alkenyl group; non-limiting examples of suitable aralkenyl groups include 2-phenethenyl and 2-naphthylethenyl;

"aralkyl" (or arylalkyl) means an aryl-alkyl- group (i.e., the bond to the parent moiety is through the alkyl group) wherein the aryl is unsubstituted or substituted as defined below and the alkyl is unsubstituted or substituted as defined above; preferred aralkyls comprise a lower alkyl group; non-limiting examples of suitable aralkyl groups include benzyl, 2-phenethyl and naphthalenylmethyl;

"aralkyloxy" (or arylalkyloxy) means an aralkyl-O- group (i.e., the bond to the parent moiety is through the ether oxygen) wherein the aralkyl group is unsubstituted or substituted as previously described; non-limiting examples of suitable aralkyloxy groups include benzyloxy and 1- or 2-naphthalenemethoxy;

"aralkoxycarbonyl" means an aralkyl-O-C(O)- group (i.e., the bond to the parent moiety is through the carbonyl) wherein the aralkyl group is unsubstituted or substituted as previously defined; a non-limiting example of a suitable aralkoxycarbonyl group is benzyloxycarbonyl;

"aralkylthio" means an aralkyl-S- group (i.e., the bond to the parent moiety is through the sulfur) wherein the aralkyl group is unsubstituted or substituted as previously described; a non-limiting example of a suitable aralkylthio group is benzylthio;

"aroyl" means an aryl-C(O)- group (i.e., the bond to the parent moiety is through the carbonyl) wherein the aryl group is unsubstituted or substituted as defined below; non-limiting examples of suitable groups include benzoyl and 1- and 2-naphthoyl;

"aryl" (sometimes abbreviated "ar") means an aromatic monocyclic or multicyclic ring system comprising about 6 to about 14 carbon atoms, preferably about 6 to about 10 carbon atoms; the aryl group can be optionally substituted with one or more independently selected "ring system substituents" (defined below). Non-limiting examples of suitable aryl groups include phenyl and naphthyl;

"arylalkynyl" means an aryl-alkynyl- group (i.e., the bond to the parent moiety is through the alkynyl group) wherein the aryl group is unsubstituted or substituted as defined above, and the alkynyl group is unsubstituted or substitutedas defined above;

"arylaminoheteroaryl" means an aryl-amino-heteroaryl group (i.e., the bond to the parent moiety is through the heteroaryl group) wherein the aryl group is unsubstituted or substituted as defined above, the amino group is as defined above (i.e., a –NH- here), and the heteroaryl group is unsubstituted or substituted as defined below;

"arylheteroaryl" means an aryl-heteroarylgroup-(i:e., the bond to the parent moiety is through the heteroaryl group) wherein the aryl group is unsubstituted or substituted as defined above, and the heteroaryl group is unsubstituted or substituted as defined below;

"aryloxy" means an aryl-O- group (i.e., the bond to the parent moiety is through the ether oxygen) wherein the aryl group is unsubstituted or substituted as defined above; non-limiting examples of suitable aryloxy groups include phenoxy and naphthoxy;

"aryloxycarbonyl" means an aryl-O-C(O)- group (i.e., the bond to the parent moiety is through the carbonyl) wherein the aryl group is unsubstituted or substituted as previously defined; non-limiting examples of suitable aryloxycarbonyl groups include phenoxycarbonyl and naphthoxycarbonyl;

"arylsulfinyl" means an aryl-S(O)- group (i.e., the bond to the parent moiety is through the sulfinyl) wherein aryl is unsubstituted or substituted as previously defined;

"arylsulfonyl" means an aryl-$S(O_2)$- group (i.e., the bond to the parent moiety is through the sulfonyl) wherein aryl is unsubstituted or substituted as previously defined;

"arylthio" means an aryl-S- group (i.e., the bond to the parent moiety is through the sulfur) wherein the aryl group is unsubstituted or substituted as previously

described; non-limiting examples of suitable arylthio groups include phenylthio and naphthylthio;

"cycloalkenyl" means a non-aromatic mono or multicyclic ring system comprising about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms that contains at least one carbon-carbon double bond; preferred cycloalkenyl rings contain about 5 to about 7 ring atoms; the cycloalkenyl can be optionally substituted with one or more independently selected "ring system substituents" (defined below); Non-limiting examples of suitable monocyclic cycloalkenyls include cyclopentenyl, cyclohexenyl, cycloheptenyl, and the like; a non-limiting example of a suitable multicyclic cycloalkenyl is norbornylenyl;

"cycloalkyl" means a non-aromatic mono- or multicyclic ring system comprising about 3 to about 7 carbon atoms, preferably about 3 to about 6 carbon atoms; the cycloalkyl can be optionally substituted with one or more independently selected "ring system substituents" (defined below); non-limiting examples of suitable monocyclic cycloalkyls include cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl and the like; non-limiting examples of suitable multicyclic cycloalkyls include 1-decalin, norbornyl, adamantyl and the like;

"cycloalkylalkyl" means a cycloalkyl-alkyl-group (i.e., the bond to the parent moiety is through the alkyl group) wherein the cycloalkyl moiety is unsubstituted or substituted as defined above, and the alkyl moiety is unsubstituted or substituted as defined above;

"halo" means fluoro, chloro, bromo, or iodo groups; preferred halos are fluoro, chloro or bromo, and more preferred are fluoro and chloro;

"halogen" means fluorine, chlorine, bromine, or iodine; preferred halogens are fluorine, chlorine and bromine;

"haloalkyl" means an alkyl, as defined above, wherein one or more hydrogen atoms on the alkyl is replaced by a halo group, as defined above;

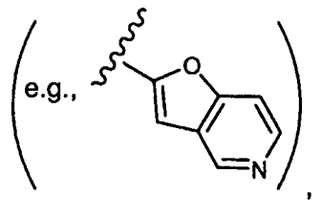
"heteroaralkenyl" means a heteroaryl-alkenyl- group (i.e., the bond to the parent moiety is through the alkenyl group) wherein the heteroaryl group is unsubstituted or substituted as defined below, and the alkenyl group is unsubstituted or substituted as defined above;

"heteroaralkyl" (or heteroarylalkyl) means a heteroaryl-alkyl- group (i.e., the bond to the parent moiety is through the alkyl group) in which the heteroaryl is unsubstituted or substituted as defined below, and the alkyl group is unsubstituted or

substituted as defined above; preferred heteroaralkyls comprise an alkyl group that is a lower alkyl group; non-limiting examples of suitable aralkyl groups include pyridylmethyl, 2-(furan-3-yl)ethyl and quinolin-3-ylmethyl;

"heteroaralkylthio" means a heteroaralkyl-S- group wherein the heteroaralkyl group is unsubstituted or substituted as defined above;

"heteroaryl" means an aromatic monocyclic or multicyclic ring system comprising about 5 to about 14 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the ring atoms is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination; preferred heteroaryls comprise about 5 to about 6 ring atoms; the "heteroaryl" can be optionally substituted by one or more independently selected "ring system substituents" (defined below); the prefix aza, oxa or thia before the heteroaryl root name means that at least a nitrogen, oxygen or sulfur atom, respectively, is present as a ring atom; a nitrogen atom of a heteroaryl can be optionally oxidized to the corresponding N-oxide; non-limiting examples of suitable heteroaryls include pyridyl; pyrazinyl; furanyl, thienyl, pyrimidinyl, isoxazolyl, isothiazolyl, oxazolyl, thiazolyl, pyrazolyl, furazanyl, pyrrolyl, pyrazolyl, triazolyl, 1,2,4-thiadiazolyl, pyrazinyl, pyridazinyl, quinoxalinyl, phthalazinyl, imidazo[1,2-a]pyridinyl, imidazo[2,1-b]thiazolyl, benzofurazanyl, indolyl, azaindolyl, benzimidazolyl, benzothienyl, quinolinyl, imidazolyl, thienopyridyl, quinazolinyl, thienopyrimidyl, pyrrolopyridyl, imidazopyridyl, isoquinolinyl, benzoazaindolyl, 1,2,4-triazinyl, benzothiazolyl, furopyridine



and the like;

"heteroarylalkynyl" (or heteroaralkynyl) means a heteroaryl-alkynyl- group (i.e., the bond to the parent moiety is through the alkynyl group) wherein the heteroaryl group is unsubstituted or substituted as defined above, and the alkynyl group is unsubstituted or substituted as defined above;

"heteroarylaryl" (or heteroararyl) means a heteroaryl-aryl- group (i.e., the bond to the parent moiety is through the aryl group) wherein the heteroaryl group is

unsubstituted or substituted as defined above, and the aryl group is unsubstituted or substituted as defined above;

"heteroarylheteroarylaryl" means a heteroaryl-heteroaryl- group (i.e., the bond to the parent moiety is through the last heteroaryl group) wherein each heteroaryl group is independently unsubstituted or substituted as defined above;

"heteroarylsulfinyl" means a heteroaryl-SO- group wherein the heteroaryl group is unsubstituted or substituted as defined above;

"heteroarylsulfonyl" means a heteroaryl-SO_2- group wherein the heteroaryl group is unsubstituted or substituted as defined above;

"heteroarylthio" means a heteroaryl-S- group wherein the heteroaryl group is unsubstituted or substituted as defined above;

"heterocyclenyl" (or heterocycloalkenyl) means a non-aromatic monocyclic or multicyclic ring system comprising about 3 to about 10 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the atoms in the ring system is an element other than carbon (for example one or more heteroatoms independently selected from the group consisting of nitrogen, oxygen and sulfur atom), and which contains at least one carbon-carbon double bond or carbon-nitrogen double bond; there are no adjacent oxygen and/or sulfur atoms present in the ring system; Preferred heterocyclenyl rings contain about 5 to about 6 ring atoms; the prefix aza, oxa or thia before the heterocyclenyl root name means that at least a nitrogen, oxygen or sulfur atom, respectively, is present as a ring atom; the heterocyclenyl can be optionally substituted by one or more independently selected "Ring system substituents" (defined below); the nitrogen or sulfur atom of the heterocyclenyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide; non-limiting examples of suitable monocyclic azaheterocyclenyl groups include 1,2,3,4-tetrahydropyridine, 1,2-dihydropyridyl, 1,4-dihydropyridyl, 1,2,3,6-tetrahydropyridine, 1,4,5,6-tetrahydropyrimidine, 2-pyrrolinyl, 3-pyrrolinyl, 2-imidazolinyl, 2-pyrazolinyl, and the like; Non-limiting examples of suitable oxaheterocyclenyl groups include 3,4-dihydro-2H-pyran, dihydrofuranyl, fluorodihydrofuranyl, and the like; A non-limiting example of a suitable multicyclic oxaheterocyclenyl group is 7-oxabicyclo[2.2.1]heptenyl; non-limiting examples of suitable monocyclic thiaheterocyclenyl rings include dihydrothiophenyl, dihydrothiopyranyl, and the like;

"heterocycloalkylalkyl" (or heterocyclylalkyl) means a heterocycloalkyl-alkyl- group (i.e., the bond to the parent moiety is through the alkyl group) wherein the

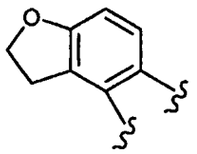
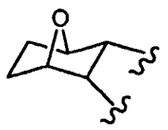
heterocycloalkyl group (i.e., the heterocyclyl group) is unsubstituted or substituted as defined below, and the alkyl group is unsubstituted or substituted as defined above;

"heterocyclyl" (or heterocycloalkyl) means a non-aromatic saturated monocyclic or multicyclic ring system comprising about 3 to about 10 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the atoms in the ring system is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination; there are no adjacent oxygen and/or sulfur atoms present in the ring system; preferred heterocyclyls contain about 5 to about 6 ring atoms; the prefix aza, oxa or thia before the heterocyclyl root name means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom; the heterocyclyl can be optionally substituted by one or more independently selected "ring system substituents" (defined below); the nitrogen or sulfur atom of the heterocyclyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide; non-limiting examples of suitable monocyclic heterocyclyl rings include piperidyl, pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,3-dioxolanyl, 1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, and the like;

"hydroxyalkyl" means a HO-alkyl- group wherein the alkyl group is substituted or unsubstituted as defined above; preferred hydroxyalkyls comprise a lower alkyl; Non-limiting examples of suitable hydroxyalkyl groups include hydroxymethyl and 2-hydroxyethyl; and

"ring system substituent" means a substituent attached to an aromatic or non-aromatic ring system that, for example, replaces an available hydrogen on the ring system; ring system substituents are each independently selected from the group consisting of: alkyl, aryl, heteroaryl, aralkyl, alkylaryl, aralkenyl, heteroaralkyl, alkylheteroaryl, heteroaralkenyl, hydroxy, hydroxyalkyl, alkoxy, aryloxy, aralkoxy, acyl, aroyl, halo, nitro, cyano, carboxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylsulfinyl, arylsulfinyl, heteroarylsulfinyl, alkylthio, arylthio, heteroarylthio, aralkylthio, heteroaralkylthio, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, $R^{60}R^{65}N$-, $R^{60}R^{65}N$-alkyl-, $R^{60}R^{65}NC(O)$- and $R^{60}R^{65}NSO_2$-, wherein R^{60} and R^{65} are each independently selected from the group consisting of: hydrogen, alkyl, aryl, and aralkyl; "Ring system substituent" also means a cyclic ring of 3 to 7 ring atoms, wherein 1-2 ring atoms can be heteroatoms, attached to an aryl, heteroaryl, heterocyclyl or heterocyclenyl ring by

simultaneously substituting two ring hydrogen atoms on said aryl, heteroaryl, heterocyclyl or heterocyclenyl ring; Non-limiting examples include:



and the like

Lines drawn into a ring mean that the indicated bond may be attached to any of the substitutable ring carbon atoms.

Any carbon or heteroatom with unsatisfied valences in the text, schemes, examples, structural formulae, and any Tables herein is assumed to have the hydrogen atom or atoms to satisfy the valences.

One or more compounds of the invention may also exist as, or optionally converted to, a solvate. Preparation of solvates is generally known. Thus, for example, M. Caira *et al*, *J. Pharmaceutical Sci.*, 93(3), 601-611 (2004) describe the preparation of the solvates of the antifungal fluconazole in ethyl acetate as well as from water. Similar preparations of solvates, hemisolvate, hydrates and the like are described by E. C. van Tonder *et al*, *AAPS PharmSciTech.*, 5(1), article 12 (2004); and A. L. Bingham *et al*, *Chem. Commun.*, 603-604 (2001). A typical, non-limiting, process involves dissolving the inventive compound in desired amounts of the desired solvent (organic or water or mixtures thereof) at a higher than ambient temperature, and cooling the solution at a rate sufficient to form crystals which are then isolated by standard methods. Analytical techniques such as, for example I. R. spectroscopy, show the presence of the solvent (or water) in the crystals as a solvate (or hydrate).

The term "pharmaceutical composition" is also intended to encompass both the bulk composition and individual dosage units comprised of more than one (e.g., two) pharmaceutically active agents such as, for example, a compound of the present invention and an additional agent selected from the lists of the additional agents described herein, along with any pharmaceutically inactive excipients. The bulk composition and each individual dosage unit can contain fixed amounts of the afore-said "more than one pharmaceutically active agents". The bulk composition is material that has not yet been formed into individual dosage units. An illustrative dosage unit is an oral dosage unit such as tablets, capsules, pills and the like. Similarly, the herein-described methods of treating a patient by administering a

pharmaceutical composition of the present invention is also intended to encompass the administration of the afore-said bulk composition and individual dosage units.

Prodrugs of the compounds of the invention are also contemplated herein. The term "prodrug", as employed herein, denotes a compound that is a drug precursor which, upon administration to a subject, undergoes chemical conversion by metabolic or chemical processes to yield a compound of formula 1.0 or a salt and/or solvate thereof. A discussion of prodrugs is provided in T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems* (1987) 14 of the A.C.S. Symposium Series, and in *Bioreversible Carriers in Drug Design,* (1987) Edward B. Roche, ed., American Pharmaceutical Association and Pergamon Press, both of which are incorporated herein by reference thereto.

For example, if a compound of formula 1.0, or a pharmaceutically acceptable salt, hydrate or solvate of the compound, contains a carboxylic acid functional group, a prodrug can comprise an ester formed by the replacement of the hydrogen atom of the acid group with a group such as, for example, (C_1–C_8)alkyl, (C_2-C_{12})alkanoyloxy-methyl, 1-(alkanoyloxy)ethyl having from 4 to 9 carbon atoms, 1-methyl-1-(alkanoyloxy)-ethyl having from 5 to 10 carbon atoms, alkoxycarbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-(alkoxycarbonyloxy)ethyl having from 5 to 8 carbon atoms, N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxy-carbonyl)amino)ethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N-(C_1-C_2)alkylamino(C_2-C_3)alkyl (such as β-dimethylaminoethyl), carbamoyl-(C_1-C_2)alkyl, N,N-di (C_1-C_2)alkylcarbamoyl-(C1-C2)alkyl and piperidino-, pyrrolidino- or morpholino(C_2-C_3)alkyl, and the like.

Similarly, if a compound of formula 1.0 contains an alcohol functional group, a prodrug can be formed by the replacement of the hydrogen atom of the alcohol group with a group such as, for example, (C_1-C_6)alkanoyloxymethyl, 1-((C_1-C_6)alkanoyl-oxy)ethyl, 1-methyl-1-((C_1-C_6)alkanoyloxy)ethyl, (C_1-C_6)alkoxycarbonyloxymethyl, N-(C_1-C_6)alkoxycarbonylaminomethyl, succinoyl, (C_1-C_6)alkanoyl, α-amino(C_1-C_4)alkanyl, arylacyl and α-aminoacyl, or α-aminoacyl-α-aminoacyl, where each α-aminoacyl group is independently selected from the naturally occurring L-amino acids, $P(O)(OH)_2$, $-P(O)(O(C_1$-$C_6)alkyl)_2$ or glycosyl (the radical resulting from the removal of a hydroxyl group of the hemiacetal form of a carbohydrate), and the like.

If a compound of formula 1.0 incorporates an amine functional group, a prodrug can be formed by the replacement of a hydrogen atom in the amine group with a group such as, for example, R^{70}-carbonyl, $R^{70}O$-carbonyl, $NR^{70}R^{75}$-carbonyl where R^{70} and R^{75} are each independently $(C_1\text{-}C_{10})$alkyl, $(C_3\text{-}C_7)$ cycloalkyl, benzyl, or R^{70}-carbonyl is a natural α-aminoacyl or natural α-aminoacyl, —C(OH)C(O)OY^{80} wherein Y^{80} is H, $(C_1\text{-}C_6)$alkyl or benzyl, —C(OY^{82})Y^{84} wherein Y^{82} is $(C_1\text{-}C_4)$ alkyl and Y^{84} is $(C_1\text{-}C_6)$alkyl, carboxy $(C_1\text{-}C_6)$alkyl, amino$(C_1\text{-}C_4)$alkyl or mono-N—or di-N,N-$(C_1\text{-}C_6)$alkylaminoalkyl, —C(Y^{86})Y^{88} wherein Y^{86} is H or methyl and Y^{88} is mono-N— or di-N,N-$(C_1\text{-}C_6)$alkylamino morpholino, piperidin-1-yl or pyrrolidin-1-yl, and the like.

This invention also includes the compounds of this invention in isolated and purified form.

Polymorphic forms of the compounds of formula 1.0, and of the salts, solvates and prodrugs of the compounds of formula 1.0, are intended to be included in the present invention.

Certain compounds of the invention may exist in different isomeric (e.g., enantiomers, diastereoisomers, atropisomers) forms. The invention contemplates all such isomers both in pure form and in admixture, including racemic mixtures. Enol forms are also included.

All stereoisomers (for example, geometric isomers, optical isomers and the like) of the present compounds (including those of the salts, solvates and prodrugs of the compounds as well as the salts and solvates of the prodrugs), such as those which may exist due to asymmetric carbons on various substituents, including enantiomeric forms (which may exist even in the absence of asymmetric carbons), rotameric forms, atropisomers, and diastereomeric forms, are contemplated within the scope of this invention. Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. The chiral centers of the present invention can have the S or R configuration as defined by the *IUPAC* 1974 Recommendations. The use of the terms "salt", "solvate" "prodrug" and the like, is intended to equally apply to the salt, solvate and prodrug of enantiomers, stereoisomers, rotamers, tautomers, racemates or prodrugs of the inventive compounds.

Diasteromeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods well known to those

skilled in the art, such as, for example, by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diasteromeric mixture by reaction with an appropriate optically active compound (e.g., chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereomers and converting (e.g., hydrolyzing) the individual diastereomers to the corresponding pure enantiomers. Also, some of the compounds of Formula (I) may be atropisomers (e.g., substituted biaryls) and are considered as part of this invention. Enantiomers can also be separated by use of chiral HPLC column.

The compounds of formula 1.0 form salts that are also within the scope of this invention. Reference to a compound of formula 1.0 herein is understood to include reference to salts thereof, unless otherwise indicated. The term "salt(s)", as employed herein, denotes acidic salts formed with inorganic and/or organic acids, as well as basic salts formed with inorganic and/or organic bases. In addition, when a compound of formula 1.0 contains both a basic moiety, such as, but not limited to a pyridine or imidazole, and an acidic moiety, such as, but not limited to a carboxylic acid, zwitterions ("inner salts") may be formed and are included within the term "salt(s)" as used herein. Pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable salts) are preferred. Salts of the compounds of the formula 1.0 may be formed, for example, by reacting a compound of formula 1.0 with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization. Acids (and bases) which are generally considered suitable for the formation of pharmaceutically useful salts from basic (or acidic) pharmaceutical compounds are discussed, for example, by S. Berge *et al*, *Journal of Pharmaceutical Sciences* (1977) 66(1) 1-19; P. Gould, *International J. of Pharmaceutics* (1986) 33 201-217; Anderson *et al*, *The Practice of Medicinal Chemistry* (1996), Academic Press, New York; in *The Orange Book* (Food & Drug Administration, Washington, D.C. on their website); and P. Heinrich Stahl, Camille G. Wermuth (Eds.), *Handbook of Pharmaceutical Salts: Properties, Selection, and Use*, (2002) Int'l. Union of Pure and Applied Chemistry, pp. 330-331. These disclosures are incorporated herein by reference thereto.

Exemplary acid addition salts include acetates, adipates, alginates, ascorbates, aspartates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, cyclopentanepropionates, digluconates, dodecylsulfates, ethanesulfonates, fumarates, glucoheptanoates, glycerophosphates,

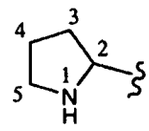
hemisulfates, heptanoates, hexanoates, hydrochlorides, hydrobromides, hydroiodides, 2-hydroxyethanesulfonates, lactates, maleates, methanesulfonates, methyl sulfates, 2-naphthalenesulfonates, nicotinates, nitrates, oxalates, pamoates, pectinates, persulfates, 3-phenylpropionates, phosphates, picrates, pivalates, propionates, salicylates, succinates, sulfates, sulfonates (such as those mentioned herein), tartarates, thiocyanates, toluenesulfonates (also known as tosylates,) undecanoates, and the like.

Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, aluminum salts, zinc salts, salts with organic bases (for example, organic amines) such as benzathines, diethylamine, dicyclohexylamines, hydrabamines (formed with N,N-bis(dehydroabietyl)ethylenediamine), N-methyl-D-glucamines, N-methyl-D-glucamides, t-butyl amines, piperazine, phenylcyclohexyl-amine, choline, tromethamine, and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quarternized with agents such as lower alkyl halides (e.g. methyl, ethyl, propyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g. dimethyl, diethyl, dibutyl, and diamyl sulfates), long chain halides (e.g. decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides), aralkyl halides (e.g. benzyl and phenethyl bromides), and others.

All such acid and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

Compounds of formula 1.0, and salts, solvates and prodrugs thereof, may exist in their tautomeric form (for example, as an amide or imino ether). All such tautomeric forms are contemplated herein as part of the present invention.

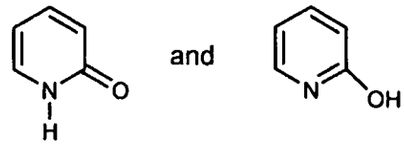
In hetero-atom containing ring systems of this invention, there are no hydroxyl groups on carbon atoms adjacent to a N, O or S, and there are no N or S groups on carbon adjacent to another heteroatom. Thus, for example, in the ring:



there is no -OH attached directly to carbons marked 2 and 5.

The compounds of formula 1.0 may exist in different tautomeric forms, and all such forms are embraced within the scope of the invention. Also, for example, all keto-enol and imine-enamine forms of the compounds are included in the invention.

Tautomeric forms such as, for example, the moieties:



are considered equivalent in certain embodiments of this invention.

The term "substituted" means that one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency under the existing circumstances is not exceeded, and that the substitution results in a stable compound. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. By "stable compound" or "stable structure" is meant a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

The term "optionally substituted" means optional substitution with the specified groups, radicals or moieties.

The term "purified", "in purified form" or "in isolated and purified form" for a compound refers to the physical state of said compound after being isolated from a synthetic process or natural source or combination thereof. Thus, the term "purified", "in purified form" or "in isolated and purified form" for a compound refers to the physical state of said compound after being obtained from a purification process or processes described herein or well known to the skilled artisan, in sufficient purity to be characterizable by standard analytical techniques described herein or well known to the skilled artisan.

When a functional group in a compound is termed "protected", this means that the group is in modified form to preclude undesired side reactions at the protected site when the compound is subjected to a reaction. Suitable protecting groups will be recognized by those with ordinary skill in the art as well as by reference to standard textbooks such as, for example, T. W. Greene *et al*, *Protective Groups in organic Synthesis* (1991), Wiley, New York.

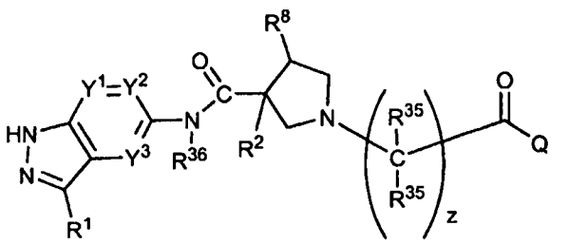
When any variable (e.g., aryl, heterocycle, R^3, etc.) occurs more than one time in any moiety or in any compound of formula 1.0, its definition on each occurrence is independent of its definition at every other occurrence.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

The present invention also embraces isotopically-labelled compounds of the present invention which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively.

Certain isotopically-labelled compounds of formula 1.0 (e.g., those labeled with ^{3}H and ^{14}C) are useful in compound and/or substrate tissue distribution assays. Tritiated (i.e., ^{3}H) and carbon-14 (i.e., ^{14}C) isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (i.e., ^{2}H) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased in vivo half-life or reduced dosage requirements) and hence may be preferred in some circumstances. Isotopically labelled compounds of formula 1.0 can generally be prepared by following procedures analogous to those disclosed in the Schemes and/or in the Examples hereinbelow, by substituting an appropriate isotopically labelled reagent for a non-isotopically labelled reagent.

This invention provides compounds of formula 1.0:



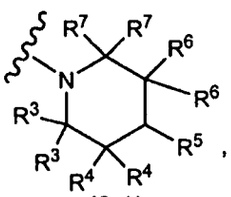
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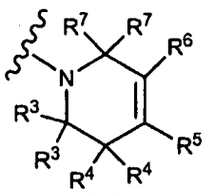
or the pharmaceutically acceptable salts, esters or solvates thereof, wherein:

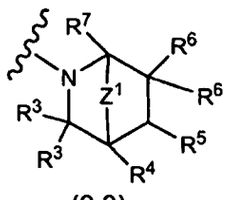
Y^1, Y^2, and Y^3 are each independently selected from the group consisting of: -CH=, -N= and $-CR^9=$ (preferably Y^1, Y^2, and Y^3 are each –CH=);

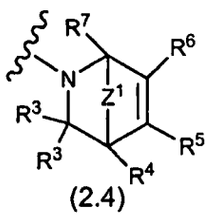
z is 1 to 3 (i.e., 1, 2 or 3, and preferably 1);

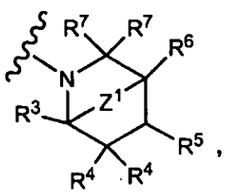
Q is a substituent selected from the group consisting of:

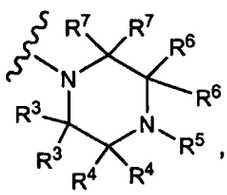

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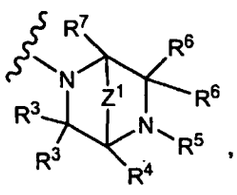

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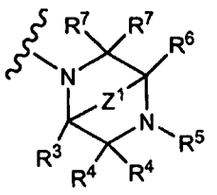

(2.3)

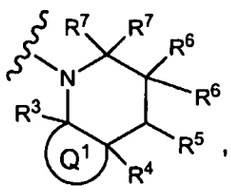

(2.4)

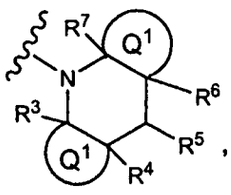

(2.5)

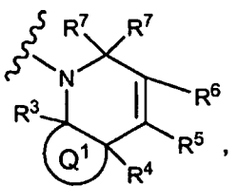

(2.6)

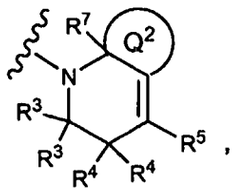

(2.7)

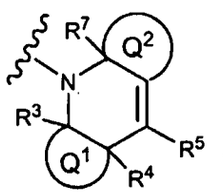

(2.8)

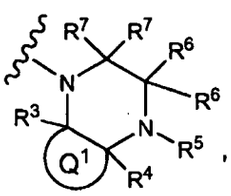

(2.9)

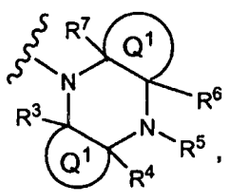

(2.10)

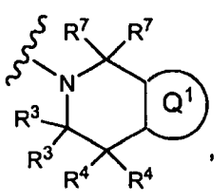

(2.11)

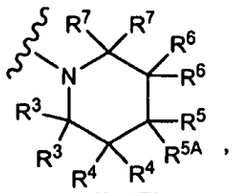

(2.12)

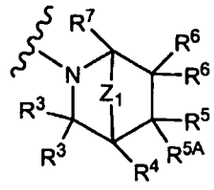

(2.13)

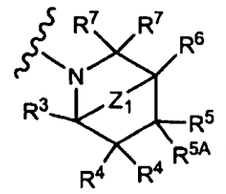

(2.14)

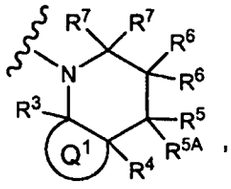

(2.15)

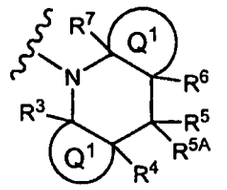

(2.16)

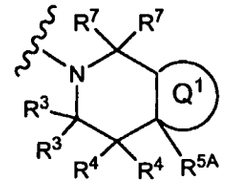

(2.17),


(2.18),


(2.19),


(2.20),


(2.21) and


(2.22);

Each Q^1 represents a ring independently selected from the group consisting of: cycloalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl, wherein said substituted rings are substituted with 1 to 3 substituents independently selected from the group consisting of: halo (e.g., Cl, F, Br) and the R^{10} moieties; provided that when Q^1 is aryl, heteroaryl, substituted aryl or substituted heteroaryl then the carbon atoms at the ring junction (i.e., the two carbon atoms common to the fused rings) are not substituted;

Q^2 represents a ring selected from the group consisting of: cycloalkyl, substituted cycloalkyl, heterocycloalkyl, and substituted heterocycloalkyl, wherein said substituted rings are substituted with 1 to 3 substituents independently selected from the group consisting of: the R^{10} moieties;

Z^1 represents $-(C(R^{24})_2)_w-$ wherein each R^{24} is independently selected from the group consisting of: H, alkyl (e.g., C_1 to C_6 alkyl, for example methyl) and F, and wherein w is 1, 2 or 3, and generally w is 1 or 2, and usually w is 1, and wherein in one example each R^{24} is H, and in another example w is 1, and in another example each R^{24} is H and w is 1, preferably w is 1 and each R^{24} is H (i.e., preferably Z^1 is $-CH_2-$);

Z^2 is selected from the group consisting of: $-N(R^{44})-$, -O- and $-C(R^{46})_2-$ (e.g., Z^2 is –NH-, -O- or $-CH_2-$);

m is 1 to 6;

n is 1 to 6;

p is 0 to 6;

t is 0, 1, or 2;

R^1 is selected from the group consisting of:

(1) -CN,

(2) $-NO_2$,

(3) $-OR^{10}$,

(4) $-SR^{10}$,

(5) $-N(R^{10})_2$,

(6) R^{10},

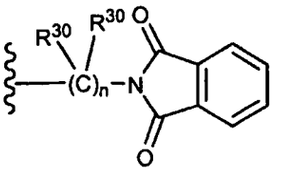
(7) $-C(O)R^{10}$ (in one example R^{10} is a 4 to 6 membered heterocycloalkyl ring, in another example R^{10} is a 4 to 6 membered heterocycloalkyl ring comprising one nitrogen atom, and in another example R^{10} is a 4 to 6 membered heterocycloalkyl ring comprising one nitrogen atom wherein said ring is bound to the carbonyl moiety (-C(O)-) through the ring nitrogen),

(8) $-(C(R^{30})_2)_n-NR^{32}-C(O)-R^{10}$ (e.g., $-(CH_2)_n-NH-C(O)-R^{10}$, for example wherein n is 1), wherein in one example n is 1, each R^{30} is H, R^{32} is H, and R^{10} is selected from the group consisting of: cycloalkyl (e.g., cyclopropyl) and alkyl (e.g., methyl and i-propyl), and wherein in another example n is 1, each R^{30} is H, R^{32} is H, and R^{10} is selected from the group consisting of: methyl, i-propyl and cyclopropyl,

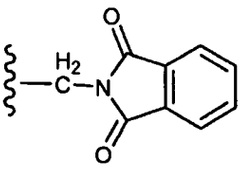
(9) $-(C(R^{30})_2)_n-NR^{32}-S(O)_t-R^{10}$ (e.g., $-(CH_2)_n-NH-S(O)_t-R^{10}$, for example wherein n is 1 and t is 2) wherein in one example n is 1, each R^{30} is H, R^{32} is H, t is 2, and R^{10} is selected from the group consisting of: cycloalkyl (e.g., cyclopropyl) and alkyl (e.g., methyl and i-propyl), and wherein in another example n is 1, each R^{30} is H, R^{32} is H, t is 2, R^{10} is selected from the group consisting of: methyl, i-propyl and cyclopropyl, and wherein in another example n is 1, each R^{30} is H, R^{32} is H, t is 2, and R^{10} is methyl,

(10) $-(C(R^{30})_2)_n-NR^{32}-C(O)-N(R^{32})-R^{10}$ (e.g., $-(CH_2)_n-NH-C(O)-NH-R^{10}$, for example wherein n is 1) wherein in one example n is 1, each R^{30} is H, each R^{32} is H, and R^{10} is alkyl (e.g., methyl and i-propyl), and wherein in another example n is 1, each R^{30} is H, each R^{32} is H, and R^{10} is selected from the group consisting of: methyl and i-propyl,

(11)



wherein in one example n is 1 and each R^{30} is H, i.e., a moiety of the formula:



(12) $-CF_3$,

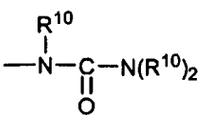
(13) $-C(O)OR^{10}$ wherein in one example R^{10} is selected from the group consisting of: H, alkyl (e.g., methyl and ispropyl) and cyclopropyl (e.g., cyclopropyl), and wherein in another example R^{10} is selected from the group consisting of: H and alkyl, and wherein in another example R^{10} is selected from the group consiting of: H and methyl,

(14) $-(C(R^{30})_2)_nR^{13}$ (e.g., $-(CH_2)_nR^{13}$) wherein in one example n is 1, each R^{30} is H, and R^{13} is selected from the group consisting of: -OH and $-N(R^{10})_2$, wherein each R^{10} is independently selected, and wherein in another example n is 1, each R^{30} is H, and R^{13} is selected from the group consisting of: -OH and $-N(R^{10})_2$, and each R^{10} is H (i.e., R^{13} is -OH or $-NH_2$),

(15) alkenyl (e.g., $-CH=CHCH_3$),

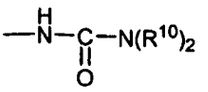
(16) $-NR^{32}-C(O)-R^{14}$ (e.g., $-NH-C(O)-R^{14}$) wherein in one example R^{32} is H and R^{14} is selected from the group consisting of: cycloalkyl (e.g., cyclopropyl), alkyl (e.g., methyl and propyl), aryl (e.g., phenyl), amino (i.e., $-NH_2$), and heteroaryl (e.g., pyridyl, such as, for example 2- pyridyl, 3-pyridyl, 4-pyridyl, pyrazolyl and imidazolyl), and wherein in another example R^{32} is H and R^{14} is selected from the group consisting of: cyclopropyl, methyl, propyl, phenyl, and amino,

(17)



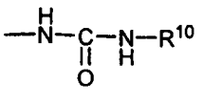
wherein each R^{10} is independently selected, for example:

(a) in one example moiety (17) is:



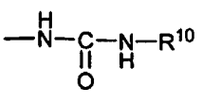
wherein each R^{10} is independently selected,

(b) in another example moiety (17) is:



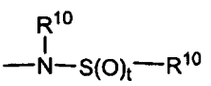
, and

(c) in another example moiety (17) is:



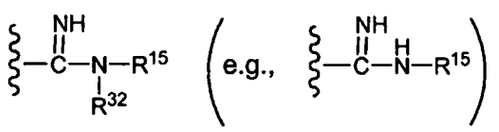
wherein R^{10} is selected from the group consisting of: aryl (e.g., phenyl) and alkyl (e.g., ethyl, and preferably R^{10} is phenyl or ethyl,

(18)



wherein each R^{10} is independently selected, and wherein in one example each R^{10} is independently selected and t is 2, and wherein in another example moiety (18) is $-NH-S(O)_t-R^{10}$, and wherein in another example moiety (18) is $-NH-S(O)_t-R^{10}$ wherein t is 2, and wherein in another example moiety (18) is $-NH-S(O)_t-R^{10}$. t is 2, and R^{10} is alkyl (e.g., methyl),

(19)



(also written as $-C(NH)N(R^{15})R^{32}$ and $-C(NH)NH(R^{15})$, respectively), wherein in one example R^{15} is –OH, and in another example R^{32} is H and R^{15} is –OH,

(20) $-C(O)-NR^{32}-(C(R^{30})_2)_p-OR^{10}$ (e.g., $-C(O)-NH-(CH_2)_p-OR^{10}$, and, for example, $-C(O)-NH-(CH_2)_p-OR^{10}$ wherein p is 2) wherein:

(a) in one example p is 2,

(b) in another example R^{32} is H,

(c) in another example R^{10} is selected from the group consisting of: H and alkyl (e.g., methyl),

(d) in another example R^{10} is selected from the group consisting of: H and alkyl (e.g., methyl), and R^{32} is H,

(e) in another example R^{10} is selected from the group consisting of: H and alkyl (e.g., methyl), R^{32} is H, an p is 2,

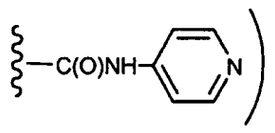
(f) in another example R^{32} is H, each R^{30} is H, and R^{10} is alkyl,

(g) in another example R^{32} is H, each R^{30} is H, and R^{10} is methyl,

(h) in another example R^{32} is H, each R^{30} is H, p is 2 and R^{10} is alkyl, and

(i) in another example R^{32} is H, each R^{30} is H, p is 2 and R^{10} is methyl,

(21) $-C(O)N(R^{10})_2$ wherein each R^{10} is independently selected, and preferably each R^{10} is independently selected from the group consisting of: (a) H, (b) alkyl (e.g., methyl, butyl, and i-propyl), (c) heteroaryl (e.g., pyridyl), (d) aryl (e.g., phenyl), and (e) cycloalkyl (e.g., cyclopropyl), wherein for example, each R^{10} is selected from the group consisting of: H, methyl, butyl, i-propyl, pyridyl, phenyl and cyclopropyl, wherein, for example, said $-C(O)N(R^{10})_2$ moiety is selected from the group consisting of: $-C(O)NH_2$, $-C(O)NH(CH_3)$, $-C(O)NH(CH)(CH_3)_2$ (i.e., -C(O)NH(i-propyl)), $-C(O)NH(C_4H_9)$, $-C(O)NH(C_6H_5)$ (i.e., -C(O)NH(phenyl)), $-C(O)NH(C_3H_5)$ (i.e., -C(O)NH(cyclopropyl), and $-C(O)NH(C_5H_4N)$ (i.e., -C(O)NH(pyridyl), such as



(22) $-C(O)-NR^{32}-C(R^{18})_3$ (e.g., $-C(O)-NH-C(R^{18})_3$) wherein each R^{18} is independently selected from the group consisting of: R^{10} and $-C(O)OR^{19}$, and R^{19} is selected from the group consisting of:alkyl (e.g., methyl) and substituted arylalkyl (e.g., $-CH_2C_6H_4OH$ (i.e.,hydroxybenzyl) such as, for example, $-p-CH_2C_6H_4OH$ (i.e., p-OHbenzyl), and wherein:

(a) in one example R^{18} and R^{19} are as defined above with the proviso that at least one R^{18} substitutent is other than H (e.g., in one example one R^{18} is H and the remaining two R^{18} groups are other than H, and in another example two R^{18} substituents are H and the remaining R^{18} substituent is other than H),

(b) in another example R^{18} is selected from the group consisting of: H, aryl (e.g., phenyl), substituted aryl (e.g., substituted phenyl, such as, for example halophenyl-, such as, for example, flurophenyl (e.g., o-F-phenyl)), and $-C(O)OR^{19}$,

(c) in another example R^{18} is selected from the group consisting of: H, phenyl, flurophenyl (e.g., o-F-phenyl), $-C(O)OCH_3$, $-C(O)OCH_2C_6H_4OH$ (i.e., -C(O)O(OHbenzyl), such as, -C(O)O(p-OHbenzyl)),

(d) in another example R^{18} is selected from the group consisting of: H, aryl (e.g., phenyl), substituted aryl (e.g., substituted phenyl, such as, for example halophenyl-, such as, for example, flurophenyl (e.g., o-F-phenyl)), and $-C(O)OR^{19}$, provided that at least one R^{18} substitutent is other than H (e.g., in one example one R^{18} is H and the remaining two R^{18} groups are other than H, and in another example two R^{18} substituents are H and the remaining R^{18} substituent is other than H),

(e) in another example R^{18} is selected from the group consisting of: H, phenyl, flurophenyl (e.g., o-F-phenyl), $-C(O)OCH_3$, $-C(O)OCH_2C_6H_4OH$ (i.e., -C(O)O(OHbenzyl), such as, -C(O)O(p-OHbenzyl)), provided that at least one R^{18} substitutent is other than H (e.g., in one example one R^{18} is H and the remaining two R^{18} groups are other than H, and in another example two R^{18} substituents are H and the remaining R^{18} substituent is other than H),

(f) in another example R^{32} is H, and each R^{18} is independently selected from the group consisting of: R^{10} and $-C(O)OR^{19}$, and R^{19} is selected from the group consisting of:alkyl (e.g., methyl) and substituted arylalkyl (e.g., $-CH_2C_6H_4OH$ (i.e.,hydroxybenzyl) such as, for example, $-p-CH_2C_6H_4OH$ (i.e., p-OHbenzyl),

(g) in another example R^{32} is H and R^{18} and R^{19} are as defined in paragraph (a),

(h) in another example R^{32} is H and R^{18} and R^{19} are as defined in paragraph (b),

(i) in another example R^{32} is H and R^{18} and R^{19} are as defined in paragraph (c),

(j) in another example R^{32} is H and R^{18} and R^{19} are as defined in paragraph (d),

(k) in another example R^{32} is H and R^{18} and R^{19} are as defined in paragraph (e), and

(l) in another example R^{32} is H and R^{18} and R^{19} are as defined in paragraph (f),

(23) $-C(O)-NR^{32}-(C(R^{30})_2)_n-C(O)-N(R^{10})_2$ (e.g., $-C(O)-NH-(CH_2)_n-C(O)-NH_2$), and wherein:

in one example R^{32} is H,

in another example each R^{30} is H,

in another example n is 1,

in another example n is 1 and R^{32} is H,

in another example each R^{10} is H,

in another example R^{32} is H and each R^{30} is H,

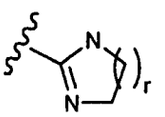
in another example R^{32} is H, each R^{30} is H and n is 1,

in another example R^{32} is H, each R^{30} is H, n is 1, and each R^{10} is H,

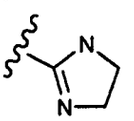
in another example R^{32} is H, n is 1, each R^{30} is independently selected from the group consisting of: H and alkyl, and each R^{10} is independently selected from the group consisting of: H and alkyl, and

in another example R^{32} is H, n is 1, and each R^{30} is independently selected from the group consisting of: H, methyl, ethyl and i-propyl (or each R^{30} is independently selected from the group consisting of H and i-propyl, or one R^{30} is i-propyl and the other R^{30} is H), and each R^{10} is independently selected from the group consisting of: H methyl, ethyl and i-propyl (or each R^{10} is H),

(24) heterocycloalkenyl, such as, for example:

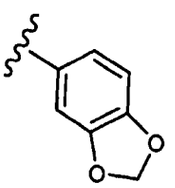


wherein r is 1 to 3, and wherein in one example r is 1, i.e., in one example the heterocycloalkenyl is dihydroimidazolyl, such as, for example:



,

(25)



, and

(26) arylalkenyl- (aralkenyl-), for example, aryl(C_2 to C_6)alkenyl-, such as for example, -CH=CH-phenyl;

R^2 is selected from the group consisting of:

(1) H,

(2) -CN,

(3) halo (e.g., F),

(4) alkyl (e.g., C_1 to C_6 alkyl, such as, for example, methyl, ethyl and propyl),

(5) substituted alkyl (e.g., substituted C_1 to C_6 alkyl, such as, for example, substituted methyl and substituted ethyl) wherein said substituted alkyl is substituted with 1 to 3 substitutents (e.g., 1 substituent) selected from the group consisting of: (a) -OH, (b) -O-alkyl (e.g., -O-(C_1-C_3alkyl), such as, for example, $-OCH_3$), (c) -O-alkyl (e.g., -O-(C_1-C_3alkyl)) substituted with 1 to 3 F atoms (examples of said –O-substituted alkyl portion include, but are not limited to, $-OCHF_2$ and $-OCF_3$), and (d) $-N(R^{40})_2$ wherein each R^{40} is independently selected from the group consisting of: (i) H, (ii) C_1-C_3 alkyl (e.g., methyl), (iii) $-CF_3$, and (e) halo (for example F, Cl, and Br, and also for example F, examples of a halo substituted alky group include, but are not limited to, $-CHF_2$), (examples of said substituted alkyl groups described in (5) include but are not limited to $-CH(OH)CH_3$, $-CH_2OH$, and $-CH_2OCH_3$),

(6) alkynyl (e.g., ethynyl),

(7) alkenyl (e.g., $-CH_2-CH=CH_2$),

(8) $-(CH_2)_mR^{11}$,

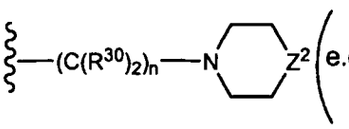
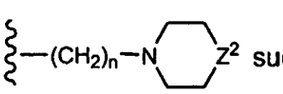
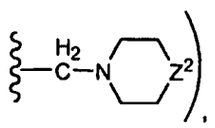
(9) $-N(R^{26})_2$,

(10) $-OR^{23}$ (e.g., -OH, $-OCH_3$ and –O-phenyl),

(11) $-N(R^{26})C(O)R^{42}$ wherein in one example R^{26} is H or C_1 to C_6 alkyl (e.g., methyl) and R^{42} is alkyl (e.g., methyl), and in another example $-N(R^{26})C(O)R^{42}$ is $-NHC(O)CH_3$,

(12) cycloalkyl (e.g., C_3 to C_6 cycloalkyl, such as, for example, cyclopropyl and cyclohexyl),

(13) cycloalkylalkyl (e.g., C_3 to C_6 cycloalkyl-(C_1 to C_3)alkyl-, such as, for example, cyclopropyl-CH_2- and cyclohexyl-CH_2-),

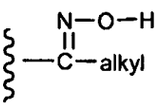
(14)  (e.g.,  such as ),

(15) –O-(substituted alkyl) wherein said substituted alkyl is substituted with 1 to 3 F atoms (examples of said –O-(substituted alkyl) moiety include, but are not limited to, $-OCHF_2$ and $-OCF_3$),

(16) $-S(O)_t$-alkyl, such as, for example, (a) -S-alkyl (i.e., t is 0) such as, for example, $-S-CH_3$, and (b) $-S(O)_2$-alkyl (i.e., t is 2) such as, for example, $-S(O)_2CH_3$,

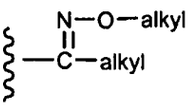
(17) –C(O)-alkyl (e.g., $-C(O)CH_3$),

(18)

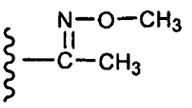


wherein methyl is an example of said alkyl moiety,

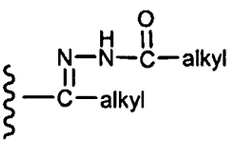
(19)



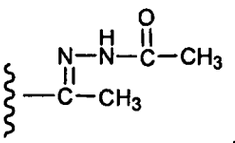
wherein each alkyl is independently selected, examples of this moiety include, but are not limited to:



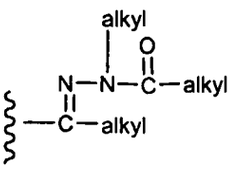
(20)



which each alkyl is independently selected, examples of this moiety include, but are not limited to,



(21)



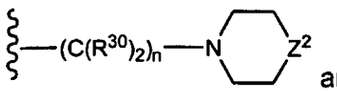
wherein each alkyl is independently selected,

(22) $-N(R^{48})-C(O)-R^{48}$ wherein each R^{48} is independently selected from the group consisting of: H and alkyl (e.g., C_1 to C_6 alkyl, such as, for example, methyl), and wherein examples of this moiety include, but are not limited to, -NH-C(O)-H, and $-N(CH_3)-C(O)H$, and

(23) $-C(O)$-alkyl, such as, for example, $-C(O)-(C_1-C_6$ alkyl), such as, for example, $-C(O)CH_3$; and

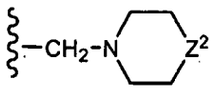
wherein:

(a) in one example said (14) moiety is



and n is 1,

(b) in another example said (14) moiety is



(i.e., n is 1, and each R^{30} is H),

(c) in another example Z^2 is –NH- in (a),

(d) in another example Z^2 is –NH- in (b),

(e) in another example Z^2 is –O- in (a),

(f) in another example Z^2 is –O- in (b),

(g) in another example Z^2 is $-CH_2-$ in (a),

(h) in another example Z^2 is $-CH_2-$ in (b),

(i) in another example R^2 is $-(CH_2)_mR^{11}$ and m is 1,

(j) in another example R^2 is $-N(R^{26})_2$,

(k) in another example R^2 is $-N(R^{26})_2$, and each R^{26} is H (i.e., R^2 is $-NH_2$),

(l) in another example R^2 is $-OR^{23}$, and

(m) in another example R^2 is –OH (i.e., R^{23} is H);

each R^3, R^4, R^5, R^6 and R^7 is independently selected from the group consisting of:

(1) H,

(2) alkenyl (e.g., $-CH_2CH=CH_2$),

(3) substituted alkenyl,

(4) alkyl,

(5) substituted alkyl,

(6) cycloalkyl,

(7) substituted cycloalkyl,

(8) cycloalkylalkyl-,

(9) substituted cycloalkylalkyl-,

(10) heterocycloalkyl,

(11) substituted heterocycloalkyl,

(12) heterocycloalkylalkyl-,

(13) substituted heterocycloalkylalkyl-,

(14) $-C(O)R^{10}$ wherein in one example R^{10} is selected from the group consisting of: alkyl (e.g., C_1 to C_6, e.g., methyl),

(15) arylheteroaryl- (e.g., phenylthiadiazolyl-),

(16) substituted arylheteroaryl- (e.g., substituted phenylthiadiazolyl-),

(17) heteroarylaryl-, such as, for example, pyrimidinylphenyl-, pyrazinylphenyl-, pyridinylphenyl- (i.e., pyridylphenyl-), furanylphenyl-, thienylphenyl-, thiazolylphenyl-, oxadiazolylphenyl-, and pyridazinylphenyl-,

(18) substituted heteroarylaryl-, such as, for example, substituted pyrimidinylphenyl-, substituted pyrazinylphenyl-, substituted pyridinylphenyl- (i.e., substituted pyridylphenyl-), substituted furanylphenyl-, substituted thienylphenyl-, substituted thiazolylphenyl-, substituted pyrimidinylphenyl, substituted oxadiazolylphenyl-, and substituted pyridazinylphenyl-,

(19) aryl (e.g., phenyl),

(20) substituted aryl (e.g., substituted phenyl),

(21) heteroaryl (e.g., thiazolyl, thienyl, pyridyl, and pyrimidinyl),

(22) substituted heteroaryl (e.g., substituted thiazolyl, substituted pyridyl and substituted pyrimidinyl), examples of substituted heteroaryl groups include, for example bromothiazolyl-, bromopyrimidinyl-, fluoropyrimidinyl-, and ethenylpyrimidinyl-,

(23) heteroarylheteroaryl- (e.g., pyrimidinylpyridyl-, pyrimidinylthiazolyl-, and pyrimidinylpyrazinyl-),

(24) substituted heteroarylheteroaryl- (e.g., substituted pyrimidinylpyridyl-, and substituted pyrimidinylpyrazinyl-),

(25) arylaminoheteroaryl- (e.g., phenyl-NH-oxadiazolyl-),

(26) substituted arylaminoheteroaryl- (e.g., substituted phenyl-NH-oxadiazolyl-),

(27) arylalkynyl- (e.g., aryl(C_2 to C_4)alkynyl such as, for example phenylethynyl-),

(28) substituted arylalkynyl- (e.g., substituted aryl(C_2 to C_4)alkynyl-, such as, for example, substituted phenylethynyl-),

(29) heteroarylalkynyl- (e.g., heteroaryl(C_2 to C_4)alkynyl-, such as, for example, pyrimidinylethynyl-),

(30) substituted heteroarylalkynyl- (e.g., substituted heteroaryl(C_2 to C_4)alkynyl-, such as, for example substituted pyrimidinylethynyl-),

(31) benzoheteroaryl (i.e., a fused phenyl and heteroaryl rings), such as, for example, benzothiazole and quinoxaline;

wherein said R^3, R^4, R^5, R^6 and R^7 substituted groups (7), (9), (11), (13), (16), (18), (20), (22), (24), (26), (28) and (30) are substituted with 1 to 3 substituents independently selected from the group consisting of: $-NH_2$, $-NHR^{20}$ (e.g., $-NHCH_2CH_3$ and $-NHCH_3$), $-N(R^{20})_2$ wherein each R^{20} is independently selected, alkyl (e.g., C_1 to C_6 alkyl, e.g., methyl, ethyl, and i-propyl), alkenyl (e.g., C_2 to C_6 alkenyl, such as, for example $-CH=CH_2$), halo (e.g., F, Cl and Br, and in another example F), $-C(O)-NH-R^{28}$ (e.g., $-C(O)-NH-CH_3$), $-C(O)OR^{28}$ (e.g., $-C(O)OC_2H_5$), $-C(O)R^{28}$ (e.g., $-C(O)CH_3$), and $-OR^{20}$ (e.g., $-OCH_3$),

wherein said R^3, R^4, R^5, R^6 and R^7 substituted groups (3) and (5) are substituted with 1 to 3 substituents independently selected from the group consisting of: $-NH_2$, halo (e.g., F, Cl and Br, and in another example F), $-C(O)-NH-R^{28}$ (e.g., $-C(O)-NH-CH_3$), $-C(O)OR^{28}$ (e.g., $-C(O)OC_2H_5$), and $-C(O)R^{28}$ (e.g., $-C(O)CH_3$), and

wherein:

in one example said substituted heteroarylaryl (moiety (18) above) is substituted with 1 to 3 substituents independently selected from the group consisting of: $-NH_2$, alkyl (e.g., C_1 to C_6 alkyl, e.g., methyl), halo (e.g., F, Cl and Br, such as, for example F),

in another example said substituted aryl (moiety (20) above) is substituted with 1 to 3 substituents independently selected from the group consisting of halo (e.g., F, Cl and Br), $-C(O)-NH-R^{28}$ (e.g., $-C(O)-NH-CH_3$), $-C(O)OR^{28}$ (e.g., $-C(O)O-C_2H_5$), and $-C(O)R^{28}$ (e.g., $-C(O)CH_3$), and

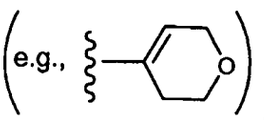
in another example said substituted heteroaryl (moiety (22) above) is substituted with 1 to 3 substitutents selected from the group consisting of: halo (e.g., Br, F, and Cl), alkenyl (e.g., C_2 to C_6 alkenyl, such as, for example, $-CH=CH_2$);

R^{5A} is selected from the group consisting of: halo (for example, F, Cl, and Br, and in another example F), -OH, alkyl (e.g., C_1 to C_6 alkyl, such as, for example, $-CH_3$), –O-alkyl (such as, for example, -O-(C_1 to C_6 alkyl), also, for example, -O-(C_1 to C_3 alkyl), also for example, -O-(C_1 to C_2 alkyl), and in one example $-O-CH_3$);

R^8 is selected from the group consisting of: H, -OH, $-N(R^{10})_2$ (e.g., $-NH_2$), $-NR^{10}C(O)R^{12}$ (e.g., $-NHC(O)CH_3$), and alkyl (e.g., methyl);

each R^9 is independently selected from the group consisting of:halogen, -CN, $-NO_2$, $-OR^{10}$, $-SR^{10}$, $-N(R^{10})_2$, and R^{10};

each R^{10} is independently selected from the group consisting of: H, alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, alkylheteroaryl-, alkylaryl-, substituted alkyl, substituted aryl, substituted arylalkyl, substituted heteroaryl, substituted heteroarylalkyl, substituted cycloalkyl, substituted cycloalkylalkyl, substituted heterocycloalkyl, substituted heterocycloalkylalkyl, substituted alkylheteroaryl-, substituted alkylaryl-, heterocycloalkenyl

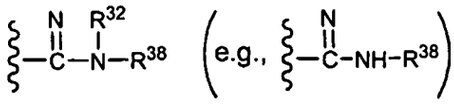


and substituted heterocycloalkenyl, and wherein:

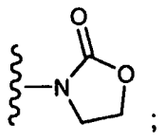
said R^{10} substituted alkyl is substituted with 1 to 3 substituents independently selected from the group consisting of: $-NH_2$, $-NHR^{20}$, $-NO_2$, -CN, $-OR^{26}$, halo (e.g., F, Cl and Br, and in another example F), -C(O)-NH-R^{26} (e.g., -C(O)-NH-CH_3, i.e., R^{26} is alkyl, such as methyl), $-C(O)OR^{26}$ (e.g., $-C(O)OC_2H_5$, i.e., R^{26} is alkyl, such as ethyl), and $-C(O)R^{26}$ (e.g., $-C(O)CH_3$, i.e., R^{26} is alkyl, such as methyl), and

said R^{10} substituted aryl, substituted arylalkyl, substituted heteroaryl, substituted heteroarylalkyl, substituted cycloalkyl, substituted cycloalkylalkyl, substituted heterocycloalkyl, substituted heterocycloalkylalkyl, substituted alkylheteroaryl- and substituted alkylaryl- are substituted with 1 to 3 substituents independently selected from the group consisting of: (1) $-NH_2$, (2) $-NO_2$, (3) -CN, (4) -OH, (5) $-OR^{20}$, (6) $-OCF_3$, (7) alkyl (e.g., C_1 to C_6 alkyl) substituted with 1 to 3 independently selected halo atoms (e.g., F, Cl and Br), examples of the substituted alkyl include, but are not limited to, $-CF_3$, $-CHF_2$ and–CH_2F, (8) $-C(O)R^{38}$ (e.g., R^{38} is H or alkyl (e.g., C_1 to C_6 alkyl, such as, for example, methyl or ethyl), for example, R^{38} is alkyl (e.g., methyl), thus, an example of $-C(O)R^{38}$ is $-C(O)CH_3$), (9) alkyl (e.g., C_1 to

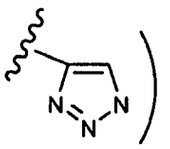
C_6 alkyl, e.g., methyl, ethyl, and i-propyl), (10) alkenyl (e.g., C_2 to C_6 alkenyl, such as, for example -CH=CH_2), (11) halo (e.g., F, Cl and Br, and in another example F), (12) -C(O)-NH-R^{26} (e.g., -C(O)-NH-CH_3), (13) -C(O)OR^{38} (e.g., R^{38} is H or alkyl (e.g., C_1 to C_6 alkyl, such as, for example, methyl or ethyl), for example, R^{38} is alkyl (e.g., methyl or ethyl), thus, for example, -C(O)OR^{38} is -C(O)OC_2H_5), (14) -C(O)-NR^{32}-$(C(R^{30})_2)_n$-$N(R^{38})_2$ (e.g., -C(O)-NH-$(CH_2)_n$-$N(R^{38})_2$) (wherein (a) in one example R^{32} is H, (b) in another example each R^{30} is H, (c) in another example n is 2, (d) in another example each R^{38} is independently selected, (e) in another example each R^{38} is independently selected from the group consisting of: H and alkyl (e.g., methyl), (f) in another example R^{32} is H, each R^{30} is H, and each R^{38} is independently selected, (g) in another example R^{32} is H, each R^{30} is H, and each R^{38} is independently selected from the group consisting of: H and alkyl (e.g., methyl), (15) -$S(O)_tR^{38}$ (wherein in one example t is 2, and in another example R^{38} is alkyl (e.g., methyl or isopropyl), and in another example t is 2 and R^{38} is alkyl (e.g., methyl or isopropyl)), (16) -C(O)-NR^{32}-R^{38} (e.g., -C(O)-NR^{32}-R^{38}) (wherein one example R^{32} is H, in another example R^{38} is alkyl (e.g., propyl), and in another example R^{32} is H and R^{38} is alkyl (e.g., propyl)), (17) -NR^{32}-C(O)-R^{38} (e.g., -NH-C(O)-R^{38}) (wherein in one example R^{32} is H, in another example R^{38} is alkyl (e.g., methyl), and in another example R^{32} is H and R^{38} is alkyl (e.g., methyl)),

(18)  (e.g.,)

(wherein in one example R^{32} is H, in another example R^{38} is H, and in another example R^{32} is H and R^{38} is H), (19) –NHR^{20} (e.g., -$NHCH_3$, -NHC_2H_5), (20) cycloalkyl (e.g., C_3 to C_6 cycloalkyl, such as, for example, cyclopropyl), (21) –O-alkyl-O-R^{20} (e.g., -O-(C_1 to C_6)alkyl-OR^{20}, such as, for example, -O-CH_2CH_2-OCH_3), (22) hydroxyalkyl (e.g., hydroxy(C_1 to C_6)alkyl, such as, for example, -CH_2OH and –$C(CH_3)_2OH$), (23) –$N(R^{20})_2$ wherein each R^{20} is independently selected (e.g., -$N(CH_3)_2$), (24) –alkyl-OR^{20} (e.g., -(C_1 to C_6)alkyl-OR^{20}, such as, for example, -CH_2OCH_3), (25) –O-alkyl-OH (e.g., -O-(C_1 to C_6)alkyl-OH, such as, for example, -O-CH_2-CH_2-OH), (26) –NH(hydroxyalkyl) (e.g., -NH(hydroxy(C_1 to C_6)alkyl, such as, for example, -$NH(CH_2CH_2OH)$), and (27) oxazolidinone, such as, for example,



R^{11} is selected from the group consisting of: F, -OH, -CN, -OR^{10}, -$NHNR^1R^{10}$, -SR^{10} and heteroaryl (e.g., triazolyl, such as, for example,



;

R^{12} is selected from the group consisting of: alkyl, aryl, heteroaryl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl and heterocycloalkylalkyl;

R^{14} is selected from the group consisting of: alkyl, aryl, heteroaryl, cycloalkyl, cycloalkylalkyl-, heterocycloalkyl, alkylheterocycloalkyl, heterocycloalkylalkyl-, alkylheteroaryl- and alkylaryl-;

R^{15} is selected from the group consisting of: H, -OH, alkyl, aryl, heteroaryl, cycloalkyl, cycloalkylalkyl-, heterocycloalkyl and heterocycloalkylalkyl-, alkylheteroaryl- and alkylaryl-;

R^{20} represents alkyl (e.g., C_1 to C_6 alkyl, such as, for example, methyl, ethyl or isopropyl);

R^{23} is selected from the group consisting of: H, alkyl (e.g., C_1 to C_6 alkyl, such as, for example, methyl and i-propyl), aryl (e.g., phenyl), cycloalkyl (e.g., C_3 to C_6 cycloalkyl, such as, for example, cyclopropyl and cyclohexyl), and cycloalkylalkyl- (e.g., C_3 to C_6 cycloalkylalkyl-, such as -$(CH_2)_n$-cycloalkyl, such as -$(CH_2)_n$-(C_3 to C_6)cycloalkyl, wherein each H of each –$(CH_2)_n$- moiety can independently be substituted with an alkyl group (e.g., C_1 to C_6 alkyl, such as, for example, methyl), and wherein in one example n is 1 and the –CH_2- moiety is not substituted, that is, -CH_2-cycloalkyl, such as, -CH_2-cyclopropyl, is an example of said cycloalkylalkyl- moiety);

each R^{26} is independently selected from the group consisting of: H and alkyl (e.g., C_1 to C_6 alkyl, such as, for example, methyl and ethyl);

R^{28} is alkyl (e.g., C_1 to C_6 alkyl, such as, for example, methyl or ethyl);

each R^{30} is independently selected from the group consisting of: H, alkyl (e.g., C_1 to C_6 alkyl, such as, for example methyl, ethyl and i-propyl), and F, and wherein in one example each R^{30} is H;

each R^{32} is independently selected from the group consisting of: H and alkyl (e.g., C_1 to C_6 alkyl, such as, for example methyl, ethyl and propyl), and wherein each R^{32} is generally H;

each R^{35} is independently selected from the group consisting of: H and C_1 to C_6 alkyl (e.g., methyl, ethyl, i-propyl, and propyl), and wherein in one example both R^{35} substitutents are the same or different alkyl groups (e.g., both R^{35} groups are the same alkyl group, such as methyl), and in another example one R^{35} group is H and the other R^{35} group is alkyl, such as methyl), and in another example each R^{35} is preferably H;

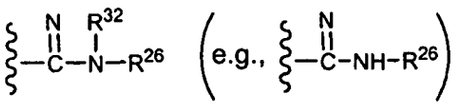
R^{36} is selected from the group consisting of: H, alkyl (e.g., C_1 to C_6 alkyl, such as, for example, methyl, ethyl and propyl), and –O-alkyl (e.g., -O-(C_1 to C_6) alkyl, such as, for example, -O-(C_1 to C_2) alkyl, such as, for example, $-OCH_3$), and preferably R^{36} is selected from the group consisting of H and methyl, and more preferably R^{36} is H;

each R^{38} is independently selected from the group consisting of: H, alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, alkylheteroaryl-, alkylaryl-, substituted alkyl, substituted aryl, substituted arylalkyl, substituted heteroaryl, substituted heteroarylalkyl, substituted cycloalkyl, substituted cycloalkylalkyl, substituted heterocycloalkyl, substituted heterocycloalkylalkyl, substituted alkylheteroaryl- and substituted alkylaryl-, and wherein:

said R^{38} substituted alkyl is substituted with 1 to 3 substituents independently selected from the group consisting of: $-NH_2$, $-NO_2$, -CN, $-OR^{26}$, halo (e.g., F, Cl and Br, and in another example F), -C(O)-NH-R^{28} (e.g., -C(O)-NH-CH_3), $-C(O)OR^{28}$ (e.g., $-C(O)OC_2H_5$), and $-C(O)R^{28}$ (e.g., $-C(O)CH_3$), and

said R^{38} substituted aryl, substituted arylalkyl, substituted heteroaryl, substituted heteroarylalkyl, substituted cycloalkyl, substituted cycloalkylalkyl, substituted heterocycloalkyl, substituted heterocycloalkylalkyl, substituted alkylheteroaryl- and substituted alkylaryl- are substituted with 1 to 3 substituents independently selected from the group consisting of: (1) $-NH_2$, (2) $-NO_2$, (3) -CN, (4) -OH, (5) $-OR^{20}$, (6) $-OCF_3$, (7) $-CF_3$, (8) $-C(O)R^{26}$ (e.g., R^{26} is H or C_1 to C_6 alkyl, such as, for example, methyl or ethyl, for example, R^{26} is alkyl (e.g., methyl), thus, an example of $-C(O)R^{26}$ is $–C(O)CH_3$), (9) alkyl (e.g., C_1 to C_6 alkyl, e.g., methyl, ethyl, and i-propyl), (10) alkenyl (e.g., C_2 to C_6 alkenyl, such as, for example $-CH=CH_2$), (11) halo (e.g., F, Cl and Br, and in another example F), (12) -C(O)-NH-R^{26} (e.g.,

$-C(O)-NH-CH_3$), (13) $-C(O)OR^{26}$ (e.g., R^{26} is H or e.g., C_1 to C_6 alkyl, such as, for example, methyl or ethyl, for example, R^{26} is alkyl (e.g., methyl or ethyl), thus, for example, $-C(O)OR^{26}$ is $-C(O)OC_2H_5$), (14) $-C(O)-NR^{32}-(C(R^{30})_2)_n-N(R^{26})_2$ (e.g., $-C(O)-NH-(CH_2)_n-N(R^{26})_2$) (wherein (a) in one example R^{32} is H, (b) in another example each R^{30} is H, (c) in another example n is 2, (d) in another example each R^{26} is independently selected, (e) in another example each R^{26} is independently selected from the group consisting of: H and methyl), (f) in another example R^{32} is H, each R^{30} is H, and each R^{26} is independently selected, (g) in another example R^{32} is H, each R^{30} is H, and each R^{26} is independently selected from the group consisting of: H and methyl), (15) $-S(O)_tR^{26}$ (wherein in one example t is 2, and in another example R^{26} is methyl, and in another example t is 2 and R^{26} is methyl), (16) $-C(O)N(R^{32})(R^{26})$ (wherein in one example R^{32} is H, in another example R^{26} is alkyl (e.g., propyl), and in another example R^{32} is H and R^{26} is alkyl (e.g., propyl)), (17) $-NR^{32}C(O)R^{26}$ (e.g., $-NHC(O)R^{26}$) (wherein in one example R^{32} is H, in another example R^{26} is alkyl (e.g., methyl), and in another example R^{32} is H and R^{26} is alkyl (e.g., methyl)),

(18)  (e.g.,)

(wherein in one example R^{32} is H, in another example R^{26} is H, and in another example R^{32} is H and R^{26} is H); and (19) $-NHR^{20}$;

R^{42} is selected from the group consisting of: alkyl (e.g., C_1 to C_6 alkyl, such as, for example $-CH_3$), aryl (e.g., phenyl), heteroaryl (e.g., thiazolyl and pyridyl), and cycloalkyl (e.g., C_3 to C_6 cycloalkyl, such as, for example, cyclopropyl);

R^{44} is selected from the group consisting of: H, alkyl (e.g., C_1 to C_6 alkyl, such as, for example, C_1 to C_3 alkyl, such as, for example, methyl, ethyl and i-propyl), cycloalkyl (e.g., C_3 to C_6 cycloalkyl, such as, for example, cyclopropyl and cyclohexyl), and cycloalkylalkyl (e.g., (C_3 to C_6)cycloalky(C_1 to C_6)alkyl, such as, for example, (C_3 to C_6)cycloalky(C_1 to C_3)alkyl, such as, for example, (C_3 to C_6)cycloalky-methyl-, such as, for example, cyclopropyl-methyl- and cyclohexyl-methyl-), and in one example, R^{44} is H;

Each R^{46} is independently selected from the group consisting of: H, alkyl (e.g., C_1 to C_6 alkyl, such as, for example, C_1 to C_3 alkyl, such as, for example, methyl, ethyl and i-propyl), cycloalkyl (e.g., C_3 to C_6 cycloalkyl, such as, for example, cyclopropyl and cyclohexyl), and cycloalkylalkyl (e.g., (C_3 to C_6)cycloalky(C_1 to C_6)alkyl, such as,

for example, (C_3 to C_6)cycloalky(C_1 to C_3)alkyl, such as, for example, (C_3 to C_6)cycloalky-methyl-, such as, for example, cyclopropyl-methyl- and cyclohexyl-methyl-), and in one example, each R^{46} is H; and

with the proviso that:

(1) Q^1 is a substituted ring wherein at least one substitutent is halo; and/or

(2) R^2 is substituted alkyl wherein said substituent is $-OCH_3$, or R^2 is selected from the group consisting of: $-CH_2OH$ and $-CH_2OCH_3$; and/or

(3) at least one of R^3, R^4, R^5, R^6, and R^7 is:

(i) selected from the group consisting of: oxadiazolylphenyl-, pyridazinylphenyl-, pyrimidinylpyrazinyl-, substituted oxadiazolylphenyl-, substituted pyridazinylphenyl-, substituted pyrimidinylpyrazinyl-, and benzoheteroaryl; or

(ii) selected from the group consisting of:

(a) substituted cycloalkyl,

(b) substituted cycloalkylalkyl-,

(c) substituted heterocycloalkyl,

(d) substituted heterocycloalkylalkyl-,

(e) substituted arylheteroaryl-,

(f) substituted heteroarylaryl-,

(g) substituted aryl,

(h) substituted heteroaryl,

(i) substituted heteroarylheteroaryl-,

(j) substituted arylaminoheteroaryl-,

(k) substituted arylalkynyl-, and

(l) substituted heteroarylalkynyl-, and

wherein at least one substitutent on at least one at least one of said (ii)(a) to (ii)(l) R^3, R^4, R^5, R^6, or R^7 group is selected from the group consisting of: $-NHR^{20}$ (e.g., $-NHCH_2CH_3$ and $-NHCH_3$), $-N(R^{20})_2$ (wherein each R^{20} is independently selected), and $-OR^{20}$ (e.g., $-OCH_3$); and/or

(4) R^{5A} is alkyl (e.g., C_1 to C_6 alkyl, such as, for example, $-CH_3$); and/or

(5) R^{10} is a substituted aryl, and at least one substitutent is selected from the group consisting of:

(a) $-S(O)_tR^{38}$ wherein R^{38} is isopropyl,

(b) $-O$-alkyl-O-R^{20},

(c) hydroxyalkyl,

(d) $-N(R^{20})_2$,

(e) –alkyl-OR^{20},

(f) –O-alkyl-OH,

(g) –NH(hydroxyalkyl), and

(h) oxazolidinone; and/or

(6) R^{20} is isopropyl.

In another embodiment of the compounds of formula 1.0 the proviso is that:

(1) Q^1 is a substituted ring wherein at least one substitutent is halo; and/or

(2) R^2 is substituted alkyl wherein said substituent is $-OCH_3$, or R^2 is selected from the group consisting of: $-CH_2OH$ and $-CH_2OCH_3$; and/or

(3) at least one of R^3, R^4, R^5, R^6, and R^7 is:

(i) selected from the group consisting of: oxadiazolylphenyl-, pyridazinylphenyl-, pyrimidinylpyrazinyl-, substituted oxadiazolylphenyl-, substituted pyridazinylphenyl-, substituted pyrimidinylpyrazinyl-, and benzoheteroaryl; or

(ii) selected from the group consisting of:

(a) substituted cycloalkyl,

(b) substituted cycloalkylalkyl-,

(c) substituted heterocycloalkyl,

(d) substituted heterocycloalkylalkyl-,

(e) substituted arylheteroaryl-,

(f) substituted heteroarylaryl-,

(g) substituted aryl,

(h) substituted heteroaryl,

(i) substituted heteroarylheteroaryl-,

(j) substituted arylaminoheteroaryl-,

(k) substituted arylalkynyl-, and

(l) substituted heteroarylalkynyl-, and

wherein at least one substitutent on at least one at least one of said (ii)(a) to (ii)(l) R^3, R^4, R^5, R^6, or R^7 group is selected from the group consisting of: $-NHR^{20}$ (e.g., $-NHCH_2CH_3$ and $-NHCH_3$), $-N(R^{20})_2$ (wherein each R^{20} is independently selected), and $-OR^{20}$ (e.g., $-OCH_3$); and/or

(4) R^{5A} is alkyl (e.g., C_1 to C_6 alkyl, such as, for example, $-CH_3$); and/or

(5) R^{10} is a substituted aryl, and at least one substitutent is selected from the group consisting of:

(a) –O-alkyl-O-R^{20},

(b) hydroxyalkyl,

(c) –N(R^{20})$_2$,

(d) –alkyl-OR^{20},

(e) –O-alkyl-OH,

(f) –NH(hydroxyalkyl), and

(g) oxazolidinone; and/or

(6) R^{20} is isopropyl.

In another embodiment of the compounds of formula 1.0 the proviso is that:

(1) Q^1 is a substituted ring wherein at least one substitutent is halo; and/or

(2) R^2 is substituted alkyl wherein said substituent is –OCH_3, or R^2 is selected from the group consisting of: -CH_2OH and –CH_2OCH_3; and/or

(3) at least one of R^3, R^4, R^5, R^6, and R^7 is:

(i) selected from the group consisting of: oxadiazolylphenyl-, pyridazinylphenyl-, pyrimidinylpyrazinyl-, substituted oxadiazolylphenyl-, substituted pyridazinylphenyl-, substituted pyrimidinylpyrazinyl-, and benzoheteroaryl; or

(ii) selected from the group consisting of:

(a) substituted cycloalkyl,

(b) substituted cycloalkylalkyl-,

(c) substituted heterocycloalkyl,

(d) substituted heterocycloalkylalkyl-,

(e) substituted arylheteroaryl-,

(f) substituted heteroarylaryl-,

(g) substituted aryl,

(h) substituted heteroaryl,

(i) substituted heteroarylheteroaryl-,

(j) substituted arylaminoheteroaryl-,

(k) substituted arylalkynyl-, and

(l) substituted heteroarylalkynyl-, and

wherein at least one substitutent on at least one at least one of said (ii)(a) to (ii)(l) R^3, R^4, R^5, R^6, or R^7 group is selected from the group consisting of: -NHR^{20} (e.g., -$NHCH_2CH_3$ and –$NHCH_3$), -N(R^{20})$_2$ (wherein each R^{20} is independently selected), and –OR^{20} (e.g., -OCH_3); and/or

(4) R^{5A} is alkyl (e.g., C_1 to C_6 alkyl, such as, for example, -CH_3); and/or

(5) R^{10} is a substituted aryl, and at least one substitutent is selected from the group consisting of:

(a) –O-alkyl-O-R^{20},

(b) hydroxyalkyl,

(c) –N(R^{20})$_2$,

(d) –alkyl-OR^{20},

(e) –O-alkyl-OH,

(f) –NH(hydroxyalkyl), and

(g) oxazolidinone.

In another embodiment of the compounds of formula 1.0 the proviso is that:

(1) Q^1 is a substituted ring wherein at least one substitutent is halo; and/or

(2) at least one of R^3, R^4, R^5, R^6, and R^7 is:

(i) selected from the group consisting of: oxadiazolylphenyl-, pyridazinylphenyl-, pyrimidinylpyrazinyl-, substituted oxadiazolylphenyl-, substituted pyridazinylphenyl-, substituted pyrimidinylpyrazinyl-, and benzoheteroaryl; or

(ii) selected from the group consisting of:

(a) substituted cycloalkyl,

(b) substituted cycloalkylalkyl-,

(c) substituted heterocycloalkyl,

(d) substituted heterocycloalkylalkyl-,

(e) substituted arylheteroaryl-,

(f) substituted heteroarylaryl-,

(g) substituted aryl,

(h) substituted heteroaryl,

(i) substituted heteroarylheteroaryl-,

(j) substituted arylaminoheteroaryl-,

(k) substituted arylalkynyl-, and

(l) substituted heteroarylalkynyl-, and

wherein at least one substitutent on at least one at least one of said (ii)(a) to (ii)(l) R^3, R^4, R^5, R^6, or R^7 group is selected from the group consisting of: -NHR^{20} (e.g., -NHCH$_2$CH$_3$ and –NHCH$_3$), -N(R^{20})$_2$ (wherein each R^{20} is independently selected), and –OR^{20} (e.g., -OCH$_3$); and/or

(3) R^{5A} is alkyl (e.g., C_1 to C_6 alkyl, such as, for example, -CH$_3$); and/or

(4) R^{10} is a substituted aryl, and at least one substitutent is selected from the group consisting of:

(a) –O-alkyl-O-R^{20},

(b) hydroxyalkyl,

(c) –N(R^{20})$_2$,

(d) –alkyl-OR^{20},

(e) –O-alkyl-OH,

(f) –NH(hydroxyalkyl), and

(g) oxazolidinone.

In another embodiment of the compounds of formula 1.0 the proviso is that:

(1) Q^1 is a substituted ring wherein at least one substitutent is halo; and/or

(2) R^2 is substituted alkyl wherein said substituent is –OCH_3, or R^2 is selected from the group consisting of: -CH_2OH and –CH_2OCH_3; and/or

(3) R^5 is:

(i) selected from the group consisting of: oxadiazolylphenyl-, pyridazinylphenyl-, pyrimidinylpyrazinyl-, substituted oxadiazolylphenyl-, substituted pyridazinylphenyl-, substituted pyrimidinylpyrazinyl-, and benzoheteroaryl; or

(ii) selected from the group consisting of:

(a) substituted cycloalkyl,

(b) substituted cycloalkylalkyl-,

(c) substituted heterocycloalkyl,

(d) substituted heterocycloalkylalkyl-,

(e) substituted arylheteroaryl-,

(f) substituted heteroarylaryl-,

(g) substituted aryl,

(h) substituted heteroaryl,

(i) substituted heteroarylheteroaryl-,

(j) substituted arylaminoheteroaryl-,

(k) substituted arylalkynyl-, and

(l) substituted heteroarylalkynyl-, and

wherein at least one substitutent on at least one at least one of said (ii)(a) to (ii)(l) R^3, R^4, R^5, R^6, or R^7 group is selected from the group consisting of: -NHR^{20} (e.g., -$NHCH_2CH_3$ and –$NHCH_3$), -N(R^{20})$_2$ (wherein each R^{20} is independently selected), and –OR^{20} (e.g., -OCH_3); and/or

(4) R^{5A} is alkyl (e.g., C_1 to C_6 alkyl, such as, for example, $-CH_3$); and/or

(5) R^{10} is a substituted aryl, and at least one substitutent is selected from the group consisting of:

(a) –O-alkyl-O-R^{20},

(b) hydroxyalkyl,

(c) $-N(R^{20})_2$,

(d) –alkyl-OR^{20},

(e) –O-alkyl-OH,

(f) –NH(hydroxyalkyl), and

(g) oxazolidinone; and/or

(6) R^{20} is isopropyl.

In another embodiment of the compounds of formula 1.0 the proviso is that:

(1) Q^1 is a substituted ring wherein at least one substitutent is halo; and/or

(2) R^2 is substituted alkyl wherein said substituent is $-OCH_3$, or R^2 is selected from the group consisting of: $-CH_2OH$ and $-CH_2OCH_3$; and/or

(3) R^5 is:

(i) selected from the group consisting of: oxadiazolylphenyl-, pyridazinylphenyl-, pyrimidinylpyrazinyl-, substituted oxadiazolylphenyl-, substituted pyridazinylphenyl-, substituted pyrimidinylpyrazinyl-, and benzoheteroaryl; or

(ii) selected from the group consisting of:

(a) substituted cycloalkyl,

(b) substituted cycloalkylalkyl-,

(c) substituted heterocycloalkyl,

(d) substituted heterocycloalkylalkyl-,

(e) substituted arylheteroaryl-,

(f) substituted heteroarylaryl-,

(g) substituted aryl,

(h) substituted heteroaryl,

(i) substituted heteroarylheteroaryl-,

(j) substituted arylaminoheteroaryl-,

(k) substituted arylalkynyl-, and

(l) substituted heteroarylalkynyl-, and

wherein at least one substitutent on at least one at least one of said (ii)(a) to (ii)(l) R^3, R^4, R^5, R^6, or R^7 group is selected from the group consisting of: $-NHR^{20}$ (e.g.,

-$NHCH_2CH_3$ and $-NHCH_3$), -$N(R^{20})_2$ (wherein each R^{20} is independently selected), and $-OR^{20}$ (e.g., $-OCH_3$); and/or

(4) R^{5A} is alkyl (e.g., C_1 to C_6 alkyl, such as, for example, $-CH_3$); and/or

(5) R^{10} is a substituted aryl, and at least one substitutent is selected from the group consisting of:

(a) $-O\text{-alkyl-}O\text{-}R^{20}$,

(b) hydroxyalkyl,

(c) $-N(R^{20})_2$,

(d) $-\text{alkyl-}OR^{20}$,

(e) –O-alkyl-OH,

(f) –NH(hydroxyalkyl), and

(g) oxazolidinone.

In another embodiment of the compounds of formula 1.0 the proviso is that:

(1) Q^1 is a substituted ring wherein at least one substitutent is halo; and/or

(2) R^5 is:

(i) selected from the group consisting of: oxadiazolylphenyl-, pyridazinylphenyl-, pyrimidinylpyrazinyl-, substituted oxadiazolylphenyl-, substituted pyridazinylphenyl-, substituted pyrimidinylpyrazinyl-, and benzoheteroaryl; or

(ii) selected from the group consisting of:

(a) substituted cycloalkyl,

(b) substituted cycloalkylalkyl-,

(c) substituted heterocycloalkyl,

(d) substituted heterocycloalkylalkyl-,

(e) substituted arylheteroaryl-,

(f) substituted heteroarylaryl-,

(g) substituted aryl,

(h) substituted heteroaryl,

(i) substituted heteroarylheteroaryl-,

(j) substituted arylaminoheteroaryl-,

(k) substituted arylalkynyl-, and

(l) substituted heteroarylalkynyl-, and

wherein at least one substitutent on at least one at least one of said (ii)(a) to (ii)(l) R^3, R^4, R^5, R^6, or R^7 group is selected from the group consisting of: $-NHR^{20}$ (e.g.,

$-NHCH_2CH_3$ and $-NHCH_3$), $-N(R^{20})_2$ (wherein each R^{20} is independently selected), and $-OR^{20}$ (e.g., $-OCH_3$); and/or

(3) R^{5A} is alkyl (e.g., C_1 to C_6 alkyl, such as, for example, $-CH_3$); and/or

(4) R^{10} is a substituted aryl, and at least one substitutent is selected from the group consisting of:

(a) $-O$-alkyl-$O-R^{20}$,

(b) hydroxyalkyl,

(c) $-N(R^{20})_2$,

(d) –alkyl-OR^{20},

(e) –O-alkyl-OH,

(f) –NH(hydroxyalkyl), and

(g) oxazolidinone.

In another embodiment of the compounds of formula 1.0, Q^1 is a substituted ring wherein at least one substitutent is halo.

In another embodiment of the compounds of formula 1.0, R^2 is substituted alkyl wherein said substituent is $-OCH_3$.

In another embodiment of the compounds of formula 1.0, R^2 is selected from the group consisting of: $-CH_2OH$ and $-CH_2OCH_3$.

In another embodiment of the compounds of formula 1.0, at least one of R^3, R^4, R^5, R^6, and R^7 is:

(i) selected from the group consisting of: oxadiazolylphenyl-, pyridazinylphenyl-, pyrimidinylpyrazinyl-, substituted oxadiazolylphenyl-, substituted pyridazinylphenyl-, substituted pyrimidinylpyrazinyl-, and benzoheteroaryl; or

(ii) selected from the group consisting of:

(a) substituted cycloalkyl,

(b) substituted cycloalkylalkyl-,

(c) substituted heterocycloalkyl,

(d) substituted heterocycloalkylalkyl-,

(e) substituted arylheteroaryl-,

(f) substituted heteroarylaryl-,

(g) substituted aryl,

(h) substituted heteroaryl,

(i) substituted heteroarylheteroaryl-,

(j) substituted arylaminoheteroaryl-,

(k) substituted arylalkynyl-, and

(l) substituted heteroarylalkynyl-, and

wherein at least one substitutent on at least one at least one of said (ii)(a) to (ii)(l) R^3, R^4, R^5, R^6, or R^7 group is selected from the group consisting of: $-NHR^{20}$ (e.g., $-NHCH_2CH_3$ and $-NHCH_3$), $-N(R^{20})_2$ (wherein each R^{20} is independently selected), and $-OR^{20}$ (e.g., $-OCH_3$).

In another embodiment of the compounds of formula 1.0 at least one of R^3, R^4, R^5, R^6, and R^7 is selected from the group consisting of: oxadiazolylphenyl-, pyridazinylphenyl-, pyrimidinylpyrazinyl-, substituted oxadiazolylphenyl-, substituted pyridazinylphenyl-, substituted pyrimidinylpyrazinyl-, and benzoheteroaryl.

In another embodiment of the compounds of formula 1.0 at least one of R^3, R^4, R^5, R^6, and R^7 is selected from the group consisting of:

(a) substituted cycloalkyl,

(b) substituted cycloalkylalkyl-,

(c) substituted heterocycloalkyl,

(d) substituted heterocycloalkylalkyl-,

(e) substituted arylheteroaryl-,

(f) substituted heteroarylaryl-,

(g) substituted aryl,

(h) substituted heteroaryl,

(i) substituted heteroarylheteroaryl-,

(j) substituted arylaminoheteroaryl-,

(k) substituted arylalkynyl-, and

(l) substituted heteroarylalkynyl-, and

wherein at least one substitutent on at least one at least one of said (ii)(a) to (ii)(l) R^3, R^4, R^5, R^6, or R^7 group is selected from the group consisting of: $-NHR^{20}$ (e.g., $-NHCH_2CH_3$ and $-NHCH_3$), $-N(R^{20})_2$ (wherein each R^{20} is independently selected), and $-OR^{20}$ (e.g., $-OCH_3$).

In another embodiment of the compounds of formula 1.0, R^5 is:

(i) selected from the group consisting of: oxadiazolylphenyl-, pyridazinylphenyl-, pyrimidinylpyrazinyl-, substituted oxadiazolylphenyl-, substituted pyridazinylphenyl-, substituted pyrimidinylpyrazinyl-, and benzoheteroaryl; or

(ii) selected from the group consisting of:

(a) substituted cycloalkyl,
(b) substituted cycloalkylalkyl-,
(c) substituted heterocycloalkyl,
(d) substituted heterocycloalkylalkyl-,
(e) substituted arylheteroaryl-,
(f) substituted heteroarylaryl-,
(g) substituted aryl,
(h) substituted heteroaryl,
(i) substituted heteroarylheteroaryl-,
(j) substituted arylaminoheteroaryl-,
(k) substituted arylalkynyl-, and
(l) substituted heteroarylalkynyl-, and

wherein at least one substitutent on at least one at least one of said (ii)(a) to (ii)(l) R^3, R^4, R^5, R^6, or R^7 group is selected from the group consisting of: $-NHR^{20}$ (e.g., $-NHCH_2CH_3$ and $-NHCH_3$), $-N(R^{20})_2$ (wherein each R^{20} is independently selected), and $-OR^{20}$ (e.g., $-OCH_3$).

In another embodiment of the compounds of formula 1.0 R^5 is selected from the group consisting of: oxadiazolylphenyl-, pyridazinylphenyl-, pyrimidinylpyrazinyl-, substituted oxadiazolylphenyl-, substituted pyridazinylphenyl-, substituted pyrimidinylpyrazinyl-, and benzoheteroaryl.

In another embodiment of the compounds of formula 1.0 R^5 is selected from the group consisting of:

(a) substituted cycloalkyl,
(b) substituted cycloalkylalkyl-,
(c) substituted heterocycloalkyl,
(d) substituted heterocycloalkylalkyl-,
(e) substituted arylheteroaryl-,
(f) substituted heteroarylaryl-,
(g) substituted aryl,
(h) substituted heteroaryl,
(i) substituted heteroarylheteroaryl-,
(j) substituted arylaminoheteroaryl-,
(k) substituted arylalkynyl-, and
(l) substituted heteroarylalkynyl-, and

wherein at least one substitutent on at least one at least one of said (ii)(a) to (ii)(l) R^3, R^4, R^5, R^6, or R^7 group is selected from the group consisting of: $-NHR^{20}$ (e.g., $-NHCH_2CH_3$ and $-NHCH_3$), $-N(R^{20})_2$ (wherein each R^{20} is independently selected), and $-OR^{20}$ (e.g., $-OCH_3$).

In another embodiment of the compounds of formula 1.0, R^{5A} is alkyl (e.g., C_1 to C_6 alkyl, such as, for example, $-CH_3$).

In another embodiment of the compounds of formula 1.0, R^{10} is a substituted aryl, and at least one substitutent is selected from the group consisting of:

(a) $-S(O)_tR^{38}$ wherein R^{38} is isopropyl,

(b) –O-alkyl-O-R^{20},

(c) hydroxyalkyl,

(d) $-N(R^{20})_2$,

(e) –alkyl-OR^{20},

(f) –O-alkyl-OH,

(g) –NH(hydroxyalkyl), and

(h) oxazolidinone.

In another embodiment of the compounds of formula 1.0, R^{10} is a substituted aryl, and at least one substitutent is selected from the group consisting of:

(a) –O-alkyl-O-R^{20},

(b) hydroxyalkyl,

(c) $-N(R^{20})_2$,

(d) –alkyl-OR^{20},

(e) –O-alkyl-OH,

(f) –NH(hydroxyalkyl), and

(g) oxazolidinone.

In another embodiment of the compounds of formula 1.0, R^{20} is isopropyl.

When R^1 is a cycloalkyl group (i.e., R^1 is R^{10} wherein R^{10} is cycloalkyl), examples of said cycloalkyl group include, but are limited to, cyclopropyl and cyclobutyl.

When R^1 is a heterocycloalkyl group (i.e., R^1 is R^{10} wherein R^{10} is heterocycloalkyl), examples of said heterocycloalkyl group include, but are limited to, morpholinyl, pyrrolidinyl, piperidinyl and piperazinyl.

When R^1 is a heteroaryl group (i.e., R^1 is R^{10} and R^{10} is heteroaryl), examples of said heteroaryl group include, but are not limited to,

(a) unsubstituted heteroaryl,

(b) heteroaryl substituted with 1 to 3 substituents independently selected from the group consisting of: $-C(O)R^{38}$ (e.g., R^{38} is alkyl such as methyl) ,$-NHR^{20}$ (e.g., $-NHCH_3$), $-OR^{20}$ (e.g., $-OCH_3$), cycloalkyl (e.g., cyclopropyl) and halo (e.g., Cl),

(c) heteroaryl selected from the group consisting of: pyrrolyl, pyrazolyl, imidazolyl, furanyl, thienyl, thiazolyl, pyridyl, pyridyl N-O, and pyrimidinyl,

(d) heteroaryl selected from the group consisting of: pyrrolyl, pyrazolyl, imidazolyl, furanyl, thienyl, thiazolyl, pyridyl, pyridyl N-O, and pyrimidinyl, wherein said heteroaryl is substituted with 1 to 3 substituents independently selected from the group consisting of: $-C(O)R^{38}$ (e.g., R^{38} is alkyl such as methyl) ,$-NHR^{20}$ (e.g., $-NHCH_3$), $-OR^{20}$ (e.g., $-OCH_3$), cycloalkyl (e.g., cyclopropyl) and halo (e.g., Cl), and

(e) heteroaryl selected from the group consisting of: thienyl substituted with $-C(O)R^{38}$ (such as, for example, thienyl substituted with $-C(O)CH_3$), thiazolyl substituted with $-NHR^{20}$ such as, for example (thazolyl substituted with-$NHCH_3$), pyridyl substituted with halo (such as, for example, pyridyl substituted with –Cl), pyridyl substituted with $-OR^{20}$ (such as, for example, pyridyl substituted with methyl), and pyrimidinyl substituted with $-OR^{20}$ (such as, for example, pyrimidinyl substituted with $-OCH_3$).

When R^1 is a heteroarylalkyl group (i.e., R^1 is R^{10} and R^{10} is heteroarylalkyl), examples of said heteroarylalkyl group include, but are not limited to,

(a) unsubstituted heteroarylalkyl-

(b) heteroarylalkyl- substituted with 1 to 3 substituents independently selected from the group consisting of: $-C(O)R^{38}$ (e.g., R^{38} is alkyl such as methyl) , $-NHR^{20}$ (e.g., $-NHCH_3$), $-OR^{20}$ (e.g., $-OCH_3$), and halo (e.g., Cl),

(c) heteroarylalkyl- selected from the group consisting of: pyrrolylalkyl- (e.g., pyrrolylCH_2-), pyrazolylalkyl- (e.g., pyrazolylCH_2-), imidazolylalkyl- (e.g., imdazolyl-CH_2-), furanylalkyl- (e.g., furanylCH_2-), thienylalkyl- (e.g., thienylCH_2-), thiazolylalkyl- (e.g., thiazolylCH_2-), pyridylalkyl- (e.g., pyridylCH_2-), pyridyl N-O alkyl- (e.g., pyridyl(N-O)CH_2-), and pyrimidinylalkyl- (e.g., pyrimidinylCH_2-),

(d) heteroarylalkyl- selected from the group consisting of: pyrrolylalkyl- (e.g., pyrrolylCH_2-), pyrazolylalkyl- (e.g., pyrazolylCH_2-), imidazolylalkyl- (e.g., imdazolylCH_2-), furanylalkyl- (e.g., furanylCH_2-), thienylalkyl- (e.g., thienylCH_2-), thiazolylalkyl- (e.g., thiazolylCH_2-), pyridylalkyl- (e.g., pyridylCH_2-), pyridyl N-O alkyl- (e.g., pyridyl(N-O)CH_2-), and pyrimidinylalkyl- (e.g., pyrimidinylCH_2-), wherein said

heteroaryl is substituted with 1 to 3 substituents independently selected from the group consisting of: $-C(O)R^{38}$ (e.g., R^{38} is alkyl such as methyl) ,$-NHR^{20}$ (e.g., $-NHCH_3$), $-OR^{20}$ (e.g., $-OCH_3$), and halo (e.g., Cl), and

(e) heteroarylalkyl- selected from the group consisting of: thienylalkyl- substituted with a $-C(O)R^{20}$ group (such as, for example, thienylCH_2- substituted with $-C(O)CH_3$), thiazolylalkyl- substituted with$-NHR^{20}$ such as, for example (thazolylCH_2- substituted with-$NHCH_3$), pyridylalkyl- substituted with halo (such as, for example, pyridylCH_2- substituted with –Cl), pyridylalkyl- substituted with $-OR^{20}$ (such as, for example, pyridylCH_2- substituted with methyl), and pyrimidinylalky- substituted with$-OR^{20}$ (such as, for example, pyrimidinylCH_2- substituted with $-OCH_3$).

When R^1 is an aryl group (i.e., R^1 is R^{10} and R^{10} is aryl), examples of said aryl group include, but are not limited to, phenyl and naphthyl, and preferably phenyl.

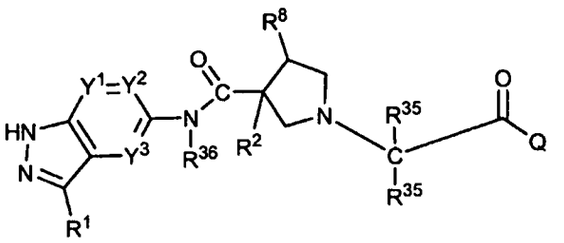
When R^1 is an arylalkyl group (i.e., R^1 is R^{10} and R^{10} is arylalkyl), examples of said arylalkyl group include, but are not limited to, $-(C(R^{30})_2)_n$phenyl (e.g., $-(CH_2)_n$phenyl), wherein in one example said arylalkyl- is $-(C(R^{30})_2)_n$phenyl wherein n is 1, and in another example said arylalkyl- is $-(CH_2)_n$phenyl wherein n is 1 (i.e., said arylalkyl- is benzyl).

When R^1 is a substituted arylalkyl group (i.e., R^1 is R^{10} and R^{10} is a substituted arylalkyl), examples of said substituted arylalkyl group include, but are not limited to, $-(C(R^{30})_2)_n$substituted phenyl (e.g., $-(CH_2)_n$substituted phenyl), wherein in one example said substituted arylalkyl- is $-(C(R^{30})_2)_n$ substituted phenyl wherein n is 1, and in another example said substituted arylalkyl- is $-(CH_2)_n$substituted phenyl wherein n is 1 (i.e., said substituted arylalkyl- is substituted benzyl), wherein the aryl moiety of said substituted arylalkyl is substituted with 1 to 3 substituents independently selected from the group consisiting of: halo (e.g., F, Cl and Br), $-CF_3$, and $-OR^{20}$ (e.g., $-OCH_3$).

Those skilled in the art will appreciate that when Q^1 is aryl, substituted aryl, heteroaryl or substituted heteroaryl the two carbon atoms common to the two fused rings are not substituted. Thus, there is no R^3 and no R^4 groups in 2.9 when Q^1 is aryl, substituted aryl, heteroaryl or substituted heteroaryl. There is no R^3 and no R^4 groups in 2.10 when Q^1 fused to the R^3 and R^4 positions is aryl, substituted aryl, heteroaryl or substituted heteroaryl. There is no R^6 and no R^7 groups in 2.10 when Q^1 fused to the R^6 and R^7 positions is aryl, substituted aryl, heteroaryl or substituted heteroaryl. There is no R^3 and no R^4 groups in 2.11 when Q^1 fused to the R^3 and R^4 positions is aryl, substituted aryl, heteroaryl or substituted heteroaryl. There is no R^3

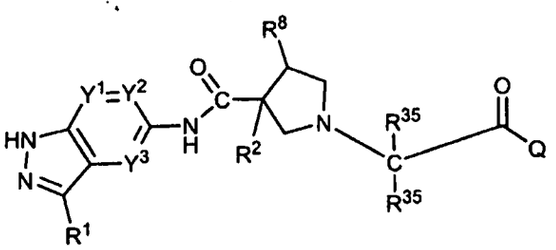
and no R^4 groups in 2.13 when Q^1 fused to the R^3 and R^4 positions is aryl, substituted aryl, heteroaryl or substituted heteroaryl. There is no R^3 and no R^4 groups in 2.14 when Q^1 fused to the R^3 and R^4 positions is aryl, substituted aryl, heteroaryl or substituted heteroaryl. There is no R^3 and no R^4 groups in 2.15 when Q^1 fused to the R^3 and R^4 positions is aryl, substituted aryl, heteroaryl or substituted heteroaryl. There is no R^6 and no R^7 groups in 2.15 when Q^1 fused to the R^3 and R^4 positions is aryl, substituted aryl, heteroaryl or substituted heteroaryl.

In one embodiment of the compounds of formula 1.0, z is 1. Thus, in this embodiment the compounds of formula 1.0 have the formula 1.0A1:



(1.0A1)

In another embodiment of the compounds of formula 1.0, z is 1 and R^{36} is H. Thus, in this embodiment the compounds of formula 1.0 have the formula 1.0A:



(1.0A)

In another embodiment of the compounds of formula 1.0, Z is 1 and and R^{36} is $-OCH_3$.

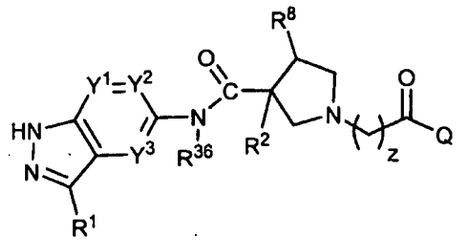
In another embodiment of the compounds of formula 1.0, z is 1, and each R^{35} is independently selected from the group consisting of: H, methyl, ethyl, i-propyl and propyl (e.g., one R^{35} is H and the other is methyl, or both R^{35} substituents are methyl, or preferably both R^{35} substitutents are H).

In another embodiment of the compounds of formula 1.0, z is 1, each R^{35} is independently selected from the group consisting of: H, methyl, ethyl, i-propyl and propyl (e.g., one R^{35} is H and the other is methyl, or both R^{35} substituents are methyl, or preferably both R^{35} substitutents are H), and R^{36} is selected from the group consisting of: H, methyl, ethyl and propyl.

In another embodiment of the compounds of formula 1.0, z is 1, each R^{35} is independently selected from the group consisting of: H, methyl, ethyl, i-propyl and propyl (e.g., one R^{35} is H and the other is methyl, or both R^{35} substituents are methyl, or preferably both R^{35} substitutents are H), and R^{36} is selected from the group consisting of: H and methyl.

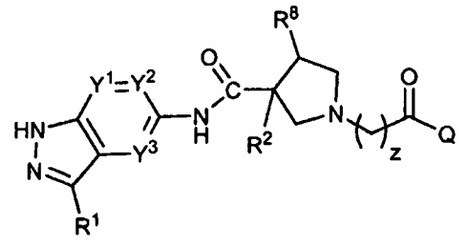
In another embodiment of the compounds of formula 1.0, z is 1, each R^{35} is independently selected from the group consisting of: H, methyl, ethyl, i-propyl and propyl (e.g., one R^{35} is H and the other is methyl, or both R^{35} substituents are methyl, or preferably both R^{35} substitutents are H), and R^{36} is: H.

In another embodiment of the compounds of formula 1.0, each R^{35} is H. Thus, in this embodiment the compounds of formula 1.0 have the formula 1.0B1:



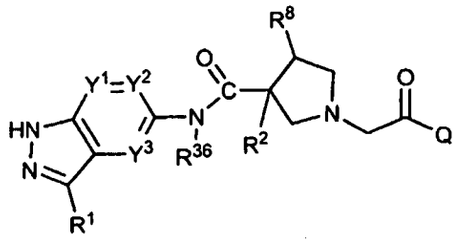
(1.0B1)

In another embodiment of the compounds of formula 1.0, each R^{35} is H and R^{36} is H. Thus, in this embodiment the compounds of formula 1.0 have the formula 1.0B:



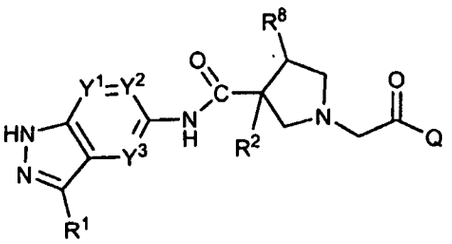
(1.0B)

In another embodiment of the compounds of formula 1.0, z is preferably 1 and each R^{35} is preferably H. Thus, in this embodiment the compounds of formula 1.0 have the formula 1.0C1:



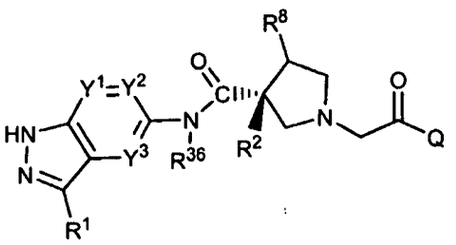
(1.0C1)

In another embodiment of the compounds of formula 1.0, z is preferably 1, each R^{35} is preferably H, and R^{36} is H. Thus, preferably the compounds of formula 1.0 have the formula 1.0C:



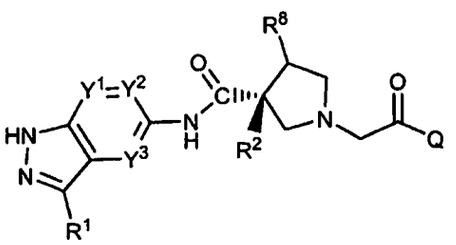
(1.0C)

Another embodiment of this invention is directed to compounds of formula 1.0 having the formula 1.1A:



(1.1A)

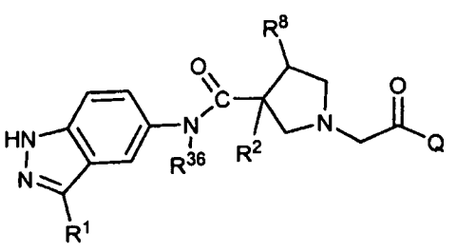
Another embodiment of this invention is directed to compounds of formula 1.0 having the formula 1.1:



(1.1)

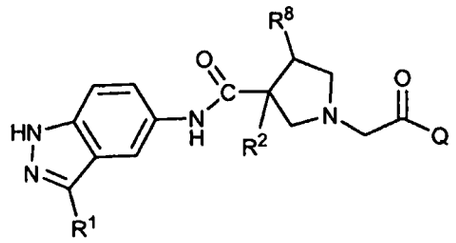
wherein all substituents are as defined for formula 1.0.

Another embodiment of this invention is directed to compounds of formulas 1.0 and 1.1A wherein Y^1, Y^2, and Y^3 are -CH=. Thus, one embodiment of this invention is directed to compounds of formula 1.2A:



(1.2A)

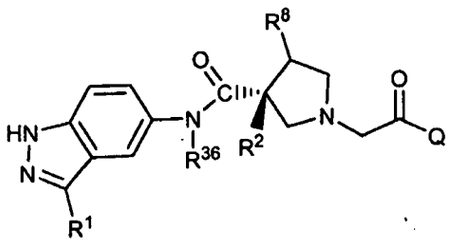
Another embodiment of this invention is directed to compounds of formulas 1.0 and 1.1 wherein Y^1, Y^2, and Y^3 are -CH=. Thus, one embodiment of this invention is directed to compounds of formula 1.2:



(1.2)

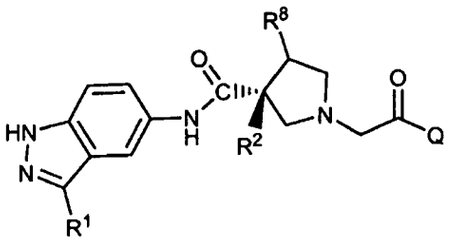
wherein all substitutents are as defined for formula 1.0.

Another embodiment of this invention is directed to compounds of formula 1.0 having the formula 1.3A:



(1.3A)

Another embodiment of this invention is directed to compounds of formula 1.0 having the formula 1.3:



(1.3)

wherein all substituents are as defined for formula 1.0.

Examples of Q include, but are not limited to: moieties 2.1, 2.2, 2.3., 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 2.10, 2.11, 2.14, or 2.15 wherein each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and alkyl (e.g., C_1 to C_6 alkyl, such as, for example methyl).

Examples of Q also include, but are not limited to: moieties 2.1, 2.2, 2.3., 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 2.10, 2.11, 2.14, or 2.15 wherein each R^3, R^4, R^6, and R^7 is H.

Examples of Q also include, but are not limited to: moieties 2.17, 2.18, 2.19, 2.20 and 2.21 wherein each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and alkyl (e.g., C_1 to C_6 alkyl, such as, for example methyl).

Examples of Q also include, but are not limited to: moieties 2.17, 2.18, 2.19, 2.20 and 2.21 wherein each R^3, R^4, R^6, and R^7 is H.

Examples of Q include, but are not limited to: moieties 2.12, 2.13, or 2.16 wherein each R^3, R^4, and R^7 is independently selected from the group consisting of: H and alkyl (e.g., C_1 to C_6 alkyl, such as, for example methyl).

Examples of Q also include, but are not limited to: moieties 2.12, 2.13, or 2.16 wherein each R^3, R^4, and R^7 is H.

Examples of Q include, but are not limited to: moiety 2.22 wherein each R^3, R^4, and R^7 is independently selected from the group consisting of: H and alkyl (e.g., C_1 to C_6 alkyl, such as, for example methyl).

Examples of Q also include, but are not limited to: moiety 2.22 wherein each R^3, R^4, and R^7 is H.

Thus, in one example of Q, Q is moiety 2.1 wherein each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and alkyl (e.g., C_1 to C_6 alkyl, such as, for example methyl).

In another example of Q, Q is moiety 2.1 wherein each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and methyl.

In another example of Q, Q is moiety 2.1 wherein each R^3, R^4, R^6, and R^7 is H.

In another example of Q, Q is moiety 2.2 wherein each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and alkyl (e.g., C_1 to C_6 alkyl, such as, for example methyl).

In another example of Q, Q is moiety 2.2 wherein each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and methyl.

In another example of Q, Q is moiety 2.2 wherein each R^3, R^4, R^6, and R^7 is H.

In another example of Q, Q is moiety 2.3 wherein each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and alkyl (e.g., C_1 to C_6 alkyl, such as, for example methyl).

In another example of Q, Q is moiety 2.3 wherein each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and methyl.

In another example of Q, Q is moiety 2.3 wherein each R^3, R^4, R^6, and R^7 is H.

In another example of Q, Q is moiety 2.4 wherein each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and alkyl (e.g., C_1 to C_6 alkyl, such as, for example methyl).

In another example of Q, Q is moiety 2.4 wherein each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and methyl.

In another example of Q, Q is moiety 2.4 wherein each R^3, R^4, R^6, and R^7 is H.

In another example of Q, Q is moiety 2.5 wherein each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and alkyl (e.g., C_1 to C_6 alkyl, such as, for example methyl).

In another example of Q, Q is moiety 2.5 wherein each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and methyl.

In another example of Q, Q is moiety 2.5 wherein each R^3, R^4, R^6, and R^7 is H.

In another example of Q, Q is moiety 2.6 wherein each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and alkyl (e.g., C_1 to C_6 alkyl, such as, for example methyl).

In another example of Q, Q is moiety 2.6 wherein each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and methyl.

In another example of Q, Q is moiety 2.7 wherein each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and alkyl (e.g., C_1 to C_6 alkyl, such as, for example methyl).

In another example of Q, Q is moiety 2.7 wherein each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and methyl.

In another example of Q, Q is moiety 2.7 wherein each R^3, R^4, R^6, and R^7 is H.

In another example of Q, Q is moiety 2.8 wherein each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and alkyl (e.g., C_1 to C_6 alkyl, such as, for example methyl).

In another example of Q, Q is moiety 2.8 wherein each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and methyl.

In another example of Q, Q is moiety 2.8 wherein each R^3, R^4, R^6, and R^7 is H.

In another example of Q, Q is moiety 2.9 or 2.10 wherein each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and alkyl (e.g., C_1 to C_6 alkyl, such as, for example methyl).

In another example of Q, Q is moiety 2.9 or 2.10 wherein each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and methyl.

In another example of Q, Q is moiety 2.9 or 2.10 wherein each R^3, R^4, R^6, and R^7 is H.

In another example of Q, Q is moiety 2.11 wherein each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and alkyl (e.g., C_1 to C_6 alkyl, such as, for example methyl).

In another example of Q, Q is moiety 2.11 wherein each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and methyl.

In another example of Q, Q is moiety 2.11 wherein each R^3, R^4, R^6, and R^7 is H.

In another example of Q, Q is moiety 2.12 or 2.13 wherein each R^3, R^4, and R^7 is independently selected from the group consisting of: H and alkyl (e.g., C_1 to C_6 alkyl, such as, for example methyl).

In another example of Q, Q is moiety 2.12 or 2.13 wherein each R^3, R^4, and R^7 is independently selected from the group consisting of: H and methyl.

In another example of Q, Q is moiety 2.12 or 2.13 wherein each R^3, R^4, and R^7 is H.

In another example of Q, Q is moiety 2.14 or 2.15 wherein each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and alkyl (e.g., C_1 to C_6 alkyl, such as, for example methyl).

In another example of Q, Q is moiety 2.14 or 2.15 wherein each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and methyl.

In another example of Q, Q is moiety 2.14 or 2.15 wherein each R^3, R^4, R^6, and R^7 is H.

In another example of Q, Q is moiety 2.16 wherein each R^3, R^4, and R^7 is H.

In another example of Q, Q is moiety 2.17 wherein each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and alkyl (e.g., C_1 to C_6 alkyl, such as, for example methyl).

In another example of Q, Q is moiety 2.17 wherein each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and methyl.

In another example of Q, Q is moiety 2.17 wherein each R^3, R^4, R^6, and R^7 is H.

In another example of Q, Q is moiety 2.18 wherein each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and alkyl (e.g., C_1 to C_6 alkyl, such as, for example methyl).

In another example of Q, Q is moiety 2.18 wherein each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and methyl.

In another example of Q, Q is moiety 2.18 wherein each R^3, R^4, R^6, and R^7 is H.

In another example of Q, Q is moiety 2.19 wherein each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and alkyl (e.g., C_1 to C_6 alkyl, such as, for example methyl).

In another example of Q, Q is moiety 2.19 wherein each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and methyl.

In another example of Q, Q is moiety 2.19 wherein each R^3, R^4, R^6, and R^7 is H.

In another example of Q, Q is moiety 2.20 wherein each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and alkyl (e.g., C_1 to C_6 alkyl, such as, for example methyl).

In another example of Q, Q is moiety 2.20 wherein each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and methyl.

In another example of Q, Q is moiety 2.20 wherein each R^3, R^4, R^6, and R^7 is H.

In another example of Q, Q is moiety 2.21 wherein each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and alkyl (e.g., C_1 to C_6 alkyl, such as, for example methyl).

In another example of Q, Q is moiety 2.21 wherein each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and methyl.

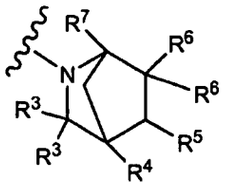
In another example of Q, Q is moiety 2.21 wherein each R^3, R^4, R^6, and R^7 is H.

In another example of Q, Q is moiety 2.22 wherein each R^3, R^4, and R^7 is independently selected from the group consisting of: H and alkyl (e.g., C_1 to C_6 alkyl, such as, for example methyl).

In another example of Q, Q is moiety 2.22 wherein each R^3, R^4, and R^7 is independently selected from the group consisting of: H and methyl.

In another example of Q, Q is moiety 2.22 wherein each R^3, R^4, and R^7 is H.

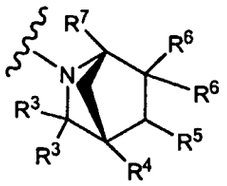
Another example of the Q substituent 2.3 is:



(2.3A)

(i.e., each R^{24} is H and w is 1).

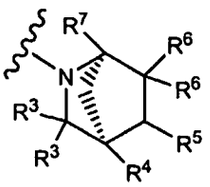
Another example of the Q substituent 2.3 is:



(2.3B)

(i.e., each R^{24} is H and w is 1).

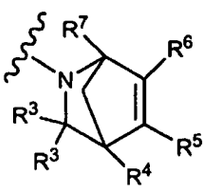
Another example of the Q substitutent 2.3 is:



(2.3C)

(i.e., each R^{24} is H and w is 1).

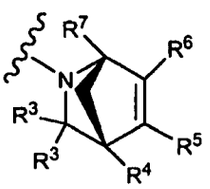
An example of the Q substituent 2.4 is:



(2.4A)

(i.e., each R^{24} is H and w is 1).

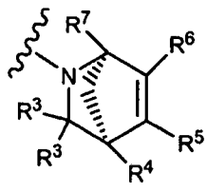
Another example of the Q substituent 2.4 is:



(2.4B)

(i.e., each R^{24} is H and w is 1).

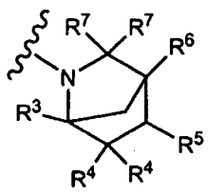
Another example of the Q substituent 2.4 is:



(2.4C)

(i.e., each R^{24} is H and w is 1).

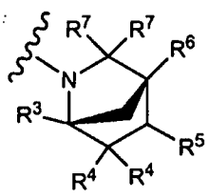
An example of the Q substituent 2.5 is:



(2.5A)

(i.e., each R^{24} is H and w is 1).

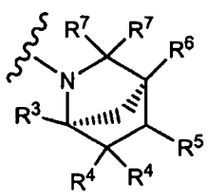
Another example of the Q substituent 2.5 is:



(2.5B)

(i.e., each R^{24} is H and w is 1).

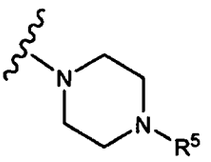
Another example of the Q substituent 2.5 is:



(2.5C)

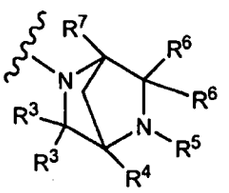
(i.e., each R^{24} is H and w is 1).

An example of the Q substituent 2.6 is:



(2.6A)

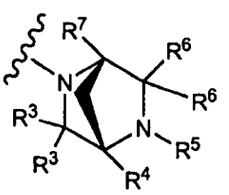
An example of the Q substituent 2.7 is:



(2.7A)

(i.e., each R^{24} is H and w is 1).

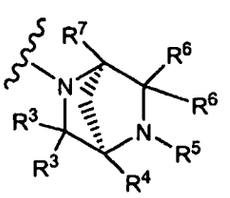
An example of the Q substituent 2.7 is:



(2.7B)

(i.e., each R^{24} is H and w is 1).

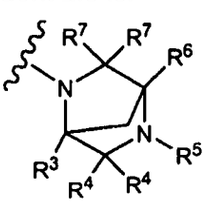
An example of the Q substituent 2.7 is:



(2.7C)

(i.e., each R^{24} is H and w is 1).

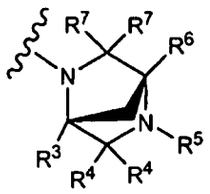
An example of the Q substituent 2.8 is:



(2.8A)

(i.e., each R^{24} is H and w is 1).

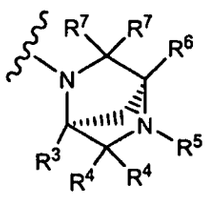
Another example of the Q substituent 2.8 is:



(2.8B)

(i.e., each R^{24} is H and w is 1).

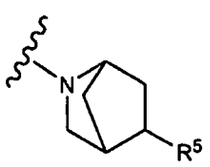
Another example of the Q substituent 2.8 is:



(2.8C)

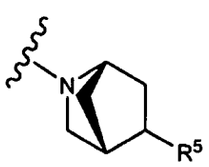
(i.e., each R^{24} is H and w is 1).

Another example of the Q substituent 2.3 is:



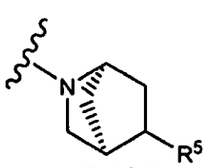
(2.3A1)

Another example of the Q substituent 2.3 is:



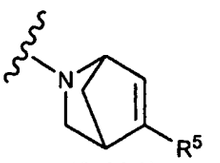
(2.3B1)

Another example of the Q substituent 2.3 is:



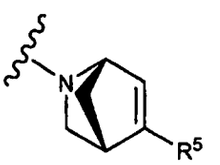
(2.3C1)

Another example of the Q substituent 2.4 is:



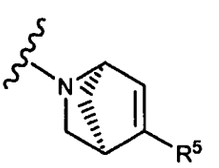
(2.4A1)

Another example of the Q substituent 2.4 is:



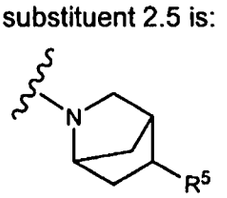
(2.4B1)

Another example of the Q substituent 2.4 is:



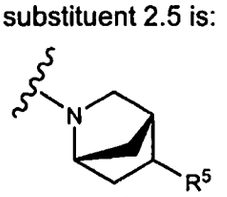
(2.4C1)

Another example of the Q substituent 2.5 is:



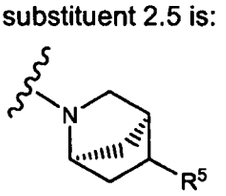
(2.5A1)

Another example of the Q substituent 2.5 is:



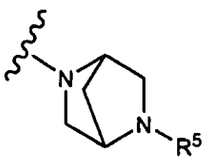
(2.5B1)

Another example of the Q substituent 2.5 is:



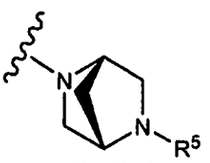
(2.5C1)

Another example of the Q substituent 2.7 is:



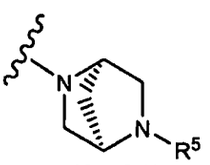
(2.7A1)

Another example of the Q substituent 2.7 is:



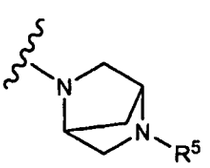
(2.7B1)

Another example of the Q substituent 2.7 is:



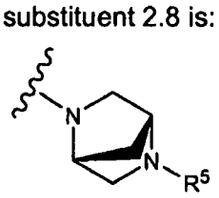
(2.7C1)

Another example of the Q substituent 2.8 is:



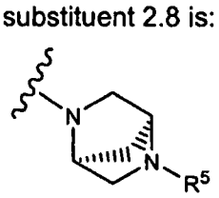
(2.8A1)

Another example of the Q substituent 2.8 is:



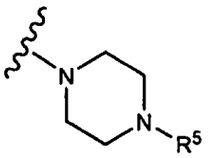
(2.8B1)

Another example of the Q substituent 2.8 is:



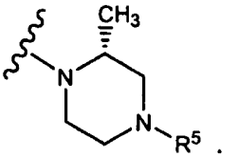
(2.8C1)

Another example of the Q substitutent is the piperazine ring:

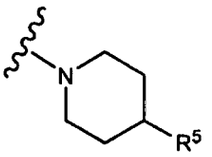


substituted with one or two substituents independently selected from the group consisting of R^3 groups, provided that said one or two substitutents are not H. In one embodiment said substituents are selected from the group consisting of alkyl groups (e.g., C_1 to C_6 alkyl, e.g., methyl). In another embodiment there is one substituent on said piperazine ring. In another embodiment there is one substituent on said piperazine ring and said substituent is methyl.

Another example of the Q substituent is the piperazine ring:

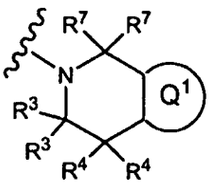


Another example of the Q substitutent is the piperidine ring:



substituted with one or two substituents independently selected from the group consisting of R^3 groups, provided that said one or two substitutents are not H. In one embodiment said substituents are selected from the group consisting of alkyl groups (e.g., C_1 to C_6 alkyl, e.g., methyl). In another embodiment there is one substituent on said piperidine ring. In another embodiment there is one substituent on said piperidine ring and said substituent is methyl.

In one example of the Q substituent 2.16

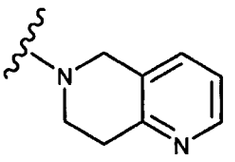


(2.16)

Q^1 is heteroaryl.

In another example of the Q substituent 2.16 Q^1 is aryl.

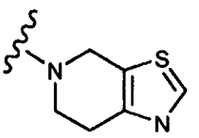
Thus, one example of the Q substituent 2.16 is 2.16A:



(2.16A)

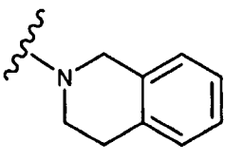
(i.e., Q^1 is pyridyl, and each R^3, R^4 and R^7 is H).

In another example, the Q substituent 2.16 is 2.16A1:



(2.16A1)

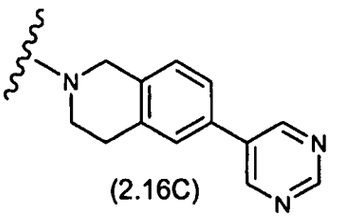
Another example of the Q substitutent 2.16 is 2.16B:



(2.16B)

(i.e., Q^1 is phenyl, and each R^3, R^4 and R^7 is H).

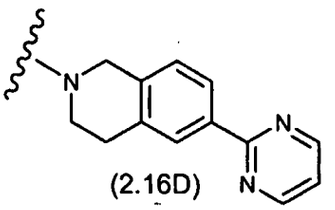
Another example of the Q substituent 2.16 is 2.16C



(2.16C)

(i.e., Q^1 is substituted phenyl, and each R^3, R^4 and R^7 is H).

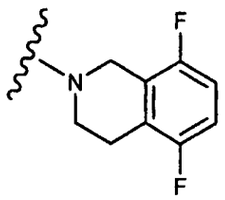
Another example of the Q substituent 2.16 is 2.16D



(2.16D)

(i.e., Q^1 is substituted phenyl, and each R^3, R^4 and R^7 is H).

Another example of the Q substituent 2.16 is 2.16E



(2.16E)

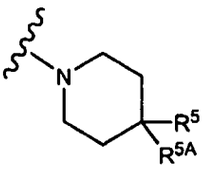
When the Q substitutent comprises two Q^1 rings, each Q^1 ring is independently selected. Generally, the Q^1 cycloalkyl rings and the Q^1 substituted cycloalkyl rings comprise 5 to 7 ring carbons. In general, the heterocycloalkyl Q^1 rings and the substituted heterocycloalky Q^1 rings comprise 5 to 7 ring carbons and comprise 1 to 3 (generally 1 or 2, or generally 1) ring heteroatoms selected from the group consisting of: O, N and S. In general, the heteroaryl Q^1 rings and the substituted heteroaryl Q^1 rings comprise 5 to 7 ring carbons and comprise 1 to 3 (generally 1 or 2, or generally 1) ring heteroatoms selected from the group consisting of: O, N and S. Examples of the Q^1 rings include, but are not limited to: piperidinyl, piperazinyl, pyranyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, pyridyl, pyrimidinyl, pyrrolyl, pyrazolyl, furanyl, thienyl, thiazolyl, imidazolyl, cyclopentyl, cyclohexyl and cycloheptyl. Examples of the Q^1 rings also include, but are not limited to: substituted piperidinyl, substituted piperazinyl, substituted pyranyl, substituted pyrrolidinyl, substituted morpholinyl, substituted thiomorpholinyl, substituted pyridyl, substituted pyrimidinyl, substituted pyrrolyl, substituted pyrazolyl, substituted furanyl, substituted thienyl, substituted thiazolyl, substituted imidazolyl, substituted cyclopentyl, substituted cyclohexyl and substituted cycloheptyl wherein said substituted Q^1 rings are substituted with 1 to 3 substitutents selected from the R^{10} moieties.

Generally, the Q^2 cycloalkyl rings and the Q^2 substituted cycloalkyl rings comprise 5 to 7 ring carbons. In general, the heterocycloalkyl Q^2 rings and the substituted heterocycloalky Q^1 rings comprise 5 to 7 ring carbons and comprise 1 to 3 (generally 1 or 2, or generally 1) ring heteroatoms selected from the group consisting of: O, N and S.

Examples of the Q^2 rings include, but are not limited to: piperidinyl, piperazinyl, pyranyl, pyrrolidinyl, cyclopentyl, cyclohexyl and cycloheptyl. Examples of the Q^2 rings also include, but are not limited to: substituted piperidinyl, substituted piperazinyl, substituted pyranyl, substituted pyrrolidinyl, substituted morpholinyl,

substituted thiomorpholinyl, substituted cyclopentyl, substituted cyclohexyl and substituted cycloheptyl wherein said substituted Q^1 rings are substituted with 1 to 3 substitutents selected from the R^{10} moieties.

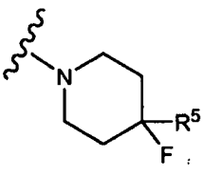
In one example the Q substituent 2.17 is:



(2.17A)

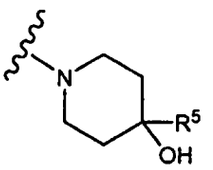
wherein R^{5A} is halo.

Another example of the Q substituent 2.17 is:



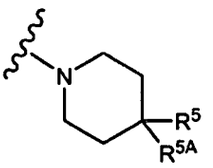
(2.17B)

Another example of the Q substituent 2.17 is:



(2.17C)

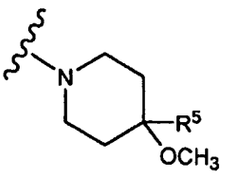
Another example of the Q substituent 2.17 is:



(2.17D)

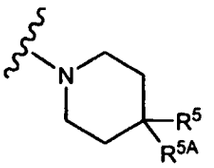
wherein R^{5A} is alkoxy, i.e., -O-(C_1 to C_6)alkyl, such as, for example, -O-(C_1 to C_3)alkyl, or -O-(C_1 to C_2)alkyl.

Another example of the Q substituent 2.17 is:



(2.17E)

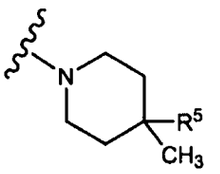
Another example of the Q substituent 2.17 is:



(2.17F)

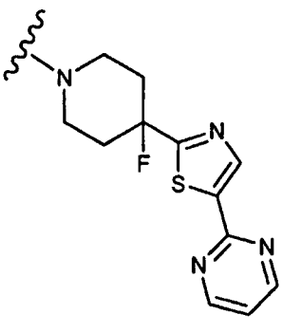
wherein R^{5A} is alkyl (e.g., -(C_1 to C_6)alkyl, such as, for example, -(C_1 to C_3)alkyl, or -(C_1 to C_2)alkyl).

Thus, another example of the Q substituent 2.17 is:

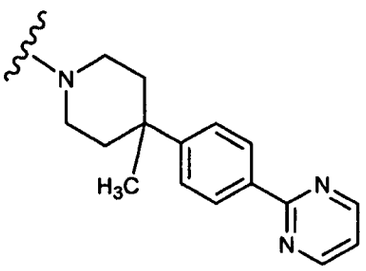


(2.17G)

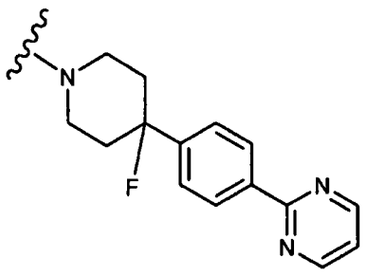
Another example of the Q substituent 2.17 is:



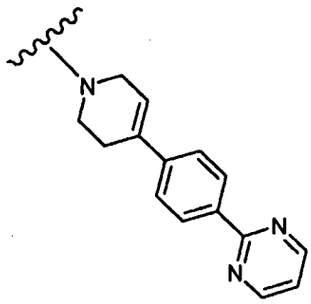
Another example of the Q substituent 2.17 is:



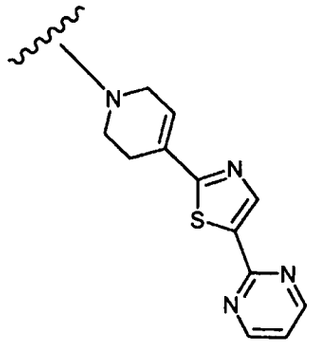
Another example of the Q substituent 2.17 is:



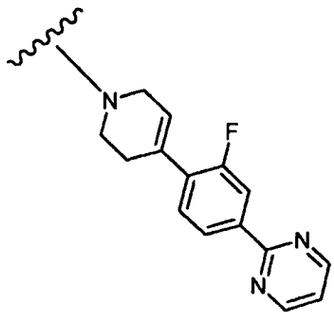
An example of the Q substituent 2.2 is:



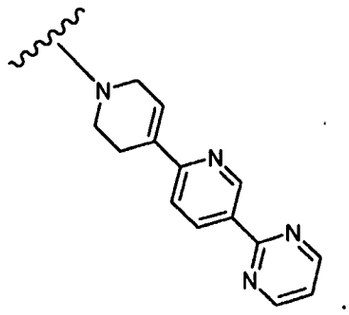
Another example of the Q substituent 2.2 is:



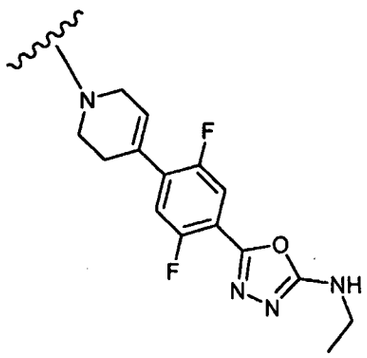
Another example of the Q substituent 2.2 is:



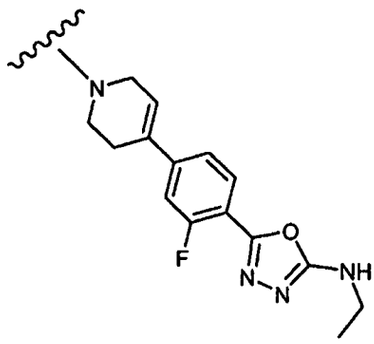
Another example of the Q substituent 2.2 is:



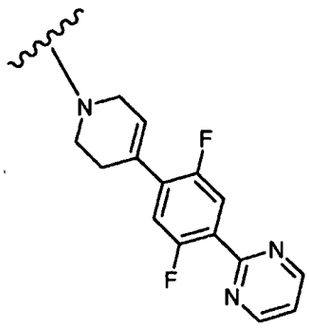
Another example of the Q substituent 2.2 is:



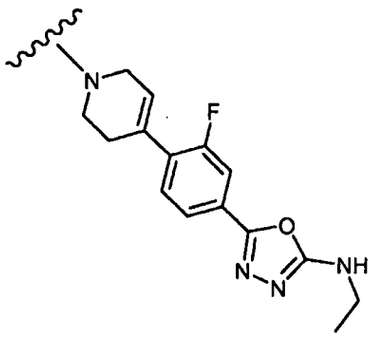
Another example of the Q substituent 2.2 is:



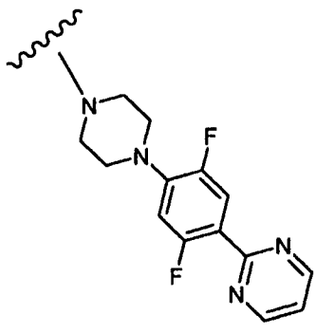
Another example of the Q substituent 2.2 is:



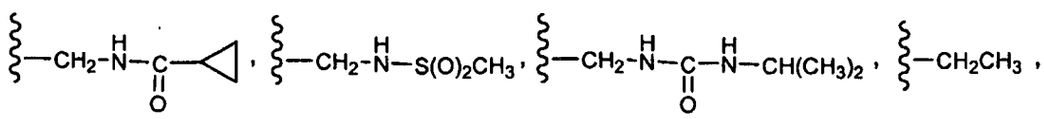
Another example of the Q substituent 2.2 is:

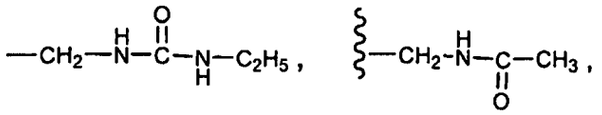


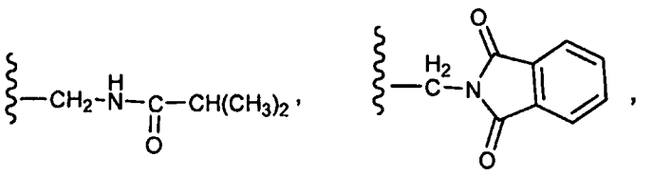
Another example of the Q substituent 2.6 is:

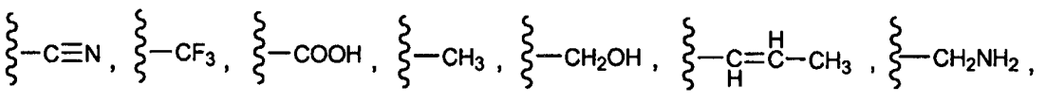


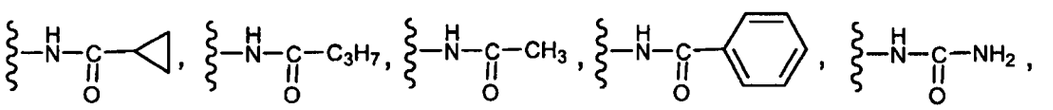
Examples of R^1 for the compounds of this invention (e.g., compounds of formulas 1.0, 1.0A1, 1.0B1, 1.0C1, 1.1, 1.1A, 1.2, 1.2A, 1.3 and 1.3A) include, but are not limited to:

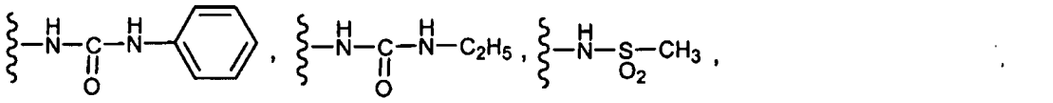


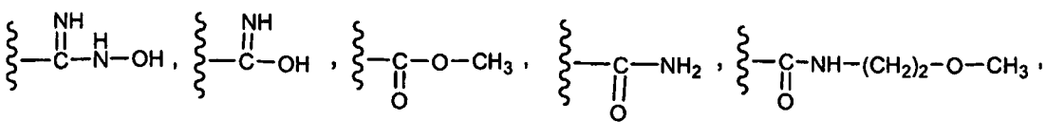


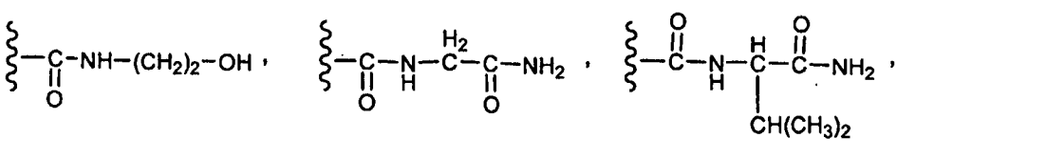


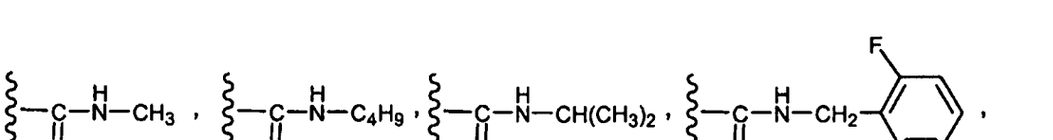


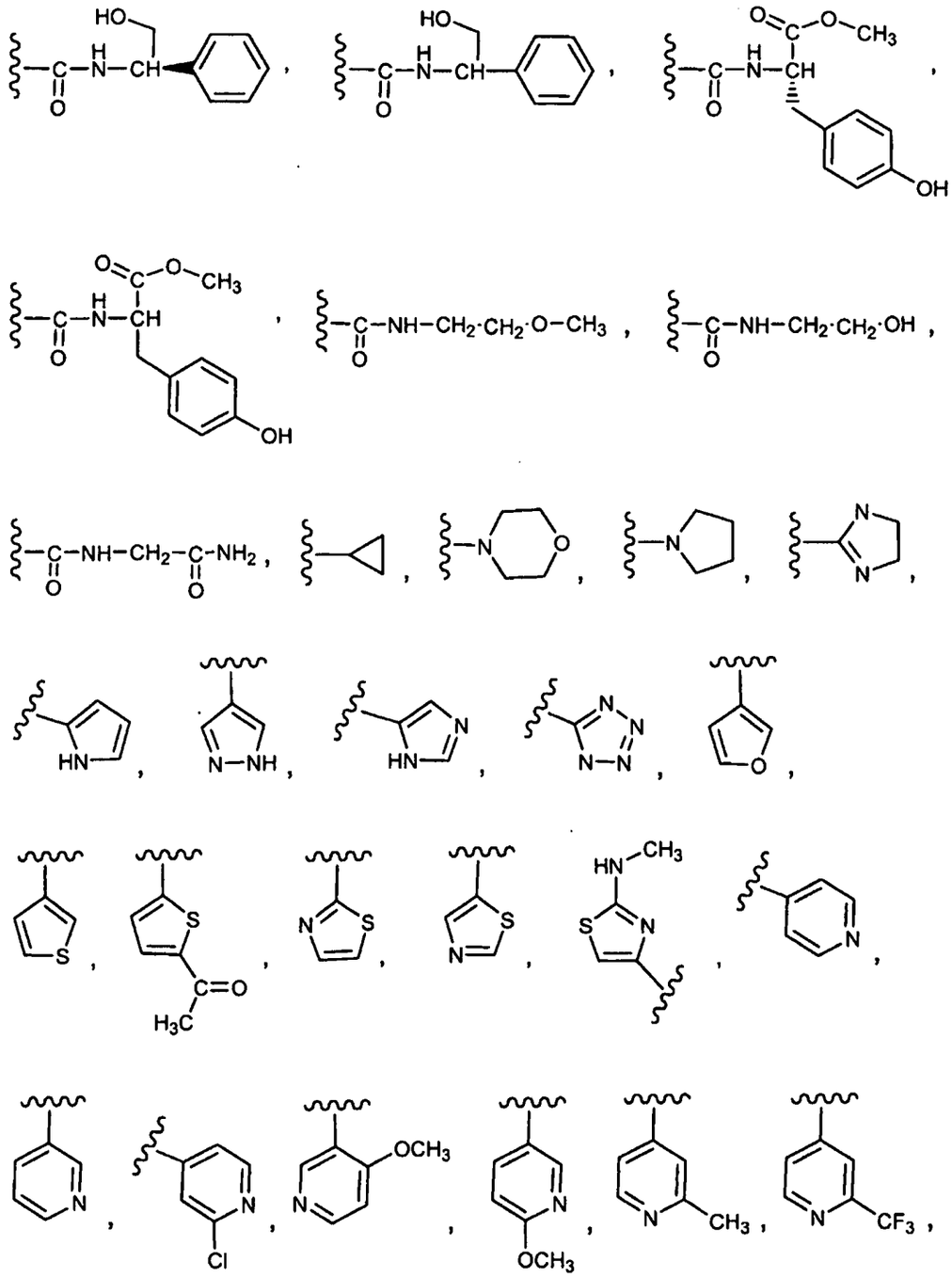


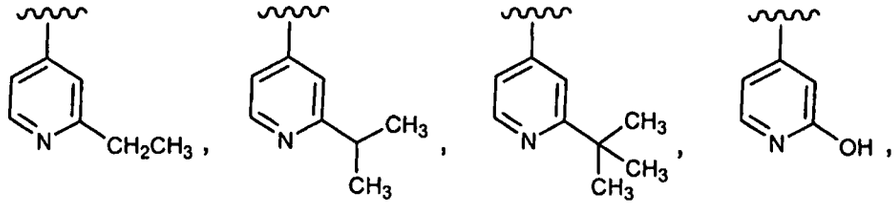


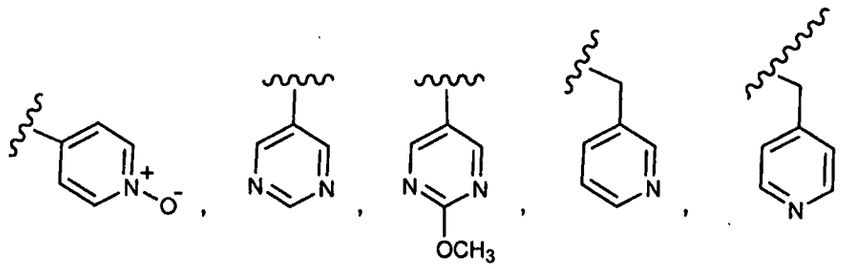


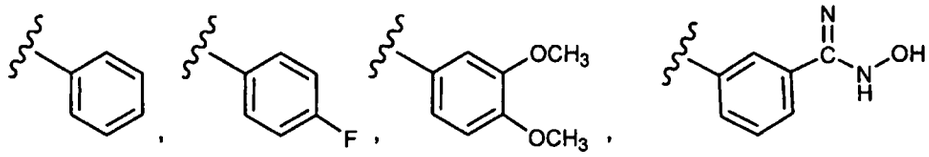


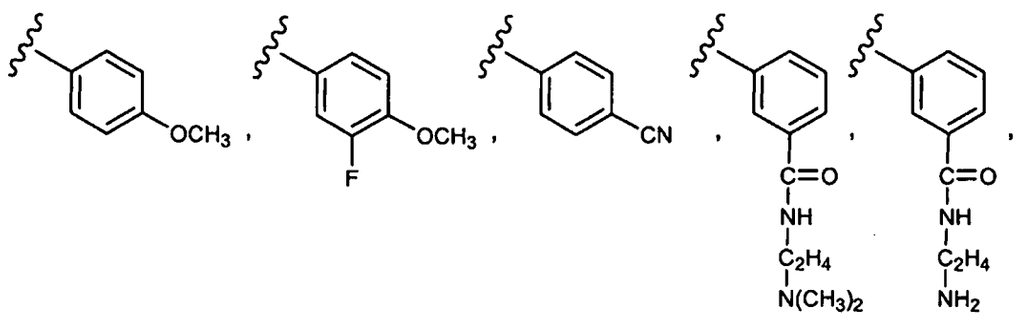


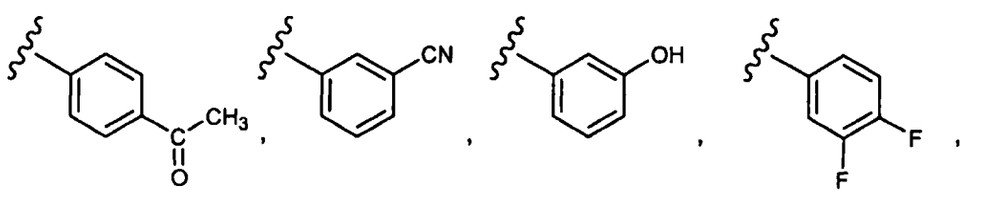


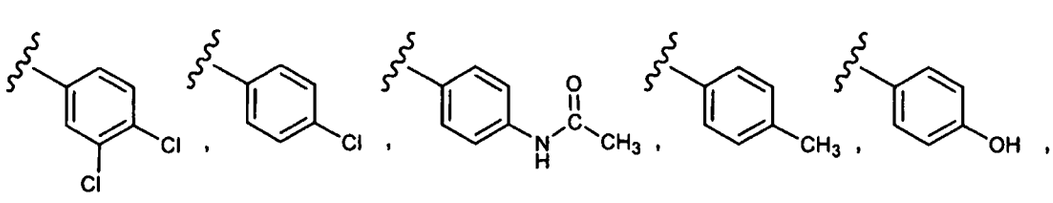


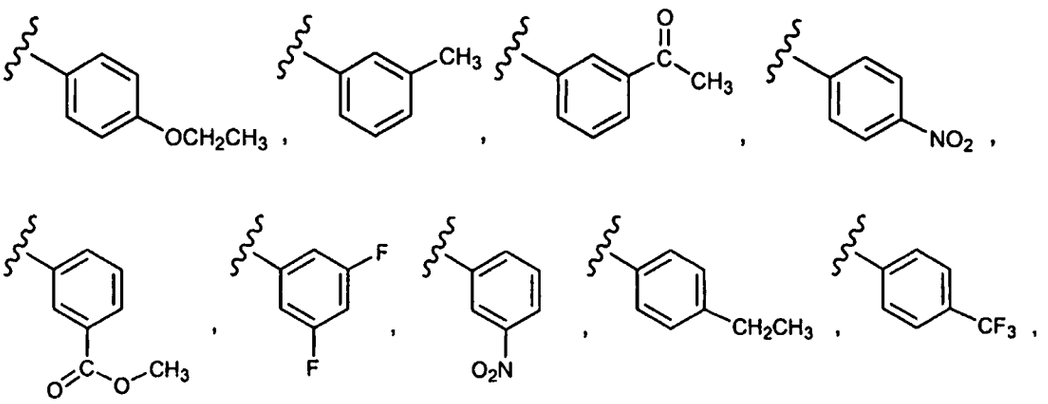


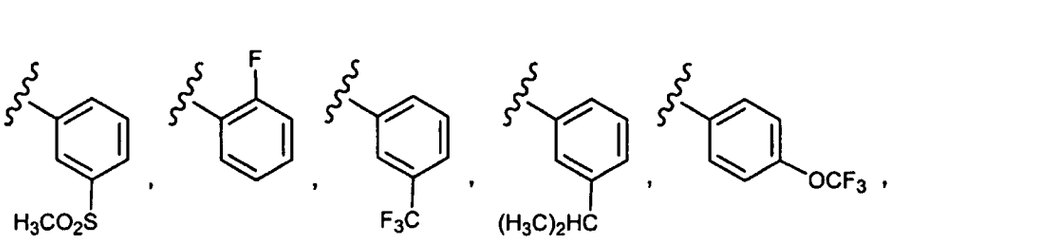


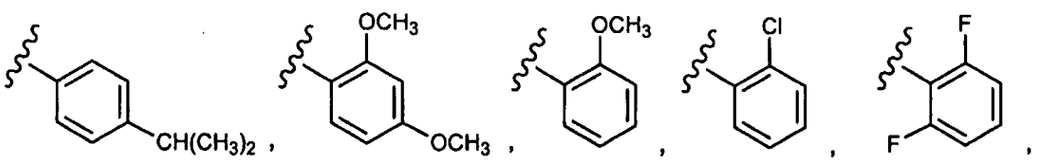


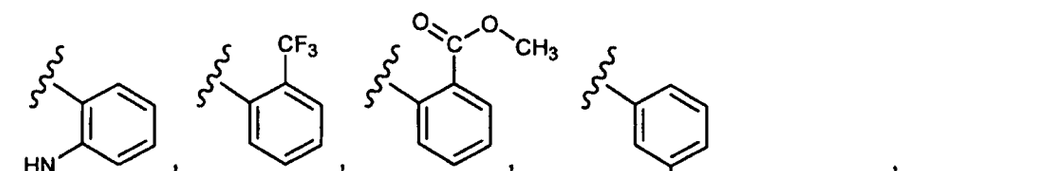


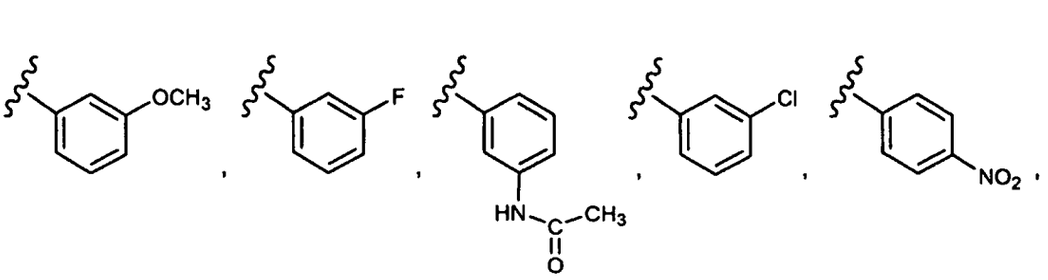


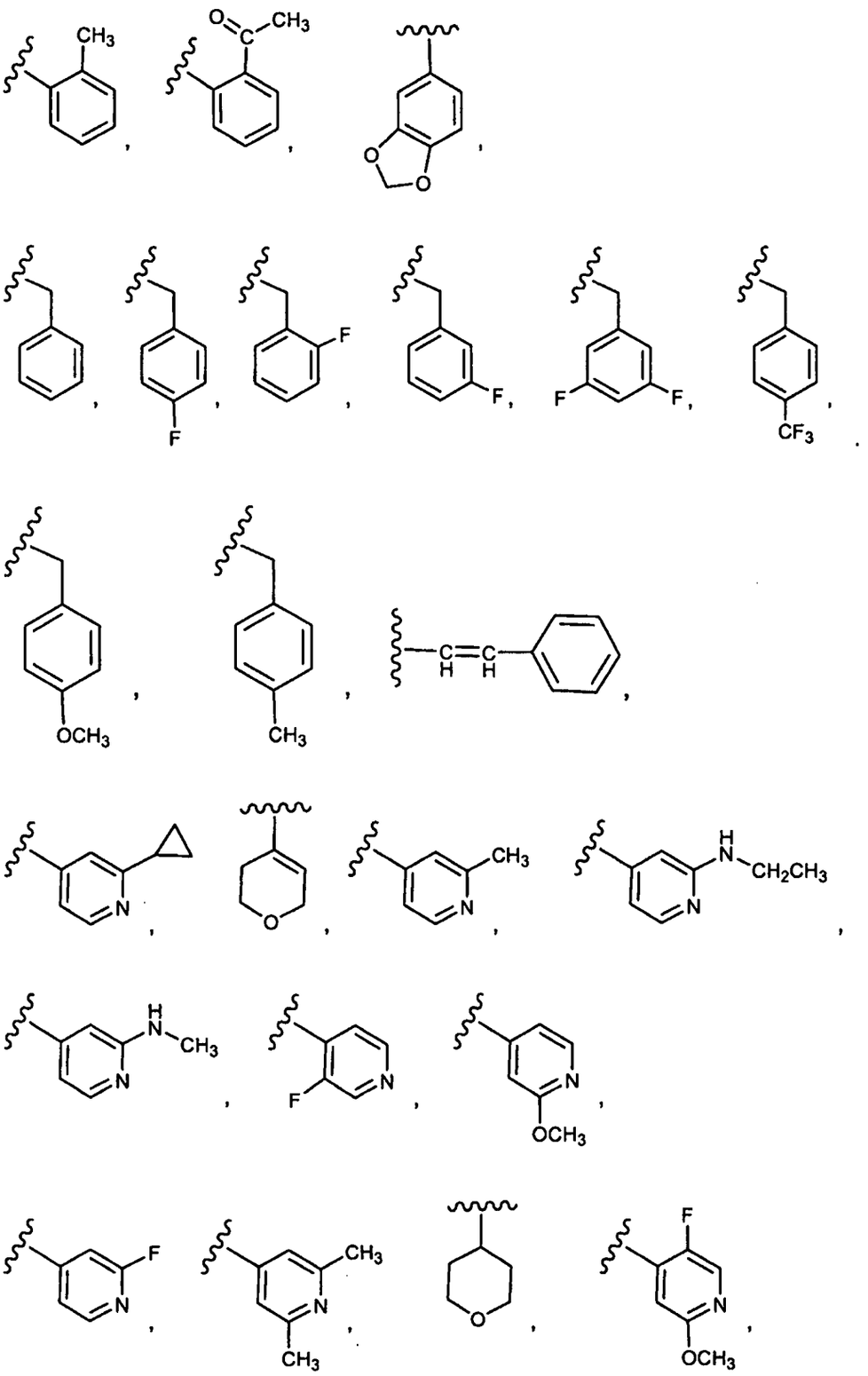


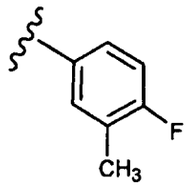
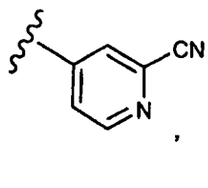
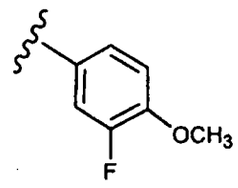
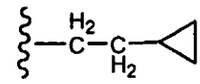
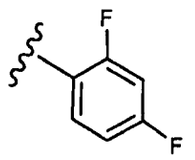
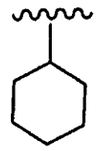
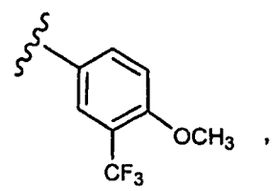
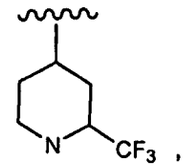
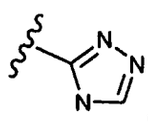
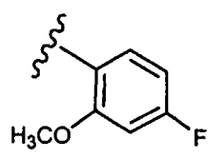
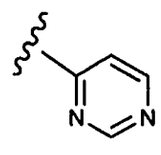
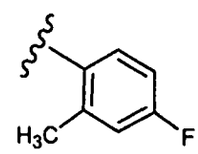
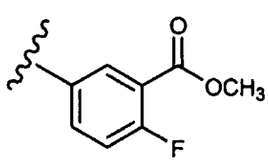
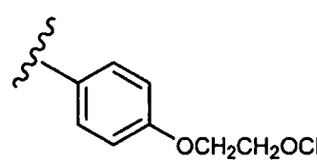
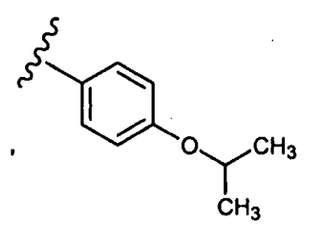
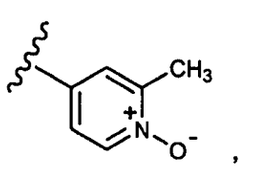
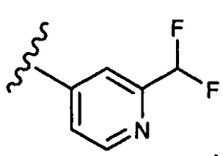
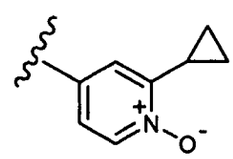






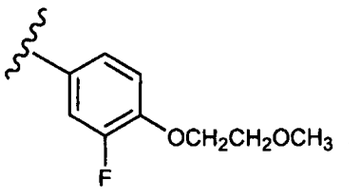
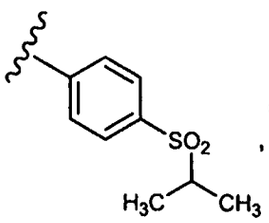
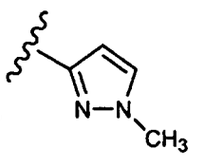
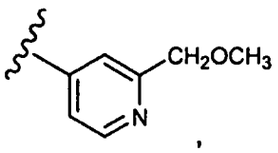
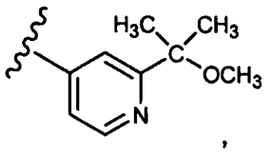
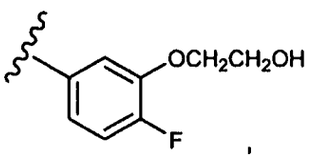
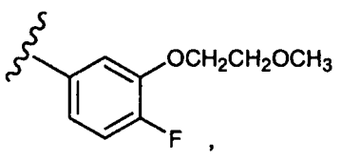
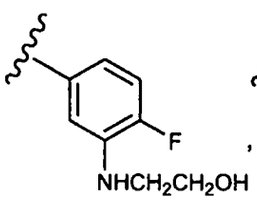
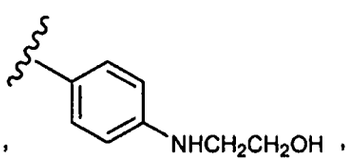
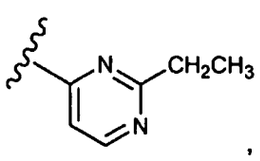
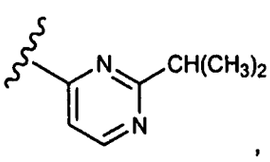
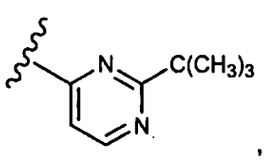
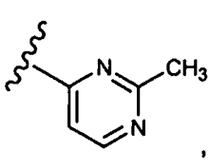
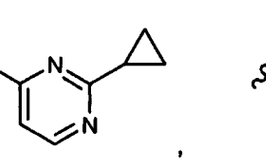
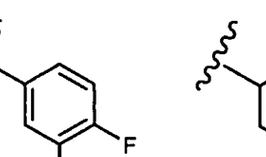
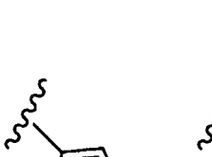


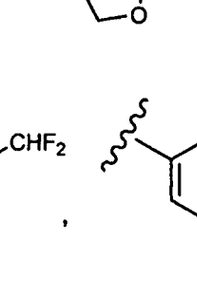
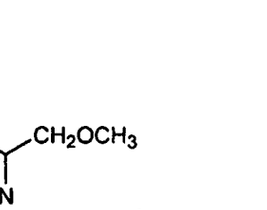


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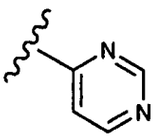
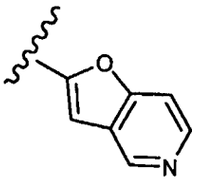
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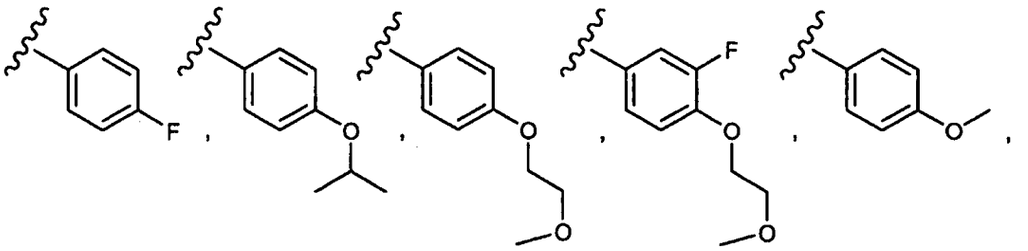



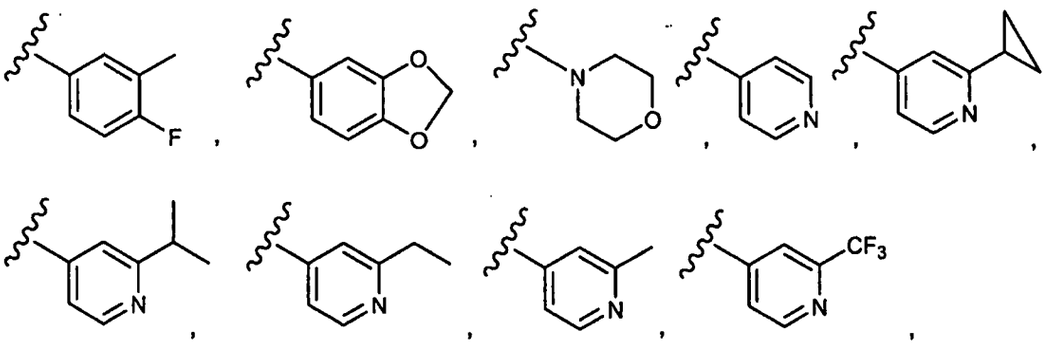
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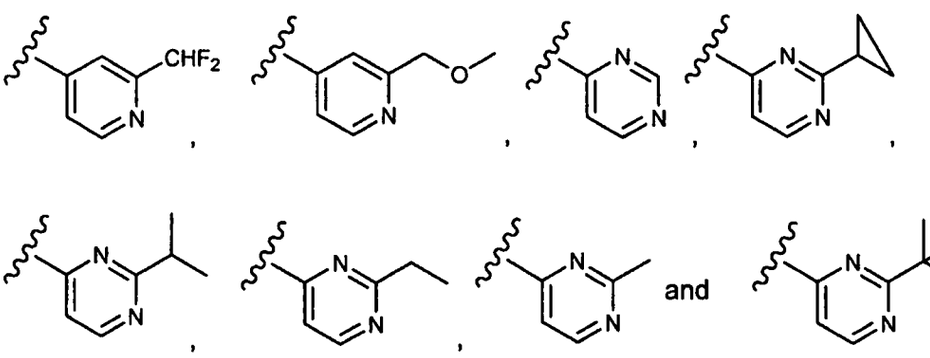
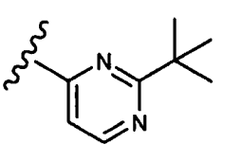
10


and


In one embodiment of this invention, R^1 is selected from the group consisting of:

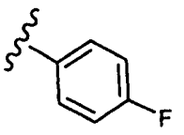




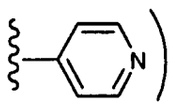

and


R^1, in one embodiment of this invention, is aryl (e.g., phenyl).

R^1, in one embodiment of this invention is substituted aryl, such as,

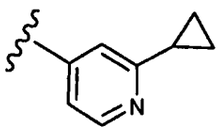


R^1, in another embodiment of this invention, is heteroaryl (e.g., in one embodiment R^1 is pyridyl N-oxide, and in another embodiment R^1 is pyridyl, such as

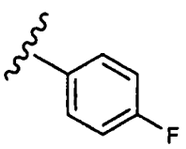


R^1, in one embodiment of this invention, is substituted heteroaryl (e.g., substituted pyridyl).

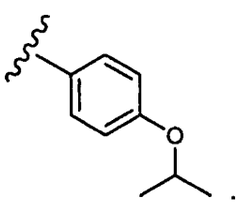
R^1, in one embodiment of this invention, is substituted heteroaryl (e.g., substituted pyridyl), such as, for example:



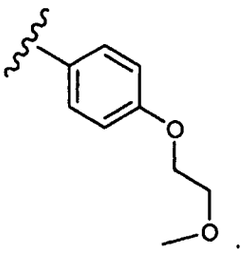
In another embodiment of this invention R^1 is:



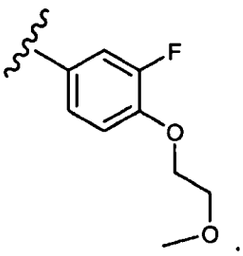
In another embodiment of this invention R^1 is:



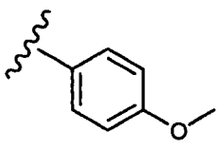
In another embodiment of this invention R^1 is:



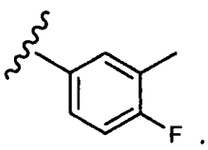
In another embodiment of this invention R^1 is:



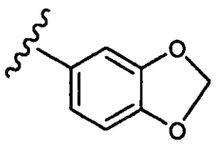
In another embodiment of this invention R^1 is:



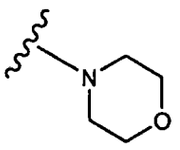
In another embodiment of this invention R^1 is:



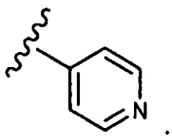
In another embodiment of this invention R^1 is:



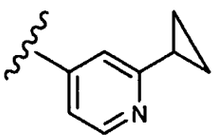
In another embodiment of this invention R^1 is:



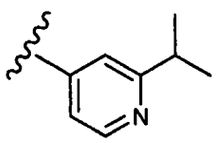
In another embodiment of this invention R^1 is:



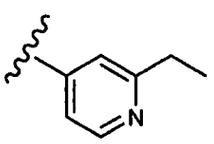
In another embodiment of this invention R^1 is:



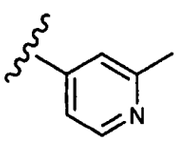
In another embodiment of this invention R^1 is:



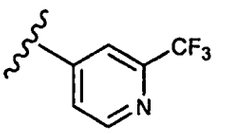
In another embodiment of this invention R^1 is:



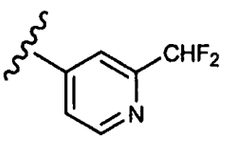
In another embodiment of this invention R^1 is:



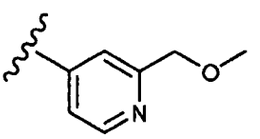
In another embodiment of this invention R^1 is:



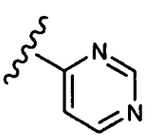
In another embodiment of this invention R^1 is:



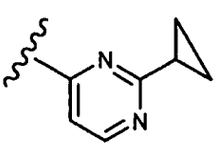
In another embodiment of this invention R^1 is:



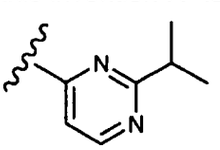
In another embodiment of this invention R^1 is:



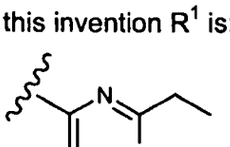
In another embodiment of this invention R^1 is:



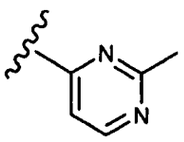
In another embodiment of this invention R^1 is:



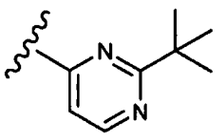
In another embodiment of this invention R^1 is:



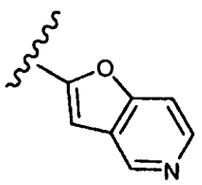
In another embodiment of this invention R^1 is:



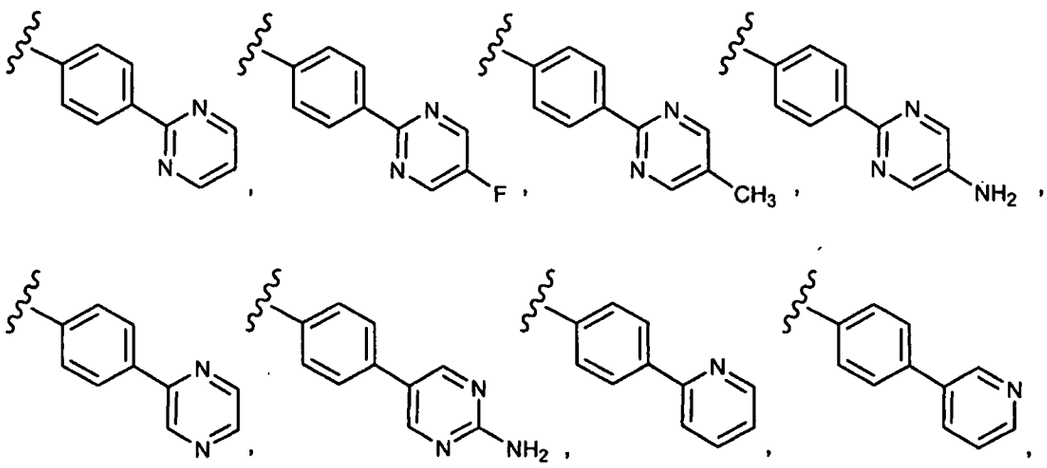
In another embodiment of this invention R^1 is:

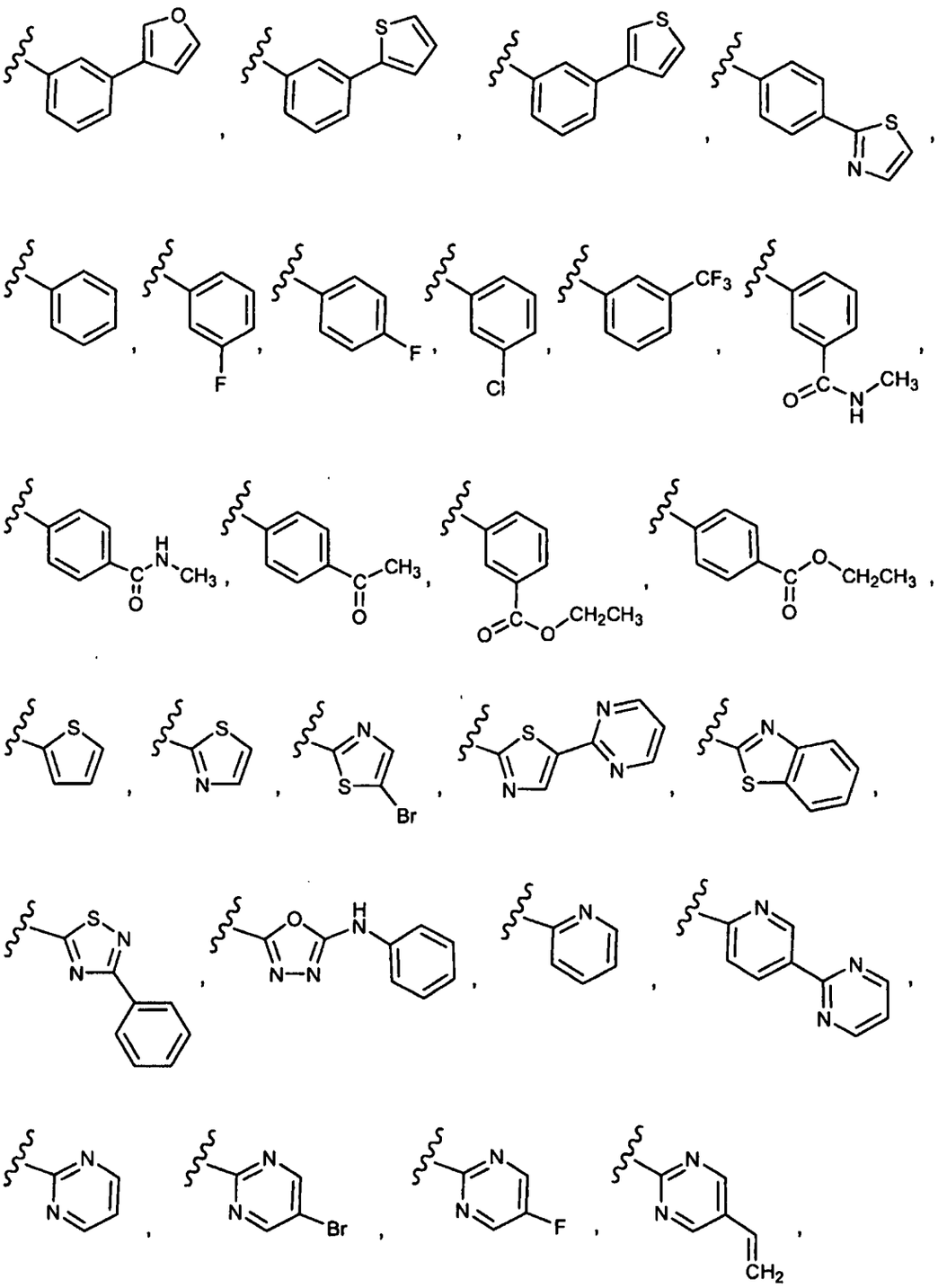


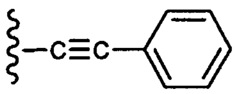
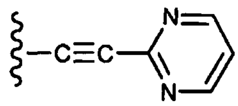
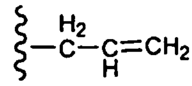
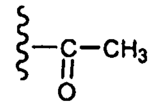
In another embodiment of this invention R^1 is:

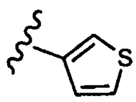
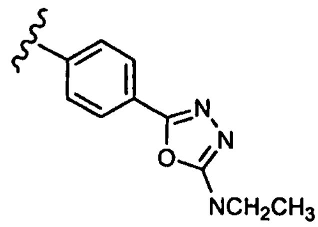
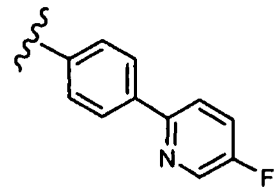


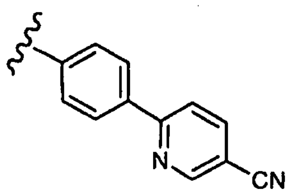
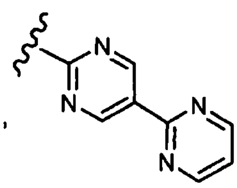
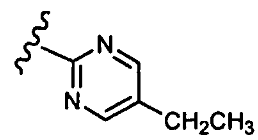
Examples of R^5 for the compounds of this invention (e.g., compounds of formulas 1.0, 1.0A1, 1.0B1, 1.0C1, 1.1, 1.1A, 1.2, 1.2A, 1.3 and 1.3A) include but are not limited to:

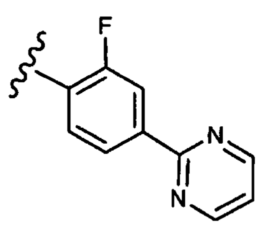
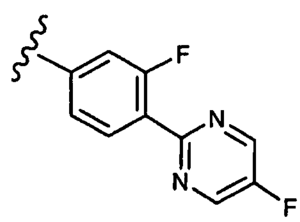


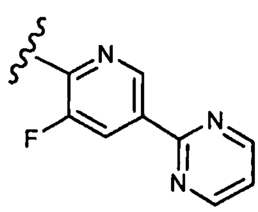
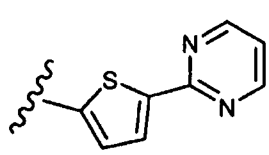
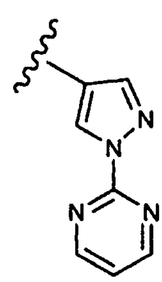
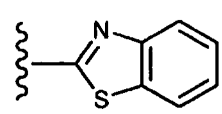


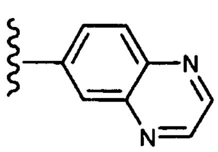
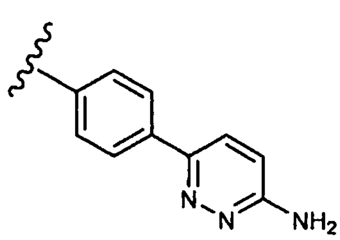
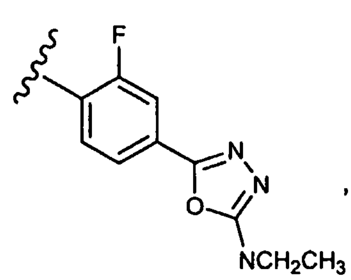
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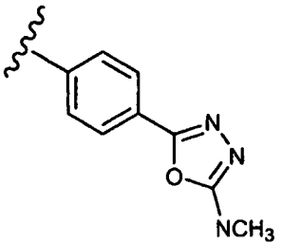
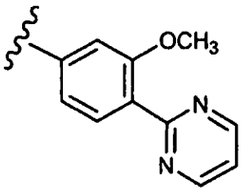
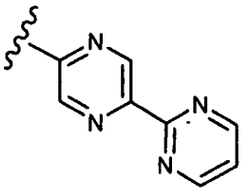
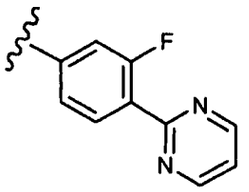
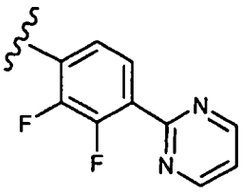
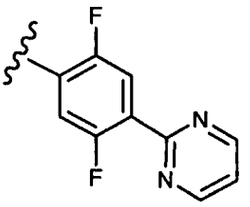
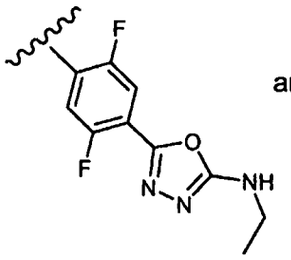
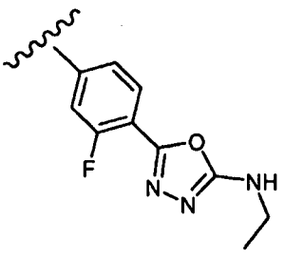
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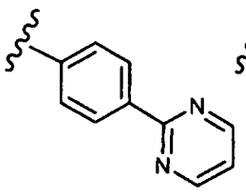
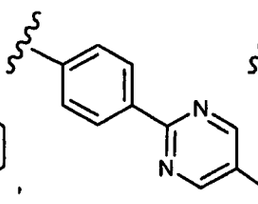
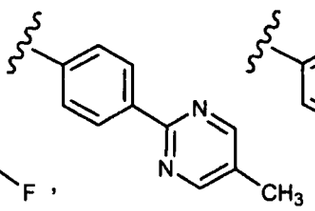
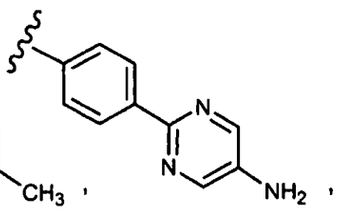
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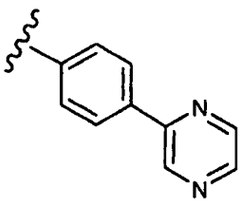
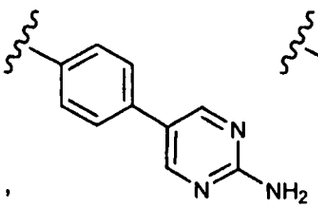
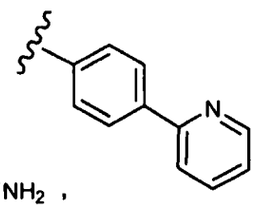
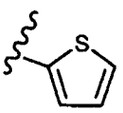
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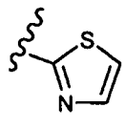
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and


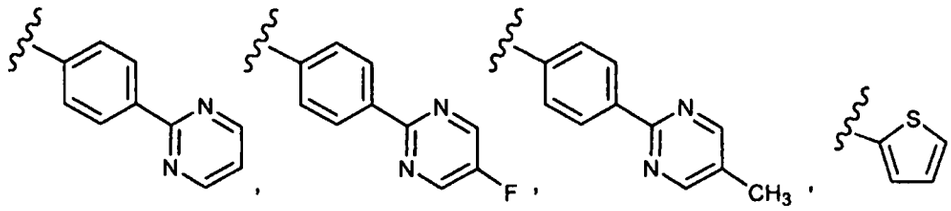
In another embodiment of this invention, R^5 is selected from the group consisting of :

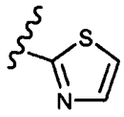





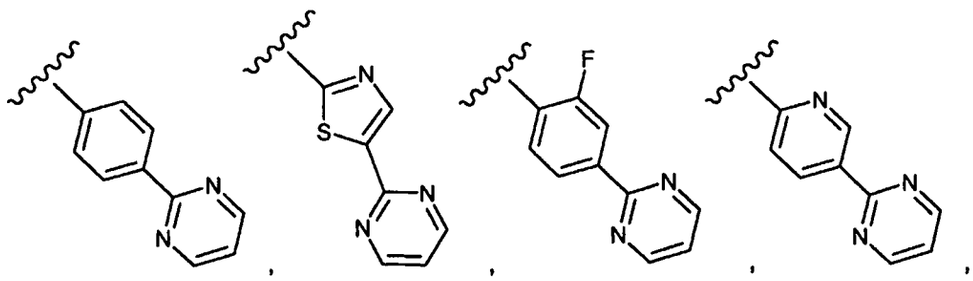
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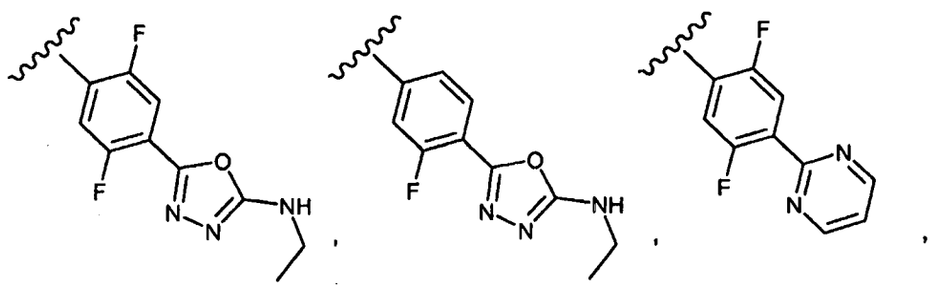
In another embodiment of this invention, R^5 is selected from the group consisting of:

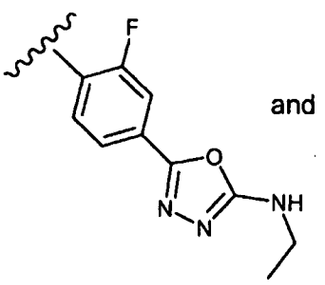


and  .

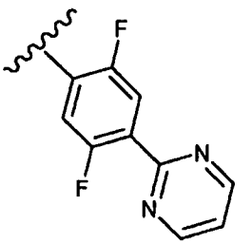
In another embodiment of this invention, R^5 is selected from the group consisting of:



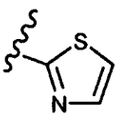




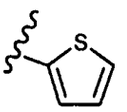
and



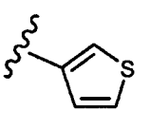
In another embodiment of this invention, R^5 is:



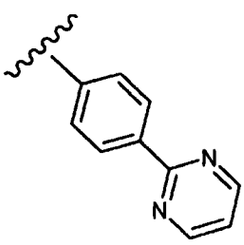
In another embodiment of this invention, R^5 is:



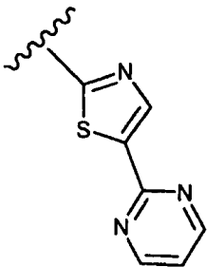
In another embodiment of this invention, R^5 is:



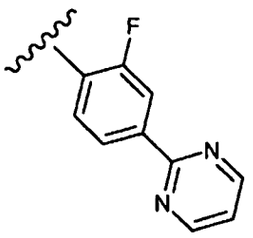
In another embodiment of this invention, R^5 is:



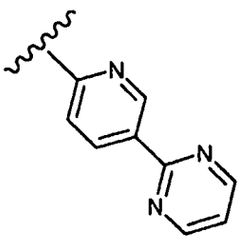
In another embodiment of this invention, R^5 is:



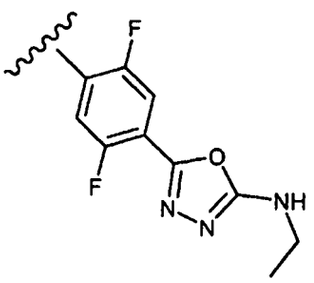
In another embodiment of this invention, R^5 is:



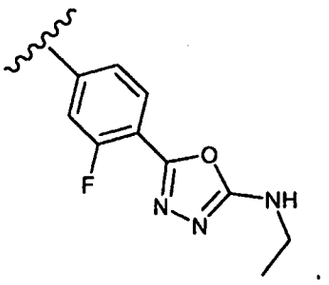
In another embodiment of this invention, R^5 is:



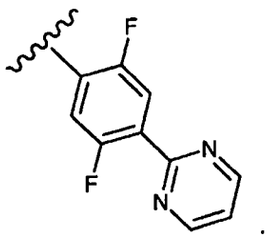
In another embodiment of this invention, R^5 is:



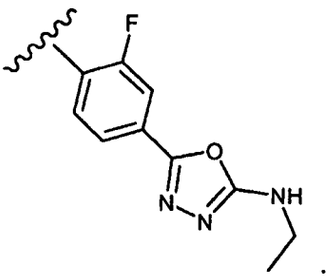
In another embodiment of this invention, R^5 is:



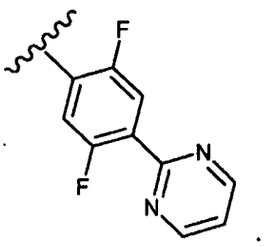
In another embodiment of this invention, R^5 is:



In another embodiment of this invention, R^5 is:



In another embodiment of this invention, R^5 is:



R^2, in one embodiment of this invention, is $-(CH_2)_mR^{11}$, wherein R^{11} is $-OR^{10}$.

R^2, in another embodiment of this invention, is $-(CH_2)_mR^{11}$, wherein R^{11} is $-OR^{10}$, and R^{10} is H or alkyl.

R^2, in another embodiment of this invention, is $-(CH_2)_mR^{11}$, wherein R^{11} is $-OR^{10}$, and R^{10} alkyl (e.g., methyl).

R^2, in another embodiment of this invention, is $-(CH_2)_mR^{11}$, wherein m is 1 and R^{11} is $-OR^{10}$.

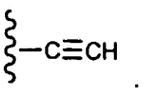
R^2, in another embodiment of this invention, is $-(CH_2)_mR^{11}$, wherein m is 1, R^{11} is $-OR^{10}$, and R^{10} is H or alkyl.

R^2, in another embodiment of this invention, is $-(CH_2)_mR^{11}$, wherein m is 1, R^{11} is $-OR^{10}$, and R^{10} alkyl.

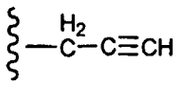
R^2, in another embodiment of this invention, is $-(CH_2)_mR^{11}$, wherein m is 1, R^{11} is $-OR^{10}$, and R^{10} methyl (i.e., R^2 is $-CH_2OCH_3$).

R^2, in another embodiment of this invention, is $-OR^{23}$ wherein R^{23} is alkyl, and said alkyl is methyl (i.e., R^2 is $-OCH_3$).

R^2, in another embodiment of this invention, is alkynyl. An example of an alkynyl group is ethynyl:



Another example of an alkynyl group is propynyl:



R^2, in another embodiment of this invention, is alkenyl. An example of an alkenyl group is $-CH_2-CH=CH_2$.

R^2, in another embodiment of this invention, is $-OCH_3$.

R^2, in another embodiment of this invention, is $-S(O)_t$-alkyl.

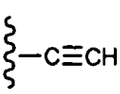
R^2, in another embodiment of this invention, is -S-alkyl (i.e., t is 0) such as, for example, $-S-CH_3$.

R^2, in another embodiment of this invention, is $-S(O)_2$-alkyl (i.e., t is 2) such as, for example, $-S(O)_2CH_3$.

R^2, in another embodiment of this invention, is $-SCH_3$.

R^2, in another embodiment of this invention, is $-S(O)_2CH_3$.

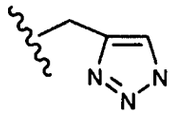
R^2, in another embodiment of this invention, is ethynyl



R^2, in another embodiment of this invention, is $-CH_2OCH_3$.

Preferably R^2 is selected from the group consisting of: ethynyl, $-OCH_3$, and $-CH_2OCH_3$.

Additional examples of the R^2 $-(CH_2)_mR^{11}$ group include, but are not limited to $-CH_2OH$, $-CH_2CN$, $-CH_2OC_2H_5$, $-(CH_2)_3OCH_3$, $-CH_2F$ and $-CH_2$-triazolyl, such as,



Additional examples of R^2 include, but are not limited to, H, $-CH_2$-morpholinyl, $-SCH_3$, $-OC_2H_5$, $-OCH(CH_3)_2$, $-CH_2N(CH_3)_2$, -CN, $-CH(OH)CH_3$, $-C(O)CH_3$, $-CH_2C{\equiv}CCH_3$, $-CH(CH_3)_2$, $-C(CH_3)=CH_2$, $-C(CH_3)=NOCH_3$, $-C(CH_3)=NOH$, $-C(CH_3)=NNHC(O)CH_3$, $-NH_2$, $-NHC(O)H$, $-NHCH_3$, $-CH_2$-O-CH_2-cyclopropyl, $-CH_2$-O-CHF_2, $-OCHF_2$, $-CHF_2$, $-CH_2C(CH_3)=CH_3$, $-CH_2CH_2CH_3$, $-N(CH_3)_2$, $-CH_2CH_3$, $-CF_3$, $-CH=CH_2$, and $-C(OH)(CH_3)_2$.

R^3, in one embodiment of this invention, is independently selected from the group consisting of: H and alkyl.

R^3, in another embodiment of this invention, is independently selected from the group consisting of: H and methyl.

R^3, in another embodiment of this invention, is H.

R^4, in one embodiment of this invention, is H.

R^4, in another embodiment of this invention, is selected from the group consisting of: H and alkyl.

R^4, in another embodiment of this invention, is selected from the group consisting of: H and methyl.

R^6, in one embodiment of this invention, is R^6 H.

R^7, in one embodiment of this invention, is independently selected from the group consisting of: H and alkyl.

R^7, in another embodiment of this invention, is independently selected from the group consisting of: H and methyl.

R^7, in one embodiment of this invention, is H.

R^8, in one embodiment of this invention, is H.

Y^1, in one embodiment of this invention, is carbon.

Y^2, in one embodiment of this invention, is carbon.

Y^3 in one embodiment of this invention, is carbon.

Y^1, Y^2 and Y^3, in one embodiment of this invention, are carbon.

One embodiment of this invention is directed to a compound of formula 1.0, preferably a compound of formula 1.0C1 and more preferably a compound of formula 1.0C, (e.g., 1.1, 1.1A, 1.2, 1.2A, 1.3 or 1.3A) wherein substituent Q is 2.16, and each R^3, R^4, and R^7 is independently selected from the group consisting of: H and methyl.

One embodiment of this invention is directed to a compound of formula 1.0, preferably a compound of formula 1.0C1 and more preferably a compound of formula 1.0C, (e.g., 1.1, 1.1A, 1.2, 1.2A, 1.3 or 1.3A) wherein substituent Q is 2.16A, and each R^3, R^4, and R^7 is independently selected from the group consisting of: H and methyl.

One embodiment of this invention is directed to a compound of formula 1.0, preferably a compound of formula 1.0C1 and more preferably a compound of formula 1.0C, (e.g., 1.1, 1.1A, 1.2, 1.2A, 1.3 or 1.3A) wherein substituent Q is 2.16B, and each R^3, R^4, and R^7 is independently selected from the group consisting of: H and methyl.

One embodiment of this invention is directed to a compound of formula 1.0, preferably a compound of formula 1.0C1 and more preferably a compound of formula 1.0C, (e.g., 1.1, 1.1A, 1.2, 1.2A, 1.3 or 1.3A) wherein substituent Q is 2.16, and each R^3, R^4, and R^7 is H.

One embodiment of this invention is directed to a compound of formula 1.0, preferably a compound of formula 1.0C1 and more preferably a compound of formula 1.0C, (e.g., 1.1, 1.1A, 1.2, 1.2A, 1.3 or 1.3A) wherein substituent Q is 2.16A, and each R^3, R^4, and R^7 is H.

One embodiment of this invention is directed to a compound of formula 1.0, preferably a compound of formula 1.0C1 and more preferably a compound of formula 1.0C, (e.g., 1.1, 1.1A, 1.2, 1.2A, 1.3 or 1.3A) wherein substituent Q is 2.16B, and each R^3, R^4, and R^7 is H.

The compounds of this invention inhibit the activity of ERK1 and ERK2 Thus, this invention further provides a method of inhibiting ERK in mammals, especially humans, by the administration of an effective amount (e.g., a therapeutically effective amount) of one or more (e.g., one) compounds of this invention. The administration of the compounds of this invention to patients, to inhibit ERK1 and/or ERK2, is useful in the treatment of cancer.

In any of the methods of treating cancer described herein, unless stated otherwise, the methods can optionally include the administration of an effective amount of one or more (e.g., 1, 2 or 3, or 1 or 2, or 1) chemotherapeutic agents. The chemotherapeutic agents can be administered currently or sequentially with the compounds of this invention.

The methods of treating cancer described herein include methods wherein a combination of drugs (i.e., compounds, or pharmaceutically active ingredients, or pharmaceutical compositions) are used (i.e., the methods of treating cancer of this invention include combination therapies). Those skilled in the art will appreciate that the drugs are generally administered individually as a pharmaceutical composition. The use of a pharmaceutical composition comprising more than one drug is within the scope of this invention.

In any of the methods of treating cancer described herein, unless stated otherwise, the methods can optionally include the administration of an effective amount of radiation therapy. For radiation therapy, γ-radiation is preferred.

Examples of cancers which may be treated by the methods of this invention include, but are not limited to: (A) lung cancer (e.g., lung adenocarcinoma and non small cell lung cancer), (B) pancreatic cancers (e.g., pancreatic carcinoma such as, for example, exocrine pancreatic carcinoma), (C) colon cancers (e.g., colorectal carcinomas, such as, for example, colon adenocarcinoma and colon adenoma), (D) myeloid leukemias (for example, acute myelogenous leukemia (AML), CML, and CMML), (E) thyroid cancer, (F) myelodysplastic syndrome (MDS), (G) bladder carcinoma, (H) epidermal carcinoma, (I) melanoma, (J) breast cancer, (K) prostate cancer, (L) head and neck cancers (e.g., squamous cell cancer of the head and neck), (M) ovarian cancer, (N) brain cancers (e.g., gliomas, such as glioma blastoma multiforme), (O) cancers of mesenchymal origin (e.g., fibrosarcomas and rhabdomyosarcomas), (P) sarcomas, (Q) tetracarcinomas, (R) nuroblastomas, (S) kidney carcinomas, (T) hepatomas, (U) non-Hodgkin's lymphoma, (V) multiple myeloma, and (W) anaplastic thyroid carcinoma.

Chemotherapeutic agents (antineoplastic agent) include but are not limited to: microtubule affecting agents, alkylating agents, antimetabolites, natural products and their derivatives, hormones and steroids (including synthetic analogs), and synthetics.

Examples of alkylating agents (including nitrogen mustards, ethylenimine derivatives, alkyl sulfonates, nitrosoureas and triazenes) include: Uracil mustard, Chlormethine, Cyclophosphamide (Cytoxan®), Ifosfamide, Melphalan, Chlorambucil, Pipobroman, Triethylene-melamine, Triethylenethiophosphoramine, Busulfan, Carmustine, Lomustine, Streptozocin, Dacarbazine, and Temozolomide.

Examples of antimetabolites (including folic acid antagonists, pyrimidine analogs, purine analogs and adenosine deaminase inhibitors) include: Methotrexate, 5-Fluorouracil, Floxuridine, Cytarabine, 6-Mercaptopurine, 6-Thioguanine, Fludarabine phosphate, Pentostatine, and Gemcitabine.

Examples of natural products and their derivatives (including vinca alkaloids, antitumor antibiotics, enzymes, lymphokines and epipodophyllotoxins) include: Vinblastine, Vincristine, Vindesine, Bleomycin, Dactinomycin, Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, Paclitaxel (paclitaxel is a microtubule affecting agent and is commercially available as Taxol®), Paclitaxel derivatives (e.g. taxotere), Mithramycin, Deoxyco-formycin, Mitomycin-C, L-Asparaginase, Interferons (especially IFN-a), Etoposide, and Teniposide.

Examples of hormones and steroids (including synthetic analogs) include: 17α-Ethinylestradiol, Diethylstilbestrol, Testosterone, Prednisone, Fluoxymesterone, Dromostanolone propionate, Testolactone, Megestrolacetate, Tamoxifen, Methylprednisolone, Methyl-testosterone, Prednisolone, Triamcinolone, Chlorotrianisene, Hydroxyprogesterone, Aminoglutethimide, Estramustine, Medroxyprogesteroneacetate, Leuprolide, Flutamide, Toremifene, and Zoladex.

Examples of synthetics (including inorganic complexes such as platinum coordination complexes): Cisplatin, Carboplatin, Hydroxyurea, Amsacrine, Procarbazine, Mitotane, Mitoxantrone, Levamisole, and Hexamethylmelamine.

Examples of other chemotherapeutics include: Navelbene, CPT-11, Anastrazole, Letrazole, Capecitabinbe, Reloxafine, and Droloxafine.

A microtubule affecting agent (e.g., paclitaxel, a paclitaxel derivative or a paclitaxel-like compound), as used herein, is a compound that interferes with cellular mitosis, i.e., having an anti-mitotic effect, by affecting microtubule formation and/or action. Such agents can be, for instance, microtubule stabilizing agents or agents which disrupt microtubule formation.

Microtubule affecting agents, useful in the methods of this invention, are well known to those skilled in the art and include, but are not limited to: Allocolchicine

(NSC 406042), Halichondrin B (NSC 609395), Colchicine (NSC 757), Colchicine derivatives (e.g., NSC 33410), Dolastatin 10 (NSC 376128), Maytansine (NSC 153858), Rhizoxin (NSC 332598), Paclitaxel (Taxol®, NSC 125973), Paclitaxel derivatives (e.g., Taxotere, NSC 608832), Thiocolchicine (NSC 361792), Trityl Cysteine (NSC 83265), Vinblastine Sulfate (NSC 49842), Vincristine Sulfate (NSC 67574), Epothilone A, Epothilone, Discodermolide (see Service, (1996) Science, 274:2009), Estramustine, Nocodazole, MAP4, and the like. Examples of such agents are described in, for example, Bulinski (1997) J. Cell Sci. 110:3055-3064, Panda (1997) Proc. Natl. Acad. Sci. USA 94:10560-10564, Muhlradt (1997) Cancer Res. 57:3344-3346, Nicolaou (1997) Nature 387:268-272, Vasquez (1997) Mol. Biol. Cell. 8:973-985, and Panda (1996) J. Biol. Chem. 271:29807-29812.

Chemotherapeutic agents with paclitaxel-like activity include, but are not limited to, paclitaxel and paclitaxel derivatives (paclitaxel-like compounds) and analogues. Paclitaxel and its derivatives (e.g. Taxol and Taxotere) are available commercially. In addition, methods of making paclitaxel and paclitaxel derivatives and analogues are well known to those of skill in the art (see, e.g., U.S. Patent Nos: 5,569,729; 5,565,478; 5,530,020; 5,527,924; 5,508,447; 5,489,589; 5,488,116; 5,484,809; 5,478,854; 5,478,736; 5,475,120; 5,468,769; 5,461,169; 5,440,057; 5,422,364; 5,411,984; 5,405,972; and 5,296,506).

More specifically, the term "paclitaxel" as used herein refers to the drug commercially available as Taxol® (NSC number: 125973). Taxol® inhibits eukaryotic cell replication by enhancing polymerization of tubulin moieties into stabilized microtubule bundles that are unable to reorganize into the proper structures for mitosis. Of the many available chemotherapeutic drugs, paclitaxel has generated interest because of its efficacy in clinical trials against drug-refractory tumors, including ovarian and mammary gland tumors (Hawkins (1992) Oncology, 6: 17-23, Horwitz (1992) Trends Pharmacol. Sci. 13: 134-146, Rowinsky (1990) J. Natl. Canc. Inst. 82: 1247-1259).

Additional microtubule affecting agents can be assessed using one of many such assays known in the art, e.g., a semiautomated assay which measures the tubulin-polymerizing activity of paclitaxel analogs in combination with a cellular assay to measure the potential of these compounds to block cells in mitosis (see Lopes (1997) Cancer Chemother. Pharmacol. 41:37-47).

Generally, activity of a test compound is determined by contacting a cell with that compound and determining whether or not the cell cycle is disrupted, in particular, through the inhibition of a mitotic event. Such inhibition may be mediated by disruption of the mitotic apparatus, e.g., disruption of normal spindle formation. Cells in which mitosis is interrupted may be characterized by altered morphology (e.g., microtubule compaction, increased chromosome number, etc.).

Compounds with possible tubulin polymerization activity can be screened in vitro. For example, the compounds are screened against cultured WR21 cells (derived from line 69-2 wap-ras mice) for inhibition of proliferation and/or for altered cellular morphology, in particular for microtubule compaction. In vivo screening of positive-testing compounds can then be performed using nude mice bearing the WR21 tumor cells. Detailed protocols for this screening method are described by Porter (1995) Lab. Anim. Sci., 45(2):145-150.

Other methods of screening compounds for desired activity are well known to those of skill in the art. Typically such assays involve assays for inhibition of microtubule assembly and/or disassembly. Assays for microtubule assembly are described, for example, by Gaskin et al. (1974) J. Molec. Biol., 89: 737-758. U.S. Patent No. 5,569,720 also provides in vitro and in vivo assays for compounds with paclitaxel-like activity.

Thus, in the methods of this invention wherein at least one chemotherapeutic agent is used, examples of said chemotherapeutic agents include those selected from the group consisting of: microtubule affecting agents, alkylating agents, antimetabolites, natural products and their derivatives, hormones and steroids (including synthetic analogs), and synthetics.

In the methods of this invention wherein at least one chemotherapeutic agent is used, examples of said chemotherapeutic agents also include: (1) taxanes, (2) platinum coordinator compounds, (3) epidermal growth factor (EGF) inhibitors that are antibodies, (4) EGF inhibitors that are small molecules, (5) vascular endolithial growth factor (VEGF) inhibitors that are antibodies, (6) VEGF kinase inhibitors that are small molecules, (7) estrogen receptor antagonists or selective estrogen receptor modulators (SERMs), (8) anti-tumor nucleoside derivatives, (9) epothilones, (10) topoisomerase inhibitors, (11) vinca alkaloids, (12) antibodies that are inhibitors of $\alpha V\beta 3$ integrins, (13) folate antagonists, (14) ribonucleotide reductase inhibitors, (15) anthracyclines, (16) biologics; (17) inhibitors of angiogenesis and/or suppressors of

tumor necrosis factor alpha (TNF-alpha) such as thalidomide (or related imid), (18) Bcr/abl kinase inhibitors, (19) MEK1 and/or MEK 2 inhibitors that are small molecules, (20) IGF-1 and IGF-2 inhibitors that are small molecules, (21) small molecule inhibitors of RAF and BRAF kinases, (22) small molecule inhibitors of cell cycle dependent kinases such as CDK1, CDK2, CDK4 and CDK6, (23) alkylating agents, and (24) farnesyl protein transferase inhibitors (also know as FPT inhibitors or FTI (i.e., farnesyl transfer inhibitors)).

In the methods of this invention wherein at least one chemotherapeutic agent is used, examples of such chemotherapeutic agents include:

(1) taxanes such as paclitaxel (TAXOL®) and/or docetaxel (Taxotere®);

(2) platinum coordinator compounds, such as, for example, carboplatin, cisplatin and oxaliplatin (e.g. Eloxatin);

(3) EGF inhibitors that are antibodies, such as: HER2 antibodies (such as, for example trastuzumab (Herceptin®), Genentech, Inc.), Cetuximab (Erbitux, IMC-C225, ImClone Systems), EMD 72000 (Merck KGaA), anti-EFGR monoclonal antibody ABX (Abgenix), TheraCIM-h-R3 (Center of Molecular Immunology), monoclonal antibody 425 (Merck KGaA), monoclonal antibody ICR-62 (ICR, Sutton, England); Herzyme (Elan Pharmaceutical Technologies and Ribozyme Pharmaceuticals), PKI 143 (Novartis), EKB 569 (Wyeth-Ayerst), GW 572016 (GlaxoSmithKline), CI 1033 (Pfizer Global Research and Development), trastuzmab-maytansinoid conjugate (Genentech, Inc.), mitumomab (Imclone Systems and Merck KGaA) and Melvax II (Imclone Systems and Merck KgaA);

(4) EGF inhibitors that are small molecules, such as, Tarceva (TM) (OSI-774, OSI Pharmaceuticals, Inc.), and Iressa (ZD 1839, Astra Zeneca);

(5) VEGF inhibitors that are antibodies such as: bevacizumab (Genentech, Inc.), and IMC-1C11 (ImClone Systems), DC 101 (a KDR VEGF Receptor 2 from ImClone Systems);

(6) VEGF kinase inhibitors that are small molecules such as SU 5416 (from Sugen, Inc), SU 6688 (from Sugen, Inc.), Bay 43-9006 (a dual VEGF and bRAF inhibitor from Bayer Pharmaceuticals and Onyx Pharmaceuticals);

(7) estrogen receptor antagonists or selective estrogen receptor modulators (SERMs), such as tamoxifen, idoxifene, raloxifene, trans-2,3-dihydroraloxifene, levormeloxifene, droloxifene, MDL 103,323, and acolbifene (Schering Corp.);

(8) anti-tumor nucleoside derivatives such as 5-fluorouracil, gemcitabine, capecitabine, cytarabine (Ara-C), fludarabine (F-Ara-A), decitabine, and chlorodeoxyadenosine (Cda, 2-Cda);

(9) epothilones such as BMS-247550 (Bristol-Myers Squibb), and EPO906 (Novartis Pharmaceuticals);

(10) topoisomerase inhibitors such as topotecan (Glaxo SmithKline), and Camptosar (Pharmacia);

(11) vinca alkaloids, such as, navelbine (Anvar and Fabre, France), vincristine and vinblastine;

(12) antibodies that are inhibitors of $\alpha V\beta 3$ integrins, such as, LM-609 (see, Clinical Cancer Research, Vol. 6, page 3056-3061, August 2000, the disclosure of which is incorporated herein by reference thereto);

(13) folate antagonists, such as Methotrexate (MTX), and Premetrexed (Alimta);

(14) ribonucleotide reductase inhibitors, such as Hydroxyurea (HU);

(15) anthracyclines, such as Daunorubicin, Doxorubicin (Adriamycin), and Idarubicin;

(16) biologics, such as interferon (e.g., Intron-A and Roferon), pegylated interferon (e.g., Peg-Intron and Pegasys), and Rituximab (Rituxan, antibody used for the treatment of non-Hodgkin's lymphoma);

(17) thalidomide (or related imid);

(18) Bcr/abl kinase inhibitors, such as, for example Gleevec (STI-571), AMN-17, ONO12380, SU11248 (Sunitinib) and BMS-354825

(19) MEK1 and/or MEK2 inhibitors, such as PD0325901 and Arry-142886 (AZD6244);

(20) IGF-1 and IGF-2 inhibitors that are small molecules, such as, for example, NVP-AEW541;

(21) small molecule inhibitors of RAF and BRAF kinases, such as, for example, BAY 43-9006 (Sorafenib);

(22) small molecule inhibitors of cell cycle dependent kinases such as CDK1, CDK2, CDK4 and CDK6, such as, for example, CYC202, BMS387032, and Flavopiridol;

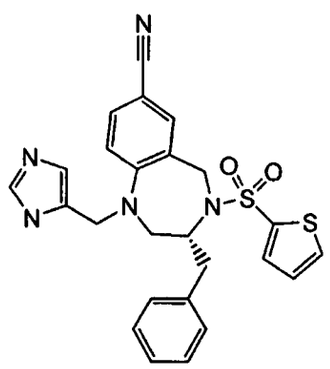
(23) alkylating agents, such as, for example, Temodar® brand of temozolomide;

(24) farnesyl protein transferase inhibitors, such as, for example:

(a) Sarasar® brand of lonifarnib (i.e., 4-[2-[4-(3,10-dibromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-*b*]byridin-11-yl)-1-piperidinyl)-2-oxoethyl]-1-piperidinecarboxamide, see for example, U.S. 5,874,442 issued February 23, 1999, and U.S. 6,632,455 issued October 14, 2003 the disclosures of each being incorporated herein by reference thereto),

(b) Zarnestra® brand of tipifarnib (i.e., (R)-6-amino[(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl)methyl]-4-(3-chlorophenyl)-1- methyl-2(1H)-quinolinone, see for example, WO 97/16443 published May 9, 1997 and U.S. 5,968,952 issued October 19, 1999, the disclosures of each being incorporated herein by reference thereto), and

(c) Bristol-Myers Squibb 214662:



(see WO97/30992 published August 28, 1997, U.S. 6,011,029 issued January 4, 2000, and U.S. 6,455,523, the disclosures of each being incorporated herein by reference thereto).

The Bcr/abl kinase inhibitors, EGF receptor inhibitors, and HER-2 antibodies (EGF receptor inhibitors that are antibodies) described above are also known as signal transduction inhibitors. Therefore, chemotherapeutic agents, as used herein, include signal transduction inhibitors.

Typical signal transduction inhibitors, that are chemotherapeutic agents, include but are not limited to: (i) Bcr/abl kinase inhibitors such as, for example, STI 571 (Gleevec), (ii) Epidermal growth factor (EGF) receptor inhibitor such as, for example, Kinase inhibitors (Iressa, OSI-774) and antibodies (Imclone: C225 [Goldstein et al. (1995), Clin Cancer Res. 1:1311-1318], and Abgenix: ABX-EGF) and (iii) HER-2/neu receptor inhibitors such as, for example, Herceptin® (trastuzumab).

Methods for the safe and effective administration of most of these chemotherapeutic agents are known to those skilled in the art. In addition, their administration is described in the standard literature. For example, the administration of many of the chemotherapeutic agents is described in the "Physicians' Desk Reference" (PDR), e.g., 1996 edition (Medical Economics Company, Montvale, NJ 07645-1742, USA), the Physician's Desk Reference, 56th Edition, 2002 (published by Medical Economics company, Inc. Montvale, NJ 07645-1742), and the Physician's Desk Reference, 57th Edition, 2003 (published by Thompson PDR, Montvale, NJ 07645-1742); the disclosures of which is incorporated herein by reference thereto.

For example, the compound of formula 1.0 (e.g., a pharmaceutical composition comprising the compound of formula 1.0); can be administered orally (e.g., as a capsule), and the chemotherapeutic agents can be administered intravenously, usually as an IV solution. The use of a pharmaceutical composition comprising more than one drug is within the scope of this invention.

The compound of formula 1.0 and the chemotherapeutic agents are administered in therapeutically effective dosages to obtain clinically acceptable results, e.g., reduction or elimination of symptoms or of the tumor. Thus, the compound of formula 1.0 and chemotherapeutic agents can be administered concurrently or consecutively in a treatment protocol. The administration of the chemotherapeutic agents can be made according to treatment protocols already known in the art.

In general when more than one chemotherapeutic agent is used in the methods of this invention, the chemotherapeutic agents are administered on the same day either concurrently or consecutively in their standard dosage form. For example, the chemotherapeutic agents are usually administered intravenously, preferably by an IV drip using IV solutions well known in the art (e.g., isotonic saline (0.9% NaCl) or dextrose solution (e.g., 5% dextrose)).

When two or more chemotherapeutic agents are used, the chemotherapeutic agents are generally administered on the same day; however, those skilled in the art will appreciate that the chemotherapeutic agents can be administered on different days and in different weeks. The skilled clinician can administer the chemotherapeutic agents according to their recommended dosage schedule from the manufacturer of the agent and can adjust the schedule according to the needs of the patient, e.g., based on the patient's response to the treatment. For example, when

gemcitabine is used in combination with a platinum coordinator compound, such as, for example, cisplatin, to treat lung cancer, both the gemcitabine and the cisplatin are given on the same day on day one of the treatment cycle, and then gemcitabine is given alone on day 8 and given alone again on day 15

The compounds of this invention and chemotherapeutic agents can be administered in a treatment protocol that usually lasts one to seven weeks, and is repeated typically from 6 to 12 times. Generally the treatment protocol can last one to four weeks. Treatment protocols of one to three weeks can also be used. A treatment protocol of one to two weeks can also be used. During this treatment protocol or cycle the compounds of this invention can be administered daily while the chemotherapeutic agents can be administered one or more times a week. Generally, a compound of this invention can be administered daily (i.e., once per day), and in one embodiment twice per day, and the chemotherapeutic agent is administered once a week or once every three weeks. For example, the taxanes (e.g., Paclitaxel (e.g., Taxol®) or Docetaxel (e.g.,Taxotere®)) can be administered once a week or once every three weeks.

However, those skilled in the art will appreciate that treatment protocols can be varied according to the needs of the patient. Thus, the combination of compounds (drugs) used in the methods of this invention can be administered in variations of the protocols described above. For example, the compounds of this invention can be administered discontinuously rather than continuously during the treatment cycle. Thus, for example, during the treatment cycle the compounds of this invention can be administered daily for a week and then discontinued for a week, with this administration repeating during the treatment cycle. Or the compounds of this invention can be administered daily for two weeks and discontinued for a week, with this administration repeating during the treatment cycle. Thus, the compounds of this invention can be administered daily for one or more weeks during the cycle and discontinued for one or more weeks during the cycle, with this pattern of administration repeating during the treatment cycle. This discontinuous treatment can also be based upon numbers of days rather than a full week. For example, daily dosing for 1 to 6 days, no dosing for 1 to 6 days with this pattern repeating during the treatment protocol. The number of days (or weeks) wherein the compounds of this invention are not dosed do not have to equal the number of days (or weeks) wherein the compounds of this invention are dosed. Usually, if a discontinuous dosing

protocol is used, the number of days or weeks that the compounds of this invention are dosed is at least equal or greater than the number of days or weeks that the compounds of this invention are not dosed.

The chemotherapeutic agent could be given by bolus or continuous infusion. The chemotherapeutic agent could be given daily to once every week, or once every two weeks, or once every three weeks, or once every four weeks during the treatment cycle. If administered daily during a treatment cycle, this daily dosing can be discontinuous over the number of weeks of the treatment cycle. For example, dosed for a week (or a number of days), no dosing for a week (or a number of days, with the pattern repeating during the treatment cycle.

The compounds of this invention can be administered orally, preferably as a solid dosage form, and in one embodiment as a capsule, and while the total therapeutically effective daily dose can be administered in one to four, or one to two divided doses per day, generally, the therapeutically effective dose is given once or twice a day, and in one embodiment twice a day. The compounds of this invention can be administered in an amount of about 50 to about 400 mg once per day, and can be administered in an amount of about 50 to about 300 mg once per day. The compounds of this invention are generally administered in an amount of about 50 to about 350 mg twice a day, usually 50 mg to about 200 mg twice a day, and in one embodiment about 75 mg to about 125 mg administered twice a day, and in another embodiment about 100 mg administered twice a day.

If the patient is responding, or is stable, after completion of the therapy cycle, the therapy cycle can be repeated according to the judgment of the skilled clinician. Upon completion of the therapy cycles, the patient can be continued on the compounds of this invention at the same dose that was administered in the treatment protocol, or, if the dose was less than 200mg twice a day, the dose can be raised to 200 mg twice a day. This maintenance dose can be continued until the patient progresses or can no longer tolerate the dose (in which case the dose can be reduced and the patient can be continued on the reduced dose).

The chemotherapeutic agents, used with the compounds of this invention, are administered in their normally prescribed dosages during the treatment cycle (i.e., the chemotherapeutic agents are administered according to the standard of practice for the administration of these drugs). For example: (a) about 30 to about 300 mg/m^2 for the taxanes; (b) about 30 to about 100 mg/m^2 for Cisplatin; (c) AUC of about 2 to

about 8 for Carboplatin; (d) about 2 to about 4 mg/m^2 for EGF inhibitors that are antibodies; (e) about 50 to about 500 mg/m^2 for EGF inhibitors that are small molecules; (f) about 1 to about 10 mg/m^2 for VEGF kinase inhibitors that are antibodies; (g) about 50 to about 2400 mg/m^2 for VEGF inhibitors that are small molecules; (h) about 1 to about 20 mg for SERMs; (i) about 500 to about 1250 mg/m^2 for the anti-tumor nucleosides 5-Fluorouracil, Gemcitabine and Capecitabine; (j) for the anti-tumor nucleoside Cytarabine (Ara-C) 100-200mg/m^2/day for 7 to 10 days every 3 to 4 weeks, and high doses for refractory leukemia and lymphoma, i.e., 1 to 3 gm/m^2 for one hour every 12 hours for 4-8 doses every 3 to four weeks; (k) for the anti-tumor nucleoside Fludarabine (F-ara-A) 10-25mg/m^2/day every 3 to 4 weeks; (l) for the anti-tumor nucleoside Decitabine 30 to 75 mg/m^2 for three days every 6 weeks for a maximum of 8 cycles; (m) for the anti-tumor nucleoside Chlorodeoxyadenosine (CdA, 2-CdA) 0.05-0.1 mg/kg/day as continuous infusion for up to 7 days every 3 to 4 weeks; (n) about 1 to about 100 mg/m^2 for epothilones; (o) about 1 to about 350 mg/m^2 for topoisomerase inhibitors; (p) about 1 to about 50 mg/m^2 for vinca alkaloids; (q) for the folate antagonist Methotrexate (MTX) 20-60 mg/m^2 by oral, IV or IM every 3 to 4 weeks, the intermediate dose regimen is 80-250 mg/m^2 IV over 60 minutes every 3 to 4 weeks, and the high dose regimen is 250-1000mg/m^2 IV given with leucovorin every 3 to 4 weeks; (r) for the folate antagonist Premetrexed (Alimta) 300-600 mg/m^2 (10 minutes IV infusion day 1) every 3 weeks; (s) for the ribonucleotide reductase inhibitor Hydroxyurea (HU) 20-50 mg/kg/day (as needed to bring blood cell counts down); (t) the platinum coordinator compound Oxaliplatin (Eloxatin) 50-100 mg/m^2 every 3 to 4 weeks (preferably used for solid tumors such as non-small cell lung cancer, colorectal cancer and ovarian cancer); (u) for the anthracycline daunorubicin 10-50 mg/m^2/day IV for 3-5 days every 3 to 4 weeks; (v) for the anthracycline Doxorubicin (Adriamycin) 50-100 mg/m^2 IV continuous infusion over 1-4 days every 3 to 4 weeks, or 10-40 mg/m^2 IV weekly; (w) for the anthracycline Idarubicin 10-30 mg/m^2 daily for 1-3 days as a slow IV infusion over 10-20 minutes every 3 to 4 weeks; (x) for the biologic interferon (Intron-A, Roferon) 5 to 20 million IU three times per week; (y) for the biologic pegylated interferon (Peg-intron, Pegasys) 3 to 4 micrograms/kg/day chronic sub cutaneous (until relapse or loss of activity); (z) for the biologic Rituximab (Rituxan) (antibody used for non-Hodgkin's lymphoma) 200-400mg/m^2 IV weekly over 4-8 weeks for 6 months; (aa) for the alkylating agent temozolomide 75 mg/m^2 to 250mg/m^2, for example, 150 mg/m^2, or for example, 200

mg/m^2, such as 200mg/m^2 for 5 days; and (bb) for the MEK1 and/or MEK2 inhibitor PD0325901, 15 mg to 30 mg, for example, 15 mg daily for 21 days every 4 weeks.

Gleevec can be used orally in an amount of about 200 to about 800 mg/day.

Thalidomide (and related imids) can be used orally in amounts of about 200 to about 800 mg/day, and can be contiuously dosed or used until releapse or toxicity. See for example Mitsiades et al., "Apoptotic signaling induced by immunomodulatory thalidomide analoqs in human multiple myeloma cells; therapeutic implications", Blood, 99(12):4525-30, June 15, 2002, the disclosure of which is incorporated herein by reference thereto.

The FPT inhibitor Sarasar® (brand of lonifarnib) can be administered orally (e.g., capsule) in amounts of about 50 to about 200 mg given twice a day, or in amounts of about 75 to about 125 mg given twice a day, or in amounts of about 100 to about 200 mg given twice a day, or in an amount of about 100 mg given twice a day.

Paclitaxel (e.g., Taxol®), for example, can be administered once per week in an amount of about 50 to about 100 mg/m^2 and in another example about 60 to about 80 mg/m^2. In another example Paclitaxel (e.g., Taxol®) can be administered once every three weeks in an amount of about 150 to about 250 mg/m^2 and in another example about 175 to about 225 mg/m^2.

In another example, Docetaxel (e.g., Taxotere®) can be administered once per week in an amount of about 10 to about 45 mg/m^2. In another example Docetaxel (e.g., Taxotere®) can be administered once every three weeks in an amount of about 50 to about 100 mg/m^2.

In another example Cisplatin can be administered once per week in an amount of about 20 to about 40 mg/m^2. In another example Cisplatin can be administered once every three weeks in an amount of about 60 to about 100 mg/m^2.

In another example Carboplatin can be administered once per week in an amount to provide an AUC of about 2 to about 3. In another example Carboplatin can be administered once every three weeks in an amount to provide an AUC of about 5 to about 8.

Other embodiments of this invention are described below. The embodiments have been numbered for the purpose of making it easier to refer to the embodiments. The term "in any one of Embodiment Nos." or the term "of any of Embodiment Nos.",

as used below, means that the particular embodiment using that term is intended to cover any one of the embodiments referred to as if any one of the referred to embodiments had been individually described. "Nos." is an abbreviation for Numbers.

Embodiment No. 1 is directed to a compound of formula 1.0, preferably a compound of formula 1.0C, wherein Q is selected from the group consisting of substituents 2.1, 2.2, 2.3, 2.3A, 2.3B, 2.3C, 2.4A, 2.4B, 2.4C, 2.5A, 2.5B, 2.5C, 2.6A, 2.7A, 2.7B, 2.7C, 2.8A, 2.8B, 2.8C, 2.9 to 2.14, 2.15, 2.16 (e.g., 2.16A or 2.16B), 2.17, 2.17A, 2.17B, 2.17C, 2.17D, 2.17E, 2.18, 2.19, 2.20, 2.21 and 2.22.

Embodiment No. 2 is directed to a compound of formula 1.1 wherein Q is selected from the group consisting of substituents 2.1, 2.2, 2.3, 2.3A, 2.3B, 2.3C, 2.4A, 2.4B, 2.4C, 2.5A, 2.5B, 2.5C, 2.6A, 2.7A, 2.7B, 2.7C, 2.8A, 2.8B, 2.8C, 2.9 to 2.14, 2.15, 2.16 (e.g., 2.16A or 2.16B), 2.17, 2.17A, 2.17B, 2.17C, 2.17D, 2.17E, 2.18, 2.19, 2.20, 2.21 and 2.22.

Embodiment No. 3 is directed to a compound of formula 1.2 wherein Q is selected from the group consisting of substituents 2.1, 2.2, 2.3, 2.3A, 2.3B, 2.3C, 2.4A, 2.4B, 2.4C, 2.5A, 2.5B, 2.5C, 2.6A, 2.7A, 2.7B, 2.7C, 2.8A, 2.8B, 2.8C, 2.9 to 2.14, 2.15, 2.16 (e.g., 2.16A or 2.16B), 2.17, 2.17A, 2.17B, 2.17C, 2.17D, 2.17E, 2.18, 2.19, 2.20, 2.21 and 2.22.

Embodiment No. 4 is directed to a compound of formula 1.3 wherein Q is selected from the group consisting of substituents 2.1, 2.2, 2.3, 2.3A, 2.3B, 2.3C, 2.4A, 2.4B, 2.4C, 2.5A, 2.5B, 2.5C, 2.6A, 2.7A, 2.7B, 2.7C, 2.8A, 2.8B, 2.8C, 2.9 to 2.14, 2.15, 2.16 (e.g., 2.16A or 2.16B), 2.17, 2.17A, 2.17B, 2.17C, 2.17D, 2.17E, 2.18, 2.19, 2.20, 2.21 and 2.22.

Embodiment No. 5 is directed to a compound of formula 1.0, preferably a compound of formula 1.0C1 and more preferably a compound of formula 1.0C, (e.g., 1.1, 1.1A, 1.2, 1.2A, 1.3 or 1.3A) wherein substituent Q is 2.1.

Embodiment No. 6 is directed to a compound of formula 1.0, preferably a compound of formula 1.0C1 and more preferably a compound of formula 1.0C, (e.g., 1.1, 1.1A, 1.2, 1.2A, 1.3 or 1.3A) wherein substituent Q is 2.2.

Embodiment No. 7 is directed to a compound of formula 1.0 (e.g., 1.1, 1.1A, 1.2, 1.2A, 1.3 or 1.3A) wherein substituent Q is 2.3 (e.g., 2.3A, 2.3B or 2.3C).

Embodiment No. 8 is directed to a compound of formula 1.0, preferably a compound of formula 1.0C, (e.g., 1.1, 1.1A, 1.2, 1.2A, 1.3 or 1.3A) wherein substituent Q is 2.4 (e.g., 2.4A, 2.4B or 2.4C).

Embodiment No. 9 is directed to a compound of formula 1.0, preferably a compound of formula 1.0C1 and more preferably a compound of formula 1.0C, (e.g., 1.1, 1.1A, 1.2, 1.2A, 1.3 or 1.3A) wherein substituent Q is 2.5 (e.g., 2.5A, 2.5B or 2.5C).

Embodiment No. 10 is directed to any of compounds of formulas to a compound of formula 1.0, preferably a compound of formula 1.0C1 and more preferably a compound of formula 1.0C, (e.g., 1.1, 1.1A, 1.2, 1.2A, 1.3 or 1.3A) wherein substituent Q is 2.6 (e.g., 2.6A).

Embodiment No. 11 is directed to a compound of formula 1.0, preferably a compound of formula 1.0C1 and more preferably a compound of formula 1.0C, (e.g., 1.1, 1.1A, 1.2, 1.2A, 1.3 or 1.3A) wherein substituent Q is 2.7.

Embodiment No. 12 is directed to a compound of formula 1.0, preferably a compound of formula 1.0C1 and more preferably a compound of formula 1.0C, (e.g., 1.1, 1.1A, 1.2, 1.2A, 1.3 or 1.3A) wherein substituent Q is 2.8.

Embodiment No. 13 is directed to a compound of formula 1.0, preferably a compound of formula 1.0C1 and more preferably a compound of formula 1.0C, (e.g., 1.1, 1.1A, 1.2, 1.2A, 1.3 or 1.3A) wherein substituent Q is 2.9.

Embodiment No. 14 is directed to a compound of formula 1.0, preferably a compound of formula 1.0C1 and more preferably a compound of formula 1.0C, (e.g., 1.1, 1.1A, 1.2, 1.2A, 1.3 or 1.3A) wherein substituent Q is 2.10.

Embodiment No. 15 is directed to a compound of formula 1.0, preferably a compound of formula 1.0C1 and more preferably a compound of formula 1.0C, (e.g., 1.1, 1.1A, 1.2, 1.2A, 1.3 or 1.3A) wherein substituent Q is 2.11.

Embodiment No. 16 is directed to a compound of formula 1.0, preferably a compound of formula 1.0C1 and more preferably a compound of formula 1.0C, (e.g., 1.1, 1.1A, 1.2, 1.2A, 1.3 or 1.3A) wherein substituent Q is 2.12.

Embodiment No. 17 is directed to a compound of formula 1.0, preferably a compound of formula 1.0C1 and more preferably a compound of formula 1.0C, (e.g., 1.1, 1.1A, 1.2, 1.2A, 1.3 or 1.3A) wherein substituent Q is 2.13.

Embodiment No. 18 is directed to a compound of formula 1.0, preferably a compound of formula 1.0C1 and more preferably a compound of formula 1.0C, (e.g., 1.1, 1.1A, 1.2, 1.2A, 1.3 or 1.3A) wherein substituent Q is 2.14.

Embodiment No. 19 is directed to a compound of formula 1.0, preferably a compound of formula 1.0C1 and more preferably a compound of formula 1.0C, (e.g., 1.1, 1.1A, 1.2, 1.2A, 1.3 or 1.3A) wherein substituent Q is 2.15.

Embodiment No. 20 is directed to a compound of formula 1.0, preferably a compound of formula 1.0C1 and more preferably a compound of formula 1.0C, (e.g., 1.1, 1.1A, 1.2, 1.2A, 1.3 or 1.3A) wherein substituent Q is 2.16.

Embodiment No. 21 is directed to a compound of formula 1.0, preferably a compound of formula 1.0C1 and more preferably a compound of formula 1.0C, (e.g., 1.1, 1.1A, 1.2, 1.2A, 1.3 or 1.3A) wherein substituent Q is 2.17 (e.g., 2.17A, 2.17B, 2.17C, 2.17D, or 2.17E).

Embodiment No. 22 is directed to a compound of formula 1.0, preferably a compound of formula 1.0C1 and more preferably a compound of formula 1.0C, (e.g., 1.1, 1.1A, 1.2, 1.2A, 1.3 or 1.3A) wherein substituent Q is 2.18.

Embodiment No. 23 is directed to a compound of formula 1.0, preferably a compound of formula 1.0C1 and more preferably a compound of formula 1.0C, (e.g., 1.1, 1.1A, 1.2, 1.2A, 1.3 or 1.3A) wherein substituent Q is 2.19.

Embodiment No. 24 is directed to a compound of formula 1.0, preferably a compound of formula 1.0C1 and more preferably a compound of formula 1.0C, (e.g., 1.1, 1.1A, 1.2, 1.2A, 1.3 or 1.3A) wherein substituent Q is 2.20.

Embodiment No. 25 is directed to a compound of formula 1.0, preferably a compound of formula 1.0C1 and more preferably a compound of formula 1.0C, (e.g., 1.1, 1.1A, 1.2, 1.2A, 1.3 or 1.3A) wherein substituent Q is 2.21.

Embodiment No. 26 is directed to a compound of formula 1.0, preferably a compound of formula 1.0C1 and more preferably a compound of formula 1.0C, (e.g., 1.1, 1.1A, 1.2, 1.2A, 1.3 or 1.3A) wherein substituent Q is 2.22.

Embodiment No. 27 is directed to a compound of formula 1.3 wherein substituent Q is 2.1.

Embodiment No. 28 is directed to a compound of formula 1.3 wherein substituent Q is 2.2.

Embodiment No. 29 is directed to a compound of formula 1.3 wherein substituent Q is 2.3.

Embodiment No. 30 is directed to a compound of formula 1.3 wherein substituent Q is 2.6.

Embodiment No. 31 is directed to a compound of formula 1.3 wherein substituent Q is 2.6A.

Embodiment No. 32 is directed to a compound of formula 1.3 wherein substituent Q is 2.7A.

Embodiment No. 33 is directed to a compound of formula 1.3 wherein substituent Q is 2.7B.

Embodiment No. 34 is directed to a compound of formula 1.3 wherein substituent Q is 2.7C.

Embodiment No. 35 is directed to a compound of formula 1.3 wherein substituent Q is 2.17.

Embodiment No. 36 is directed to a compound of formula 1.3 wherein substituent Q is 2.17A.

Embodiment No. 37 is directed to a compound of formula 1.3 wherein substituent Q is 2.17B.

Embodiment No. 38 is directed to a compound of formula 1.3 wherein substituent Q is 2.17C.

Embodiment No. 39 is directed to a compound of formula 1.3 wherein substituent Q is 2.17D.

Embodiment No. 40 is directed to a compound of formula 1.3 wherein substituent Q is 2.17E.

Embodiment No. 41 is directed to a compound of formula 1.0, preferably a compound of formula 1.0C1 and more preferably a compound of formula 1.0C, (e.g., 1.1, 1.1A, 1.2, 1.2A, 1.3 or 1.3A) wherein each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and alkyl.

Embodiment No. 42 is directed to a compound of formula 1.0, preferably a compound of formula 1.0C1 and more preferably a compound of formula 1.0C, (e.g., 1.1, 1.1A, 1.2, 1.2A, 1.3 or 1.3A) wherein each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and methyl.

Embodiment No. 43 is directed to a compound of formula 1.0, preferably a compound of formula 1.0C1 and more preferably a compound of formula 1.0C, (e.g., 1.1, 1.1A, 1.2, 1.2A, 1.3 or 1.3A) wherein each R^3, R^4, R^6, and R^7 is H.

Embodiment No. 44 is directed to a compound of formula 1.0, preferably a compound of formula 1.0C1 and more preferably a compound of formula 1.0C, (e.g.,

1.1, 1.1A, 1.2, 1.2A, 1.3 or 1.3A) wherein substituent Q is selected from the group consisting of: moieties 2.1, 2.2, 2.3A, 2.3B, and 2.3C.

Embodiment No. 45 is directed to a compound of formula 1.0, preferably a compound of formula 1.0C1 and more preferably a compound of formula 1.0C, (e.g., 1.1, 1.1A, 1.2, 1.2A, 1.3 or 1.3A) wherein substituent Q is selected from the group consisting of: moieties 2.1, 2.2, 2.3A, 2.3B, and 2.3C, and each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and alkyl.

Embodiment No. 46 is directed to a compound of formula 1.0, preferably a compound of formula 1.0C1 and more preferably a compound of formula 1.0C, (e.g., 1.1, 1.1A, 1.2, 1.2A, 1.3 or 1.3A) wherein substituent Q is selected from the group consisting of: moieties 2.1, 2.2, 2.3A, 2.3B, and 2.3C, and each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and methyl.

Embodiment No. 47 is directed to a compound of formula 1.0, preferably a compound of formula 1.0C1 and more preferably a compound of formula 1.0C, (e.g., 1.1, 1.1A, 1.2, 1.2A, 1.3 or 1.3A) wherein substituent Q is selected from the group consisting of: moieties 2.1, 2.2, 2.3A, 2.3B, and 2.3C, and each R^3, R^4, R^6, and R^7 is H.

Embodiment No. 48 is directed to a compound of formula 1.0, preferably a compound of formula 1.0C1 and more preferably a compound of formula 1.0C, (e.g., 1.1, 1.1A, 1.2, 1.2A, 1.3 or 1.3A) wherein substituent Q is selected from the group consisting of: moiety 2.17.

Embodiment No. 49 is directed to a compound of formula 1.0, preferably a compound of formula 1.0C1 and more preferably a compound of formula 1.0C, (e.g., 1.1, 1.1A, 1.2, 1.2A, 1.3 or 1.3A) wherein substituent Q is selected from the group consisting of: moiety 2.17, and each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and alkyl.

Embodiment No. 50 is directed to a compound of formula 1.0, preferably a compound of formula 1.0C1 and more preferably a compound of formula 1.0C, (e.g., 1.1, 1.1A, 1.2, 1.2A, 1.3 or 1.3A) wherein substituent Q is selected from the group consisting of: moiety 2.17, and each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and methyl.

Embodiment No. 51 is directed to a compound of formula 1.0, preferably a compound of formula 1.0C1 and more preferably a compound of formula 1.0C, (e.g.,

1.1, 1.1A, 1.2, 1.2A, 1.3 or 1.3A) wherein substituent Q is selected from the group consisting of: moiety 2.17, and each R^3, R^4, R^6, and R^7 is H.

Embodiment No. 52 is directed to a compound of formula 1.0, preferably a compound of formula 1.0C1 and more preferably a compound of formula 1.0C, (e.g., 1.1, 1.1A, 1.2, 1.2A, 1.3 or 1.3A) wherein substituent Q is selected from the group consisting of: moieties 2.1, and: (1) each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and alkyl, or (2) each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and methyl, or (3) each R^3, R^4, R^6, and R^7 is H.

Embodiment No. 53 is directed to a compound of formula 1.0, preferably a compound of formula 1.0C1 and more preferably a compound of formula 1.0C, (e.g., 1.1, 1.1A, 1.2, 1.2A, 1.3 or 1.3A) wherein substituent Q is selected from the group consisting of: moieties 2.2, and: (1) each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and alkyl, or (2) each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and methyl, or (3) each R^3, R^4, R^6, and R^7 is H.

Embodiment No. 54 is directed to a compound of formula 1.0, preferably a compound of formula 1.0C1 and more preferably a compound of formula 1.0C, (e.g., 1.1, 1.1A, 1.2, 1.2A, 1.3 or 1.3A) wherein substituent Q is selected from the group consisting of: moieties 2.3A, 2.3B, 2.3C, and: (1) each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and alkyl, or (2) each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and methyl, or (3) each R^3, R^4, R^6, and R^7 is H.

Embodiment No. 55 is directed to a compound of formula 1.2 or 1.3 wherein each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and alkyl.

Embodiment No. 56 is directed to a compound of formula 1.2 or 1.3 wherein each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and methyl.

Embodiment No. 57 is directed to a compound of formula 1.2 or 1.3 wherein each R^3, R^4, R^6, and R^7 is H.

Embodiment No. 58 is directed to a compound of formula 1.2 or 1.3 wherein substituent Q is selected from the group consisting of: moieties 2.1, 2.2, 2.3A, 2.3B and 2.3C.

Embodiment No. 59 is directed to a compound of formula 1.2 or 1.3 wherein substituent Q is selected from the group consisting of: moieties 2.1, 2.2, 2.3A, 2.3B and 2.3C, and each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and alkyl.

Embodiment No. 60 is directed to a compound of formula 1.2 or 1.3 wherein substituent Q is selected from the group consisting of: moieties 2.1, 2.2, 2.3A, 2.3B and 2.3C, and each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and methyl.

Embodiment No. 61 is directed to a compound of formula 1.2 or 1.3 wherein substituent Q is selected from the group consisting of: moieties 2.1, 2.2, 2.3A, 2.3B and 2.3C, and each R^3, R^4, R^6, and R^7 is H.

Embodiment No. 62 is directed to a compound of formula 1.2 or 1.3 wherein substituent Q is moiety 2.17.

Embodiment No. 63 is directed to a compound of formula 1.2 or 1.3 wherein substituent Q is moiety 2.17, and each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and alkyl.

Embodiment No. 64 is directed to a compound of formula 1.2 or 1.3 wherein substituent Q is moiety 2.17, and each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and methyl.

Embodiment No. 65 is directed to a compound of formula 1.2 or 1.3 wherein substituent Q is moiety 2.17, and each R^3, R^4, R^6, and R^7 is H.

Embodiment No. 66 is directed to a compound of formula 1.2 or 1.3 wherein substituent Q is selected from the group consisting of: moiety 2.1, and: (1) each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and alkyl, or (2) each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and methyl, or (3) each R^3, R^4, R^6, and R^7 is H.

Embodiment No. 67 is directed to a compound of formula 1.2 or 1.3 wherein substituent Q is selected from the group consisting of: moiety 2.2, and: (1) each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and alkyl, or (2) each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and methyl, or (3) each R^3, R^4, R^6, and R^7 is H.

Embodiment No. 68 is directed to a compound of formula 1.2 or 1.3 wherein substituent Q is selected from the group consisting of: moieties 2.3A, 2.3B and 2.3C, and: (1) each R^3, R^4, R^6, and R^7 is independently selected from the group consisting

of: H and alkyl, or (2) each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and methyl, or (3) each R^3, R^4, R^6, and R^7 is H.

Embodiment No. 69 is directed to a compound of formula 1.3 wherein each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and alkyl.

Embodiment No. 70 is directed to a compound of formula 1.3 wherein each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and methyl.

Embodiment No. 71 is directed to a compound of formula 1.3 wherein each R^3, R^4, R^6, and R^7 is H.

Embodiment No. 72 is directed to a compound of formula 1.3 wherein substituent Q is selected from the group consisting of: moieties 2.1, 2.2, 2.3A, 2.3B and 2.3C.

Embodiment No. 73 is directed to a compound of formula 1.3 wherein substituent Q is selected from the group consisting of: moieties 2.1, 2.2, 2.3A, 2.3B and 2.3C, and each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and alkyl.

Embodiment No. 74 is directed to a compound of formula 1.3 wherein substituent Q is selected from the group consisting of: moieties 2.1, 2.2, 2.3A, 2.3B and 2.3C, and each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and methyl.

Embodiment No. 75 is directed to a compound of formula 1.3 wherein substituent Q is selected from the group consisting of: moieties 2.1, 2.2, 2.3A, 2.3B and 2.3C, and each R^3, R^4, R^6, and R^7 is H.

Embodiment No. 76 is directed to a compound of formula 1.3 wherein substituent Q is moiety 2.17.

Embodiment No. 77 is directed to a compound of formula 1.3 wherein substituent Q is moiety 2.17, and each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and alkyl.

Embodiment No. 78 is directed to a compound of formula 1.3 wherein substituent Q is moiety 2.17, and each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and methyl.

Embodiment No. 79 is directed to a compound of formula 1.3 wherein substituent Q is moiety 2.17, and each R^3, R^4, R^6, and R^7 is H.

Embodiment No. 80 is directed to a compound of formula 1.3 wherein substituent Q is selected from the group consisting of: moiety 2.1, and: (1) each R^3,

R^4, R^6, and R^7 is independently selected from the group consisting of: H and alkyl, or (2) each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and methyl, or (3) each R^3, R^4, R^6, and R^7 is H.

Embodiment No. 81 is directed to a compound of formula 1.3 wherein substituent Q is selected from the group consisting of: moiety 2.2, and: (1) each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and alkyl, or (2) each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and methyl, or (3) each R^3, R^4, R^6, and R^7 is H.

Embodiment No. 82 is directed to a compound of formula 1.3 wherein substituent Q is selected from the group consisting of: moieties 2.3A1, 2.3B and 2.3C, and: (1) each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and alkyl, or (2) each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and methyl, or (3) each R^3, R^4, R^6, and R^7 is H.

Embodiment No. 83 is directed to a compound of formula 1.0, preferably a compound of formula 1.0C1 and more preferably a compound of formula 1.0C, (e.g., 1.1, 1.1A, 1.2, 1.2A, 1.3 or 1.3A) wherein substituent Q is selected from the group consisting of: moieties 2.6, 2.7A, 2.7B and 2.7C.

Embodiment No. 84 is directed to a compound of formula 1.0, preferably a compound of formula 1.0C1 and more preferably a compound of formula 1.0C, (e.g., 1.1, 1.1A, 1.2, 1.2A, 1.3 or 1.3A) wherein substituent Q is selected from the group consisting of: moieties 2.6, 2.7A, 2.7B and 2.7C, and each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and alkyl.

Embodiment No. 85 is directed to a compound of formula 1.0, preferably a compound of formula 1.0C1 and more preferably a compound of formula 1.0C, (e.g., 1.1, 1.1A, 1.2, 1.2A, 1.3 or 1.3A) wherein substituent Q is selected from the group consisting of: moieties 2.6, 2.7A, 2.7B and 2.7C, and each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and methyl.

Embodiment No. 86 is directed to a compound of formula 1.0, preferably a compound of formula 1.0C1 and more preferably a compound of formula 1.0C, (e.g., 1.1, 1.1A, 1.2, 1.2A, 1.3 or 1.3A) wherein substituent Q is selected from the group consisting of: moieties 2.6, 2.7A, 2.7B and 2.7C, and each R^3, R^4, R^6, and R^7 is H.

Embodiment No. 87 is directed to a compound of formula 1.0, preferably a compound of formula 1.0C1 and more preferably a compound of formula 1.0C, (e.g., 1.1, 1.1A, 1.2, 1.2A, 1.3 or 1.3A) wherein substituent Q is selected from the group

consisting of: moiety 2.6, and: (1) each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and alkyl, or (2) each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and methyl, or (3) each R^3, R^4, R^6, and R^7 is H.

Embodiment No. 88 is directed to a compound of formula 1.0, preferably a compound of formula 1.0C1 and more preferably a compound of formula 1.0C, (e.g., 1.1, 1.1A, 1.2, 1.2A, 1.3 or 1.3A) wherein substituent Q is selected from the group consisting of: moiety 2.7A, and: (1) each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and alkyl, or (2) each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and methyl, or (3) each R^3, R^4, R^6, and R^7 is H.

Embodiment No. 89 is directed to a compound of formula 1.0, preferably a compound of formula 1.0C1 and more preferably a compound of formula 1.0C, (e.g., 1.1, 1.1A, 1.2, 1.2A, 1.3 or 1.3A) wherein substituent Q is selected from the group consisting of: moieties 2.7B and 2.7C, and: (1) each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and alkyl, or (2) each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and methyl, or (3) each R^3, R^4, R^6, and R^7 is H.

Embodiment No. 90 is directed to a compound of formula 1.2 or 1.3 wherein substituent Q is selected from the group consisting of: moieties 2.6, 2.7A, 2.7B and 2.7C.

Embodiment No. 91 is directed to a compound of formula 1.2 or 1.3 wherein substituent Q is selected from the group consisting of: moieties 2.6, 2.7A, 2.7B and 2.7C, and each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and alkyl.

Embodiment No. 92 is directed to a compound of formula 1.2 or 1.3 wherein substituent Q is selected from the group consisting of: moieties 2.6, 2.7A, 2.7B and 2.7C, and each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and methyl.

Embodiment No. 93 is directed to a compound of formula 1.2 or 1.3 wherein substituent Q is selected from the group consisting of: moieties 2.6, 2.7A, 2.7B and 2.7C, and each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H.

Embodiment No. 94 is directed to a compound of formula 1.2 or 1.3 wherein substituent Q is selected from the group consisting of: moiety 2.6, and: (1) each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and alkyl, or (2) each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and methyl, or (3) each R^3, R^4, R^6, and R^7 is H.

Embodiment No. 95 is directed to a compound of formula 1.2 or 1.3 wherein substituent Q is selected from the group consisting of: moiety 2.7A, and: (1) each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and alkyl, or (2) each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and methyl, or (3) each R^3, R^4, R^6, and R^7 is H.

Embodiment No. 96 is directed to a compound of formula 1.2 or 1.3 wherein substituent Q is selected from the group consisting of: moieties 2.7A and 2.7B, and: (1) each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and alkyl, or (2) each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and methyl, or (3) each R^3, R^4, R^6, and R^7 is H.

Embodiment No. 97 is directed to a compound of formula 1.3 wherein substituent Q is selected from the group consisting of: moieties 2.6, 2.7A, 2.7B and 2.7C.

Embodiment No. 98 is directed to a compound of formula 1.3 wherein substituent Q is selected from the group consisting of: moieties 2.6, 2.7A, 2.7B and 2.7C, and each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and alkyl.

Embodiment No. 99 is directed to a compound of formula 1.3 wherein substituent Q is selected from the group consisting of: moieties 2.6, 2.7A, 2.7B and 2.7C, and each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and methyl.

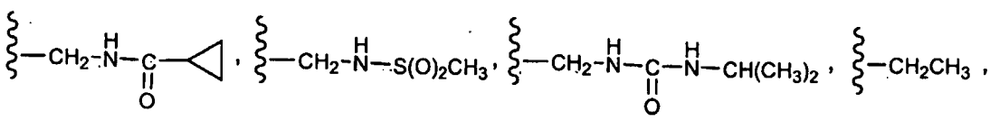
Embodiment No. 100 is directed to a compound of formula 1.3 wherein substituent Q is selected from the group consisting of: moieties 2.6, 2.7A, 2.7B and 2.7C, and each R^3, R^4, R^6, and R^7 is H.

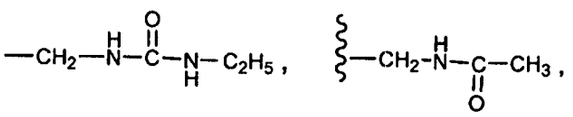
Embodiment No. 101 is directed to a compound of formula 1.3 wherein substituent Q is selected from the group consisting of: moiety 2.6, and: (1) each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and alkyl, or (2) each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and methyl, or (3) each R^3, R^4, R^6, and R^7 is H.

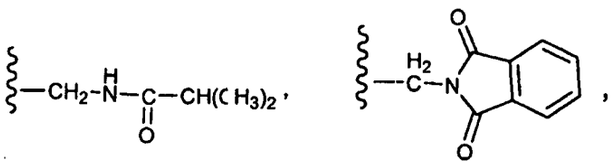
Embodiment No. 102 is directed to a compound of formula 1.3 wherein substituent Q is selected from the group consisting of: moiety 2.7A, and: (1) each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and alkyl, or (2) each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and methyl, or (3) each R^3, R^4, R^6, and R^7 is H.

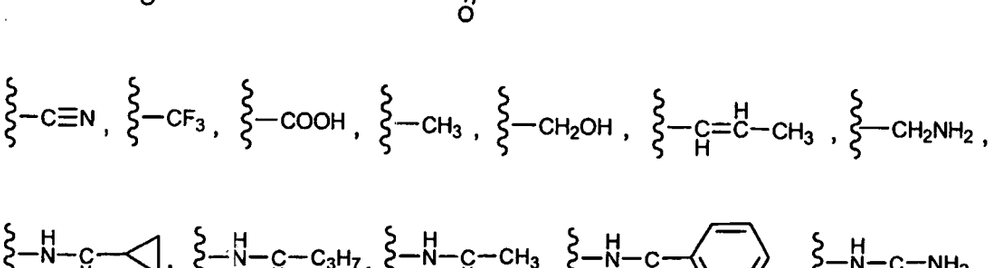
Embodiment No. 103 is directed to a compound of formula 1.3 wherein substituent Q is selected from the group consisting of: moieties 2.7B and 2.7C, and: (1) each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and alkyl, or (2) each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and methyl, or (3) each R^3, R^4, R^6, and R^7 is H.

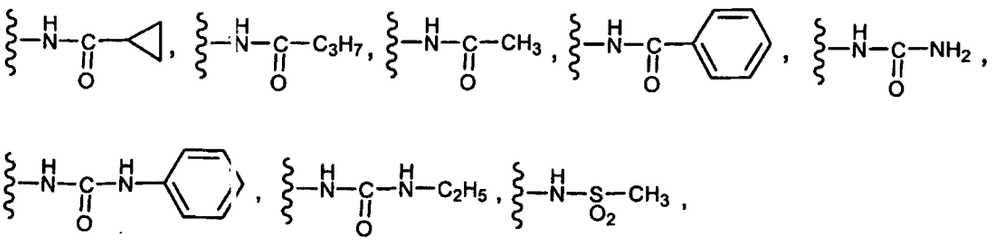
Embodiment No. 104 is directed to a compound of any one of Embodiment Nos. 1 to 103, wherein R^1 is selected from the group consisting of:

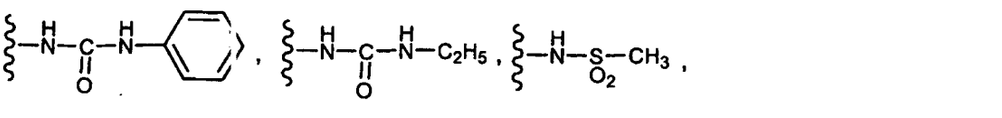


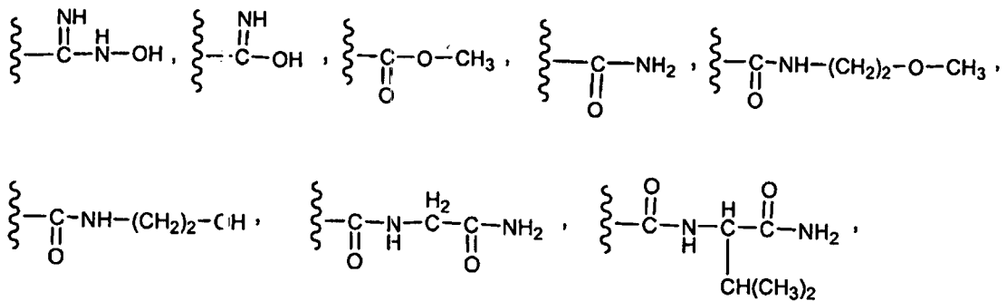


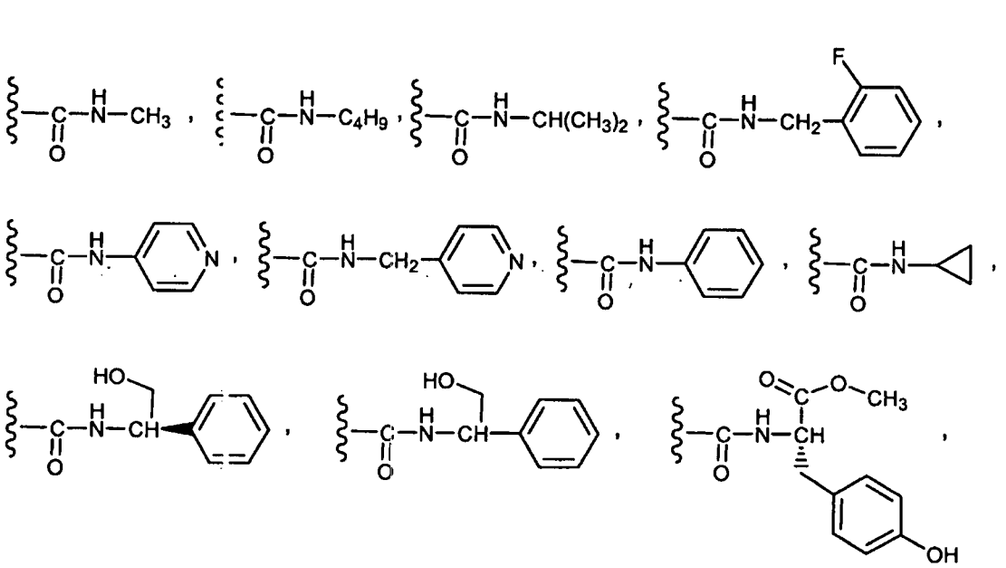


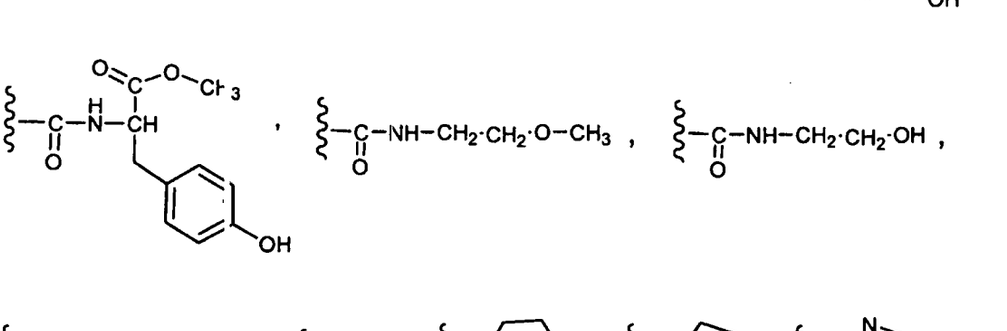


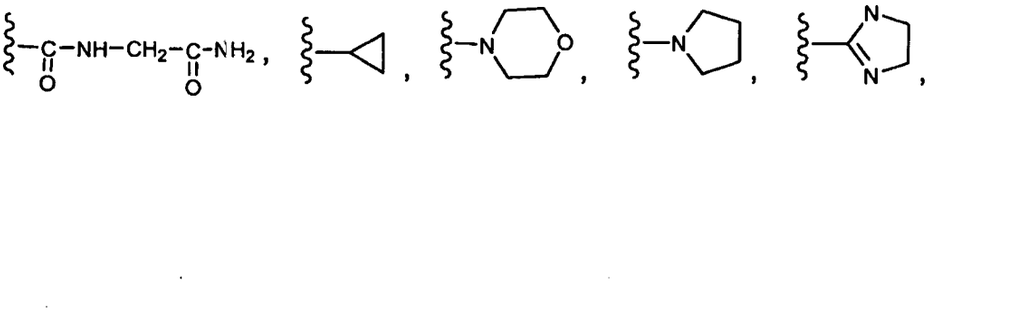


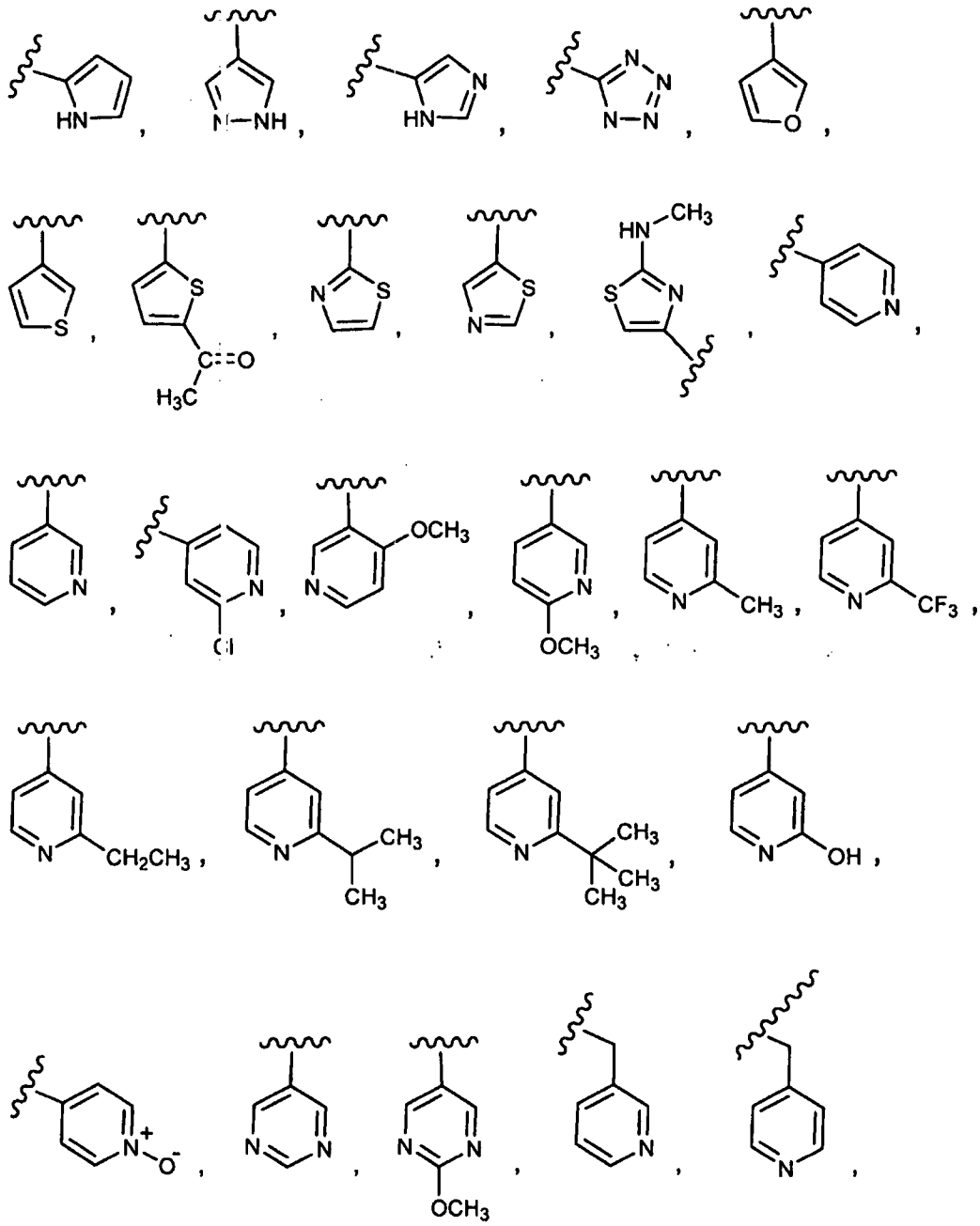






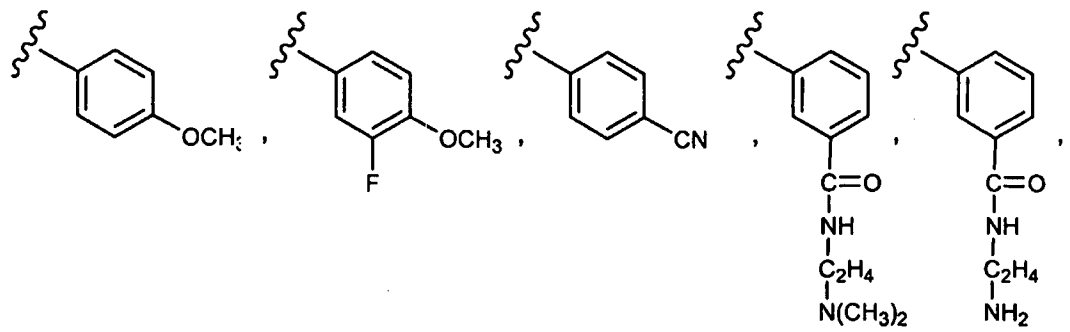


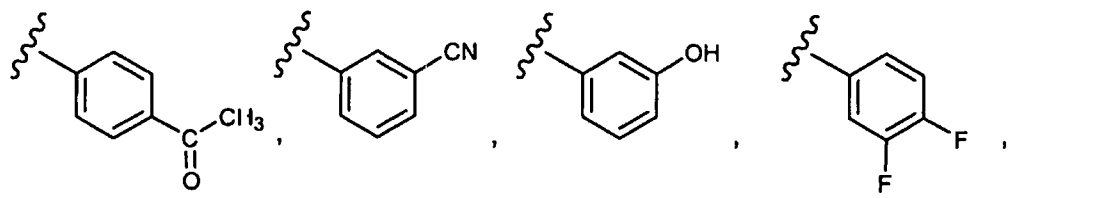


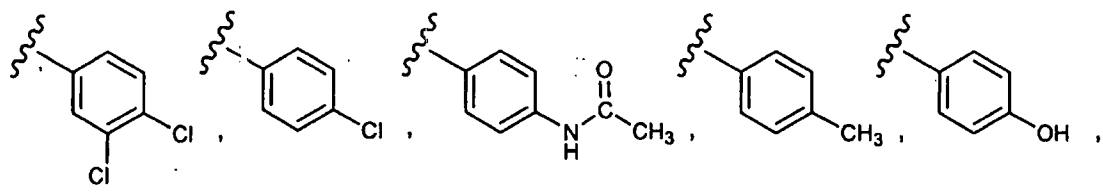


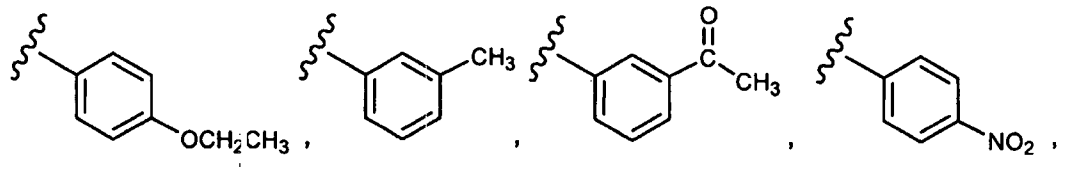
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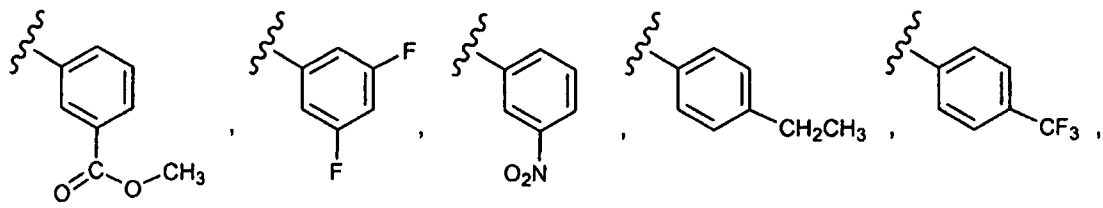
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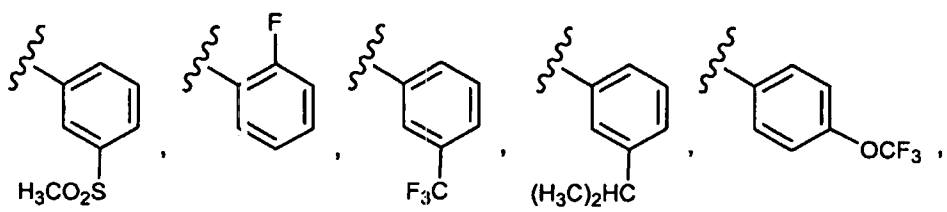

OCH3
OCH3
F
CN
C=O
NH
C2H4
N(CH3)2
C=O
NH
C2H4
NH2

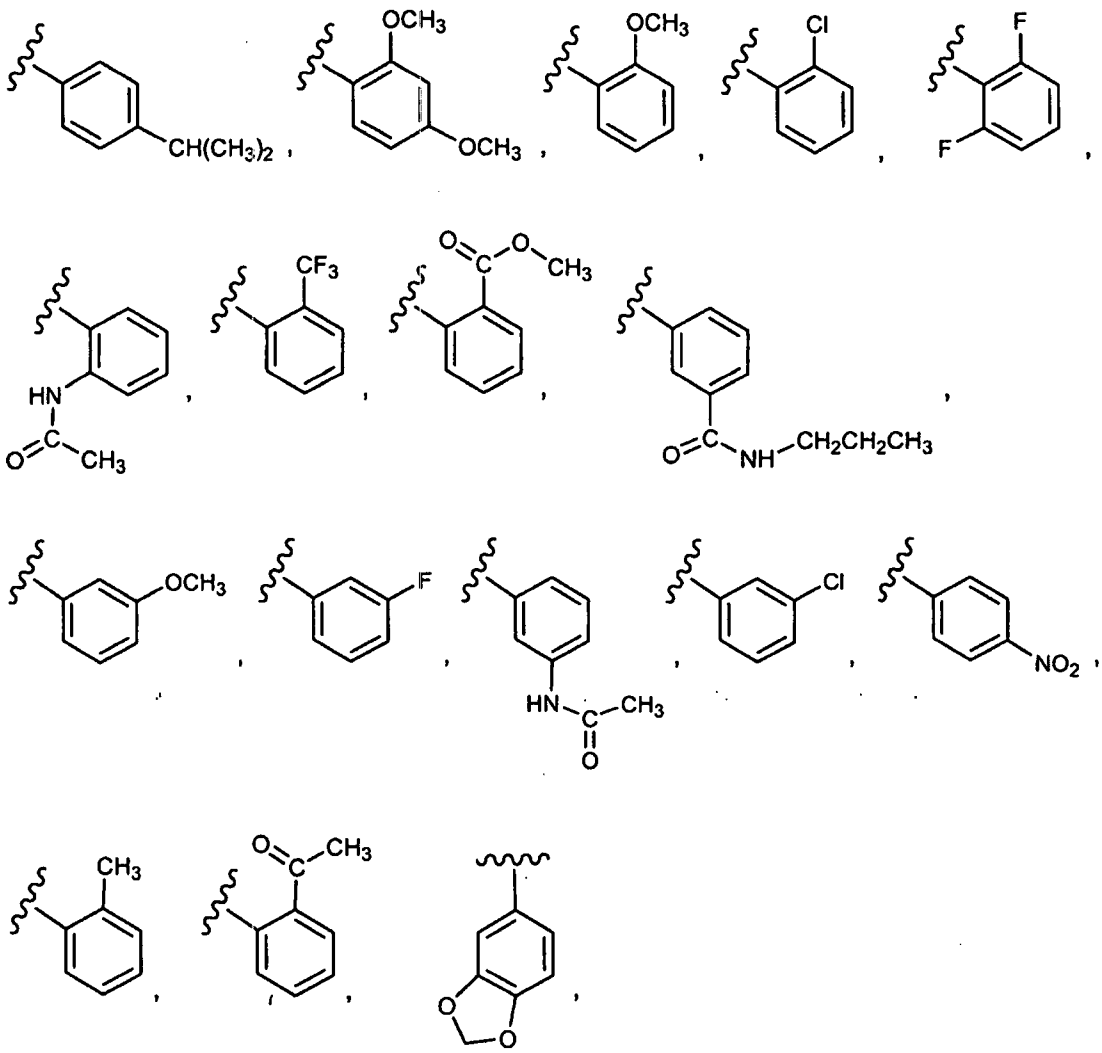

CH3
C
O
CN
OH
F
F

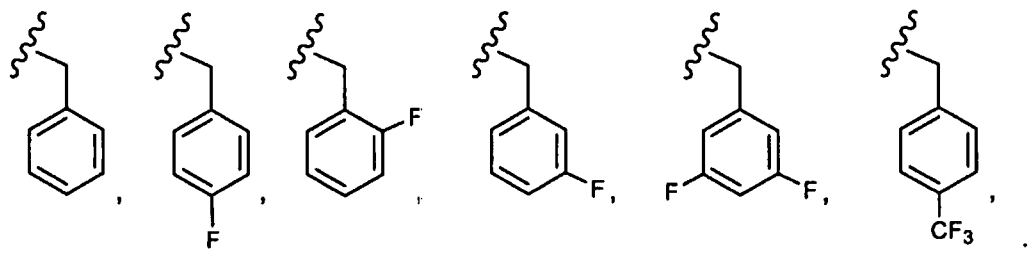

Cl
Cl
Cl
N
H
O
C
CH3
CH3
OH

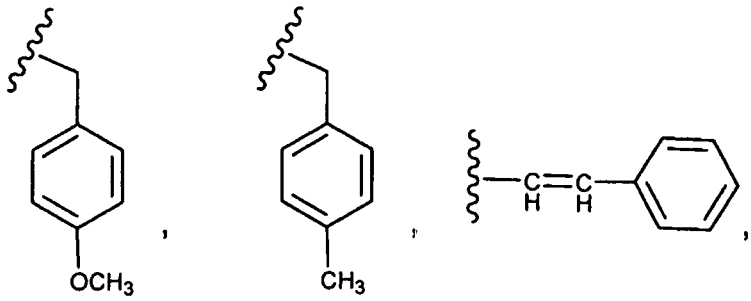

OCH2CH3
CH3
O
C
CH3
NO2

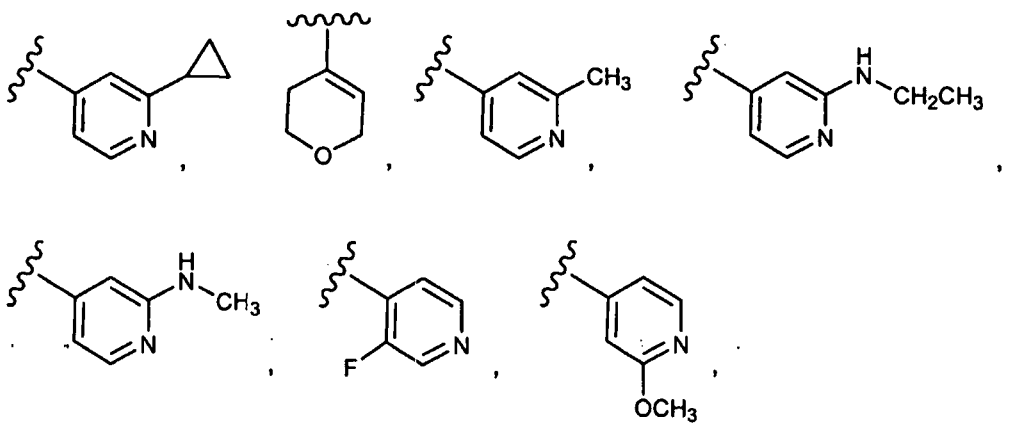

O
C
O
CH3
F
F
O2N
CH2CH3
CF3

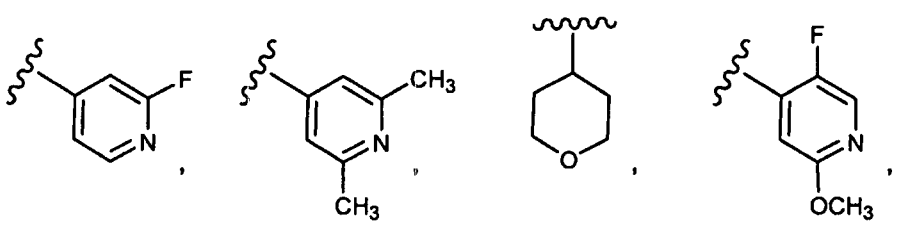

H3CO2S
F
F3C
(H3C)2HC
OCF3

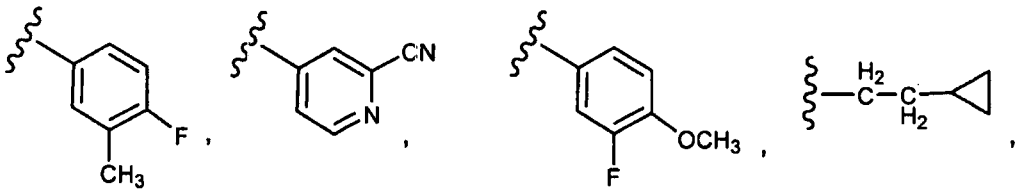


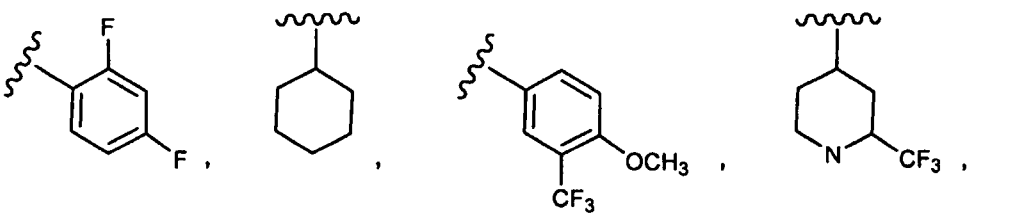


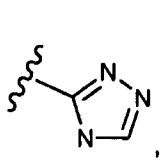
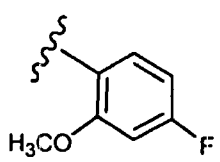
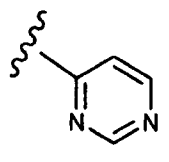
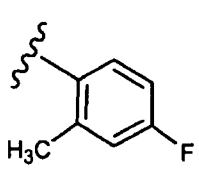


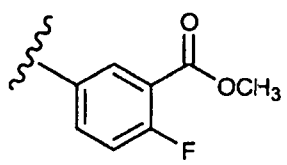
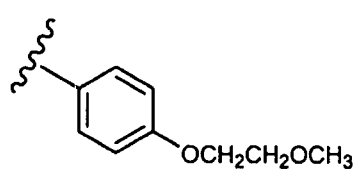
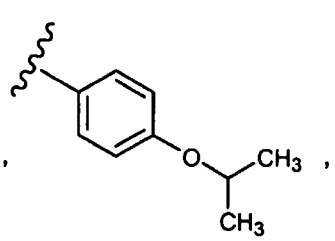




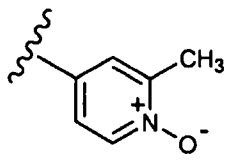
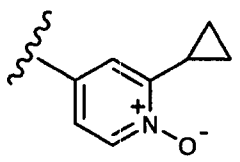
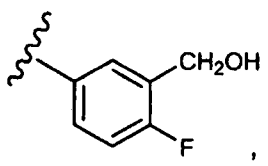


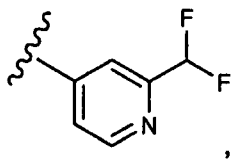
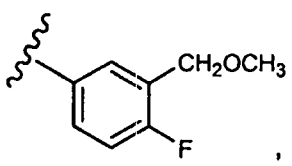



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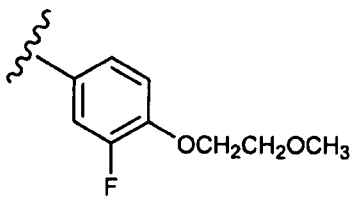
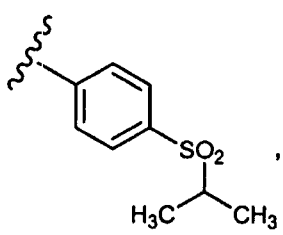
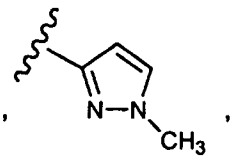

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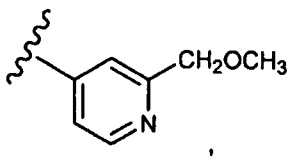
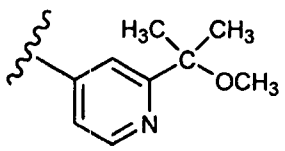
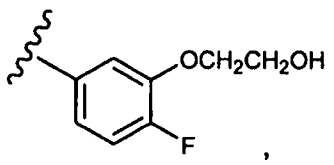
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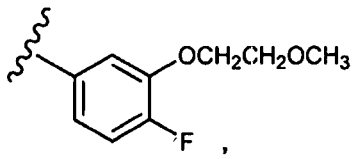
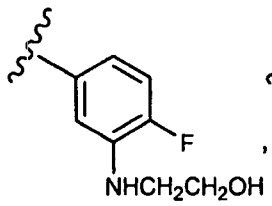
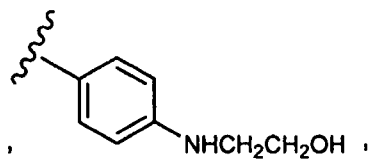
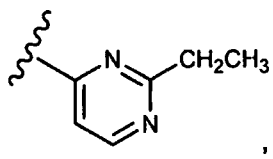
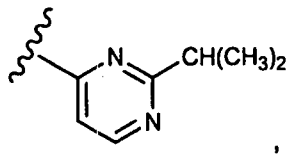
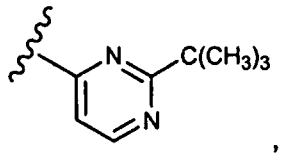
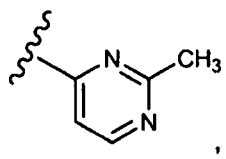
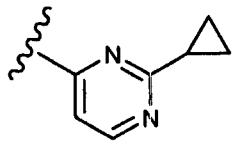
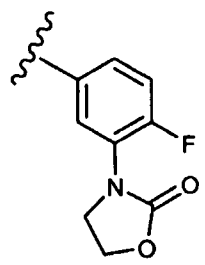
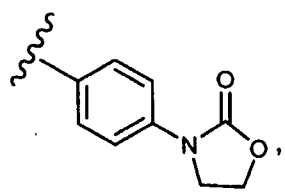

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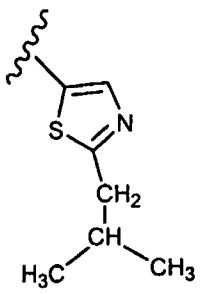
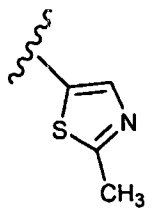
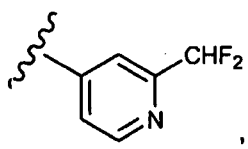
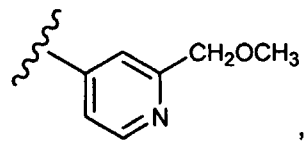
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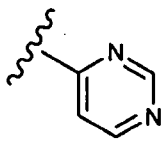
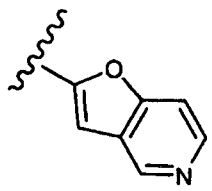

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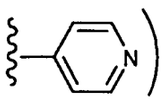

and


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Embodiment No. 105 is directed to a compound of any one of Embodiment Nos. 1 to 103, wherein R^1 is aryl (e.g., phenyl).

Embodiment No. 106 is directed to a compound of any one of Embodiment Nos. 1 to 103, wherein R^1 is substituted aryl (e.g., substituted phenyl).

Embodiment No. 107 is directed to a compound of any one of Embodiment Nos. 1 to 103, wherein R^1 is heteroaryl (e.g., pyridyl, such as

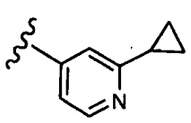


Embodiment No. 108 is directed to a compound of any one of Embodiment Nos. 1 to 103, wherein R^1 is substituted heteroaryl (e.g., substituted pyridyl).

Embodiment No. 109 is directed to a compound of any one of Embodiment Nos. 1 to 103, wherein R^1 is pyridyl substituted with cycloalkyl (e.g., cyclopropyl).

Embodiment No. 110 is directed to a compound of any one of Embodiment Nos. 1 to 103, wherein R^1 is pyridyl substituted with cyclopropyl.

Embodiment No. 111 is directed to a compound of any one of Embodiment Nos. 1 to 103, wherein R^1 is:



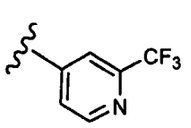
Embodiment No. 112 is directed to a compound of any one of Embodiment Nos. 1 to 103, wherein R^1 is phenyl substituted with halo.

Embodiment No. 113 is directed to a compound of any one of Embodiment Nos. 1 to 103, wherein R^1 is phenyl substituted with F.

Embodiment No. 114 is directed to a compound of any one of Embodiment Nos. 1 to 103, wherein R^1 is p-F-phenyl.

Embodiment No. 115 is directed to a compound of any one of Embodiment Nos. 1 to 103, wherein R^1 is pyridyl substituted with $-CF_3$.

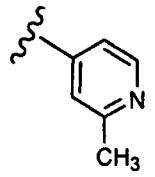
Embodiment No. 116 is directed to a compound of any one of Embodiment Nos. 1 to 103, wherein R^1 is:



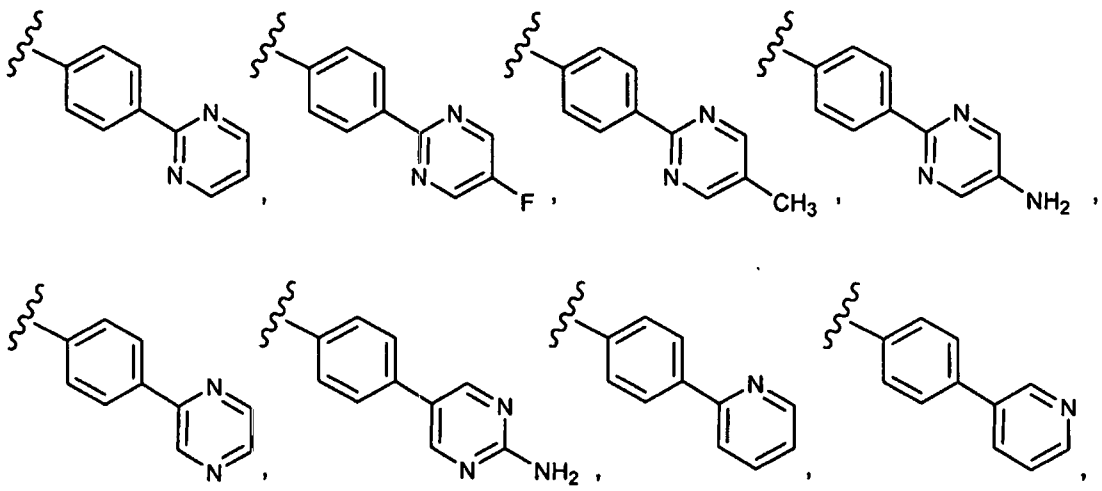
Embodiment No. 117 is directed to a compound of any one of Embodiment Nos. 1 to 103, wherein R^1 is pyridyl substituted with alkyl.

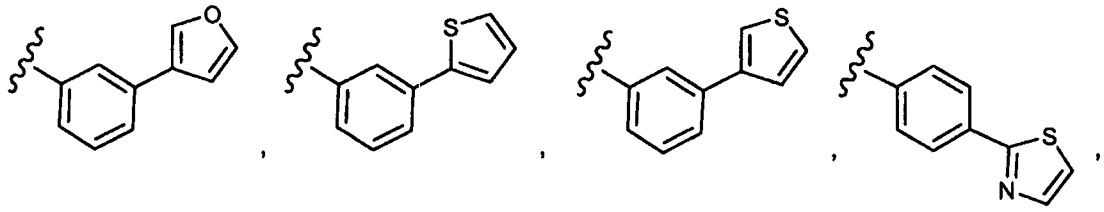
Embodiment No. 118 is directed to a compound of any one of Embodiment Nos. 1 to 103, wherein R^1 is pyridyl substituted with methyl.

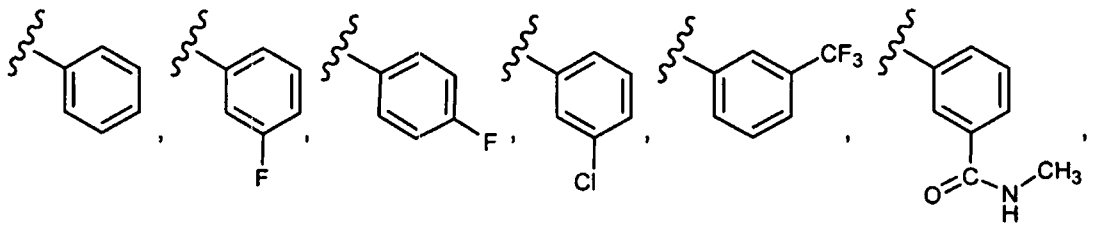
Embodiment No. 119 is directed to a compound of any one of Embodiment Nos. 1 to 103, wherein R^1 is:

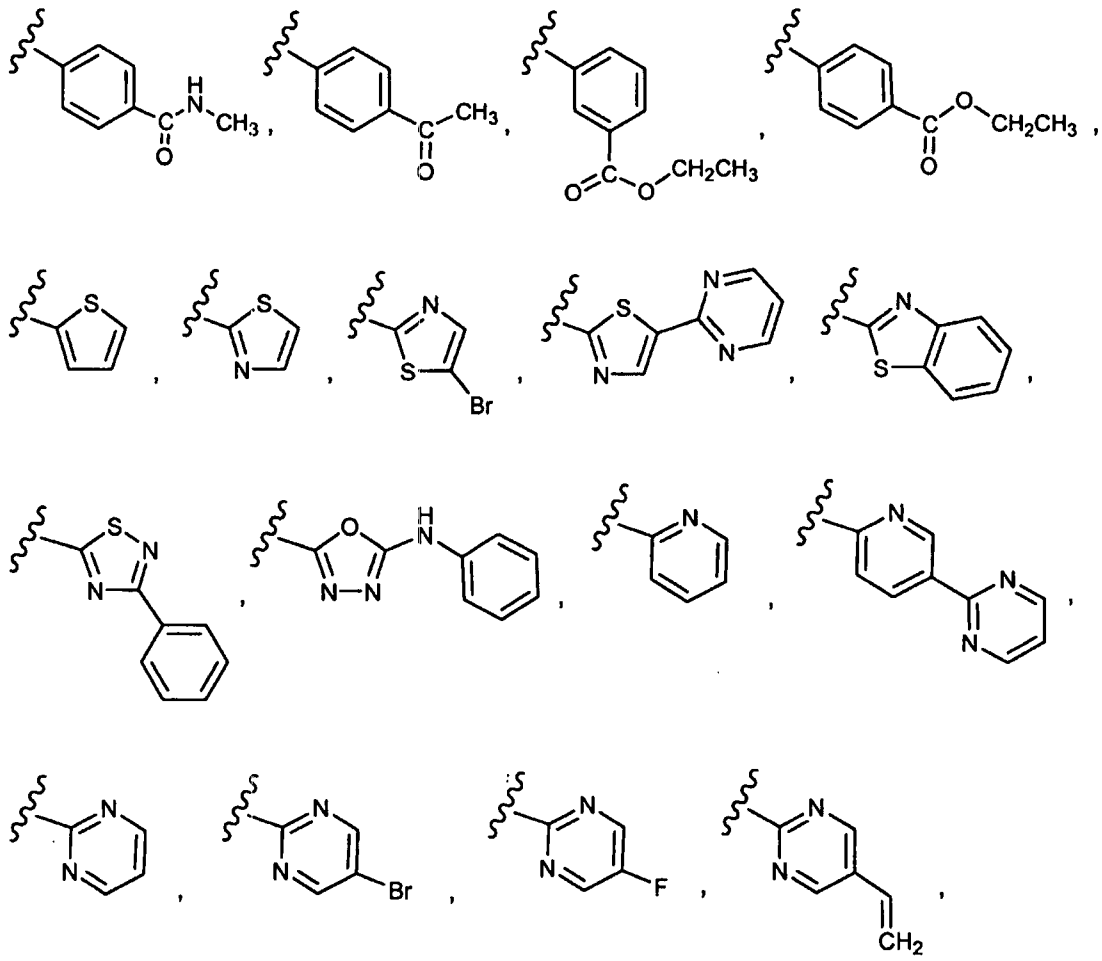


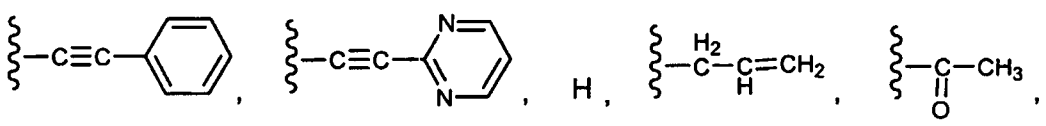
Embodiment No. 120 is directed to a compound of any one of Embodiment Nos. 1 to 103 wherein R^5 is selected from the group consisting of:

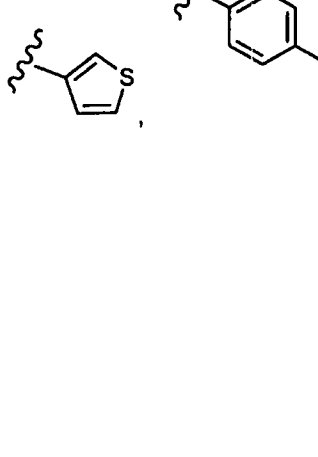




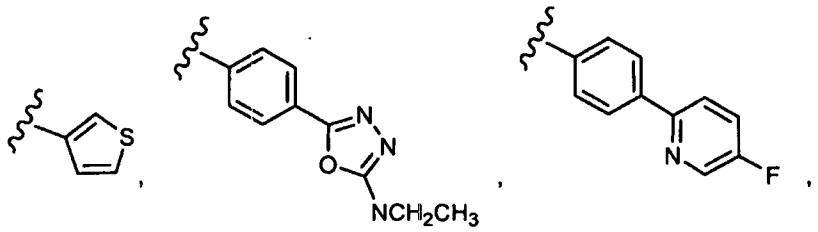


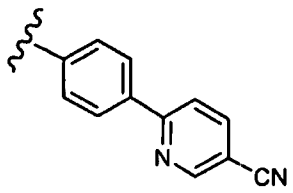
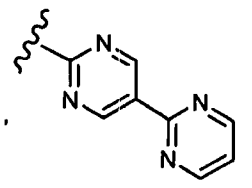
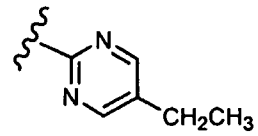
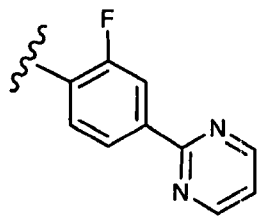
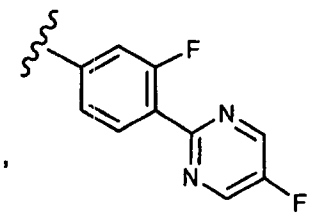
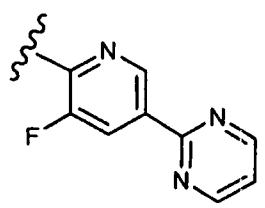
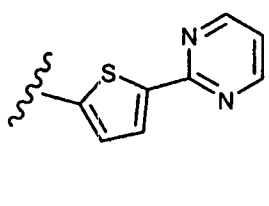
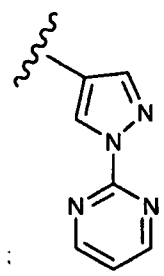
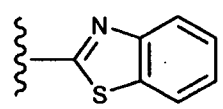
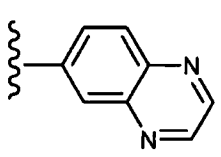
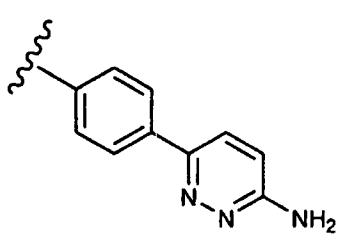
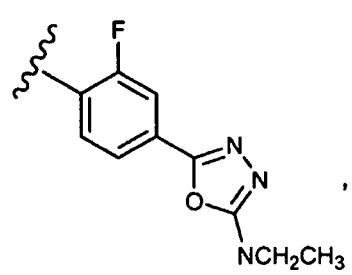
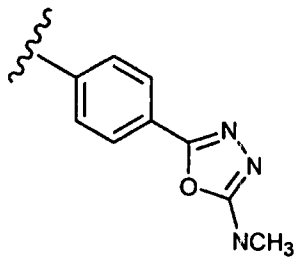
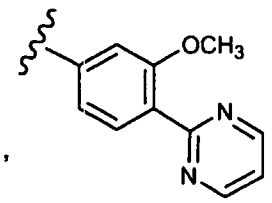
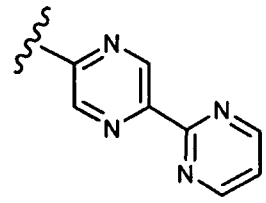




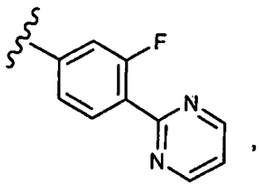
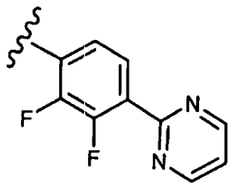
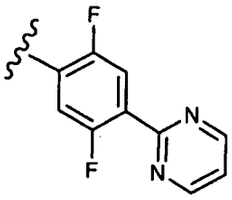
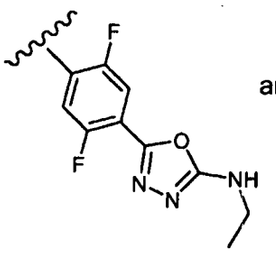
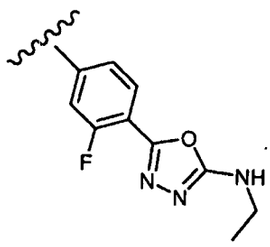


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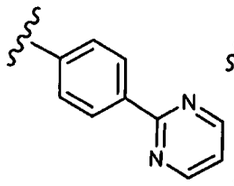
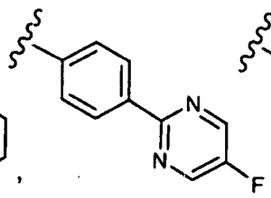
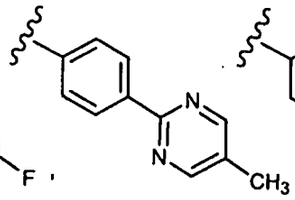
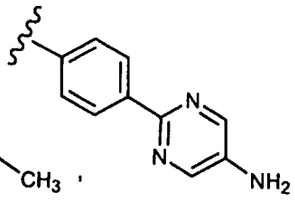
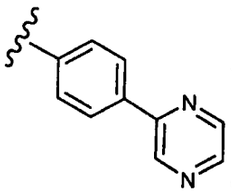
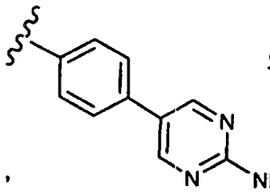
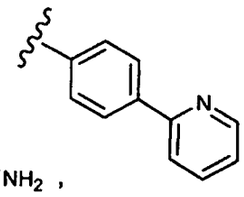
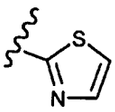


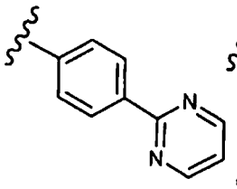
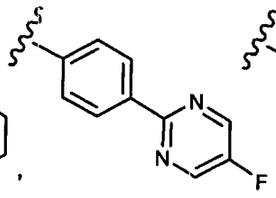
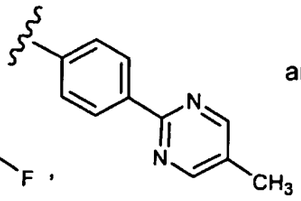
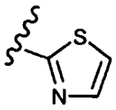
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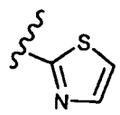
Embodiment No. 121 is directed to a compound of any one of Embodiment Nos. 1 to 103 wherein R^5 is selected from the group consisting of:


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and

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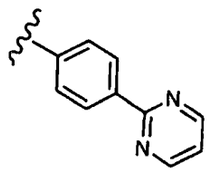
Embodiment No. 122 is directed to a compound of any one of Embodiment Nos. 1 to 103 wherein R^5 is selected from the group consisting of:


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and

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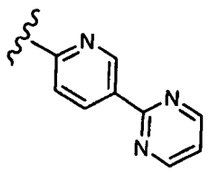
Embodiment No. 123 is directed to a compound of any one of Embodiment Nos. 1 to 103 wherein R^5 is



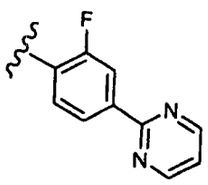
Embodiment No. 124 is directed to a compound of any one of Embodiment Nos. 1 to 103 wherein R^5 is



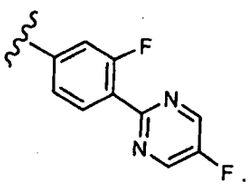
Embodiment No. 125 is directed to a compound of any one of Embodiment Nos. 1 to 103 wherein R^5 is



Embodiment No. 126 is directed to a compound of any one of Embodiment Nos. 1 to 103 wherein R^5 is



Embodiment No. 127 is directed to a compound of any one of Embodiment Nos. 1 to 103 wherein R^5 is



Embodiment No. 128 is directed to a compound of any one of Embodiment Nos. 1 to 103 wherein R^1 is selected from the group consisting of the R^1 groups of any one of Embodiment Nos. 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, or 119 and wherein R^5 is selected from the group consisting of the R^5 groups in any one of Embodiment Nos. 120, 121, 122, 123, 124, 125, 126, or 127.

Embodiment No. 129 is directed to a compound of any one of Embodiment Nos. 1 to 128 wherein R^2 is selected from the group consisting of H, $-CH_2OH$ and $-CH_2F$.

Embodiment No. 130 is directed to a compound of any one of Embodiment Nos. 1 to 128 wherein R^2 is H.

Embodiment No. 131 is directed to a compound of any one of Embodiment Nos. 1 to 128 wherein R^2 is $-OR^{23}$ wherein R^{23} is alkyl.

Embodiment No. 132 is directed to a compound of any one of Embodiment Nos. 1 to 128 wherein R^2 is $-OCH_3$.

Embodiment No. 133 is directed to a compound of any one of Embodiment Nos. 1 to 128 wherein R^2 is –CN.

Embodiment No. 134 is directed to a compound of any one of Embodiment Nos. 1 to 128 wherein R^2 is $-OCHF_2$.

Embodiment No. 135 is directed to a compound of any one of Embodiment Nos.1 to 30, 32 to 35, 41, 42, 44 to 46, 48 to 50, 52 to 56, 58 to 60, 62 to 64, 66 to 70, 72 to 74, 76 to 78, 80 to 85, 87 to 92, 94 to 99 and 101 to 134 wherein R^3 is $-CH_3$, provided that, as those skilled in the art will appreciate, Embodiment No. 135 does not apply to any previous embodiment wherein R^3 has already been limited to H.

Embodiment No. 136 is directed to a compound of any one of Embodiment Nos.1 to 30, 32 to 35, 41, 42, 44 to 46, 48 to 50, 52 to 56, 58 to 60, 62 to 64, 66 to 70, 72 to 74, 76 to 78, 80 to 85, 87 to 92, 94 to 99 and 101 to 134 wherein R^4 is $-CH_3$, provided that, as those skilled in the art will appreciate, Embodiment No. 135 does not apply to any previous embodiment wherein R^4 has already been limited to H.

Embodiment No. 137 is directed to a compound of any one of Embodiment Nos.1 to 15, 18 to 19, 21 to 30, 32 to 35, 41 to 42, 44 to 46, 48 to 50, 52 to 56, 58 to 60, 62, 64, 66 to 70, 72 to 74, 76 to 78, 80 to 85, 87 to 92, 94 to 99 and 101 to 134 wherein R^6 is$-CH_3$, provided that, as those skilled in the art will appreciate, Embodiment No. 135 does not apply to any previous embodiment wherein R^6 has already been limited to H, or wherein R^6 is absent from the formula (e.g., when Q is 2.12, 2.13 or 2.16).

Embodiment No. 138 is directed to a compound of any one of Embodiment Nos.1 to 30, 32 to 35, 41, 42, 44 to 46, 48 to 50, 52 to 56, 58 to 60, 62 to 64, 66 to 70, 72 to 74, 76 to 78, 80 to 85, 87 to 92, 94 to 99 and 101 to 134 wherein R^7 is

$-CH_3$, provided that, as those skilled in the art will appreciate, Embodiment No. 135 does not apply to any previous embodiment wherein R^7 has already been limited to H.

Embodiment No. 139 is directed to a compound selected from the group consisting of the final compounds of Examples 612 to 827.

Thus one embodiment is directed to the final compound of Example 612. Another embodiment is directed to the final compound of Example 613. Another embodiment is directed to the final compound of Example 614. Another embodiment is directed to the final compound of Example 615. Another embodiment is directed to the final compound of Example 616. Another embodiment is directed to the final compound of Example 617. Another embodiment is directed to the final compound of Example 618. Another embodiment is directed to the final compound of Example 619. Another embodiment is directed to the final compound of Example 620. Another embodiment is directed to the final compound of Example 621. Another embodiment is directed to the final compound of Example 622. Another embodiment is directed to the final compound of Example 623. Another embodiment is directed to the final compound of Example 624. Another embodiment is directed to the final compound of Example 625. Another embodiment is directed to the final compound of Example 626. Another embodiment is directed to the final compound of Example 627. Another embodiment is directed to the final compound of Example 628. Another embodiment is directed to the final compound of Example 629. Another embodiment is directed to the final compound of Example 630. Another embodiment is directed to the final compound of Example 631. Another embodiment is directed to the final compound of Example 632. Another embodiment is directed to the final compound of Example 633. Another embodiment is directed to the final compound of Example 634. Another embodiment is directed to the final compound of Example 635. Another embodiment is directed to the final compound of Example 636. Another embodiment is directed to the final compound of Example 637. Another embodiment is directed to the final compound of Example 638. Another embodiment is directed to the final compound of Example 639. Another embodiment is directed to the final compound of Example 640. Another embodiment is directed to the final compound of Example 641. Another embodiment is directed to the final compound of Example 642. Another embodiment is directed to the final compound of Example 643. Another embodiment is directed to the final compound of Example 644. Another embodiment is directed to the final compound of Example 645. Another

embodiment is directed to the final compound of Example 646. Another embodiment is directed to the final compound of Example 647. Another embodiment is directed to the final compound of Example 648. Another embodiment is directed to the final compound of Example 649. Another embodiment is directed to the final compound of Example 650. Another embodiment is directed to the final compound of Example 651. Another embodiment is directed to the final compound of Example 652. Another embodiment is directed to the final compound of Example 653. Another embodiment is directed to the final compound of Example 654. Another embodiment is directed to the final compound of Example 655. Another embodiment is directed to the final compound of Example 656. Another embodiment is directed to the final compound of Example 657. Another embodiment is directed to the final compound of Example 658. Another embodiment is directed to the final compound of Example 659. Another embodiment is directed to the final compound of Example 660. Another embodiment is directed to the final compound of Example 661. Another embodiment is directed to the final compound of Example 662. Another embodiment is directed to the final compound of Example 663. Another embodiment is directed to the final compound of Example 664. Another embodiment is directed to the final compound of Example 665. Another embodiment is directed to the final compound of Example 666. Another embodiment is directed to the final compound of Example 667. Another embodiment is directed to the final compound of Example 668. Another embodiment is directed to the final compound of Example 669. Another embodiment is directed to the final compound of Example 670. Another embodiment is directed to the final compound of Example 671. Another embodiment is directed to the final compound of Example 672. Another embodiment is directed to the final compound of Example 673. Another embodiment is directed to the final compound of Example 674. Another embodiment is directed to the final compound of Example 675. Another embodiment is directed to the final compound of Example 676. Another embodiment is directed to the final compound of Example 677. Another embodiment is directed to the final compound of Example 678. Another embodiment is directed to the final compound of Example 679. Another embodiment is directed to the final compound of Example 680. Another embodiment is directed to the final compound of Example 681. Another embodiment is directed to the final compound of Example 682. Another embodiment is directed to the final compound of Example 683. Another embodiment is directed to the final compound of Example 684.

Another embodiment is directed to the final compound of Example 685. Another embodiment is directed to the final compound of Example 686. Another embodiment is directed to the final compound of Example 687. Another embodiment is directed to the final compound of Example 688. Another embodiment is directed to the final compound of Example 689. Another embodiment is directed to the final compound of Example 690. Another embodiment is directed to the final compound of Example 691. Another embodiment is directed to the final compound of Example 692. Another embodiment is directed to the final compound of Example 693. Another embodiment is directed to the final compound of Example 694. Another embodiment is directed to the final compound of Example 695. Another embodiment is directed to the final compound of Example 696. Another embodiment is directed to the final compound of Example 697. Another embodiment is directed to the final compound of Example 698. Another embodiment is directed to the final compound of Example 699. Another embodiment is directed to the final compound of Example 700. Another embodiment is directed to the final compound of Example 701. Another embodiment is directed to the final compound of Example 702. Another embodiment is directed to the final compound of Example 703. Another embodiment is directed to the final compound of Example 704. Another embodiment is directed to the final compound of Example 705. Another embodiment is directed to the final compound of Example 706. Another embodiment is directed to the final compound of Example 707. Another embodiment is directed to the final compound of Example 708. Another embodiment is directed to the final compound of Example 709. Another embodiment is directed to the final compound of Example 710. Another embodiment is directed to the final compound of Example 711. Another embodiment is directed to the final compound of Example 712. Another embodiment is directed to the final compound of Example 713. Another embodiment is directed to the final compound of Example 714. Another embodiment is directed to the final compound of Example 715. Another embodiment is directed to the final compound of Example 716. Another embodiment is directed to the final compound of Example 717. Another embodiment is directed to the final compound of Example 718. Another embodiment is directed to the final compound of Example 719. Another embodiment is directed to the final compound of Example 720. Another embodiment is directed to the final compound of Example 721. Another embodiment is directed to the final compound of Example 722. Another embodiment is directed to the final compound of Example

723. Another embodiment is directed to the final compound of Example 724. Another embodiment is directed to the final compound of Example 725. Another embodiment is directed to the final compound of Example 726. Another embodiment is directed to the final compound of Example 727. Another embodiment is directed to the final compound of Example 728. Another embodiment is directed to the final compound of Example 729. Another embodiment is directed to the final compound of Example 730. Another embodiment is directed to the final compound of Example 731. Another embodiment is directed to the final compound of Example 732. Another embodiment is directed to the final compound of Example 733. Another embodiment is directed to the final compound of Example 734. Another embodiment is directed to the final compound of Example 735. Another embodiment is directed to the final compound of Example 736. Another embodiment is directed to the final compound of Example 737. Another embodiment is directed to the final compound of Example 738. Another embodiment is directed to the final compound of Example 739. Another embodiment is directed to the final compound of Example 740. Another embodiment is directed to the final compound of Example 741. Another embodiment is directed to the final compound of Example 742. Another embodiment is directed to the final compound of Example 743. Another embodiment is directed to the final compound of Example 744. Another embodiment is directed to the final compound of Example 745. Another embodiment is directed to the final compound of Example 746. Another embodiment is directed to the final compound of Example 747. Another embodiment is directed to the final compound of Example 748. Another embodiment is directed to the final compound of Example 749. Another embodiment is directed to the final compound of Example 750. Another embodiment is directed to the final compound of Example 751. Another embodiment is directed to the final compound of Example 752. Another embodiment is directed to the final compound of Example 753. Another embodiment is directed to the final compound of Example 754. Another embodiment is directed to the final compound of Example 755. Another embodiment is directed to the final compound of Example 756. Another embodiment is directed to the final compound of Example 757. Another embodiment is directed to the final compound of Example 758. Another embodiment is directed to the final compound of Example 759. Another embodiment is directed to the final compound of Example 760. Another embodiment is directed to the final compound of Example 761. Another embodiment is directed to the final compound of

Example 762. Another embodiment is directed to the final compound of Example 763. Another embodiment is directed to the final compound of Example 764. Another embodiment is directed to the final compound of Example 765. Another embodiment is directed to the final compound of Example 766. Another embodiment is directed to the final compound of Example 767. Another embodiment is directed to the final compound of Example 768. Another embodiment is directed to the final compound of Example 769. Another embodiment is directed to the final compound of Example 770. Another embodiment is directed to the final compound of Example 671. Another embodiment is directed to the final compound of Example 772. Another embodiment is directed to the final compound of Example 773. Another embodiment is directed to the final compound of Example 774. Another embodiment is directed to the final compound of Example 775. Another embodiment is directed to the final compound of Example 776. Another embodiment is directed to the final compound of Example 777. Another embodiment is directed to the final compound of Example 778. Another embodiment is directed to the final compound of Example 779. Another embodiment is directed to the final compound of Example 780. Another embodiment is directed to the final compound of Example 781. Another embodiment is directed to the final compound of Example 782. Another embodiment is directed to the final compound of Example 783. Another embodiment is directed to the final compound of Example 784. Another embodiment is directed to the final compound of Example 785. Another embodiment is directed to the final compound of Example 786. Another embodiment is directed to the final compound of Example 787. Another embodiment is directed to the final compound of Example 788. Another embodiment is directed to the final compound of Example 789. Another embodiment is directed to the final compound of Example 790. Another embodiment is directed to the final compound of Example 791. Another embodiment is directed to the final compound of Example 792. Another embodiment is directed to the final compound of Example 793. Another embodiment is directed to the final compound of Example 794. Another embodiment is directed to the final compound of Example 795. Another embodiment is directed to the final compound of Example 796. Another embodiment is directed to the final compound of Example 797. Another embodiment is directed to the final compound of Example 798. Another embodiment is directed to the final compound of Example 799. Another embodiment is directed to the final compound of Example 800. Another embodiment is directed to the final

compound of Example 801. Another embodiment is directed to the final compound of Example 802. Another embodiment is directed to the final compound of Example 803. Another embodiment is directed to the final compound of Example 804. Another embodiment is directed to the final compound of Example 805. Another embodiment is directed to the final compound of Example 806. Another embodiment is directed to the final compound of Example 807. Another embodiment is directed to the final compound of Example 808. Another embodiment is directed to the final compound of Example 809. Another embodiment is directed to the final compound of Example 810. Another embodiment is directed to the final compound of Example 811. Another embodiment is directed to the final compound of Example 812. Another embodiment is directed to the final compound of Example 813. Another embodiment is directed to the final compound of Example 814. Another embodiment is directed to the final compound of Example 815. Another embodiment is directed to the final compound of Example 816. Another embodiment is directed to the final compound of Example 817. Another embodiment is directed to the final compound of Example 818. Another embodiment is directed to the final compound of Example 819. Another embodiment is directed to the final compound of Example 820. Another embodiment is directed to the final compound of Example 821. Another embodiment is directed to the final compound of Example 822. Another embodiment is directed to the final compound of Example 823. Another embodiment is directed to the final compound of Example 824. Another embodiment is directed to the final compound of Example 825. Another embodiment is directed to the final compound of Example 826. Another embodiment is directed to the final compound of Example 827.

Embodiment No. 140 is directed to the final compound of Example 622.

Embodiment No. 141 is directed to the final compound of Example 613.

Embodiment No. 142 is directed to the final compound of Example 825.

Embodiment No. 143 is directed to a compound of any one of Embodiment Nos. 1 to 142 in pure and isolated form.

Embodiment No. 144 is directed to a pharmaceutical composition comprising an effective amount of at least one compound (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) of formula 1.0, preferably a compound of formula 1.0C, and a pharmaceutically acceptable carrier.

Embodiment No. 145 is directed to a pharmaceutical composition comprising an effective amount of a compound of formula 1.0, preferably a compound of formula 1.0C, and a pharmaceutically acceptable carrier.

Embodiment No. 146 is directed to a pharmaceutical composition comprising an effective amount of at least one compound (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) of formula 1.1, and a pharmaceutically acceptable carrier.

Embodiment No. 147 is directed to a pharmaceutical composition comprising an effective amount of a compound of formula 1.1 and a pharmaceutically acceptable carrier.

Embodiment No. 148 is directed to a pharmaceutical composition comprising an effective amount of at least one compound (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) of formula 1.2, and a pharmaceutically acceptable carrier.

Embodiment No. 149 is directed to a pharmaceutical composition comprising an effective amount of a compound of formula 1.2 and a pharmaceutically acceptable carrier.

Embodiment No. 150 is directed to a pharmaceutical composition comprising an effective amount of at least one compound (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) of formula 1.3, and a pharmaceutically acceptable carrier.

Embodiment No. 151 is directed to a pharmaceutical composition comprising an effective amount of a compound of formula 1.3 and a pharmaceutically acceptable carrier.

Embodiment No. 152 is directed to a pharmaceutical composition comprising an effective amount of at least one compound (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) of any one of Embodiment Nos. 1 to 142 and a pharmaceutically acceptable carrier.

Embodiment No. 153 is directed to a pharmaceutical composition comprising an effective amount of a compound of any one of Embodiment Nos. 1 to 142 and a pharmaceutically acceptable carrier.

Embodiment No. 154 is directed to a pharmaceutical composition comprising an effective amount of at least one compound (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) of Embodiment No. 143 and a pharmaceutically acceptable carrier.

Embodiment No. 155 is directed to a pharmaceutical composition comprising an effective amount of one compound of Embodiment No. 143 and a pharmaceutically acceptable carrier.

Embodiment No. 156 is directed to a pharmaceutical composition of any one of Embodiment Nos. 144 to 155 further comprising an effective amount of at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) other active pharmaceutically active ingredient.

Embodiment No. 157 is directed to a pharmaceutical composition of any one of Embodiment Nos. 144 to 155 further comprising an effective amount of another (i.e., one other) pharmaceutically active ingredient.

Embodiment No. 158 is directed to a pharmaceutical composition of any one of Embodiment Nos. 144 to 155 further comprising an effective amount of at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) chemotherapeutic agent.

Embodiment No. 159 is directed to a pharmaceutical composition of any one of Embodiment Nos. 144 to 155 further comprising an effective amount of a chemotherapeutic agent.

Embodiment No. 160 is directed to a method of treating cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.0 (preferably formula 1.0C).

Embodiment No. 161 is directed to a method of treating cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of one compound of formula 1.0 (preferably formula 1.0C).

Embodiment No. 162 is directed to a method of treating cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.1.

Embodiment No. 163 is directed to a method of treating cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of one compound of formula 1.1.

Embodiment No. 164 is directed to a method of treating cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.2.

Embodiment No. 165 is directed to a method of treating cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of one compound of formula 1.2.

Embodiment No. 166 is directed to a method of treating cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.3.

Embodiment No. 167 is directed to a method of treating cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of one compound of formula 1.3.

Embodiment No. 168 is directed to a method of treating cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of any one of Embodiment Nos. 1 to 143.

Embodiment No. 169 is directed to a method of treating cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a compound of any one of Embodiment Nos. 1 to 143.

Embodiment No. 170 is directed to a method of treating cancer in any one of Embodiment Nos. 160 to 169 further comprising the administration of an effective amount of at least one (1, 2 or 3, or 1 or 2, or 1, and usually 1) chemotherapeutic agent.

Embodiment No. 171 is directed to a method of treating cancer in any one of Embodiment Nos. 160 to 169 further comprising the administration of an effective amount of a chemotherapeutic agent.

Embodiment No. 172 is directed to a method of treating cancer in a patient in need of such treatment comprising administering to said patient an effective amount of a pharmaceutical composition of any one of Embodiment Nos. 144 to 159.

Embodiment No. 173 is directed to a method of treating cancer in a patient in need of such treatment comprising administering to said patient an effective amount of a pharmaceutical composition of any one of Embodiment Nos. 144 to 155.

Embodiment No. 174 is directed to a method of treating cancer in a patient in need of such treatment comprising administering to said patient an effective amount of a pharmaceutical composition of any one of Embodiment Nos. 144 to 155, in combination with an effective amount of at least one (1, 2 or 3, or 1 or 2, or 1, and usually 1) chemotherapeutic agent

Embodiment No. 175 is directed to a method of treating cancer in a patient in need of such treatment comprising administering to said patient an effective amount

of a pharmaceutical composition of any one of Embodiment Nos. 144 to 155, in combination with an effective amount of one chemotherapeutic agent.

Embodiment No. 176 is directed to a method of treating cancer of any one of Embodiment Nos. 170, 171, 174 and 175 wherein the chemotherapeutic agent is selected from the group consisting of: paclitaxel, docetaxel, carboplatin, cisplatin, gemcitabine, tamoxifen, Herceptin, Cetuximab, Tarceva, Iressa, bevacizumab, navelbine, IMC-1C11, SU5416 and SU6688.

Embodiment No. 177 is directed to a method of treating cancer of any one of Embodiment Nos. 170, 171, 174 and 175 wherein the chemotherapeutic agent is selected from the group consisting of: paclitaxel, docetaxel, carboplatin, cisplatin, navelbine, gemcitabine, and Herceptin.

Embodiment No. 178 is directed to a method of treating cancer of any one of Embodiment Nos. 170, 171, 174 and 175 wherein the chemotherapeutic agent is selected from the group consisting of: Cyclophasphamide, 5-Fluorouracil, Temozolomide, Vincristine, Cisplatin, Carboplatin, and Gemcitabine.

Embodiment No. 179 is directed to a method of treating cancer of any one of Embodiment Nos. 170, 171, 174 and 175 wherein the chemotherapeutic agent is selected from the group consisting of: Gemcitabine, Cisplatin and Carboplatin.

This invention also provides a method of treating cancer in a patient in need of such treatment, said treatment comprising administering to said patient a therapeutically effective amount at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), and therapeutically effective amounts of at least one (e.g., 1, 2 or 3, or 1 or 2, or 2, or 1) chemotherapeutic agent selected from the group consisting of: (1) taxanes, (2) platinum coordinator compounds, (3) epidermal growth factor (EGF) inhibitors that are antibodies, (4) EGF inhibitors that are small molecules, (5) vascular endolithial growth factor (VEGF) inhibitors that are antibodies, (6) VEGF kinase inhibitors that are small molecules, (7) estrogen receptor antagonists or selective estrogen receptor modulators (SERMs), (8) anti-tumor nucleoside derivatives, (9) epothilones, (10) topoisomerase inhibitors, (11) vinca alkaloids, (12) antibodies that are inhibitors of $\alpha V\beta 3$ integrins, (13) folate antagonists, (14) ribonucleotide reductase inhibitors, (15) anthracyclines, (16) biologics; (17) inhibitors of angiogenesis and/or suppressors of tumor necrosis factor alpha (TNF-alpha) such as thalidomide (or related imid), (18) Bcr/abl kinase inhibitors, (19) MEK1 and/or MEK

2 inhibitors that are small molecules, (20) IGF-1 and IGF-2 inhibitors that are small molecules, (21) small molecule inhibitors of RAF and BRAF kinases, (22) small molecule inhibitors of cell cycle dependent kinases such as CDK1, CDK2, CDK4 and CDK6, (23) alkylating agents, and (24) farnesyl protein transferase inhibitors (also know as FPT inhibitors or FTI (i.e., farnesyl transfer inhibitors)).

This invention also provides a method of treating cancer in a patient in need of such treatment, said treatment comprising administering to said patient a therapeutically effective amount at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), and therapeutically effective amounts of at least two (e.g., 2 or 3, or 2, and usually 2) different antineoplastic agents selected from the group consisting of: (1) taxanes, (2) platinum coordinator compounds, (3) epidermal growth factor (EGF) inhibitors that are antibodies, (4) EGF inhibitors that are small molecules, (5) vascular endolithial growth factor (VEGF) inhibitors that are antibodies, (6) VEGF kinase inhibitors that are small molecules, (7) estrogen receptor antagonists or selective estrogen receptor modulators (SERMs), (8) anti-tumor nucleoside derivatives, (9) epothilones, (10) topoisomerase inhibitors, (11) vinca alkaloids, (12) antibodies that are inhibitors of $\alpha V\beta 3$ integrins, (13) folate antagonists, (14) ribonucleotide reductase inhibitors, (15) anthracyclines, (16) biologics; (17) inhibitors of angiogenesis and/or suppressors of tumor necrosis factor alpha (TNF-alpha) such as thalidomide (or related imid), (18) Bcr/abl kinase inhibitors, (19) MEK1 and/or MEK 2 inhibitors that are small molecules, (20) IGF-1 and IGF-2 inhibitors that are small molecules, (21) small molecule inhibitors of RAF and BRAF kinases, (22) small molecule inhibitors of cell cycle dependent kinases such as CDK1, CDK2, CDK4 and CDK6, (23) alkylating agents, and (24) farnesyl protein transferase inhibitors (also know as FPT inhibitors or FTI (i.e., farnesyl transfer inhibitors)).

This invention also provides a method of treating cancer in a patient in need of such treatment, said method comprising administering to said patient therapeutically effective amounts at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), and an antineoplastic agent selected from the group consisting of: (1) EGF inhibitors that are antibodies, (2) EGF inhibitors that are small molecules, (3) VEGF inhibitors that are antibodies, and (4) VEGF inhibitors that are small molecules. Radiation therapy can also be used in conjunction with this above combination

therapy, i.e., the above method using a combination of compounds of the invention and antineoplastic agent can also comprise the administration of a therapeutically effect amount of radiation.

This invention also provides a method of treating leukemias (e.g., acute myeloid leukemia (AML), and chronic myeloid leukemia (CML)) in a patient in need of such treatment, said method comprising administering to said patient therapeutically effective amounts at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), and: (1) Gleevec and interferon to treat CML; (2) Gleevec and pegylated interferon to treat CML; (3) Gleevec to treat CML; (4) an anti-tumor nucleoside derivative (e.g., Ara-C) to treat AML; or (5) an anti-tumor nucleoside derivative (e.g., Ara-C) in combination with an anthracycline to treat AML.

This invention also provides a method of treating non-Hodgkin's lymphoma in a patient in need of such treatment, said method comprising administering therapeutically effective amounts at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) and: (1) a biologic (e.g., Rituxan); (2) a biologic (e.g., Rituxan) and an anti-tumor nucleoside derivative (e.g., Fludarabine); or (3) Genasense (antisense to BCL-2).

This invention also provides a method of treating multiple myeloma in a patient in need of such treatment, said method comprising administering to said patient therapeutically effective amounts of at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) and: (1) a proteosome inhibitor (e.g., PS-341 from Millenium); or (2) Thalidomide (or related imid).

This invention also provides a method of treating cancer in a patient in need of such treatment, said method comprising administering to said patient therapeutically effective amounts of: (a) at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), and (b) at least one (e.g., 1, 2 or 3, or 1 or 2, or 2, or 1) antineoplastic agent selected from the group consisting of: (1) taxanes, (2) platinum coordinator compounds, (3) EGF inhibitors that are antibodies, (4) EGF inhibitors that are small molecules, (5) VEGF inhibitors that are antibodies, (6) VEGF kinase inhibitors that are small molecules, (7) estrogen receptor antagonists or selective estrogen receptor

modulators, (8) anti-tumor nucleoside derivatives, (9) epothilones, (10) topoisomerase inhibitors, (11) vinca alkaloids, and (12) antibodies that are inhibitors of αVβ3 integrins.

This invention also provides a method of treating non small cell lung cancer in a patient in need of such treatment, said method comprising administering to said patient therapeutically effective amounts of: (a) at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), and (b) at least one (e.g., 1, 2 or 3, or 1 or 2, or 2, or 1) antineoplastic agent selected from the group consisting of: (1) taxanes, (2) platinum coordinator compounds, (3) EGF inhibitors that are antibodies, (4) EGF inhibitors that are small molecules, (5) VEGF inhibitors that are antibodies, (6) VEGF kinase inhibitors that are small molecules, (7) estrogen receptor antagonists or selective estrogen receptor modulators, (8) anti-tumor nucleoside derivatives, (9) epothilones, (10) topoisomerase inhibitors, (11) vinca alkaloids, and (12) antibodies that are inhibitors of αVβ3 integrins.

This invention also provides a method of treating non small cell lung cancer in a patient in need of such treatment, said method comprising administering to said patient therapeutically effective amounts of: (a) at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), and (b) at least one (e.g., 1, 2 or 3, or 1 or 2, or 2, or 1) antineoplastic agent selected from the group consisting of: (1) taxanes, (2) platinum coordinator compounds, (3) anti-tumor nucleoside derivatives, (4) topoisomerase inhibitors, and (5) vinca alkaloids.

This invention also provides a method of treating non small cell lung cancer in a patient in need of such treatment, said method comprising administering therapeutically effective amounts of: (a) at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), (b) carboplatin, and (c) paclitaxel.

This invention also provides a method of treating non small cell lung cancer in a patient in need of such treatment, said method comprising administering to said patient therapeutically effective amounts of: (a) at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), (b) cisplatin, and (c) gemcitabine.

This invention also provides a method of treating non small cell lung cancer in a patient in need of such treatment, said method comprising administering therapeutically effective amounts of: (a) at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), (b) carboplatin, and (c) gemcitabine.

This invention also provides a method of treating non small cell lung cancer in a patient in need of such treatment, said method comprising administering therapeutically effective amounts of: (a) at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), (b) Carboplatin, and (c) Docetaxel.

This invention also provides a method of treating cancer in a patient in need of such treatment, said method comprising administering therapeutically effective amounts of: (a) at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), and (b) an antineoplastic agent selected from the group consisting of: (1) EGF inhibitors that are antibodies, (2) EGF inhibitors that are small molecules, (3) VEGF inhibitors that are antibodies, (4) VEGF kinase inhibitors that are small molecules.

This invention also provides a method of treating squamous cell cancer of the head and neck, in a patient in need of such treatment, said method comprising administering to said patient therapeutically effective amounts of: (a) at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), and (b) at least one (e.g., 1, 2 or 3, or 1 or 2, or 2, or 1) antineoplastic agent selected from the group consisting of: (1) taxanes, and (2) platinum coordinator compounds.

This invention also provides a method of treating squamous cell cancer of the head and neck, in a patient in need of such treatment, said method comprising administering to said patient therapeutically effective amounts of: (a) at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), and (b) at least one (e.g., 1, 2 or 3, or 1 or 2, or 2, or 1) antineoplastic agent selected from the group consisting of: (1) taxanes, (2) platinum coordinator compounds, and (3) anti-tumor nucleoside derivatives (e.g., 5-Fluorouracil).

This invention also provides a method of treating CML in a patient in need of such treatment, said method comprising administering therapeutically effective

amounts of: (a) at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), (b) Gleevec, and (c) interferon (e.g., Intron-A).

This invention also provides a method of treating CML in a patient in need of such treatment comprising administering therapeutically effective amounts of: (a) at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), (b) Gleevec; and (c) pegylated interferon (e.g., Peg-Intron, and Pegasys).

This invention also provides a method of treating CML in a patient in need of such treatment comprising administering therapeutically effective amounts of: (a) at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) and (b) Gleevec.

This invention also provides a method of treating CMML in a patient in need of such treatment, said method comprising administering to said patient therapeutically effective amounts of at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143).

This invention also provides a method of treating AML in a patient in need of such treatment, said method comprising administering to said patient therapeutically effective amounts of: (a) at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), and (b) an anti-tumor nucleoside derivative (e.g., Cytarabine (i.e., Ara-C)).

This invention also provides a method of treating AML in a patient in need of such treatment, said method comprising administering to said patient therapeutically effective amounts of: (a) at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), (b) an anti-tumor nucleoside derivative (e.g., Cytarabine (i.e., Ara-C)), and (c) an anthracycline.

This invention also provides a method of treating non-Hodgkin's lymphoma in a patient in need of such treatment, said method comprising administering to said patient therapeutically effective amounts of: (a) at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), and (b) Rituximab (Rituxan).

This invention also provides a method of treating non-Hodgkin's lymphoma in a patient in need of such treatment, said method comprising administering to said patient therapeutically effective amounts of: (a) at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), (b) Rituximab (Rituxan), and (c) an anti-tumor nucleoside derivative (e.g., Fludarabine (i.e., F-ara-A).

This invention also provides a method of treating non-Hodgkin's lymphoma in a patient in need of such treatment, said method comprising administering to said patient therapeutically effective amounts of: (a) at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), and (b) Genasense (antisense to BCL-2).

This invention also provides a method of treating multiple myeloma in a patient in need of such treatment, said method comprising administering therapeutically effective amounts of: (a) at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), and (b) a proteosome inhibitor (e.g., PS-341 (Millenium)).

This invention also provides a method of treating multiple myeloma in a patient in need of such treatment, said method comprising administering to said patient therapeutically effective amounts of: (a) at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), and (b) Thalidomide or related imid.

This invention also provides a method of treating multiple myeloma in a patient in need of such treatment, said method comprising administering therapeutically effective amounts of: (a) at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), and (b) Thalidomide.

This invention is also directed to the methods of treating cancer described herein, particularly those described above, wherein in addition to the administration of the compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) and antineoplastic agents, radiation therapy is also administered prior to, during, or after the treatment cycle.

This invention also provides a method for treating cancer (e.g., lung cancer, prostate cancer and myeloid leukemias) in a patient in need of such treatment, said method comprising administering to said patient (1) an effective amount of at least

one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), in combination with (2) at least one (e.g., 1, 2 or 3, or 1 or 2, or 2, or 1) antineoplastic agent, microtubule affecting agent and/or radiation therapy.

This invention also provides a method of treating cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) in combination with an effective amount of at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) signal transduction inhibitor.

Thus, in one example (e.g., treating non small cell lung cancer): (1) the compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) is administered in an amount of about 50 mg to about 200 mg twice a day, and in another example about 75 mg to about 125 mg administered twice a day, and in yet another example about 100 mg administered twice a day, (2) Paclitaxel (e.g., Taxol® is administered once per week in an amount of about 50 to about 100 mg/m^2, and in another example about 60 to about 80 mg/m^2, and (3) Carboplatin is administered once per week in an amount to provide an AUC of about 2 to about 3.

In another example (e.g., treating non small cell lung cancer): (1) the compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) is administered in an amount of about 50 mg to about 200 mg twice a day, and in another example about 75 mg to about 125 mg administered twice a day, and yet in another example about 100 mg administered twice a day, (2) Paclitaxel (e.g., Taxol® is administered once per week in an amount of about 50 to about 100 mg/m^2, and in another example about 60 to about 80 mg/m^2, and (3) Cisplatin is administered once per week in an amount of about 20 to about 40 mg/m^2.

In another example (e.g., treating non small cell lung cancer): (1) the compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) is administered in an amount of about 50 mg to about 200 mg twice a day, and in another example about 75 mg to about 125 mg administered twice a day, and in yet another example about 100 mg administered twice a day, (2) Docetaxel (e.g., Taxotere®) is administered once per week in an amount of about 10 to about 45

mg/m^2, and (3) Carboplatin is administered once per week in an amount to provide an AUC of about 2 to about 3.

In another example (e.g., treating non small cell lung cancer): (1) the compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) is administered in an amount of about 50 mg to about 200 mg twice a day, and in another example about 75 mg to about 125 mg administered twice a day, and in yet another example about 100 mg administered twice a day, (2) Docetaxel (e.g., Taxotere®) is administered once per week in an amount of about 10 to about 45 mg/m^2, and (3) Cisplatin is administered once per week in an amount of about 20 to about 40 mg/m^2.

In another example (e.g., treating non small cell lung cancer): (1) the compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) is administered in an amount of about 50 mg to about 200 mg twice a day, and in another example about 75 mg to about 125 mg administered twice a day, and in yet another example about 100 mg administered twice a day, (2) Paclitaxel (e.g., Taxol® is administered once every three weeks in an amount of about 150 to about 250 mg/m^2, and in another example about 175 to about 225 mg/m^2, and in yet another example 175 mg/m^2, and (3) Carboplatin is administered once every three weeks in an amount to provide an AUC of about 5 to about 8, and in another example 6.

In another example of treating non small cell lung cancer: (1) the compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) is administered in an amount of 100 mg administered twice a day, (2) Paclitaxel (e.g., Taxol® is administered once every three weeks in an amount of 175 mg/m^2, and (3) Carboplatin is administered once every three weeks in an amount to provide an AUC of 6.

In another example (e.g., treating non small cell lung cancer): (1) the compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) is administered in an amount of about 50 mg to about 200 mg twice a day, and in another example about 75 mg to about 125 mg administered twice a day, and in yet another example about 100 mg administered twice a day, (2) Paclitaxel (e.g., Taxol® is administered once every three weeks in an amount of about 150 to about 250 mg/m^2, and in another example about 175 to about 225 mg/m^2, and (3) Cisplatin

is administered once every three weeks in an amount of about 60 to about 100 mg/m^2.

In another example (e.g., treating non small cell lung cancer): (1) the compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) is administered in an amount of about 50 mg to about 200 mg twice a day, and in another example about 75 mg to about 125 mg administered twice a day, and in yet another example about 100 mg administered twice a day, (2) Docetaxel (e.g., Taxotere® is administered once every three weeks in an amount of about 50 to about 100 mg/m^2, and (3) Carboplatin is administered once every three weeks in an amount to provide an AUC of about 5 to about 8.

In another example (e.g., treating non small cell lung cancer): (1) the compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) is administered in an amount of about 50 mg to about 200 mg twice a day, in another example about 75 mg to about 125 mg administered twice a day, and in yet another example about 100 mg administered twice a day, (2) Docetaxel (e.g., Taxotere® is administered once every three weeks in an amount of about 50 to about 100 mg/m^2, and (3) Cisplatin is administered once every three weeks in an amount of about 60 to about 100 mg/m^2.

In another example for treating non small cell lung cancer using the compounds of formula 1.0, Docetaxel and Carboplatin: (1) the compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) is administered in an amount of about 50 mg to about 200 mg twice a day, and in another example about 75 mg to about 125 mg administered twice a day, and in yet another example about 100 mg administered twice a day, (2) Docetaxel (e.g., Taxotere® is administered once every three weeks in an amount of about 75 mg/m^2, and (3) Carboplatin is administered once every three weeks in an amount to provide an AUC of about 6.

In another example of the treatments of non-small cell lung cancer described above the Docetaxel (e.g., Taxotere®) and Cisplatin, the Docetaxel (e.g., Taxotere®) and Carboplatin, the Paclitaxel (e.g., Taxol®) and Carboplatin, or the Paclitaxel (e.g., Taxol®) and Cisplatin are administered on the same day.

In another example (e.g., CML): (1) the compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) is administered in an amount

of about 100 mg to about 200 mg administered twice a day, (2) Gleevec is administered in an amount of about 400 to about 800 mg/day orally, and (3) interferon (Intron-A) is administered in an amount of about 5 to about 20 million IU three times per week.

In another example (e.g., CML): (1) the compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) is administered in an amount of about 100 mg to about 200 mg administered twice a day, (2) Gleevec is administered in an amount of about 400 to about 800 mg/day orally, and (3) pegylated interferon (Peg-Intron or Pegasys) is administered in an amount of about 3 to about 6 micrograms/kg/day.

In another example (e.g., non-Hodgkin's lymphoma): (1) the compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) is administered in an amount of about 50 mg to about 200 mg twice a day, and in another example about 75 mg to about 125 mg administered twice a day, and in yet another example about 100 mg administered twice a day, and (2) Genasense (antisense to BCL-2) is administered as a continuous IV infusion at a dose of about 2 to about 5 mg/kg/day (e.g., 3 mg/kg/day) for 5 to 7 days every 3 to 4 weeks.

In another example (e.g., multiple myeloma): (1) the compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) is administered in an amount of about 50 mg to about 200 mg twice a day, and in another example about 75 mg to about 125 mg administered twice a day, and in yet another example about 100 mg administered twice a day, and (2) the proteosome inhibitor (e.g., PS-341 – Millenium) is administered in an amount of about 1.5mg/m^2 twice weekly for two consecutive weeks with a one week rest period.

In another example (e.g., multiple myeloma): (1) the compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) is administered in an amount of about 50 mg to about 200 mg twice a day, and in another example about 75 mg to about 125 mg administered twice a day, and in yet another example about 100 mg administered twice a day, and (2) the Thalidomide (or related imid) is administered orally in an amount of about 200 to about 800 mg/day, with dosing being continuous until relapse or toxicity.

In one embodiment of the methods of treating cancer of this invention, the chemotherapeutic agents are selected from the group consisting of: paclitaxel,

docetaxel, carboplatin, cisplatin, gemcitabine, tamoxifen, Herceptin, Cetuximab, Tarceva, Iressa, bevacizumab, navelbine, IMC-1C11, SU5416 and SU6688.

In another embodiment of the methods of treating cancer of this invention, the chemotherapeutic agents are selected from the group consisting of: paclitaxel, docetaxel, carboplatin, cisplatin, navelbine, gemcitabine, and Herceptin.

Thus, one embodiment of this invention is directed to a method of treating cancer comprising administering to a patient in need of such treatment therapeutically effective amounts of the compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), a taxane, and a platinum coordination compound.

Another embodiment of this invention is directed to a method of treating cancer comprising administering to a patient in need of such treatment therapeutically effective amounts of the compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), a taxane, and a platinum coordination compound, wherein said compound of formula 1.0 is administered every day, said taxane is administered once per week per cycle, and said platinum coordinator compound is administered once per week per cycle. In another embodiment the treatment is for one to four weeks per cycle.

Another embodiment of this invention is directed to a method of treating cancer comprising administering to a patient in need of such treatment therapeutically effective amounts of the compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), a taxane, and a platinum coordination compound, wherein said compound of formula 1.0 is administered every day, said taxane is administered once every three weeks per cycle, and said platinum coordinator compound is administered once every three weeks per cycle. In another embodiment the treatment is for one to three weeks per cycle.

Another embodiment of this invention is directed to a method of treating cancer comprising administering to a patient in need of such treatment therapeutically effective amounts of the compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), paclitaxel, and carboplatin. In another embodiment, said compound of formula 1.0 is administered every day, said paclitaxel is administered once per week per cycle, and said carboplatin is administered once per week per cycle. In another embodiment the treatment is for one to four weeks per cycle.

Another embodiment of this invention is directed to a method of treating cancer comprising administering to a patient in need of such treatment therapeutically effective amounts of the compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), paclitaxel, and carboplatin. In another embodiment, said compound of formula 1.0 is administered every day, said paclitaxel is administered once every three weeks per cycle, and said carboplatin is administered once every three weeks per cycle. In another embodiment the treatment is for one to three weeks per cycle.

Another embodiment of this invention is directed to a method for treating non small cell lung cancer in a patient in need of such treatment comprising administering daily a therapeutically effective amount of the compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), administering a therapeutically effective amount of carboplatin once a week per cycle, and administering a therapeutically effective amount of paclitaxel once a week per cycle, wherein the treatment is given for one to four weeks per cycle. In another embodiment said compound of formula 1.0 is administered twice per day. In another embodiment said carboplatin and said paclitaxel are administered on the same day, and in another embodiment said carboplatin and said paclitaxel are administered consecutively, and in another embodiment said carboplatin is administered after said paclitaxel.

Another embodiment of this invention is directed to a method for treating non small cell lung cancer in a patient in need of such treatment comprising administering daily a therapeutically effective amount of a compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), administering a therapeutically effective amount of carboplatin once every three weeks per cycle, and administering a therapeutically effective amount of paclitaxel once every three weeks per cycle, wherein the treatment is given for one to three weeks. In another embodiment compound of formula 1.0 is administered twice per day. In another embodiment said carboplatin and said paclitaxel are administered on the same day, and in another embodiment said carboplatin and said paclitaxel are administered consecutively, and in another embodiment said carboplatin is administered after said paclitaxel.

Another embodiment of this invention is directed to a method for treating non small cell lung cancer in a patient in need of such treatment comprising administering about 50 to about 200 mg of a compound of formula 1.0 (for example, as described in

any one of Embodiment Nos. 1 to 143) twice a day, administering carboplatin once per week per cycle in an amount to provide an AUC of about 2 to about 8 (and in another embodiment about 2 to about 3), and administering once per week per cycle about 60 to about 300 mg/m^2 (and in another embodiment about 50 to 100mg/m^2, and in yet another embodiment about 60 to about 80 mg/m^2) of paclitaxel, wherein the treatment is given for one to four weeks per cycle. In another embodiment said compound of formula 1.0 is administered in amount of about 75 to about 125 mg twice a day, and in another embodiment about 100 mg twice a day. In another embodiment said carboplatin and said paclitaxel are administered on the same day, and in another embodiment said carboplatin and said paclitaxel are administered consecutively, and in another embodiment said carboplatin is administered after said paclitaxel.

In another embodiment, this invention is directed to a method for treating non small cell lung cancer in a patient in need of such treatment comprising administering about 50 to about 200 mg of a compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) twice a day, administering carboplatin once every three weeks per cycle in an amount to provide an AUC of about 2 to about 8 (in another embodiment about 5 to about 8, and in another embodiment 6), and administering once every three weeks per cycle about 150 to about 250 mg/m^2 (and in another embodiment about 175 to about 225 mg/m^2, and in another embodiment 175 mg/m^2) of paclitaxel, wherein the treatment is given for one to three weeks. In another embodiment said compound of formula 1.0 is administered in an amount of about 75 to about 125 mg twice a day, and in another embodiment about 100 mg twice a day. In another embodiment said carboplatin and said paclitaxel are administered on the same day, and in another embodiment said carboplatin and said paclitaxel are administered consecutively, and in another embodiment said carboplatin is administered after said paclitaxel.

Other embodiments of this invention are directed to methods of treating cancer as described in the above embodiments (i.e., the embodiments directed to treating cancer and to treating non small cell lung cancer with a taxane and platinum coordinator compound) except that in place of paclitaxel and carboplatin the taxanes and platinum coordinator compounds used together in the methods are: (1) docetaxel (Taxotere®) and cisplatin; (2) paclitaxel and cisplatin; and (3) docetaxel and carboplatin. In another embodiment of the methods of this invention cisplatin is used

in amounts of about 30 to about 100 mg/m^2. In another embodiment of the methods of this invention docetaxel is used in amounts of about 30 to about 100 mg/m^2.

In another embodiment this invention is directed to a method of treating cancer comprising administering to a patient in need of such treatment therapeutically effective amounts of a compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), a taxane, and an EGF inhibitor that is an antibody. In another embodiment the taxane used is paclitaxel, and the EGF inhibitor is a HER2 antibody (in one embodiment Herceptin) or Cetuximab, and in another embodiment Herceptin is used. The length of treatment, and the amounts and administration of said compound of formula 1.0 and the taxane are as described in the embodiments above. The EGF inhibitor that is an antibody is administered once a week per cycle, and in another embodiment is administered on the same day as the taxane, and in another embodiment is administered consecutively with the taxane. For example, Herceptin is administered in a loading dose of about 3 to about 5 mg/m^2 (in another embodiment about 4 mg/m^2), and then is administered in a maintenance dose of about 2 mg/m^2 once per week per cycle for the remainder of the treatment cycle (usually the cycle is 1 to 4 weeks). In one embodiment the cancer treated is breast cancer.

In another embodiment this invention is directed to a method of treating cancer comprising administering to a patient in need of such treatment therapeutically effective amounts of: (1) a compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), (2) a taxane, and (3) an antineoplastic agent selected from the group consisting of: (a) an EGF inhibitor that is a small molecule, (b) a VEGF inhibitor that is an antibody, and (c) a VEGF kinase inhibitor that is a small molecule. In another embodiment, the taxane paclitaxel or docetaxel is used. In another embodiment the antineoplastic agent is selected from the group consisting of: tarceva, Iressa, bevacizumab, SU5416, SU6688 and BAY 43-9006. The length of treatment, and the amounts and administration of said compound of formula 1.0 and the taxane are as described in the embodiments above. The VEGF kinase inhibitor that is an antibody is usually given once per week per cycle. The EGF and VEGF inhibitors that are small molecules are usually given daily per cycle. In another embodiment, the VEGF inhibitor that is an antibody is given on the same day as the taxane, and in another embodiment is administered concurrently with the taxane. In another embodiment, when the EGF inhibitor that is a small molecule or the VEGF

inhibitor that is a small molecule is administered on the same day as the taxane, the administration is concurrently with the taxane. The EGF or VEGF kinase inhibitor is generally administered in an amount of about 10 to about 500 mg/m^2.

In another embodiment this invention is directed to a method of treating cancer comprising administering to a patient in need of such treatment therapeutically effective amounts of a compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), an anti-tumor nucleoside derivative, and a platinum coordination compound.

Another embodiment of this invention is directed to a method of treating cancer comprising administering to a patient in need of such treatment therapeutically effective amounts of a compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), an anti-tumor nucleoside derivative, and a platinum coordination compound, wherein said compound of formula 1.0 is administered every day, said anti-tumor nucleoside derivative is administered once per week per cycle, and said platinum coordinator compound is administered once per week per cycle. Although the treatment can be for one to four weeks per cycle, in one embodiment the treatment is for one to seven weeks per cycle.

Another embodiment of this invention is directed to a method of treating cancer comprising administering to a patient in need of such treatment therapeutically effective amounts of a compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), an anti-tumor nucleoside derivative, and a platinum coordination compound, wherein said compound of formula 1.0 is administered every day, said an anti-tumor nucleoside derivative is administered once per week per cycle, and said platinum coordinator compound is administered once every three weeks per cycle. Although the treatment can be for one to four weeks per cycle, in one embodiment the treatment is for one to seven weeks per cycle.

Another embodiment of this invention is directed to a method of treating cancer comprising administering to a patient in need of such treatment therapeutically effective amounts of a compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), gemcitabine, and cisplatin. In another embodiment, said compound of formula 1.0 is administered every day, said gemcitabine is administered once per week per cycle, and said cisplatin is administered once per week per cycle. In one embodiment the treatment is for one to seven weeks per cycle.

Another embodiment of this invention is directed to a method of treating cancer comprising administering to a patient in need of such treatment therapeutically effective amounts of a compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), gemcitabine, and cisplatin. In another embodiment, said compound of formula 1.0 is administered every day, said gemcitabine is administered once per week per cycle, and said cisplatin is administered once every three weeks per cycle. In another embodiment the treatment is for one to seven weeks.

Another embodiment of this invention is directed to a method of treating cancer comprising administering to a patient in need of such treatment therapeutically effective amounts of a compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), gemcitabine, and carboplatin. In another embodiment said compound of formula 1.0 is administered every day, said gemcitabine is administered once per week per cycle, and said carboplatin is administered once per week per cycle. In another embodiment the treatment is for one to seven weeks per cycle.

Another embodiment of this invention is directed to a method of treating cancer comprising administering to a patient in need of such treatment therapeutically effective amounts of a compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), gemcitabine, and carboplatin. In another embodiment said compound of formula 1.0 is administered every day, said gemcitabine is administered once per week per cycle, and said carboplatin is administered once every three weeks per cycle. In another embodiment the treatment is for one to seven weeks per cycle.

In the above embodiments using gemcitabine, the compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) and the platinum coordinator compound are administered as described above for the embodiments using taxanes. Gemcitabine is administered in an amount of about 500 to about 1250 mg/m^2. In one embodiment the gemcitabine is administered on the same day as the platinum coordinator compound, and in another embodiment consecutively with the platinum coordinator compound, and in another embodiment the gemcitabine is administered after the platinum coordinator compound.

Another embodiment of this invention is directed to a method of treating cancer in a patient in need of such treatment comprising administering to said patient a

compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) and an antineoplastic agent selected from: (1) EGF inhibitors that are antibodies, (2) EGF inhibitors that are small molecules, (3) VEGF inhibitors that are antibodies, and (4) VEGF kinase inhibitors that are small molecules all as described above. The treatment is for one to seven weeks per cycle, and generally for one to four weeks per cycle. The compound of formula 1.0 is administered in the same manner as described above for the other embodiments of this invention. The small molecule antineoplastic agents are usually administered daily, and the antibody antineoplastic agents are usually administered once per week per cycle. In one embodiment the antineoplastic agents are selected from the group consisting of: Herceptin, Cetuximab, Tarceva, Iressa, bevacizumab, IMC-1C11, SU5416, SU6688 and BAY 43-9006.

In the embodiments of this invention wherein a platinum coordinator compound is used as well as at least one other antineoplastic agent, and these drugs are administered consecutively, the platinum coordinator compound is generally administered after the other antineoplastic agents have been administered.

Other embodiments of this invention include the administration of a therapeutically effective amount of radiation to the patient in addition to the administration of a compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) and antineoplastic agents in the embodiments described above. Radiation is administered according to techniques and protocols well know to those skilled in the art.

Another embodiment of this invention is directed to a pharmaceutical composition comprising at least two different chemotherapeutic agents and a pharmaceutically acceptable carrier for intravenous administration. Preferably the pharmaceutically acceptable carrier is an isotonic saline solution (0.9% NaCl) or a dextrose solution (e.g., 5% dextrose).

Another embodiment of this invention is directed to a pharmaceutical composition comprising a compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) and at least two different antineoplastic agents and a pharmaceutically acceptable carrier for intravenous administration. Preferably the pharmaceutically acceptable carrier is an isotonic saline solution (0.9% NaCl) or a dextrose solution (e.g., 5% dextrose).

Another embodiment of this invention is directed to a pharmaceutical composition comprising a compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) and at least one antineoplastic agent and a pharmaceutically acceptable carrier for intravenous administration. Preferably the pharmaceutically acceptable carrier is an isotonic saline solution (0.9% NaCl) or a dextrose solution (e.g., 5% dextrose).

Other embodiments of this invention are directed to the use of a combination of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) and drugs for the treatment of breast cancer, i.e., this invention is directed to a combination therapy for the treatment of breast cancer. Those skilled in the art will appreciate that the compounds of formula 1.0 and drugs are generally administered as individual pharmaceutical compositions. The use of a pharmaceutical composition comprising more than one drug is within the scope of this invention.

Thus, another embodiment of this invention is directed to a method of treating (or preventing) breast cancer (i.e., postmenopausal and premenopausal breast cancer, e.g., hormone-dependent breast cancer) in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) and a therapeutically effective amount of at least one antihormonal agent selected from the group consisting of: (a) aromatase inhibitors, (b) antiestrogens, and (c) LHRH analogues; and said treatment optionally including the administration of at least one chemotherapeutic agent.

The compound of formula 1.0 is preferably administered orally, and in one embodiment is administered in capsule form.

Examples of aromatase inhibitors include but are not limited to: Anastrozole (e.g., Arimidex), Letrozole (e.g., Femara), Exemestane (Aromasin), Fadrozole and Formestane (e.g., Lentaron).

Examples of antiestrogens include but are not limited to: Tamoxifen (e.g., Nolvadex), Fulvestrant (e.g., Faslodex), Raloxifene (e.g., Evista), and Acolbifene.

Examples of LHRH analogues include but are not limited to: Goserelin (e.g., Zoladex) and Leuprolide (e.g., Leuprolide Acetate, such as Lupron or Lupron Depot).

Examples of chemotherapeutic agents include but are not limited to: Trastuzumab (e.g., Herceptin), Gefitinib (e.g., Iressa), Erlotinib (e.g., Erlotinib HCl,

such as Tarceva), Bevacizumab (e.g., Avastin), Cetuximab (e.g., Erbitux), and Bortezomib (e.g., Velcade).

Preferably, when more than one antihormonal agent is used, each agent is selected from a different category of agent. For example, one agent is an aromatase inhibitor (e.g., Anastrozole, Letrozole, or Exemestane) and one agent is an antiestrogen (e.g., Tamoxifen or Fulvestrant).

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) and at least one antihormonal agent selected from the group consisting of: (a) aromatase inhibitors, (b) antiestrogens, and (c) LHRH analogues; and administering an effective amount of at least one chemotherapeutic agent.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) and at least one antihormonal agent selected from the group consisting of: (a) aromatase inhibitors, (b) antiestrogens, and (c) LHRH analogues.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) and at least one antihormonal agent selected from the group consisting of: (a) aromatase inhibitors, and (b) antiestrogens.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), at least one antihormonal agent selected from the group consisting of: (a) aromatase inhibitors and (b) antiestrogens; and at least one chemotherapeutic agent.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) and at least one aromatase inhibitor.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), at least one aromatase inhibitor, and at least one chemotherapeutic agent.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of: (1) at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143); and (2) at least one antihormonal agent selected from the group consisting of: (a) aromatase inhibitors that are selected from the group consisting of Anastrozole, Letrozole, Exemestane, Fadrozole and Formestane, (b) antiestrogens that are selected from the group consisting of: Tamoxifen, Fulvestrant, Raloxifene, and Acolbifene, and (c) LHRH analogues that are selected from the group consisting of: Goserelin and Leuprolide; and administering an effective amount of at least one chemotherapeutic agent selected from the group consisting of: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, and Bortezomib.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of: (1) at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143); and (2) at least one antihormonal agent selected from the group consisting of: (a) aromatase inhibitors that are selected from the group consisting of Anastrozole, Letrozole, Exemestane, Fadrozole and Formestane, (b) antiestrogens that are selected from the group consisting of: Tamoxifen, Fulvestrant, Raloxifene, and Acolbifene, and (c) LHRH analogues that are selected from the group consisting of: Goserelin and Leuprolide.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of: (1) at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143); and (2) at least one antihormonal agent selected from the group consisting of: (a) aromatase inhibitors that are selected from the group consisting of Anastrozole, Letrozole, Exemestane, Fadrozole and Formestane, and (b) antiestrogens that are selected from the group consisting of: Tamoxifen, Fulvestrant, Raloxifene, and Acolbifene.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of: (1) at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143); and (2) at least one antihormonal agent selected from the group consisting of: (a) aromatase inhibitors that are selected from the group consisting of Anastrozole, Letrozole, Exemestane, Fadrozole and Formestane, (b) antiestrogens that are selected from the group consisting of: Tamoxifen, Fulvestrant, Raloxifene, and Acolbifene; and administering an effective amount of at least one chemotherapeutic agents are selected from the group consisting of: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, and Bortezomib.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of: (1) at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143); and (2) at least one aromatase inhibitor selected from the group consisting of Anastrozole, Letrozole, Exemestane, Fadrozole and Formestane.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of: (1) at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143); (2) at least one aromatase inhibitor that is selected from the group consisting of Anastrozole, Letrozole, Exemestane, Fadrozole and Formestane; and (3) administering an effective amount of at least one

chemotherapeutic agent selected from the group consisting of: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, and Bortezomib.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of: (1) at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143); (2) at least one aromatase inhibitor; and (3) at least one LHRH analogue.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of:(1) at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143); (2) at least one antiestrogen ; and (3) at least one LHRH analogue.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of: (1) at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143); (2) at least one aromatase inhibitor that is selected from the group consisting of Anastrozole, Letrozole, Exemestane, Fadrozole and Formestane; and (3) at least one LHRH analogue that is selected from the group consisting of: Goserelin and Leuprolide.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of: (1) at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143); (2) at least one antiestrogen that is selected from the group consisting of: Tamoxifen, Fulvestrant, Raloxifene, and Acolbifene; and (3) at least one LHRH analogue that is selected from the group consisting of: Goserelin and Leuprolide.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one

(e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) and Anastrozole.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) and Letrazole.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) and Exemestane.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) and and Fadrozole.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) and Formestane.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) and Tamoxifen.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) Fulvestrant.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said

treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) and Raloxifene.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) and Acolbifene.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) and Goserelin.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) and and Leuprolide.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), Anastrozole, and an antiestrogen selected from the group consisting of: Tamoxifen, Fulvestrant, Raloxifene, and Acolbifene.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), Letrozole, and an antiestrogen selected from the group consisting of: Tamoxifen, Fulvestrant, Raloxifene, and Acolbifene.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of

Embodiment Nos. 1 to 143), Exemestane, and an antiestrogen selected from the group consisting of: Tamoxifen, Fulvestrant, Raloxifene, and Acolbifene.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), Fadrozole, and an antiestrogen selected from the group consisting of: Tamoxifen, Fulvestrant, Raloxifene, and Acolbifene.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), Formestane, and an antiestrogen selected from the group consisting of: Tamoxifen, Fulvestrant, Raloxifene, and Acolbifene.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), Anastrozole, and Tamoxifen.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), Letrozole, and Tamoxifen.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), Exemestane, and Tamoxifen.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), Fadrozole, and Tamoxifen.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), Formestane, and Tamoxifen.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), Anastrozole, and Fulvestrant.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), Letrozole, and Fulvestrant.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), Exemestane, and Fulvestrant.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), Fadrozole, and Fulvestrant.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), Formestane, and Fulvestrant.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of

Embodiment Nos. 1 to 143), Anastrozole, and a chemotherapeutic agent selected from the group consisting of: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, and Bortezomib.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), Letrozole, and a chemotherapeutic agent selected from the group consisting of: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, and Bortezomib.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), Exemestane, and a chemotherapeutic agent selected from the group consisting of: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, and Bortezomib.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), Fadrozole, and a chemotherapeutic agent selected from the group consisting of: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, and Bortezomib.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), Formestane, and a chemotherapeutic agent selected from the group consisting of: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, and Bortezomib.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one

(e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), Tamoxifen, and a chemotherapeutic agent selected from the group consisting of: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, and Bortezomib.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), Fulvestrant, and a chemotherapeutic agent selected from the group consisting of: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, and Bortezomib.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), Raloxifene, and a chemotherapeutic agent selected from the group consisting of: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, and Bortezomib.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), Acolbifene, and a chemotherapeutic agent selected from the group consisting of: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, and Bortezomib.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), Goserelin, and a chemotherapeutic agent selected from the group consisting of: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, and Bortezomib.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said

treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), Leuprolein, and a chemotherapeutic agent selected from the group consisting of: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, and Bortezomib.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), Anastrozole, an antiestrogen selected from the group consisting of: Tamoxifen, Fulvestrant, Raloxifene, and Acolbifene, and a chemotherapeutic agent selected from the group consisting of: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, and Bortezomib.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), Letrozole, an antiestrogen selected from the group consisting of: Tamoxifen, Fulvestrant, Raloxifene, and Acolbifene, and a chemotherapeutic agent selected from the group consisting of: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, and Bortezomib.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), Exemestane, an antiestrogen selected from the group consisting of: Tamoxifen, Fulvestrant, Raloxifene, and Acolbifene, and a chemotherapeutic agent selected from the group consisting of: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, and Bortezomib.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), Fadrozole, an antiestrogen selected from the group

consisting of: Tamoxifen, Fulvestrant, Raloxifene, and Acolbifene, and a chemotherapeutic agent selected from the group consisting of: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, and Bortezomib.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), Formestane, an antiestrogen selected from the group consisting of: Tamoxifen, Fulvestrant, Raloxifene, and Acolbifene, and a chemotherapeutic agent selected from the group consisting of: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, and Bortezomib.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), Anastrozole, Tamoxifen, and a chemotherapeutic agent selected from the group consisting of: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, and Bortezomib.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), Letrozole, Tamoxifen, and a chemotherapeutic agent selected from the group consisting of: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, and Bortezomib.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), Exemestane, Tamoxifen, and a chemotherapeutic agent selected from the group consisting of: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, and Bortezomib.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said

treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), Fadrozole, Tamoxifen, and a chemotherapeutic agent selected from the group consisting of: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, and Bortezomib.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), Formestane, Tamoxifen, and a chemotherapeutic agent selected from the group consisting of: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, and Bortezomib.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), Anastrozole, Fulvestrant, and a chemotherapeutic agent selected from the group consisting of: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, and Bortezomib.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), Letrozole, Fulvestrant, and a chemotherapeutic agent selected from the group consisting of: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, and Bortezomib.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), Exemestane, Fulvestrant, and a chemotherapeutic agent selected from the group consisting of: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, and Bortezomib.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), Fadrozole, Fulvestrant, and a chemotherapeutic agent selected from the group consisting of: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, and Bortezomib.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), Formestane, Fulvestrant, and a chemotherapeutic agent selected from the group consisting of: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, and Bortezomib.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), Goserelin and Tamoxifen.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), Goserelin, and Fulvestrant.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), Goserelin, and Raloxifene.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), Goserelin and Acolbifene.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), Leuprolide, and Tamoxifen.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), Leuprolide, and Fulvestrant.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), Leuprolide, and Raloxifene.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), Leuprolide and Acolbifene.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), Goserelin and Anastrozole.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), Goserelin and Letrozole.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one

(e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), Goserelin and Exemestane.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), Goserelin and Fadrozole.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), Goserelin and Formestane.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), Leuprolide and Anastrozole.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), Leuprolide and Letrozole.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), Leuprolide and Exemestane.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), Leuprolide and Fadrozole.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said

treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), Leuprolide and Formestane.

Another embodiment of this invention is directed to the treatment or prevention of breast cancer in a patient in need of such treatment, said treatment comprising the administration of a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) and Anastrozole.

Another embodiment of this invention is directed to the treatment or prevention of breast cancer in a patient in need of such treatment, said treatment comprising the administration of a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) and Letrozole.

Another embodiment of this invention is directed to the treatment or prevention of breast cancer in a patient in need of such treatment, said treatment comprising the administration of a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) and Exemestane.

Another embodiment of this invention is directed to the treatment or prevention of breast cancer in a patient in need of such treatment, said treatment comprising the administration of a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) and Tamoxifen.

Another embodiment of this invention is directed to the treatment or prevention of breast cancer in a patient in need of such treatment, said treatment comprising the administration of a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) and Fulvestrant.

Another embodiment of this invention is directed to the treatment or prevention of breast cancer in a patient in need of such treatment, said treatment comprising the administration of a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), Anastrozole, and Fulvestrant.

Another embodiment of this invention is directed to the treatment or prevention of breast cancer in a patient in need of such treatment, said treatment comprising the administration of a therapeutically effective amount of at least one compound of formula I (e.g., one), Letrozole, and Fulvestrant.

Another embodiment of this invention is directed to the treatment or prevention of breast cancer in a patient in need of such treatment, said treatment comprising the administration of a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), Exemestane, and Fulvestrant.

Another embodiment of this invention is directed to the treatment or prevention of breast cancer in a patient in need of such treatment, said treatment comprising the administration of a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), Anastrozole, and Tamoxifen.

Another embodiment of this invention is directed to the treatment or prevention of breast cancer in a patient in need of such treatment, said treatment comprising the administration of a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), Letrozole, and Tamoxifen.

Another embodiment of this invention is directed to the treatment or prevention of breast cancer in a patient in need of such treatment, said treatment comprising the administration of a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), Exemestane, and Tamoxifen.

Other embodiments of this invention are directed to any of the above described embodiments for the treatment of Breast Cancer wherein the chemotherapeutic agent is Trastuzumab.

Other embodiments of this invention are directed to any of the above described embodiments for the treatment or prevention of Breast Cancer wherein the method is directed to the treatment of breast cancer.

The compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), antihormonal agents and chemotherapeutic agents can be administered concurrently or sequentially.

The antihormonal agents and optional chemotherapeutic agents are administered according to their protocols, dosage amounts, and dosage forms that are well know to those skilled in the art (e.g., the Physician's Desk Reference or published literature). For example, for Tamoxifen, Fulvestrant, Raloxifene, Anastrozole, Letrozole, Exemestane, Leuprolide and Goserelin, see the Physician's Desk Reference, 57th Edition, 2003, published by Thomas PDR at Montvale, N.J. 07645-1742, the disclosure of which is incorporated herein by reference thereto.

In general, in the embodiments directed to the methods of treating Breast Cancer: (1) the compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) can be administered daily (e.g., once per day, and in one embodiment twice a day), (2) the aromatase inhibitors can be administered in accordance with the known protocol for the aromatase inhibitor used (e.g., once per day), (3) the antiestrogens can be administered in accordance with the known protocol for the antiestrogen used (e.g., from once a day to once a month), (4) the LHRH analogue can be administered in accordance with the known protocol for the LHRH analogue used (e.g., once a month to once every three months), and (5) the chemotherapeutic agent can be administered in accordance with the known protocol for the chemotherapeutic agent used (e.g., from once a day to once a week).

Radiation therapy, if administered in the above treatments for breast cancer, is generally administered according to known protocols before administration of the compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), antihormonal agents and optional chemotherapeutic agents.

Treatment according to the methods of treating breast cancer is continuous (i.e., a continuous dosing schedule is followed). The treatment is continued until there is a complete response, or until the skilled clinician determines that the patient is not benefiting from the treatment (for example, when there is disease progression).

The continuous treatment protocol for breast cancer can be changed to a discontinuous treatment schedule if, in the judgment of the skilled clinician, the patient would benefit from a discontinuous treatment schedule with one or more of the administered drugs. For example, the compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) can be given using a discontinous treatment schedule while the remaining drugs used in the treatment are given as described herein. An example of a discontinuous treatment protocol for the compound of formula 1.0 (for example, as described in any one of Embodiment Nos.

1 to 143) is a repeating cycle of three weeks with the compound of formula 1.0 followed by one week without the compound of formula 1.0.

After a complete response is achieved with the breast cancer treatment, maintenance therapy with the compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) can be continued using the dosing described in the methods of this invention. Maintenance therapy can also include administration of the antihormonal agents using the dosing described in the methods of this invention. Maintenance therapy can just be with the antihormonal agents. For example, after a complete response is achieved, an aromatase inhibitor (e.g., Anastrozole, Letrozole or Exemestane) can be continued for up to five years. Or, for example, an antiestrogen, e.g., Tamoxifen, may be used for up to five years after a complete response is achieved. Or, for example, an antiestrogen (e.g., Tamoxifen) can be used for up to five years after a complete response is achieved followed by the use of an aromatase inhibitor (e.g., Anastrozole, Letrozole or Exemestane) for up to five years.

In the embodiments directed to the treatment of breast cancer described above, the compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) is administered continuously in a total daily dose of about 100 mg to about 600 mg. Usually this amount is administered in divided doses, and in one embodiment this amount is administered twice a day. In one embodiment the compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) is dosed twice a day in an amount of about 50 mg to about 300 mg per dose. In another embodiment the compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) is dosed twice a day in an amount of about 100 mg to about 200 mg per dose. Examples include the compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) being dosed twice a day at 100 mg per dose. Examples also include the compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) being dosed twice a day at 200 mg per dose.

Anastrozole is administered p.o. and is dosed once a day in amounts of about 0.5 to about 10 mg per dose, and in one embodiment in an amount of about 1.0 mg per dose.

Letrozole is administered p.o. and is dosed once a day in amounts of about 1.0 to about 10 mg per dose, and in one embodiment in an amount of about 2.5 mg per dose.

Exemestane is administered p.o. and is dosed once a day in amounts of about 10 to about 50 mg per dose, and in one embodiment in an amount of about 25 mg per dose.

Fadrozole is administered p.o. and is dosed twice a day in amounts of about 0.5 to about 10 mg per dose, and in one embodiment in an amount of about 2.0 mg per dose.

Formestane is administered i.m. and is dosed once every two weeks in amounts of about 100 to about 500 mg per dose, and in one embodiment in an amount of about 250 mg per dose.

Tamoxifen is administered p.o. and is dosed once a day in amounts of about 10 to about 100 mg per dose, and in one embodiment in an amount of about 20 mg per dose.

Fulvestrant is administered i.m. and is dosed once a month in amounts of about 100 to about 1000 mg per dose, and in one embodiment in an amount of about 250 mg per dose.

Raloxifene is administered p.o. and is dosed once a day in amounts of about 10 to about 120 mg per dose, and in one embodiment in an amount of about 60 mg per dose.

Acolbifene is administered p.o. and is dosed once a day in amounts of about 5 to about 20 mg per dose, and in one embodiment in an amount of about 20 mg per dose.

Goserelin is administered s.c. and is dosed once a month, or once every three months, in amounts of about 2 to about 20 mg per dose, and in one embodiment in an amount of about 3.6 mg per dose when administered once a month, and in another embodiment in an amount of about 10.8 mg per dose when administered once every three months.

Leuprolide is administered s.c. and is dosed once a month, or once every three months, in amounts of about 2 to about 20 mg per dose, and in one embodiment in an amount of about 3.75 mg per dose when administered once a month, and in another embodiment in an amount of about 11.25 mg per dose when administered once every three months.

Trastuzumab is administered by i.v. and is dosed once a week in amounts of about 2 to about 20 mpk per dose, and in one embodiment in an amount of about 2 mpk per dose. Trastuzumab is generally initially administered in a loading dose that is generally twice the dose of the weekly dose. Thus, for example, a 4 mpk loading dose is administered and then dosing is 2 mpk per dose per week.

Gefitinib is administered p.o. and is dosed once a day in amounts of about 100 to about 1000 mg per dose, and in one embodiment in an amount of about 250 mg per dose.

Erlotinib is administered p.o. and is dosed once a day in amounts of about 100 to about 500 mg per dose, and in one embodiment in an amount of about 150 mg per dose.

Bevacizumab is administered i.v. and is dosed once every two weeks in amounts of about 2.5 to about 15 mg per kilogram of body weight per dose, and in one embodiment in an amount of about 10 mg per kilogram per dose.

Cetuximab is administered i.v. and is dosed once a week in amounts of about 200 to about 500 mg per meter squared dose, and in one embodiment in an amount of about 250 mg per meter squared per dose.

Bortezomib is administered i.v. and is dosed twice a week for 2 weeks followed by a 10 day rest period (21 day treatment cycle) for a maximum of 8 treatment cycles in amounts of about 1.0 to about 2.5 mg per meter squared per dose, and in one embodiment in an amount of about 1.3 mg per meter squared per dose.

Thus in one embodiment of this invention breast cancer is treated (or prevented) in a patient in need of such treatment wherein said treatment comprises administering to said patient: (1) the compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) orally in an amount of about 50 mg to about 300 mg per dose wherein each dose is administered twice a day, and (2) Anastrozole p.o. in an amount of about 0.5 to about 10 mg per dose wherein each dose is given once a day.

In another embodiment of this invention breast cancer is treated (or prevented) in a patient in need of such treatment wherein said treatment comprises administering to said patient: (1) the compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) orally in an amount of about 100 to 200 mg per dose, wherein each dose is administered twice a day, and (2) Anastrozole in an amount of about 1.0 mg per dose wherein each dose is given once a day.

In another embodiment of this invention breast cancer is treated (or prevented) in a patient in need of such treatment wherein said treatment comprises administering to said patient: (1) the compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) orally in an amount of about 50 mg to about 300 mg per dose wherein each dose is administered twice a day, and (2) Letrozole p.o. in an amount of about 1.0 to about 10 mg per dose wherein each dose is given once a day.

In another embodiment of this invention breast cancer is treated (or prevented) in a patient in need of such treatment wherein said treatment comprises administering to said patient: (1) the compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) orally in an amount of about 100 to 200 mg per dose, wherein each dose is administered twice a day, and (2) Letrozole p.o. in an amount of about 2.5 mg per dose wherein each dose is given once a day.

In another embodiment of this invention breast cancer is treated (or prevented) in a patient in need of such treatment wherein said treatment comprises administering to said patient: (1) the compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) orally in an amount of about 50 mg to about 300 mg per dose wherein each dose is administered twice a day, and (2) Exemestane p.o. in an amount of about 10 to about 50 mg per dose wherein each dose is given once a day.

In another embodiment of this invention breast cancer is treated (or prevented) in a patient in need of such treatment wherein said treatment comprises administering to said patient: (1) the compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) orally in an amount of about 100 to 200 mg per dose, wherein each dose is administered twice a day, and (2) Exemestane in an amount of about 25 mg per dose wherein each dose is given once a day.

In another embodiment of this invention breast cancer is treated (or prevented) in a patient in need of such treatment wherein said treatment comprises administering to said patient: (1) the compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) orally in an amount of about 50 mg to about 300 mg per dose wherein each dose is administered twice a day, and (2) Fulvestrant i.m. in an amount of about 100 to about 1000 mg per dose wherein each dose is given once a month.

In another embodiment of this invention breast cancer is treated (or prevented) in a patient in need of such treatment wherein said treatment comprises administering

to said patient: (1) the compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) orally in an amount of about 100 to 200 mg per dose, wherein each dose is administered twice a day, and (2) Fulvestrant i.m. in an amount of about 250 mg per dose wherein each dose is given once a month.

In another embodiment of this invention breast cancer is treated (or prevented) in a patient in need of such treatment wherein said treatment comprises administering to said patient: (1) the compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) p.o. in an amount of about 50 mg to about 300 mg per dose wherein each dose is administered twice a day, and (2) Tamoxifen p.o. in an amount of about 10 to about 100 mg per dose wherein each dose is given once a day.

In another embodiment of this invention breast cancer is treated (or prevented) in a patient in need of such treatment wherein said treatment comprises administering to said patient: (1) the compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) p.o. in an amount of about 100 to 200 mg per dose, wherein each dose is administered twice a day, and (2) Tamoxifen p.o. in an amount of about 20 mg per dose wherein each dose is given once a day.

In other embodiments of the invention breast cancer is treated in a patient in need of such treatment wherein said treatment comprises the administration of the compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), one of the aromatase inhibitors (e.g., Anastrozole, Letrozole, or Exemestane, and in one embodiment Anastrozole), and one of the antiestrogens (e.g., Fulvestrant or Tamoxifen), wherein the compound of formula 1.0, aromatase inhibitor and antiestrogen are administered in the dosages described above.

Thus, for example in another embodiment of this invention breast cancer is treated (or prevented) in a patient in need of such treatment wherein said treatment comprises administering to said patient : (1) the compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) p.o. in an amount of about 50 mg to about 300 mg per dose wherein each dose is administered twice a day, (2) Anastrozole p.o. in an amount of about 0.5 to about 10 mg per dose wherein each dose is given once a day, and (3) Fulvestrant i.m. in an amount of about 100 to about 1000 mg per dose wherein each dose is given once a month.

In another embodiment of this invention breast cancer is treated (or prevented) in a patient in need of such treatment wherein said treatment comprises administering

to said patient: (1) the compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) p.o in an amount of about 100 to 200 mg per dose, wherein each dose is administered twice a day, (2) Anastrozole p.o. in an amount of about 1.0 mg per dose wherein each dose is given once a day, and (3) Fulvestrant i.m. in an amount of about 250 mg per dose wherein each dose is given once a month.

In another embodiment of this invention breast cancer is treated (or prevented) in a patient in need of such treatment wherein said treatment comprises administering to said patient: (1) the compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) p.o. in an amount of about 50 mg to about 300 mg per dose wherein each dose is administered twice a day, (2) Letrozole p.o in an amount of about 1.0 to about 10 mg per dose wherein each dose is given once a day, and (3) Fulvestrant in an amount of about 100 to about 1000 mg per dose wherein each dose is given once a month.

In another embodiment of this invention breast cancer is treated (or prevented) in a patient in need of such treatment wherein said treatment comprises administering to said patient: (1) the compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) p.o. in an amount of about 100 to 200 mg per dose, wherein each dose is administered twice a day, (2) Letrozole p.o. in an amount of about 2.5 mg per dose wherein each dose is given once a day, and (3) Fulvestrant i.m. in an amount of about 250 mg per dose wherein each dose is given once a month.

In another embodiment of this invention breast cancer is treated (or prevented) in a patient in need of such treatment wherein said treatment comprises administering to said patient: (1) the compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) p.o. in an amount of about 50 mg to about 300 mg per dose wherein each dose is administered twice a day, (2) Exemestane p.o. in an amount of about 10 to about 50 mg per dose wherein each dose is given once a day, and (3) Fulvestrant i.m. in an amount of about 100 to about 1000 mg per dose wherein each dose is given once a month.

In another embodiment of this invention breast cancer is treated (or prevented) in a patient in need of such treatment wherein said treatment comprises administering to said patient: (1) the compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) p.o. in an amount of about 100 to 200 mg per dose,

wherein each dose is administered twice a day, (2) Exemestane p.o. in an amount of about 25 mg per dose wherein each dose is given once a day, and (3) Fulvestrant i.m. in an amount of about 250 mg per dose wherein each dose is given once a month.

In another embodiment of this invention breast cancer is treated (or prevented) in a patient in need of such treatment wherein said treatment comprises administering to said patient: (1) the compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) p.o. in an amount of about 50 mg to about 300 mg per dose wherein each dose is administered twice a day, (2) Anastrozole p.o. in an amount of about 0.5 to about 10 mg per dose wherein each dose is given once a day, and (3) Tamoxifen p.o.in an amount of about 10 to about 100 mg per dose wherein each dose is given once a day.

In another embodiment of this invention breast cancer is treated (or prevented) in a patient in need of such treatment wherein said treatment comprises administering to said patient: (1) the compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) p.o. in an amount of about 100 to 200 mg per dose, wherein each dose is administered twice a day, (2) Anastrozole p.o. in an amount of about 1.0 mg per dose wherein each dose is given once a day, and (3) Tamoxifen p.o. in an amount of about 20 mg per dose wherein each dose is given once a day.

In another embodiment of this invention breast cancer is treated (or prevented) in a patient in need of such treatment wherein said treatment comprises administering to said patient: (1) the compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) p.o. in an amount of about 50 mg to about 300 mg per dose wherein each dose is administered twice a day, (2) Letrozole p.o. in an amount of about 1.0 to about 10 mg per dose wherein each dose is given once a day, and (3) Tamoxifen p.o. in an amount of about 10 to about 100 mg per dose wherein each dose is given once a day.

In another embodiment of this invention breast cancer is treated (or prevented) in a patient in need of such treatment wherein said treatment comprises administering to said patient: (1) the compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) p.o. in an amount of about 100 to 200 mg per dose, wherein each dose is administered twice a day, (2) Letrozole p.o. in an amount of about 2.5 mg per dose wherein each dose is given once a day, and (3) Tamoxifen p.o. in an amount of about 20 mg per dose wherein each dose is given once a day.

In another embodiment of this invention breast cancer is treated (or prevented) in a patient in need of such treatment wherein said treatment comprises administering to said patient: (1) the compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) p.o. in an amount of about 50 mg to about 300 mg per dose wherein each dose is administered twice a day, (2) Exemestane p.o. in an amount of about 10 to about 50 mg per dose wherein each dose is given once a day, and (3) Tamoxifen p.o. in an amount of about 10 to about 100 mg per dose wherein each dose is given once a day.

In another embodiment of this invention breast cancer is treated (or prevented) in a patient in need of such treatment wherein said treatment comprises administering to said patient: (1) the compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) p.o. in an amount of about 100 to 200 mg per dose, wherein each dose is administered twice a day, (2) Exemestane p.o. in an amount of about 25 mg per dose wherein each dose is given once a day, and (3) Tamoxifen p.o. in an amount of about 20 mg per dose wherein each dose is given once a day.

Those skilled in the art will appreciate that when other combinations of antihormonal agents are used, the individual antihormonal agent is used in the amounts specified above for that individual antihormonal agent.

Other embodiments of the treatment of Breast Cancer are directed to the methods of treating Breast Cancer described above wherein the compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) is dosed twice a day in an amount of about 100 mg per dose.

Other embodiments of the treatment of Breast Cancer are directed to the methods of treating Breast Cancer described above wherein the compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) is dosed twice a day in an amount of about 200 mg per dose.

Other embodiments of the treatment of Breast Cancer are directed to the methods of treating Breast Cancer described above wherein a chemotherapeutic agent is administered in addition to the compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) and antihormonal agent (or antihormonal agents). In these embodiments the dosage ranges of the compound of formula 1.0 and antihormonal agents are as those described above in the combination therapies, or those described above for the individual compound of formula I and antihormonal agents, and the dosages of the chemotherapeutic agents

are those described above for the individual chemotherapeutic agent. The dosages for the chemotherapeutic agents are well known in the art.

Other embodiments of this invention are directed to pharmaceutical compositions comprising the compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143) and at least one antihormonal agent and a pharmaceutically acceptable carrier.

Other embodiments of this invention are directed to pharmaceutical compositions comprising the compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), at least one antihormonal agent, at least one chemotherapeutic agent, and a pharmaceutically acceptable carrier.

Other embodiments of this invention are directed to pharmaceutical compositions comprising the compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 143), at least one chemotherapeutic agent, and a pharmaceutically acceptable carrier.

Those skilled in the art will appreciate that the compounds (drugs) used in the methods of this invention are available to the skilled clinician in pharmaceutical compositions (dosage forms) from the manufacturer and are used in those compositions. So, the recitation of the compound or class of compounds in the above described methods can be replaced with a recitation of a pharmaceutical composition comprising the particular compound or class of compounds. For example, the embodiment directed to a method of treating cancer comprising administering to a patient in need of such treatment therapeutically effective amounts of the compound of formula 1.0, a taxane, and a platinum coordination compound, includes within its scope a method of treating cancer comprising administering to a patient in need of such treatment therapeutically effective amounts of a pharmaceutical composition comprising the compound of formula 1.0, a pharmaceutical composition comprising a taxane, and a pharmaceutical composition comprising a platinum coordination compound.

Those skilled in the art will recognize that the actual dosages and protocols for administration employed in the methods of this invention may be varied according to the judgment of the skilled clinician. The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage for a particular situation is within the skill of the art. A determination to vary the dosages and protocols for

administration may be made after the skilled clinician takes into account such factors as the patient's age, condition and size, as well as the severity of the cancer being treated and the response of the patient to the treatment.

The amount and frequency of administration of the compound of formula 1.0 and the chemotherapeutic agents will be regulated according to the judgment of the attending clinician (physician) considering such factors as age, condition and size of the patient as well as severity of the cancer being treated.

The chemotherapeutic agent can be administered according to therapeutic protocols well known in the art. It will be apparent to those skilled in the art that the administration of the chemotherapeutic agent can be varied depending on the cancer being treated and the known effects of the chemotherapeutic agent on that disease. Also, in accordance with the knowledge of the skilled clinician, the therapeutic protocols (e.g., dosage amounts and times of administration) can be varied in view of the observed effects of the administered therapeutic agents on the patient, and in view of the observed responses of the cancer to the administered therapeutic agents.

The initial administration can be made according to established protocols known in the art, and then, based upon the observed effects, the dosage, modes of administration and times of administration can be modified by the skilled clinician.

The particular choice of chemotherapeutic agent will depend upon the diagnosis of the attending physicians and their judgement of the condition of the patient and the appropriate treatment protocol.

The determination of the order of administration, and the number of repetitions of administration of the chemotherapeutic agent during a treatment protocol, is well within the knowledge of the skilled physician after evaluation of the cancer being treated and the condition of the patient.

Thus, in accordance with experience and knowledge, the practicing physician can modify each protocol for the administration of an chemotherapeutic agent according to the individual patient's needs, as the treatment proceeds. All such modifications are within the scope of the present invention.

The particular choice of antihormonal agents, optional chemotherapeutic agents and optional radiation will depend upon the diagnosis of the attending physicians and their judgment of the condition of the patient and the appropriate treatment protocol.

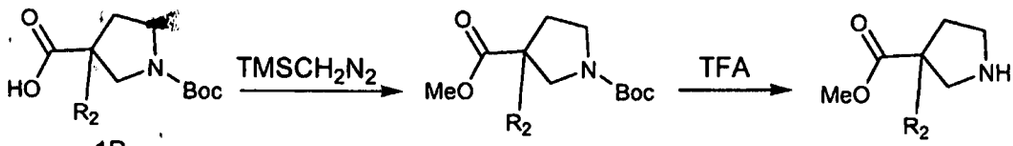
The determination of the order of administration, and the number of repetitions of administration of the antihormonal agents, optional chemotherapeutic agents and optional radiation during a treatment protocol, is well within the knowledge of the skilled physician after evaluation of the breast cancer being treated and the condition of the patient.

Thus, in accordance with experience and knowledge, the practicing physician can modify each protocol for the administration of antihormonal agents, optional chemotherapeutic agents and optional radiation according to the individual patient's needs, as the treatment proceeds. All such modifications are within the scope of the present invention.

The attending clinician, in judging whether treatment is effective at the dosage administered, will consider the general well-being of the patient as well as more definite signs such as relief of cancer-related symptoms (e.g., pain, cough (for lung cancer), and shortness of breath (for lung cancer)), inhibition of tumor growth, actual shrinkage of the tumor, or inhibition of metastasis. Size of the tumor can be measured by standard methods such as radiological studies, e.g., CAT or MRI scan, and successive measurements can be used to judge whether or not growth of the tumor has been retarded or even reversed. Relief of disease-related symptoms such as pain, and improvement in overall condition can also be used to help judge effectiveness of treatment.

The compounds of this invention can be made according to the processes described in WO2007/070398 published on June 21, 2007, and the compounds of the invention can be made according to the processes described below.

Scheme 1



1B 2B 3B

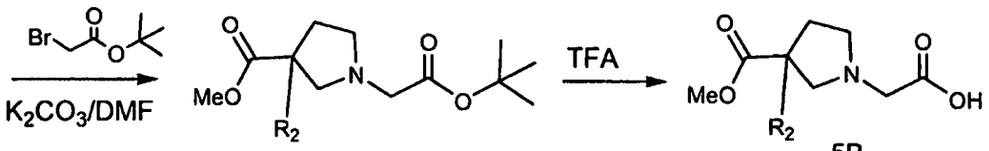
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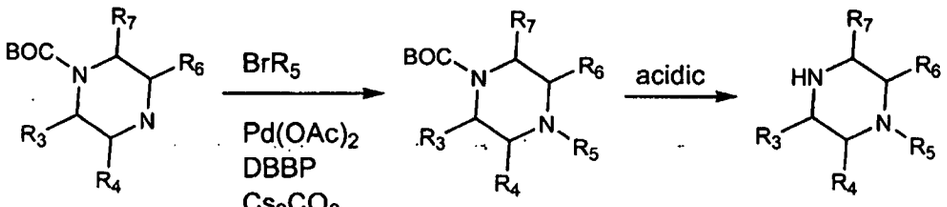
2/4



4B 5B

The appropriately substituted pyrrolidine is prepared as follows. The methyl ester of pyrrolidine 1B is prepared by reaction with TMSdiazomethane. After removing the BOC protecting group, compound 3B is reacted with bromo-tert.butylacetate to obtain 4B. The tert.butyl ester is then removed to obtain intermediate 5B.

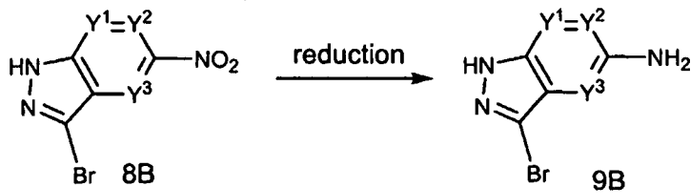
Scheme 2



6B 7B 7C

The R^5 substituted piperazine is prepared by Buchwald type coupling of the piperazine 6B with an aryl bromide in the presence of palladium to obtain the piperazine 7B. The BOC group is removed using acidic conditions (e.g., TFA) to give piperazine 7C.

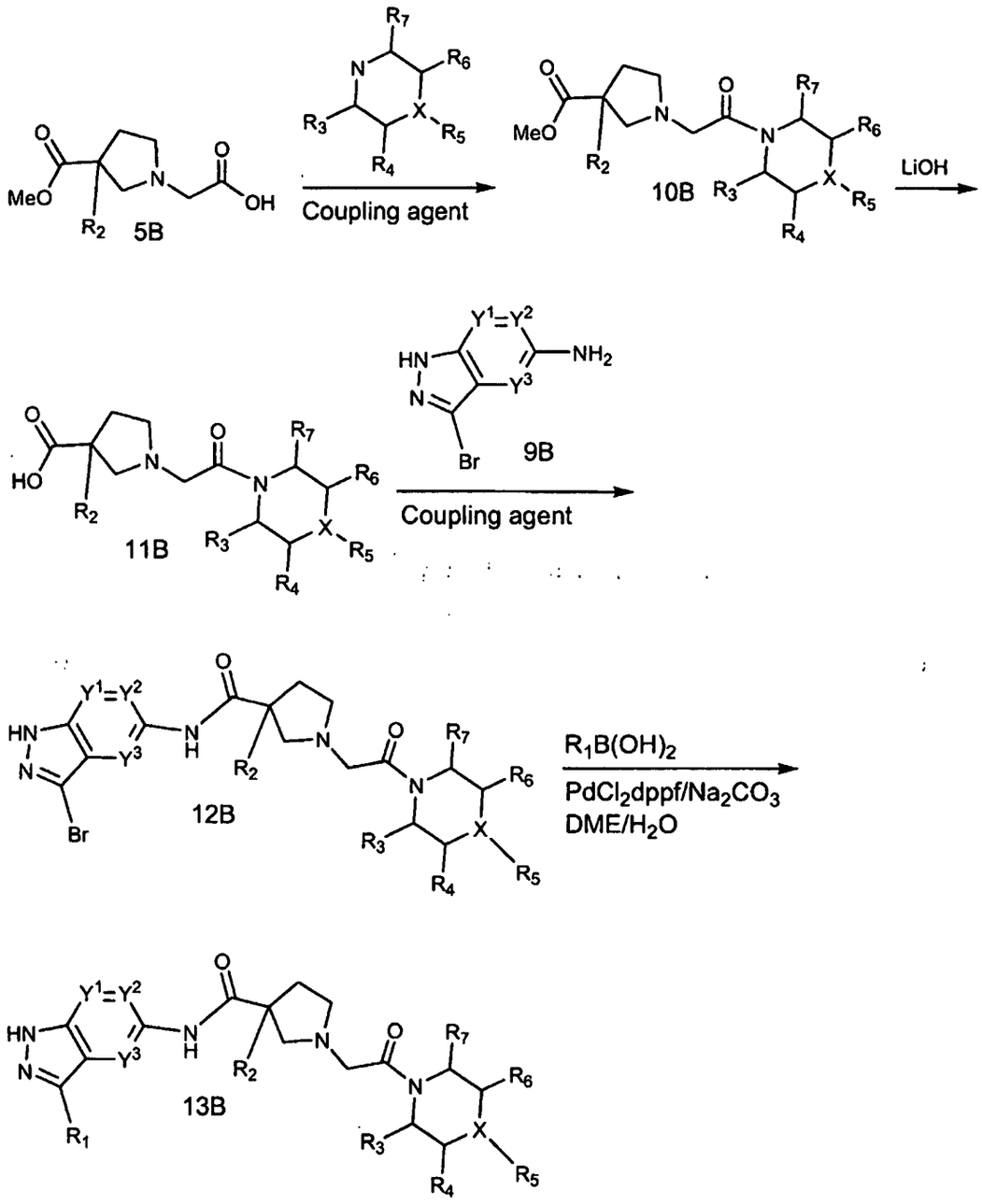
Scheme 3



8B 9B

The indazole bromide 9B is prepared by reduction of the indazole nitro compound 8B using reducing conditions such as palladium on carbon in the presence of hydrogen atmosphere.

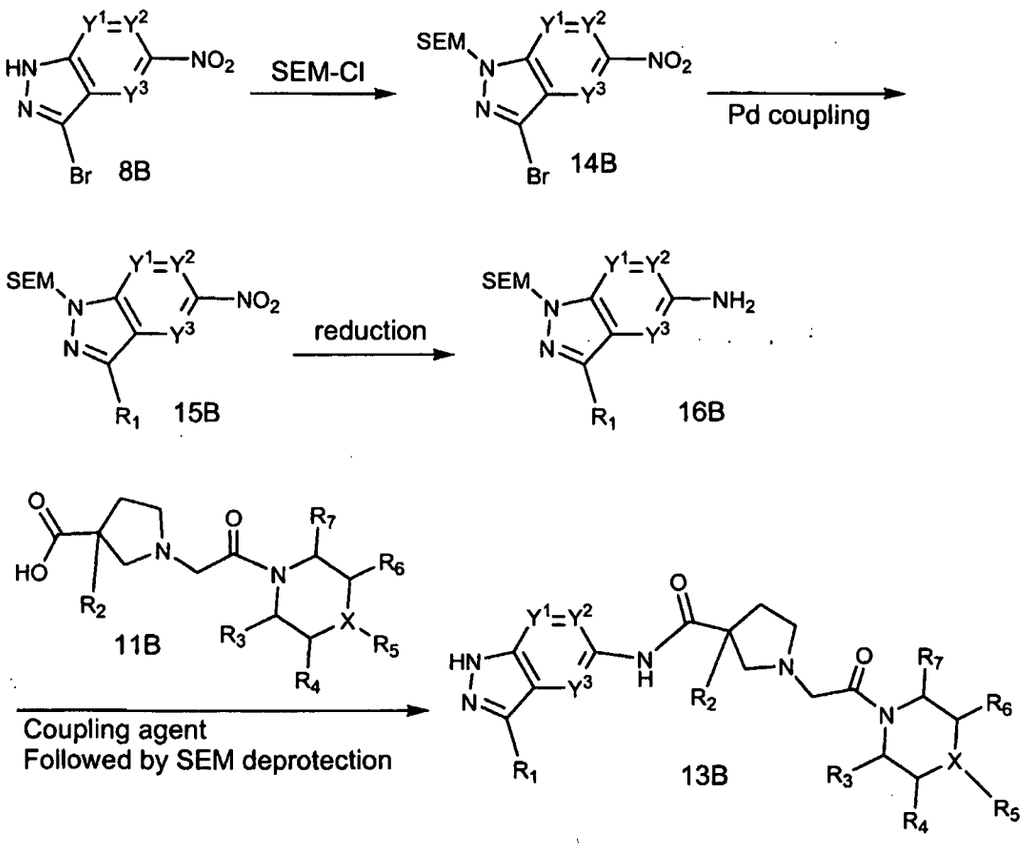
Scheme 4



The final molecule is assembled by coupling the pyrrolidine 5B with the piperazine (X is N, see compound 7C from Scheme 2), or with the piperidine (X is C, prepared in Schemes 11 or 12, or prepared according to the Examples described herein, or prepared according to methods well known to those skilled in the art), using

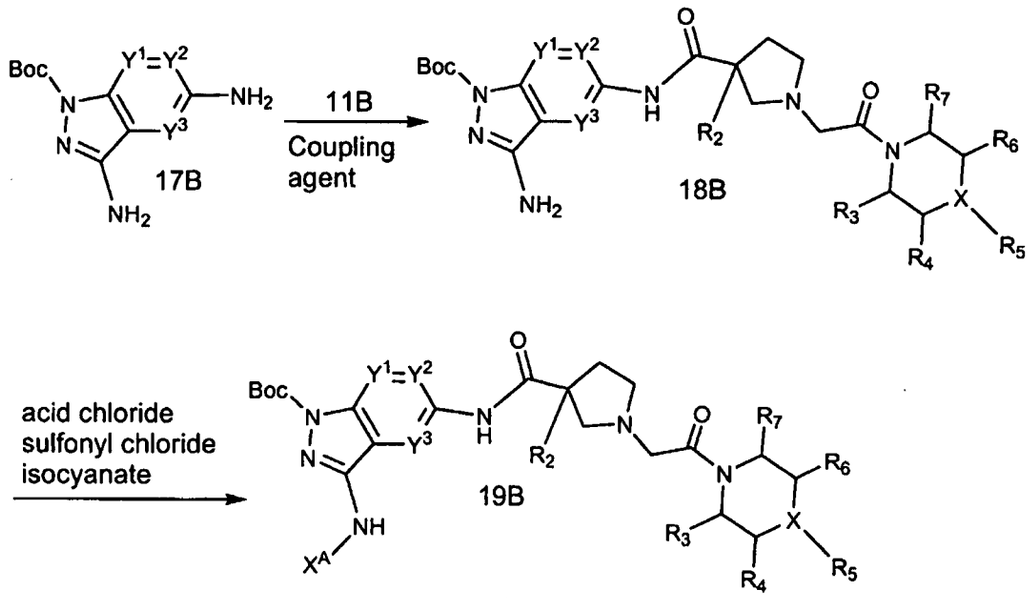
standard coupling conditions such as HATU in DMF to obtain 10B. After hydrolysis of the methyl ester to obtain 11B, the indazole intermediate 9B is then coupled using standard coupling conditions such as HATU in DMF to obtain 12B. The indazole is then derivatized at the 3 position by suzuki coupling with an a boronic acid to obtain the final product 13B.

Scheme 5



Alternatively, the final product 13B can be prepared by protecting the indazole 8B as the SEM (or trityl) derivative followed by Suzuki coupling to give the appropriately substituted indazole intermediate 15B. After reduction using reducing conditions such as palladium on carbon in the presence of hydrogen atmosphere to obtain 16B, the amine 16B can be coupled to 11B using standard coupling conditions such as HATU in DMF to obtain 13B.

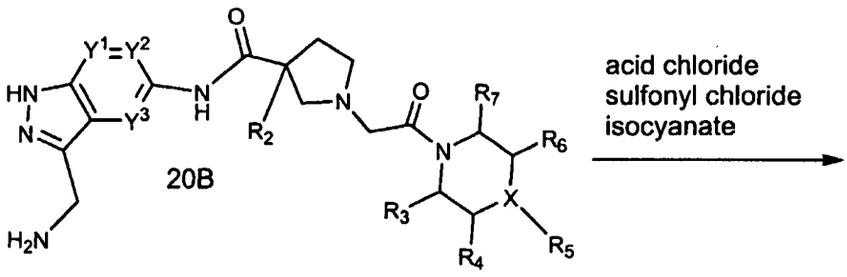
Scheme 6

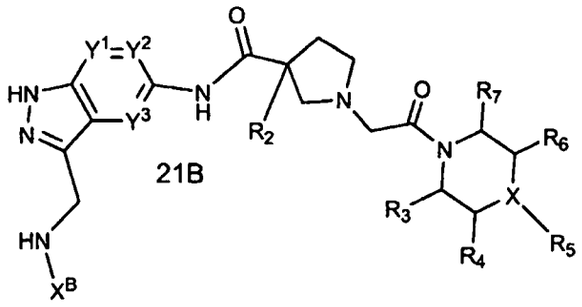


3-Amino substituted indazole derivatives can be prepared according to general Scheme 6 by coupling the Boc protected 3,5-diamino indazole 17B with 11B under standard coupling conditions such as HATU in DMF to obtain 18B. The 3-amino group can then be reacted with acid chlorides, sulfonyl chlorides and isocyanates to prepare the corresponding amides, sulfonamides and ureas 19B respectively.

Those skilled in the art will appreciate that the moiety $-NHX^A$ represents the amino substituted R^1 groups, such as, $-N(R^{10})_2$, $-NR^{32}-C(O)-R^{14}$, $-N(R^{10})C(O)N(R^{10})_2$, and $-N(R^{10})S(O)_tR^{10}$.

Scheme 7



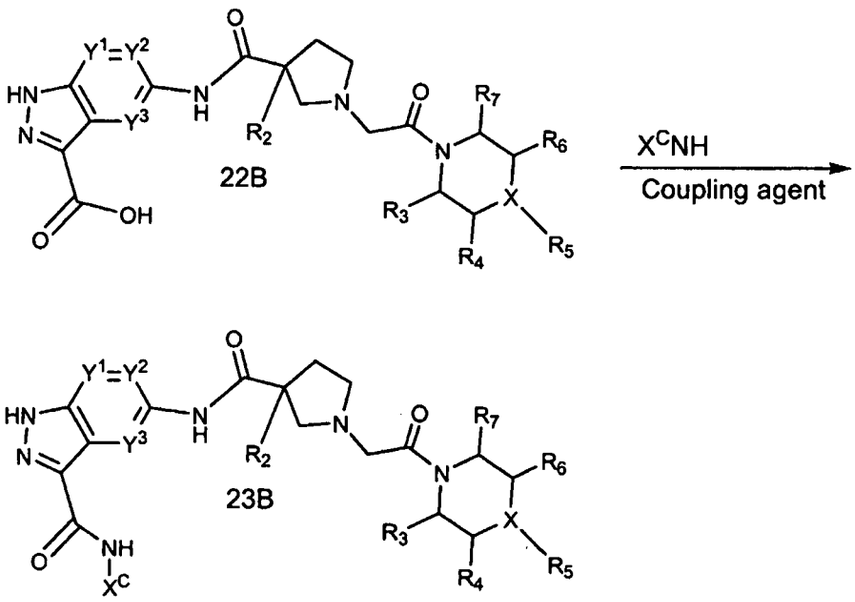


21B

The amino methyl indazole derivative 20B can be prepared according to Example 76 step 1 through 4 by substituting the appropriately substituted rings. The 3-aminomethyl group can then be reacted with acid chlorides, sulfonyl chlorides and isocyanates to prepare the corresponding amides, sulfonamides and ureas 21B respectively.

Those skilled in the art will appreciate that the moiety $-CH_2NHX^B$ represents the amino substituted methyl R^1 groups, such as, $-(C(R^{30})_2)_n-NR^{32}-C(O)-R^{10}$ (wherein n is 1 and each R^{30} is H), $-(C(R^{30})_2)_n-NR^{32}-S(O)_t-R^{10}$ (wherein n is 1 and each R^{30} is H), $-(C(R^{30})_2)_n-NR^{32}-C(O)-N(R^{32})-R^{10}$ (wherein n is 1 and each R^{30} is H), $-(C(R^{30})_2)_nR^{13}$ (wherein n is 1, each R^{30} is H and R^{13} is $-N(R^{10})_2$),

Scheme 8



22B

X^CNH

Coupling agent

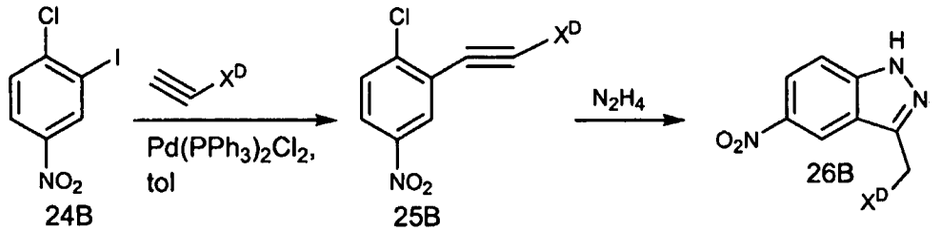
23B

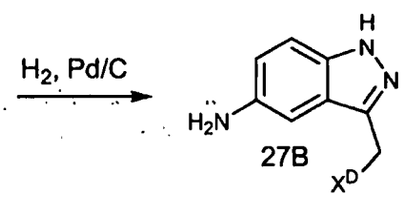
The amide compound 23B can be prepared by following Example 87 substituting the appropriate compound 11B (General Scheme 4). The resulting acid

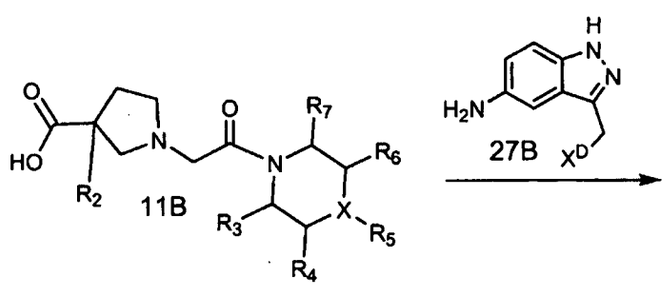
22B is then coupled with the appropriate amine under standard coupling conditions such as in the presence of EDC/HOBt to obtain 23B.

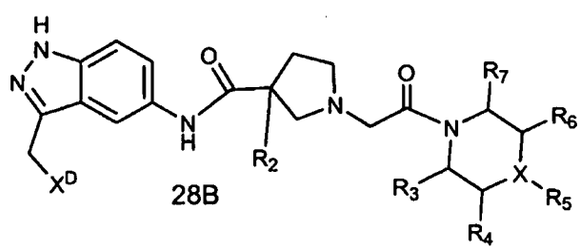
Those skilled in the art will appreciate that the moiety $-C(O)NHX^C$ represents the amide R^1 groups, such as, $-C(O)N(R^{10})_2$ and $-C(O)-NR^{32}-C(R^{18})_3$

Scheme 9







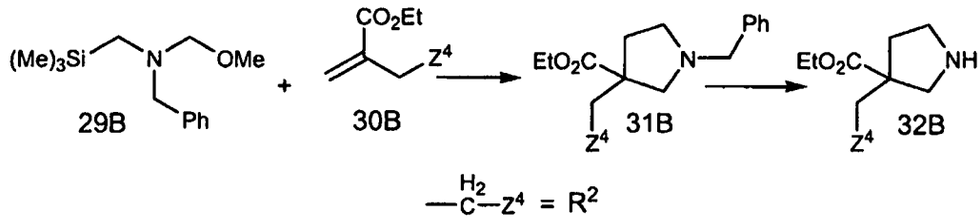


Indazoles of type 27B can be prepared by reacting 24B with the appropriately substituted acetylene in the presence of $Pd(PPh_3)_2Cl_2$ in toluene to obtain 25B. After heating with hydrazine to obtain 26B, 27B is obtained after hydrogenation. Coupling

of 27B with 11B under standard coupling conditions such as HATU or EDC/HOBt gives 28B.

The moiety $-CH_2X^D$ represents R^1 groups that are an R^{10} substituent, such as, alkyl, heteroarylalkyl, and arylalkyl.

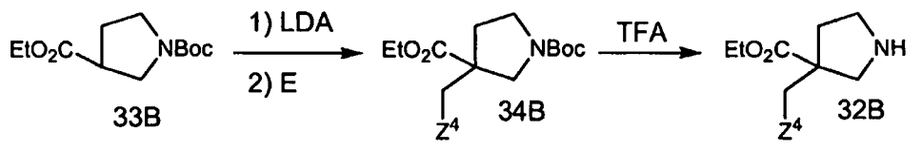
Scheme 10



$-\overset{H_2}{\underset{}{C}}-Z^4 = R^2$

The appropriately substituted pyrrolidine 32B can be obtained by reacting 29B with the appropriately substituted compound 30B in the presence of trifluoroacetic acid to obtain 31B. Compound 31B can then be deprotection under hydrogenation conditions (Pd/C, H_2 to obtain 32B).

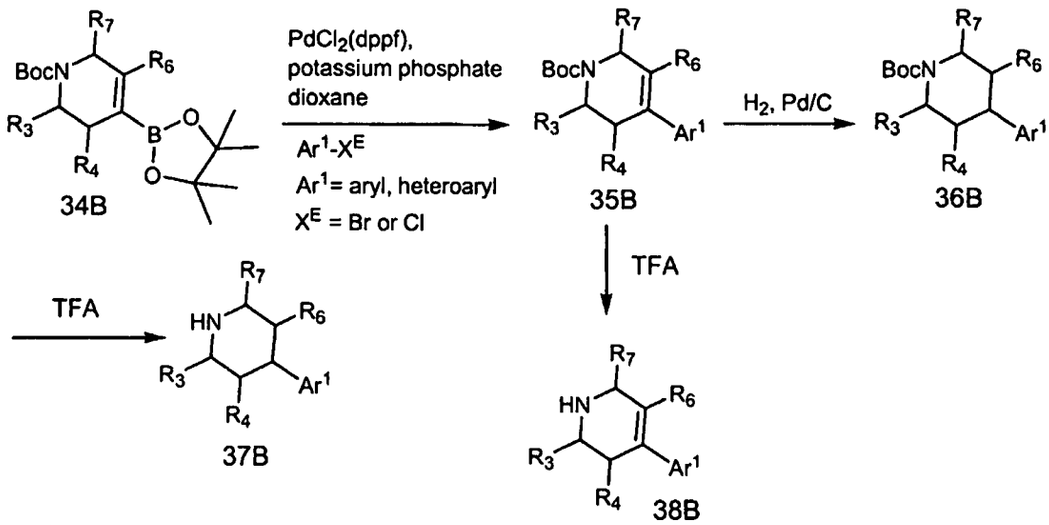
Alternative Process For Scheme 10



(E = electrophile)

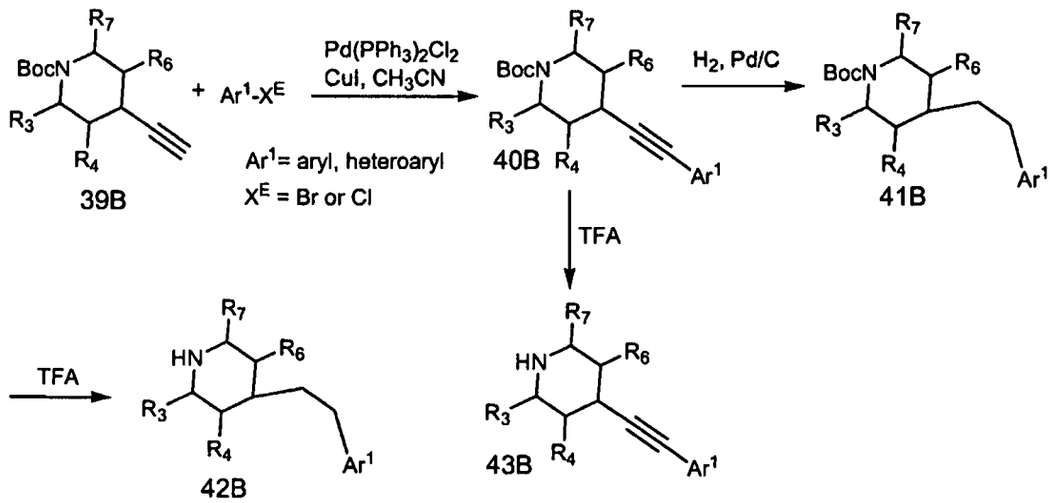
Alternatively, 32B can be obtain by reaction 33B with LDA followed by the addition of a suitable electrophile such as allylbromide, as in example 127, to obtain 34B. Treatment of 34B with trifluoroacetic acid yields 32B.

Scheme 11



Aryl or heteroaryl substituted piperidines can be prepared by Suzuki coupling of an aryl or heteroaryl halide with the pinicolboronate 34B to obtain 35B. The ring double bond can then be hydrogenated to obtain 36B followed by removal of the Boc protecting group under trifluoroacetic acid conditions. Alternatively the double bond can be retained and the Boc group removed to give 38B.

Scheme 12



Similarly aryl or heteroaryl substituted piperizines with a 2 carbon spacer can be prepared as shown in Scheme 12 by coupling an aryl or heteroaryl halide with an acetylene derivative 39B that can be prepared according to procedures known in the

art to obtain 40B. 40B can then be reduced to 41B followed by by removal of the Boc protecting group under trifluoroacetic acid conditions. Alternatively the Boc protecting group from 40B can be removed under trifluoroacetic acid conditions to give 43B.

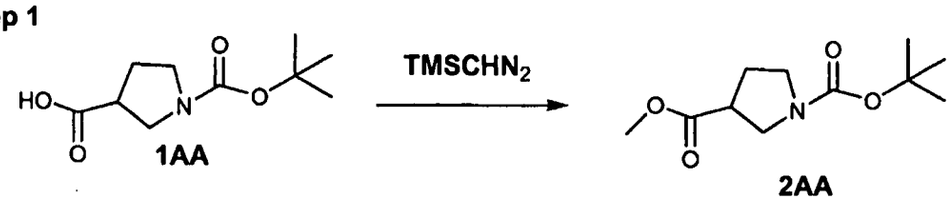
Compounds of this invention are exemplified in the following examples, which should not be construed as limiting the scope of the disclosure. Alternative mechanistic pathways and analogous structures within the scope of the invention may be apparent to those skilled in the art.

The LCMS conditions are: (1) column: C-18 reverse phase, 5um, 4.6 x 50 mm, (2) MS:PE Sciex API-150EX, and (3) HPLC: Shimadzu LC-10 ADvp, 1ml/min, linerar gradient 10% acetonitirle in water to 95% acetonitrile in water, both contain 0.05% TFA

Examples 1 to 611 are disclosed in WO2007/070398 (published on June 21, 2007) on page 188 at about line 15 to page 453 at about line 10, which pages are copied herein in their entirety and should be considered as part of the present disclosure, even though the said published pages are not reproduced here for the sake of brevity.

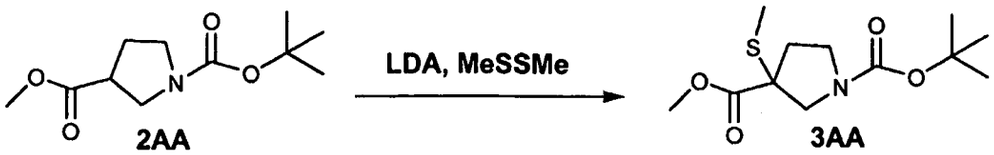
EXAMPLE 612

Step 1



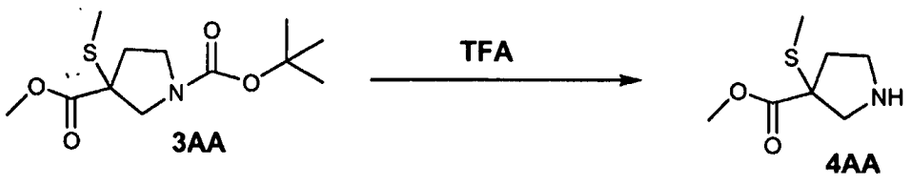
Pyrrolidine-1,3-dicarboxylic acid 1-tert-butyl ester **1AA**(4.3 gm, 20 mmol) was dissolved in 28 mL of toluene and 3.5 ml of methanol. Trimethylsilyldiazomethane 2N solution in hexanes(13 ml, 26 mmol) was added dropwise at 0 C and the reaction mixture stirred for 10 min at ambient temperature. The mixture was evaporated to obtain 4.3 gm of oil.

Step 2



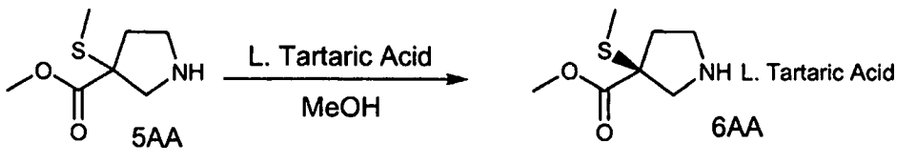
To the oil **2** (0.5 gm, 2.1 mmol) dissolved in tetrahydrofuran (15 ml) 1.2 ml of lithium diisopropylamide 2N solution in hexanes was added dropwise and the reaction mixture stirred for 1 hr at -78 C. Dimethyldisulfide (0.48 mL, 5.4 mmol) was added slowly and let warm to ambient temperature gradually. The reaction mixture was stirred for 18 hrs. A saturated solution of Ammonium chloride (25 ml) was added and the reaction mixture stirred for 5 min. The reaction mixture was extracted with ethyl acetate three times (3x25 ml), dried over magnesium sulfate, filtered and evaporated to give 0.386g of title product **3AA** after column chromatography.

Step 3



3-Methylsulfanyl-pyrrolidine-1,3-dicarboxylic acid 1-tert-butyl ester 3-methyl ester **3AA** (2.15 gm, 8.8 mmol) was dissolved in 20 ml of 50% trifluoroacetic acid/dichloromethane and stirred for 2 hrs. The reaction mixture was evaporated to an oil and exchanged with hydrochloric acid by dissolving in 20 ml of dichloromethane and adding 10 ml of 1N HCl in ether to obtain 3.35 gm **4AA** gummy solid.

Step 4

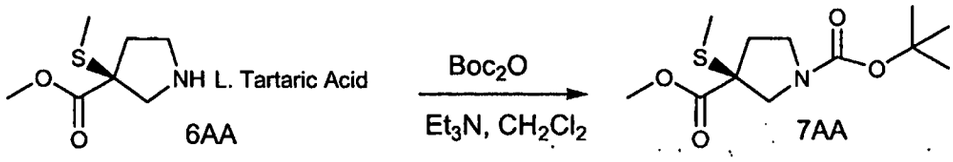


Compound A (42.9g, 244.8 mmol) and 1 eq. of L-tartaric acid were placed in a 1L rbf (round bottom flask) and dissolved with 250 mL of MeOH. The flask was then attached to a rotavapor at 75°C. The mixture was allowed to gently spin at this

temperature for about 20 mins. to ensure complete dissolution. After the formation of a clear solution, about 10mg of pure crystals were added (to aid the crystal formation) was allowed to settle gently settle down for crystal formation. After 3 days, 19.4g of crystals were recovered which was then washed with cold MeOH to give 18.2g of crystals.

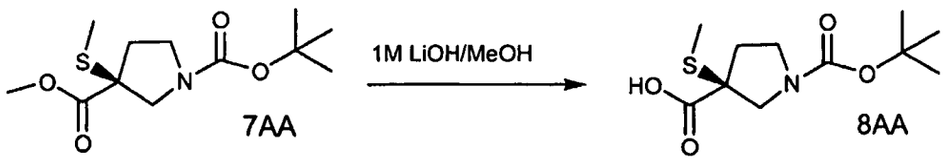
The chiral purity of the crystals was determined by derivatizing with 4-nitrobenzyl chloroformate and subjecting it to HPLC under the conditions of chiral AD column, 20% isopropanol/hexane solvent system and a flow rate of 1mL/min. The purity was found to be ~ 99.9% with a retention time of 16.58 min.

Step 5



Compound 6AA (3.0g, 9.2 mmol) was dissolved in 100mL of CH_2Cl_2 at rt. 2.5 eq. of Et_3N was added followed by 1.2 eq. of Boc_2O. The reaction mixture was allowed to stir for 1 day after it was diluted with CH_2Cl_2 and washed with sat. $NaHCO_3$ followed by sat. NaCl. The organic layer was dried over anhydrous MgSO4 and evaporated to dryness. The crude product was column purified (20% EtAOc/Hex) and evaporated to give 2.43g of pure product in the yield of ~ 96%.

Step 5



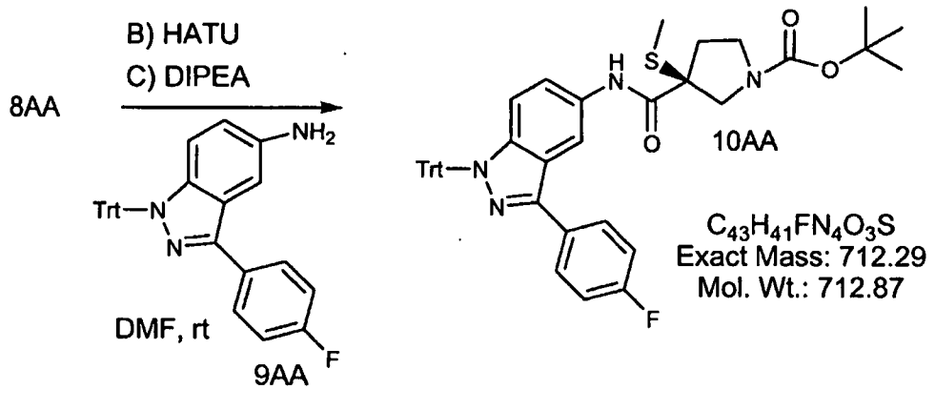
$C_{12}H_{21}NO_4S$
Exact Mass: 275.12
Mol. Wt.: 275.36

$C_{11}H_{19}NO_4S$
Exact Mass: 261.10
Mol. Wt.: 261.34

Compound 7AA (0.75g, 2.73 mmol) was dissolved in 20 mL of MeOH. 6 mL of 1M LiOH was added to the reaction flask and the resulting solution was allowed to stir at rt for 1 overnight. Upon completion of the reaction (determined by TLC), 6 mL of 1N HCl was added to neutralize the LiOH present in the reaction mixture. The mixture

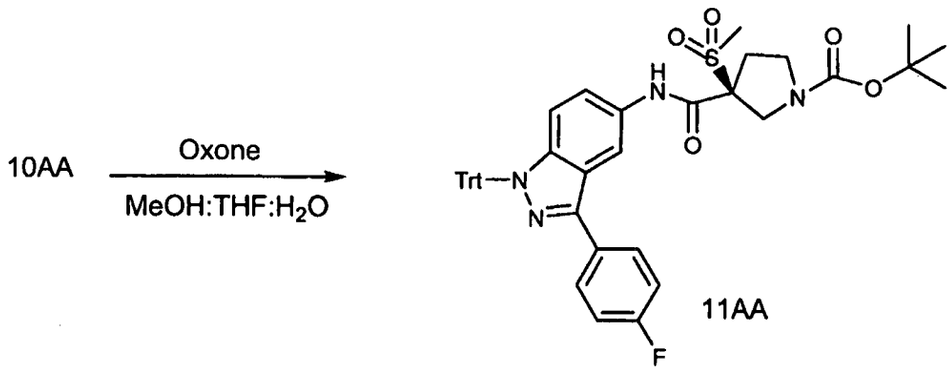
was then evaporated to dryness and azeotroped with dioxane to give 1.6g of 8AA as a white solid.

Step 7



In a rbf equipped with septum inlet was placed 0.26g of 8AA (0.994 mMol) and 0.467g of 9AA (0.994 mMol). These 2 components were dissolved in DMF. DIPEA was added to the reaction mixture followed by HATU. The mixture was stirred rt under a stream of nitrogen for 2 days. The crude was then quenched with 50 mL of sat. $NaHCO_3$ and extracted (3x50 mL) with EtOAc. The combined organic extracts was washed with brine and dried over Na_2SO_4. It was then filtered and evaporated to dryness to give a crude product which was column purified (30% E/H) to give 0.605 of product.

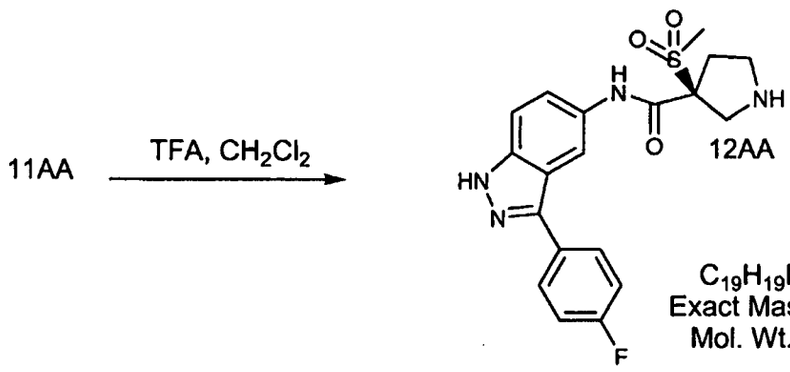
Step 8



$C_{43}H_{41}FN_4O_5S$
Exact Mass: 744.28
Mol. Wt.: 744.87

Compound 10AA (0.9g, 1.26 mMol) was dissolved in 6 mL each of MeOH:THF:H_2O. Oxone was added and the resulting mixture was allowed to stir for an overnight. Upon completion, the mixture was filtered through a glass fritz and washed with MeOH. The filtrate was then concentrated to give a crude product which was then subjected to the next step.

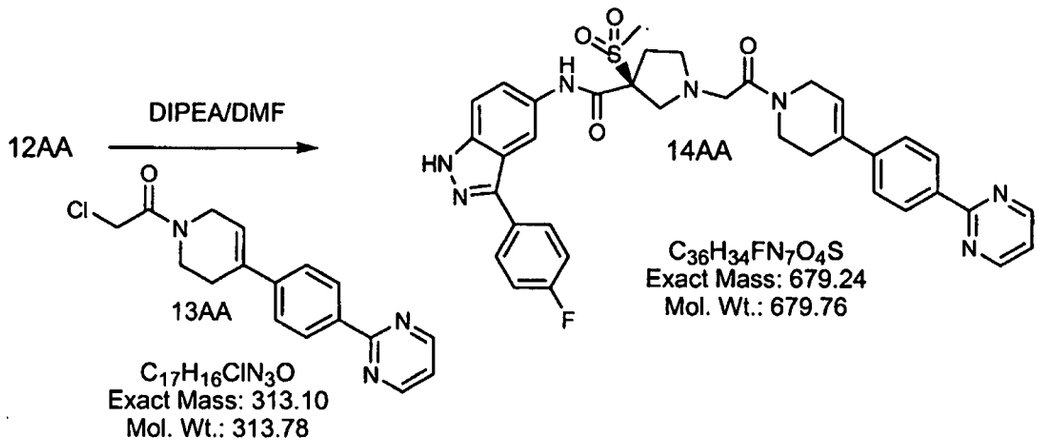
Step 9



$C_{19}H_{19}FN_4O_3S$
Exact Mass: 402.12
Mol. Wt.: 402.44

The starting material 11AA (0.64g, 0.858 mmol) was dissolved in 20 mL of anhydrous CH_2Cl_2. 2.5 mL of TFA was added slowly and was allowed to stir at rt under a stream of nitrogen for 1 overnight. The mixture was evaporated to dryness and column purified (7% 2N NH_3, MeOH/CH_2Cl_2) to give 0.31g of product in the yield of 91%.

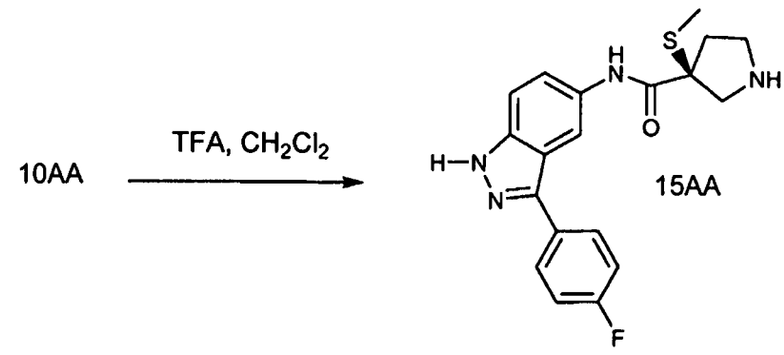
Step 10



Compound 12AA (0.105g, 0.261 mmol) was dissolved in 5 mL of DMF. 3 eq. of DIPEA was added followed by 1.1 eq. of 13AA. The reaction mixture was stirred for 3 days at rt under a stream of nitrogen. Upon completion, 25 mL of brine was added to the reaction mixture which was then extracted 3 times with EtOAc. The combined organic extracts was dried over anhydrous $MgSO_4$, filtered and evaporated to obtain crude title product. The crude product was purified by PTLC (6% 2N NH_3, $MeOH/CH_2Cl_2$) to give 132 mg of pure product.

EXAMPLE 613

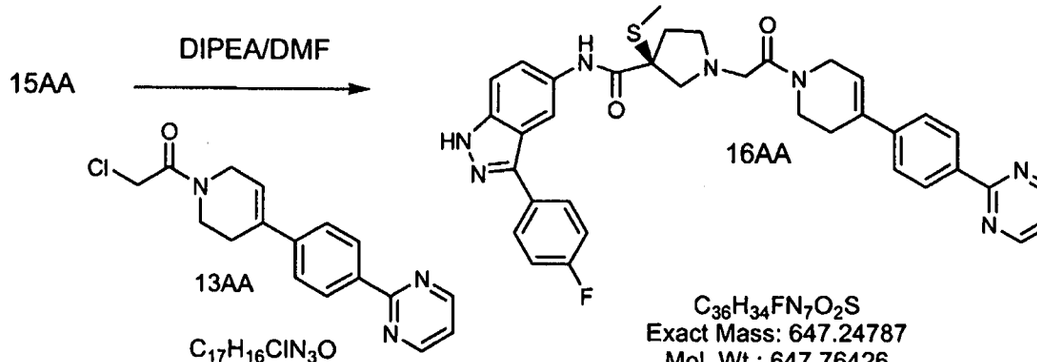
Step 1



$C_{19}H_{19}FN_4OS$
Exact Mass: 370.12636
Mol. Wt.: 370.44376

The starting material 10AA (see Example 612, Step 8) (0.712g, 1.0 mmol) was dissolved in 20 mL of anhydrous CH_2Cl_2. 2 mL of TFA was added slowly and was allowed to stir at rt under a stream of nitrogen for 1 overnight. The mixture was evaporated to dryness and treated with 30 mL of 2% 2N NH_3, MeOH to give 0.612g of product.

Step 2



$C_{17}H_{16}ClN_3O$
Exact Mass: 313.10
Mol. Wt.: 313.78

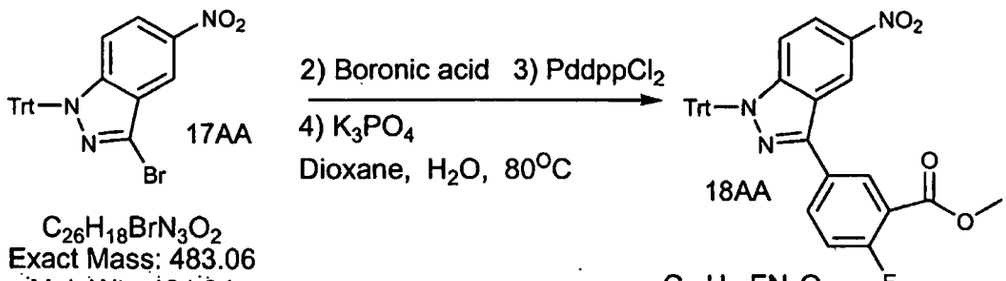
$C_{36}H_{34}FN_7O_2S$
Exact Mass: 647.24787
Mol. Wt.: 647.76426

Compound 15AA (0.300g, 0.81 mmol) was dissolved in 5 mL of DMF. 3 eq. of DIPEA was added followed by 1.1 eq. of 13AA. The reaction mixture was stirred for 2

days at rt under a stream of nitrogen. Upon completion, 25 mL of brine was added to the reaction mixture which was then extracted 3 times with EtOAc. The combined organic extracts was dried over anhydrous $MgSO_4$, filtered and evaporated to obtain crude title product. The crude product was purified by PTLC (6% 2N NH_3, $MeOH/CH_2Cl_2$) to give 431 mg of pure product.

Preparation 46

Step 1

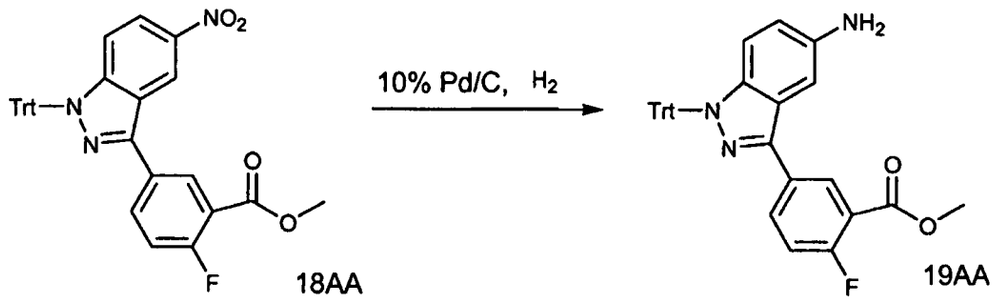


$C_{26}H_{18}BrN_3O_2$
Exact Mass: 483.06
Mol. Wt.: 484.34

$C_{34}H_{24}FN_3O_4$
Exact Mass: 557.18
Mol. Wt.: 557.57

In a flame dried sealed tube was placed 3.0g of compound 17AA (6.19 mMol). 1.5 eq. of 2, 0.1 eq. of 3 and 2.5 eq. of 4 were also added. 65 mL of dioxane and 30 mL of H_2O were added to the mixture. The mixture was degassed under nitrogen and then heated to 80°C for 1 day. After completion, mixture was diluted with EtOAc and filtered through celite. The ethyl acetate layer was washed with water, dried over anhydrous Mg SO_4 and evaporated to dryness. The crude product was column purified (5%E/H) to give 1.1g of product.

Step 2

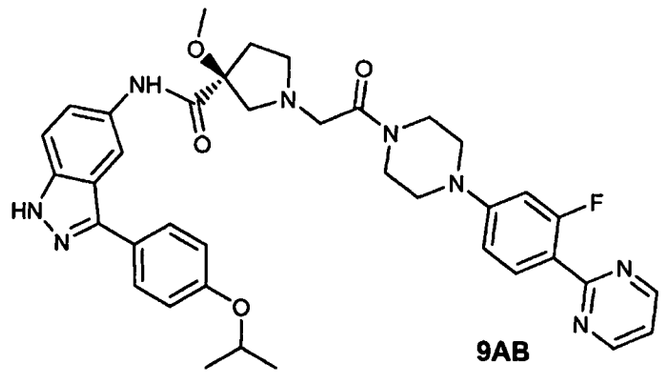


$C_{34}H_{24}FN_3O_4$
Exact Mass: 557.18
Mol. Wt.: 557.57

$C_{34}H_{26}FN_3O_2$
Exact Mass: 527.20
Mol. Wt.: 527.59

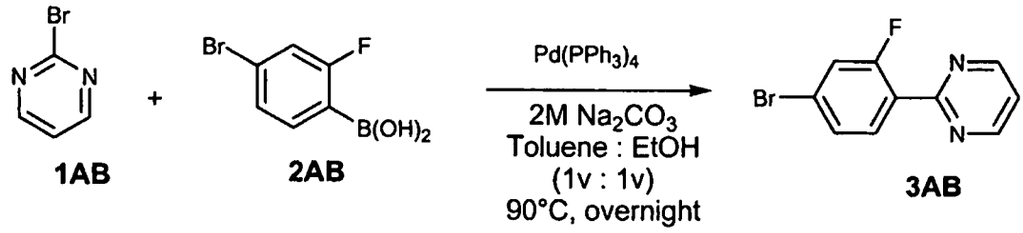
Compound 18AA (1.2g, 2.15 mmol) was dissolved in 20 mL each of MeOH:Toluene. 20% of 10% Pd/C catalyst was added and the mixture was subjected to H_2 in the form of ballon. After degassing for a number of times, mixture was allowed to stir for 1 day. After completion, the mixture was diluted with CH_2Cl_2 and filtered through celite. It was then washed with 50% E/H. The filtrate was evaporated to dryness to give 1.18g of title product.

EXAMPLE 614



9AB

Step 1: Synthesis of 2-(4-Bromo-2-fluoro-phenyl)-pyrimidine (3AB)



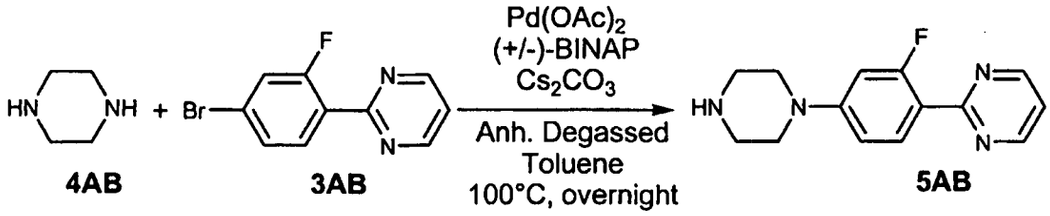
1AB **2AB** **3AB**

4-Bromo-2-fluorophenyl boronic acid **(2AB)** (3.0g, 13.71 mmol, 1 equiv), 2-bromopyrimidine **(1AB)** (6.54 g, 41.13 mmol, 3 equiv), and 2M sodium carbonate (34 mL) were added in a pressure vessel (350 mL) and a (1v : 1v) mixture of toluene and ethanol (45 mL : 45 mL) was added. The mixture was then bubbled with nitrogen gas for about 10 minutes. Tetrakistriphenylphosphine palladium (0) (793mg, 0.686 mmol, 0.05 equiv) was added to the mixture. The reaction vessel was tightly capped, placed in an oil bath at 90°C and stirred overnight.

The reaction mixture was cooled down to room temperature and the content was filtered into a flask and the solvent mixture was evaporated off on the rotovap. The residue was then taken up in one to one mixture of toluene and ethyl acetate and washed with (3v : 1v) mixture of brine and DI water twice. The organic layer was separated and combined and dried over magnesium sulfate. The crude product was then filtered into a flask and the solvent was removed on rotovap. The residue was taken up in as little dichloromethane as possible and purified by column chromatography using Analogix purification system with the following conditions: Solvent A: Hexanes; Solvent B: Ethylacetate. Flow Rate: 65 mL/min. Gradient: 0% Solvent B to 50% Solvent B in 60 minutes.

Yield= 2.79 g (80.4%)

Step 2: Synthesis of 2-(2-Fluoro-4-piperazin-1-yl-phenyl)-pyrimidine (5AB)



4AB **3AB** **5AB**

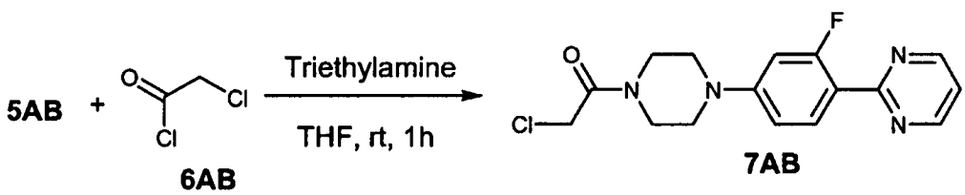
2-(4-Bromo-2-fluoro-phenyl)-pyrimidine **(3AB)** (2.0 g, 7.9 mmol, 1 equiv), piperazine **(4AB)** (2.72 g, 31.6 mmol, 4 equiv), cesium carbonate (20.6 g, 63.2 mmol, 8 equiv), racemic (+/-) BINAP (492 mg, 0.79 mmol, 0.1 equiv), and palladium (II)

acetate (89 mg, 0.395 mmol, 0.05 equiv) were all weighed out in a flamed dried pressure vessel and the vessel was sealed with a rubber septa and the content of the reaction vessel was kept under vacuum for 2 hours. Anhydrous degassed toluene (100 mL) was added to the reaction vessel using a cannula. The rubber septa was replaced with a Teflon cap and the vessel was tightly sealed and placed in an oil bath at 100°C to stir the content overnight.

The reaction vessel was cooled down to room temperature and the content was transferred into a flask. Some water was added to solubilize the excess inorganic base along with some ethyl acetate. The organic layer was then washed with water and brine twice, and separated and dried over magnesium sulfate. The crude product was then filtered into a flask and the solvent was removed on rotovap. The residue was taken up in as little dichloromethane as possible and purified by column chromatography using Analogix purification system with the following conditions: Solvent A: Dichloromethane; Solvent B: 40% 7N NH_3 in Methanol. Flow Rate: 65 mL/min. Gradient: 0% Solvent B to 30% Solvent B in 52 minutes and stayed at 30% Solvent B for 10 minutes.

Yield= 889 mg (44%).

Step 3: Synthesis of 2-Chloro-1-[4-(3-fluoro-4-pyrimidin-2-yl-phenyl)-piperazin-1-yl]-ethanone (7AB)



6AB 7AB

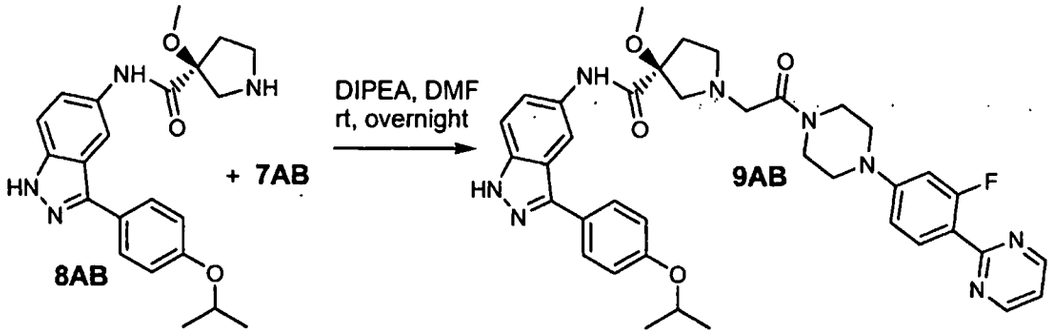
2-(2-Fluoro-4-piperazin-1-yl-phenyl)-pyrimidine **(5AB)** (889 mg, 3.442 mmol, 1 equiv) was dissolved in anhydrous tetrahydrofuran (5 mL) and triethylamine (697 mg, 959 uL, 6.884 mmol, 2 equiv) was added, followed by slow addition of a solution of chloroacetyl chloride **(6AB)** (466.5 mg, 330 uL, 4.13 mmol, 1.2 equiv) in tetrahydrofuran at room temperature. The mixture was then stirred for about 1 hour at room temperature.

Upon the completion of the reaction, the solvent was removed on rotovap and the residue was taken up in dichloromethane and washed with a (1v : 1v) mixture of

brine and water in a seperatory funnel. The organic layer was separated, concentrated down, and dried on pump. The crude residue was then taken up in dichloromethane and purified by column chromatography using Analogix purification system with the following conditions: Solvent A: Dichloromethane; Solvent B: 40% 7N NH_3 in Methanol. Flow Rate: 65 mL/min. Gradient: 0% Solvent B to 30% Solvent B in 52 minutes and stayed at 30% Solvent B for 10 minutes.

Yield= 1.05 g (91.1%)

Step 4: Synthesis of 1-{2-[4-(3-Fluoro-4-pyrimidin-2-yl-phenyl)-piperazin-1-yl]-2-oxo-ethyl}-3-methoxy-pyrrolidine-3-carboxylic acid [3-(4-isopropoxy-phenyl)-1H-indazol-5-yl]-amide (9AB)



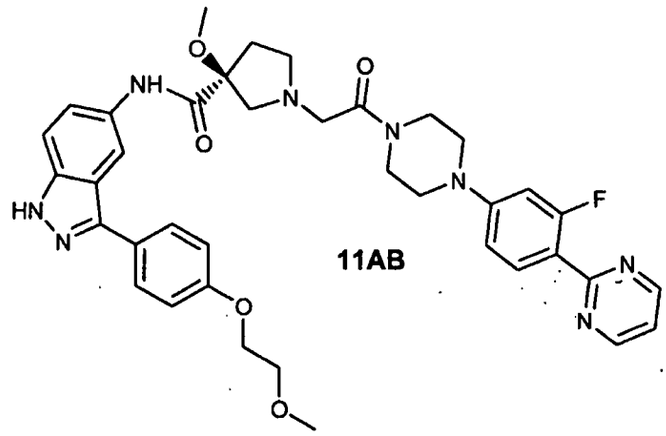
3-Methoxy-pyrrolidine-3-carboxylic acid [3-(4-isopropoxy-phenyl)-1H-indazol-5-yl]-amide **(8AB)** (40 mg, 0.086 mmol, 1 equiv) and 2-Chloro-1-[4-(3-fluoro-4-pyrimidin-2-yl-phenyl)-piperazin-1-yl]-ethanone **(7AB)** (35 mg, 0.103 mmol, 1.2 equiv) were weighed out in a flask, and to it was added N,N-dimethylformamide (3 mL) and diisopropylethylamine (22 mg, 30 uL, 0.172 mmol, 2 equiv). The reaction content was stirred at room temperature, overnight.

The crude reaction mixture was diluted out with enough amount of ethylacetate and the organic phase was washed with a (1v : 1v) mixture of brine and water twice. The organic layer was separated and concentrated down on rotovap to dryness, and further dried on a high vacuum pump. The residue was taken up in as little dichloromethane as possible and purified by column chromatography using Analogix purification system with the following conditions: Solvent A: Dichloromethane; Solvent B: 40% 7N NH_3 in Methanol. Flow Rate: 30 mL/min. Gradient: 0% Solvent B to 20%

Solvent B in 30 minutes. The clean fractions were combined in a flask and concentrated down on rotovap. The residue was then dissolved in methanol and acidified with 4N HCl in 1,4-dioxane (80 uL) to make it into HCl salt form before submitting it to biological assay.

Yield= 46.4 mg, LCMS $[M+H^+]$ = 693.4.

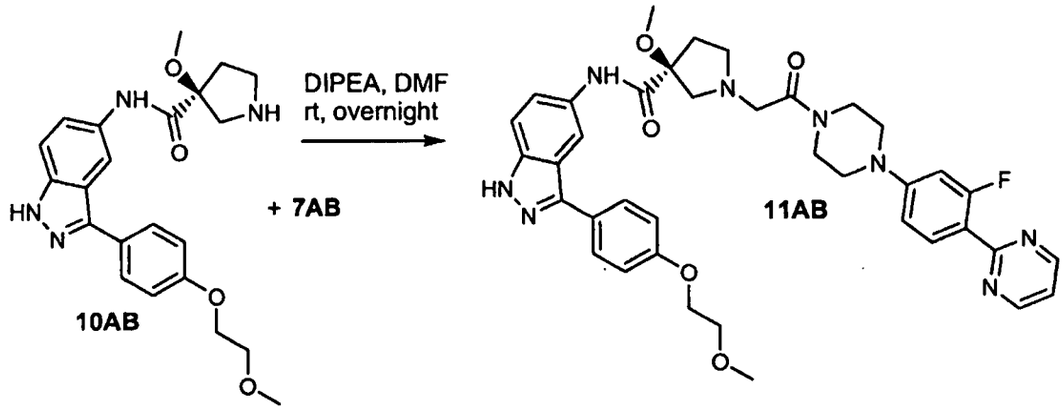
EXAMPLE 615



Steps 1 to 3

Steps 1 to 3 are similar to Steps 1 to 3 of Example 614. .

Step 4: Synthesis of 1-{2-[4-(3-Fluoro-4-pyrimidin-2-yl-phenyl)-piperazin-1-yl]-2-oxo-ethyl}-3-methoxy-pyrrolidine-3-carboxylic acid {3-[4-(2-methoxy-ethoxy)-phenyl]-1H-indazol-5-yl}-amide (11AB)



3-Methoxy-pyrrolidine-3-carboxylic acid {3-[4-(2-methoxy-ethoxy)-phenyl]-1H-indazol-5-yl}-amide **(10AB)** (50 mg, 0.103 mmol, 1 equiv) and 2-Chloro-1-[4-(3-fluoro-4-pyrimidin-2-yl-phenyl)-piperazin-1-yl]-ethanone **(7AB)** (42 mg, 0.124 mmol, 1.2 equiv) were weighed out in a flask and to it was added N,N-dimethylformamide (3 mL) and diisopropylethylamine (26.6 mg, 36 uL, 0.206 mmol, 2 equiv). The reaction content was stirred at room temperature, overnight.

The crude reaction mixture was diluted out with enough amount of ethylacetate and the organic phase was washed with a (1v : 1v) mixture of brine and water twice. The organic layer was separated and concentrated down on rotovap to dryness, and further dried on a high vacuum pump. The residue was taken up in as little dichloromethane as possible and purified by column chromatography using Analogix purification system with the following conditions: Solvent A: Dichloromethane; Solvent B: 40% 7N NH_3 in Methanol. Flow Rate: 30 mL/min. Gradient: 0% Solvent B to 20% Solvent B in 30 minutes. The clean fractions were combined in a flask and concentrated down on rotovap. The residue was then dissolved in methanol and acidified with 4N HCl in 1,4-dioxane (100 uL) to make it into HCl salt form before submitting it to biological assay.

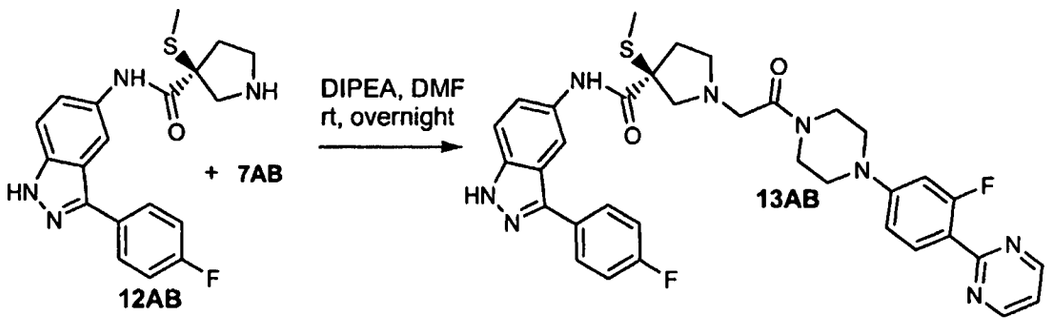
Yield= 46.4 mg, LCMS $[M+H^+]$ = 709.4.

EXAMPLE 616

Steps 1 to 3

Steps 1 to 3 are similar to Steps 1 to 3 of Example 614. .

Step 4: Synthesis of 1-{2-[4-(3-Fluoro-4-pyrimidin-2-yl-phenyl)-piperazin-1-yl]-2-oxo-ethyl}-3-methylsulfanyl-pyrrolidine-3-carboxylic acid [3-(4-fluoro-phenyl)-1H-indazol-5-yl]-amide (13AB)



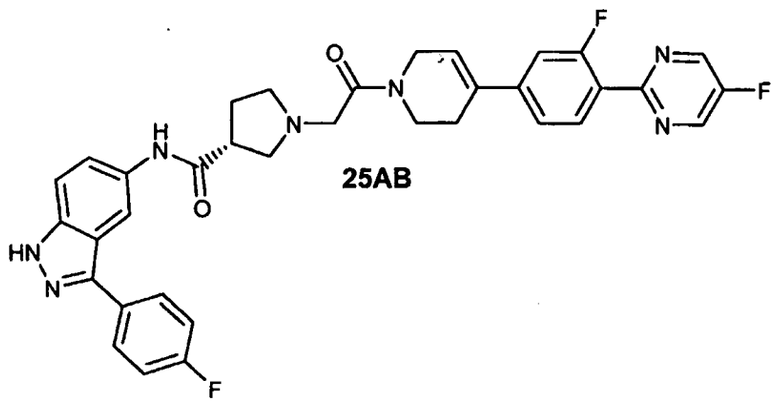
3-Methylsulfanyl-pyrrolidine-3-carboxylic acid [3-(4-fluoro-phenyl)-1H-indazol-5-yl]-amide **(12AB)** (40 mg, 0.09 mmol, 1 equiv) and 2-Chloro-1-[4-(3-fluoro-4-pyrimidin-2-yl-phenyl)-piperazin-1-yl]-ethanone **(7AB)** (37 mg, 0.11 mmol, 1.2 equiv) were weighed out in a flask, and to it was added N,N-dimethylformamide (3 mL) and diisopropylethylamine (23 mg, 32 uL, 0.18 mmol, 2 equiv). The reaction content was stirred at room temperature overnight.

The crude reaction mixture was diluted out with enough amount of ethylacetate and the organic phase was washed with a (1v : 1v) mixture of brine and water twice. The organic layer was separated and concentrated down on rotovap to dryness, and further dried on a high vacuum pump. The residue was taken up in as little dichloromethane as possible and purified by column chromatography using Analogix purification system with the following conditions: Solvent A: Dichloromethane; Solvent B: 40% 7N NH_3 in Methanol. Flow Rate: 30 mL/min. Gradient: 0% Solvent B to 20% Solvent B in 30 minutes. The clean fractions were combined in a flask and concentrated down on rotovap. The residue was then dissolved in methanol and acidified with 4N HCl in 1,4-dioxane (100 uL) to make it into HCl salt form before submitting it to biological assay.

Yield= 58 mg, LCMS $[M+H^+]$ = 669.4.

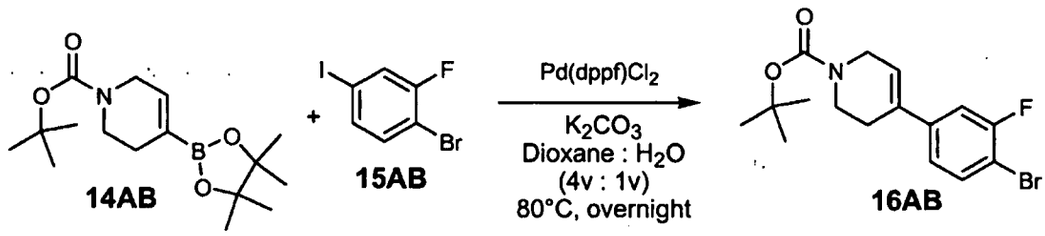
245

EXAMPLE 617



25AB

Step 1: Synthesis of 4-(4-Bromo-3-fluoro-phenyl)-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester (16AB)



14AB **15AB** **16AB**

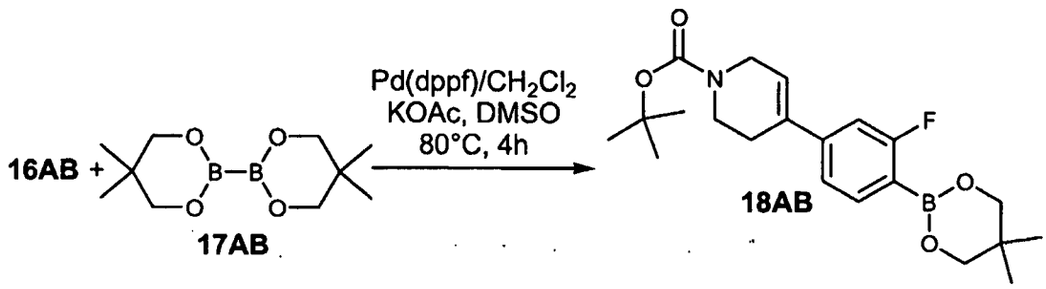
4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester **(14AB)** (4.0g, 12.9 mmol, 1 equiv), 1-Bromo-2-fluoro-4-iodo-benzene **(15AB)** (5.84 g, 19.4 mmol, 1.5 equiv), potassium carbonate (5.4 g, 38.8 mmol, 3 equiv), and a (4v : 1 v) mixture of 1,4-dioxane and water (120 mL : 30 mL) were all added in a pressure vessel (350 mL) and the mixture was bubbled with nitrogen gas for about 10 minutes. To this mixture was added dichloro[1, 1'-bis(diphenylphosphino)ferrocene] palladium (II)/dichloromethane adduct (1.05 g, 1.29 mmol, 0.1 equiv), and the reaction vessel was tightly capped, placed in an oil bath at 80°C, and stirred overnight.

The reaction mixture was cooled down to room temperature and the content was transferred into a flask and concentrated down on rotovap. The residue was then taken up in ethyl acetate and, in a seperatory funnel; the crude mixture was washed with water, 10% sodium carbonate and brine. The organic layer was dried on magnesium sulfate and passed through a Celite plug. The filtrate was then treated with activated carbon at 65°C in an Erlenmeyer in a water bath for about 10 minutes to decolorize the solution. The charcoal was separated by a Celite plug. The solvent

was removed on rotovap and the residue was dried on pump overnight. The residue was taken up in as little dichloromethane as possible and purified by column chromatography using Analogix purification system with the following conditions: Solvent A: Hexanes; Solvent B: Ethylacetate. Flow Rate: 65 mL/min. Gradient: 0% Solvent B to 50% Solvent B in 60 minutes.

Yield= 3.12 g (68%)

Step 2: Synthesis of 4-[4-(5,5-Dimethyl-[1,3,2]dioxaborinan-2-yl)-3-fluoro-phenyl]-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester (18AB):

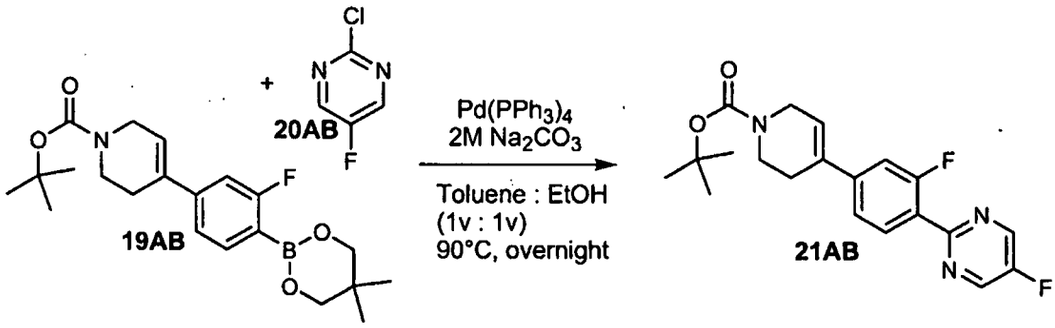


4-(4-Bromo-3-fluoro-phenyl)-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester **(16AB)**(2.3 g, 6.59 mmol, 1 equiv), bis(neopentylglycolato)diboron **(17AB)**(1.79 g, 7.91 mmol, 1.2 equiv), and potassium acetate (1.94 g, 19.77 mmol, 3 equiv) were all weighed out in a dry pressure vessel and dissolved in dimethylsulfoxide (50 mL). The mixture was bubbled with nitrogen gas for 10 minutes. Dichloro[1, 1'-bis(diphenylphosphino) ferrocene]palladium (II)/dichloromethane adduct (540 mg, 0.66 mmol, 0.1 equiv) was added and the reaction vessel was sealed tightly with a cap and placed in on oil bath at 80°C for 4 hours.

Upon the completion of 4 hours, the reaction vessel was cooled down to room temperature and the content was transferred into a flask. Some water was added to solubilize the excess inorganic base along with some ethyl acetate. The organic layer was then washed with water and brine twice, and separated and dried over magnesium sulfate. The organic layer was concentrated down on rotovap and taken up with dichloromethane. In an Erlenmeyer the crude compound was treated with activated carbon at 65°C in a water bath for about 10 minutes to decolorize the solution. The charcoal was separated by a Celite plug. The solvent was removed on rotovap and the residue was dried on pump overnight. The residue was taken up in as little dichloromethane as possible and purified by column chromatography using

Analogix purification system with the following conditions: Solvent A: Hexanes; Solvent B: Ethylacetate. Flow Rate: 65 mL/min. Gradient: 0% Solvent B to 50% Solvent B in 60 minutes. Relatively clean fractions were combined and the solvent was concentrated down. The product spot on TLC was streaking; that is probably because during the purification of this compound on a silica gel column some of the boronic acid ester was getting hydrolyzed to boronic acid. Therefore, even though the separation was not as desirable, the compound was used as-is in the next reaction after the purification step.

Step 3: Synthesis 4-[3-Fluoro-4-(5-fluoro-pyrimidin-2-yl)-phenyl]-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester (21AB)



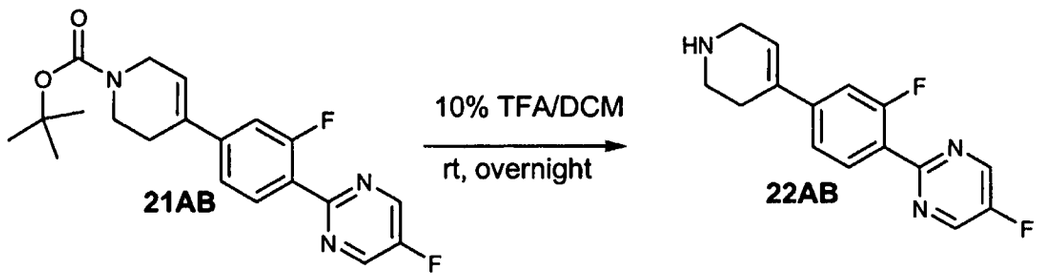
4-[4-(5,5-Dimethyl-[1,3,2]dioxaborinan-2-yl)-3-fluoro-phenyl]-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester **(19AB)**(1.55g, 3.98 mmol, 1 equiv), 2-Chloro-5-fluoro-pyrimidine **(20AB)**(634 mg, 591 uL, 4.78 mmol, 1.2 equiv), and 2M sodium carbonate (9.95 mL) were added in a pressure vessel (350 mL) and a (1v : 1v) mixture of toluene and ethanol (25 mL : 25 mL) was added. The mixture was then bubbled with nitrogen gas for about 10 minutes. Tetrakis(triphenylphosphine) palladium (0) (462 mg, 0.4 mmol, 0.1 equiv) was added to the mixture. The reaction vessel was tightly capped, placed in an oil bath at 90°C, and stirred overnight.

The reaction mixture was cooled down to room temperature and diluted with ethyl acetate. The crude mixture was transferred into a seperatory funnel and washed with a (1v : 1v) brine and water mixture. The organic layer was separated and combined and dried over magnesium sulfate. The crude product was then filtered into a flask and the solvent was removed on rotovap. The residue was taken up in as little dichloromethane as possible and purified by column chromatography using Analogix

purification system with the following conditions: Solvent A: Dichloromethane; Solvent B: Methanol. Flow Rate: 45 mL/min. Gradient: 0% Solvent B to 10% Solvent B in 60 minutes.

Yield= 677 mg (46%)

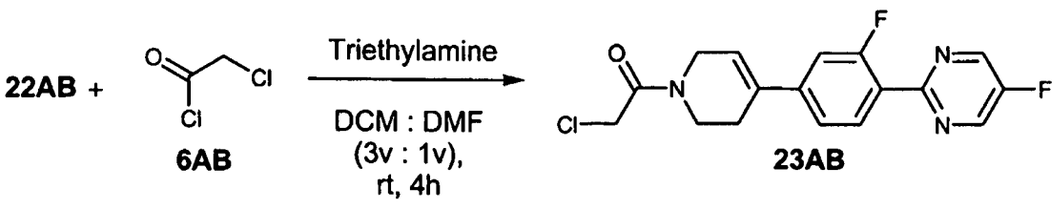
Step 4: Synthesis of 5-Fluoro-2-[2-fluoro-4-(1,2,3,6-tetrahydro-pyridin-4-yl)-phenyl]-pyrimidine (22AB)



4-[3-Fluoro-4-(5-fluoro-pyrimidin-2-yl)-phenyl]-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester **(21AB)** (717 mg, 1.92 mmol, 1 equiv) was treated with 10% solution of trifluoroacetic acid in dichloromethane at room temperature overnight.

The solvent was concentrated down and the residue was taken up in ethyl acetate and washed with 10% aqueous sodium carbonate twice. Water layers were combined and saturated with sodium chloride and the remaining product in water layer thus extracted with ethyl acetate. The organic layers were combined and evaporated to dryness on a rotovap. The residue was taken up in as little dichloromethane as possible and purified by column chromatography using Analogix purification system with the following conditions: Solvent A: Dichloromethane; Solvent B: 40% 7N NH_3 in Methanol. Flow Rate: 65 mL/min. Gradient: 0% Solvent B to 30% Solvent B in 60 minutes and stayed at 30% Solvent B for 10 minutes. LCMS [$M+H^+$] = 274.2.

STEP 5: Synthesis of 2-Chloro-1-{4-[3-fluoro-4-(5-fluoro-pyrimidin-2-yl)-phenyl]-3,6-dihydro-2H-pyridin-1-yl}-ethanone (23)

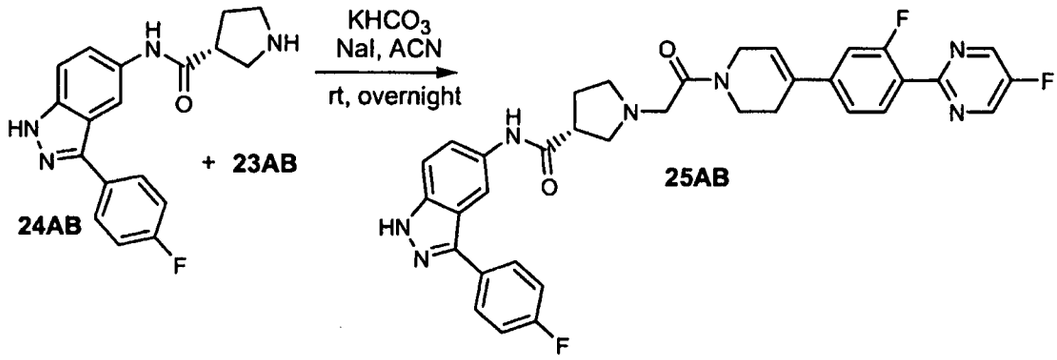


5-Fluoro-2-[2-fluoro-4-(1,2,3,6-tetrahydro-pyridin-4-yl)-phenyl]-pyrimidine **(22AB)** (1.94 g, 7.1 mmol, 1 equiv) was dissolved in a (3v : 1v) mixture of dichloromethane (30 mL) and N,N-dimethyl formamide (10 mL) and triethylamine (862 mg, 1.19 mL, 8.52 mmol, 1.2 equiv) was added, followed by slow addition of chloroacetyl chloride (962 mg, 678 uL, 8.52 mmol, 1.2 equiv) at room temperature. The mixture was then stirred for about 4 hours at room temperature.

Upon the completion of the reaction, the solvent mixture was removed on rotovap and the residue was taken up in dichloromethane and washed with saturated solution of sodium bicarbonate and a (1v : 1v) mixture of brine and water in a seperatory funnel. The organic layer was separated, concentrated down, and dried on pump. The crude residue was then taken up in dichloromethane and purified by column chromatography using Analogix purification system with the following conditions: Solvent A: Dichloromethane; Solvent B: 40% 7N NH_3 in Methanol. Flow Rate: 65 mL/min. Gradient: 0% Solvent B to 30% Solvent B in 52 minutes and stayed at 30% Solvent B for 10 minutes.

Yield= 851 mg (34%)

Step 6: Synthesis of 1-(2-{4-[3-Fluoro-4-(5-fluoro-pyrimidin-2-yl)-phenyl]-3,6-dihydro-2H-pyridin-1-yl}-2-oxo-ethyl)-pyrrolidine-3-carboxylic acid [3-(4-fluoro-phenyl)-1H-indazol-5-yl]-amide (25AB)



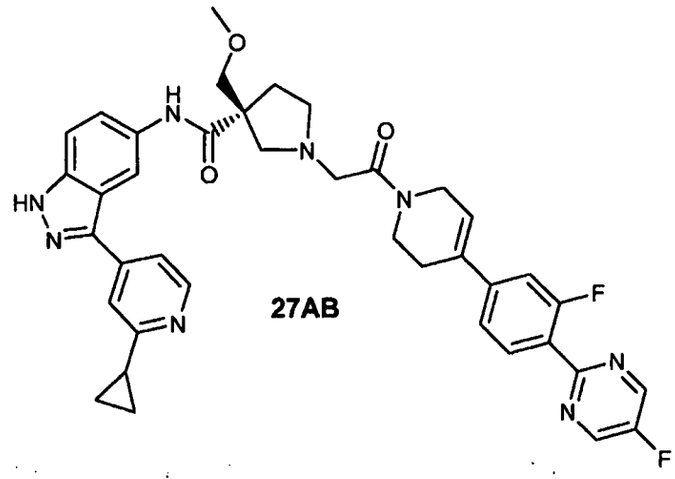
Pyrrolidine-3-carboxylic acid [3-(4-fluoro-phenyl)-1H-indazol-5-yl]-amide **(24AB)** (30 mg, 0.093 mmol, 1 equiv), 2-Chloro-1-{4-[3-fluoro-4-(5-fluoro-pyrimidin-2-yl)-phenyl]-3,6-dihydro-2H-pyridin-1-yl}-ethanone **(23AB)** (36 mg, 0.102 mmol, 1.1 equiv), potassium bicarbonate (47 mg, 0.465 mmol, 5 equiv), and sodium iodide (3 mg, 0.019 mmol, 0.2 equiv) were all weighed out in a flask and to it was added acetonitrile (3 mL). The reaction content was stirred at room temperature overnight.

The crude reaction mixture was concentrated down on rotovap and the residue was taken up in ethyl acetate. In a seperatory funnel, the organic phase was washed with a (1v : 1v) mixture of brine and water twice. The organic layer was separated and concentrated down on rotovap to dryness, and further dried on a high vacuum pump. The residue was taken up in as little dichloromethane as possible and purified by column chromatography using Analogix purification system with the following conditions: Solvent A: Dichloromethane; Solvent B: 40% 7N NH_3 in Methanol. Flow Rate: 30 mL/min. Gradient: 0% Solvent B to 20% Solvent B in 30 minutes. The clean fractions were combined in a flask and concentrated down on rotovap. The residue was then dissolved in methanol and acidified with 4N HCl in 1,4-dioxane (100 uL) to make it into HCl salt form before submitting it to biological assay.

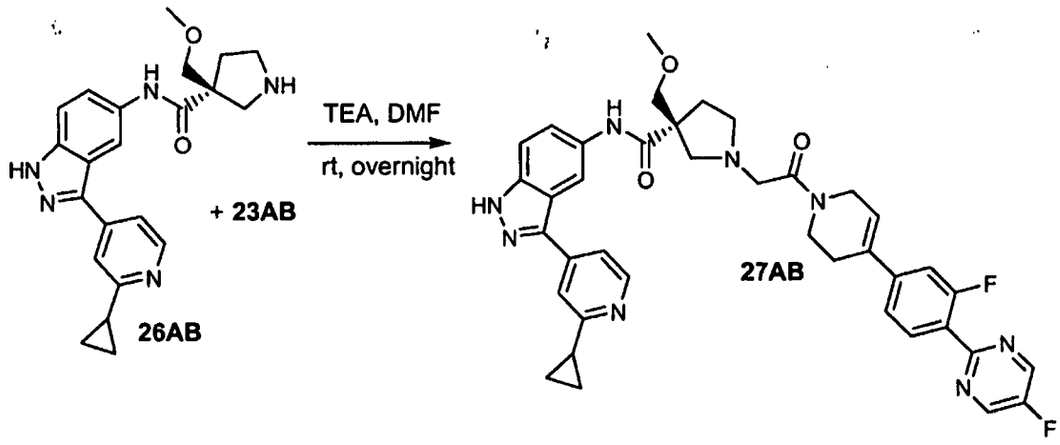
Yield= 16.9 mg, LCMS $[M+H^+]$ = 638.4.

Example 618

Synthesis of 1-(2-{4-[3-Fluoro-4-(5-fluoro-pyrimidin-2-yl)-phenyl]-3,6-dihydro-2H-pyridin-1-yl}-2-oxo-ethyl)-3-methoxymethyl-pyrrolidine-3-carboxylic acid [3-(2-cyclopropyl-pyridin-4-yl)-1H-indazol-5-yl]-amide (27AB)



27AB

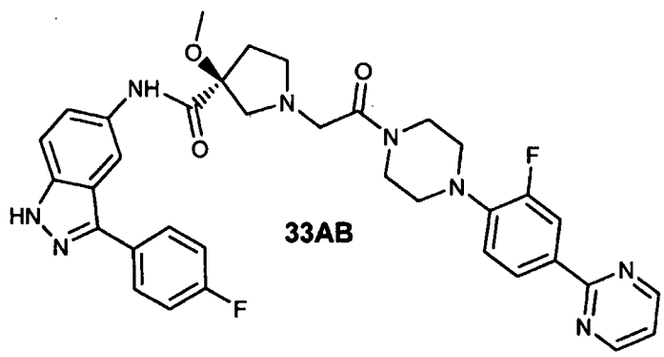


3-Methoxymethyl-pyrrolidine-3-carboxylic acid [3-(2-cyclopropyl-pyridin-4-yl)-1H-indazol-5-yl]-amide **(26AB)** (85 mg, 0.217 mmol, 1 equiv) and 2-Chloro-1-{4-[3-fluoro-4-(5-fluoro-pyrimidin-2-yl)-phenyl]-3,6-dihydro-2H-pyridin-1-yl}-ethanone **(23AB)** (84 mg, 0.239 mmol, 1.1 equiv)were weighed out in a flask and dissolved in anhydrous N,N-dimethylformamide (5 mL). Triethyl amine (33 mg, 46 uL, 0.326 mmol, 1.5 equiv) was added to the reaction mixture and the reaction content was stirred at room temperature overnight.

The crude reaction mixture was diluted out with enough amount of ethylacetate and the organic phase was washed with a saturated solution of sodium bicarbonate and a (1v : 1v) mixture of (brine : water) twice. The organic layer was separated and concentrated down on rotovap to dryness, and further dried on a high vacuum pump. The residue was taken up in as little dichloromethane as possible and purified by column chromatography using Analogix purification system with the following conditions: Solvent A: Dichloromethane; Solvent B: 40% 7N NH_3 in Methanol. Flow Rate: 30 mL/min. Gradient: 0% Solvent B to 20% Solvent B in 30 minutes. The clean fractions were combined in a flask and concentrated down on rotovap. The residue was then dissolved in methanol and acidified with 4N HCl in 1,4-dioxane (100 uL) to make it into HCl salt form before submitting it to biological assay.

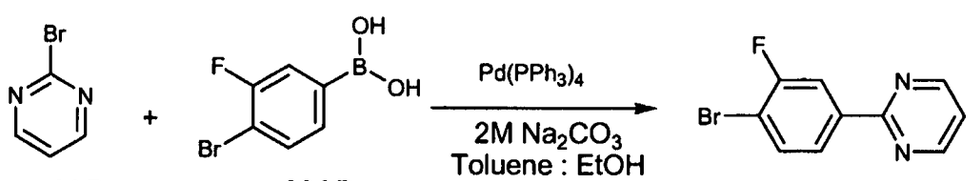
Yield= 75 mg (49%), LCMS $[M+H^+]$ = 705.4.

Example 619



33AB

Step 1: Synthesis of 2-(4-Bromo-3-fluoro-phenyl)-pyrimidine (29AB)



1AB **28AB** **29AB**

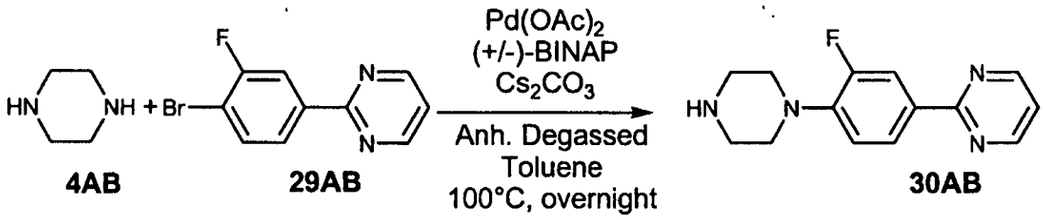
4-Bromo-3-fluorophenyl boronic acid **(28AB)** (1.0g, 4.57 mmol, 1 equiv), 2-bromopyrimidine **(1AB)** (2.18 g, 13.7 mmol, 3 equiv), and 2M sodium carbonate (12 mL) were added in a pressure vessel (150 mL) and a (1v : 1v) mixture of toluene and ethanol (25 mL : 25 mL) was added. The mixture was then bubbled with nitrogen gas

for about 10 minutes. Tetrakistriphenylphosphine palladium (0) (266 mg, 0.23 mmol, 0.05 equiv) was added to the mixture. The reaction vessel was tightly capped, placed in an oil bath at 90°C, and stirred overnight.

The reaction mixture was cooled down to room temperature and the content was filtered into a flask and the solvent mixture was evaporated off on the rotovap. The residue was then taken up in one to one mixture of toluene and ethyl acetate and washed with (3v : 1v) mixture of brine : DI water twice. The organic layer was separated and combined and dried over magnesium sulfate. The crude product was then filtered into a flask and the solvent was removed on rotovap. The residue was taken up in as little dichloromethane as possible and purified by column chromatography using Analogix purification system with the following conditions: Solvent A: Hexanes; Solvent B: Ethylacetate. Flow Rate: 65 mL/min. Gradient: 0% Solvent B to 50% Solvent B in 60 minutes.

Yield= 1.08 g (94%)

Step 2: Synthesis of 2-(3-Fluoro-4-piperazin-1-yl-phenyl)-pyrimidine (30AB)



4AB **29AB** **30AB**

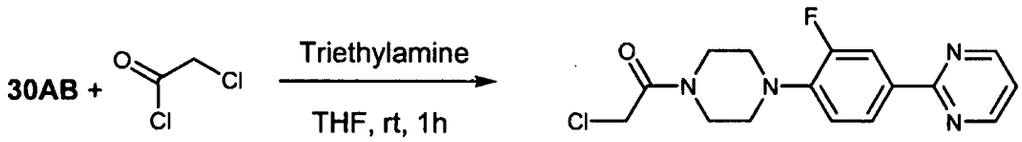
2-(4-Bromo-3-fluoro-phenyl)-pyrimidine **(29AB)** (874 mg, 3.45 mmol, 1 equiv), piperazine (1.19 g, 13.8 mmol, 4 equiv), cesium carbonate (9.0 g, 27.6 mmol, 8 equiv), racemic (+/-) BINAP (215 mg, 0.345 mmol, 0.1 equiv), and palladium (II) acetate (38.8 mg, 0.173 mmol, 0.05 equiv) were all weighed out in a flamed dried pressure vessel and the vessel was sealed with a rubber septa and the all-solid mixture was kept under vacuum for 2 hours. Anhydrous degassed toluene (30 mL) was added to the reaction vessel using a cannula. The rubber septa was replaced with a Teflon cap and the vessel was tightly sealed and placed in an oil bath at 100°C to stir the content overnight.

The reaction vessel was cooled down to room temperature and the content was transferred into a flask. Some water was added to solubilize the excess inorganic base along with some ethyl acetate. The organic layer was then washed with water and brine twice, and separated and dried over magnesium sulfate. The crude product

was then filtered into a flask and the solvent was removed on rotovap. The residue was taken up in as little dichloromethane as possible and purified by column chromatography using Analogix purification system with the following conditions: Solvent A: Dichloromethane; Solvent B: 40% 7N NH_3 in Methanol. Flow Rate: 40 mL/min. Gradient: 0% Solvent B to 30% Solvent B in 52 minutes and stayed at 30% Solvent B for 10 minutes.

Yield= 675 mg (76%)

Step 3: Synthesis of 2-Chloro-1-[4-(2-fluoro-4-pyrimidin-2-yl-phenyl)-piperazin-1-yl]-ethanone (31AB)



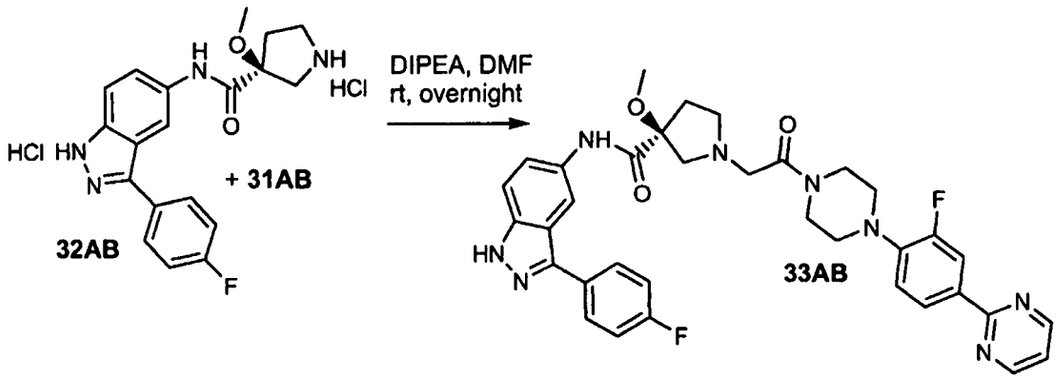
6AB **31AB**

2-(3-Fluoro-4-piperazin-1-yl-phenyl)-pyrimidine **(29AB)** (675 mg, 2.61 mmol, 1 equiv) was dissolved in anhydrous tetrahydrofuran (5 mL), and triethylamine (1.32 mg, 1.82 mL, 13.05 mmol, 5 equiv) was added, followed by slow addition of a solution of chloroacetyl chloride (591 mg, 417 uL, 5.23 mmol, 2 equiv) in tetrahydrofuran at room temperature. The mixture was then stirred for about 1 hour at room temperature.

Upon the completion of the reaction, the solvent was removed on rotovap and the residue was taken up in dichloromethane and washed with a (1v : 1v) mixture of brine and water in a seperatory funnel. The organic layer was separated, concentrated down, and dried on pump. The crude residue was then taken up in dichloromethane and purified by column chromatography using Analogix purification system with the following conditions: Solvent A: Dichloromethane; Solvent B: 40% 7N NH_3 in Methanol. Flow Rate: 40 mL/min. Gradient: 0% Solvent B to 30% Solvent B in 52 minutes and stayed at 30% Solvent B for 10 minutes.

Yield= 821 mg (94%)

Step 4: Synthesis of 1-{2-[4-(2-Fluoro-4-pyrimidin-2-yl-phenyl)-piperazin-1-yl]-2-oxo-ethyl}-3-methoxy-pyrrolidine-3-carboxylic acid [3-(4-fluoro-phenyl)-1H-indazol-5-yl]-amide (33AB)



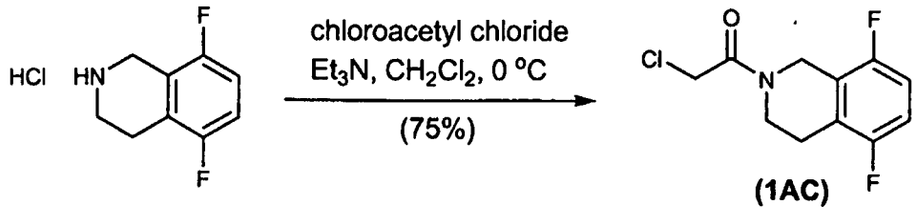
3-Methoxy-pyrrolidine-3-carboxylic acid [3-(4-fluoro-phenyl)-1H-indazol-5-yl]-amide 2.HCl Salt **(32AB)** (30 mg, 0.07 mmol, 1 equiv) and 2-Chloro-1-[4-(2-fluoro-4-pyrimidin-2-yl-phenyl)-piperazin-1-yl]-ethanone **(31AB)** (28 mg, 0.08 mmol, 1.2 equiv) were weighed out in a flask and to it was added N,N-dimethylformamide (3 mL) and diisopropylethylamine (54.3 mg, 73 uL, 0.42 mmol, 6 equiv). The reaction content was stirred at room temperature overnight.

The crude reaction mixture was diluted out with enough amount of ethylacetate and the organic phase was washed with a (1v : 1v) mixture of brine and water twice. The organic layer was separated and concentrated down on rotovap to dryness, and further dried on a high vacuum pump. The residue was taken up in as little dichloromethane as possible and purified by column chromatography using Analogix purification system with the following conditions: Solvent A: Dichloromethane; Solvent B: 40% 7N NH_3 in Methanol. Flow Rate: 30 mL/min. Gradient: 0% Solvent B to 15% Solvent B in 30 minutes. The clean fractions were combined in a flask and concentrated down on rotovap. The residue was then dissolved in methanol and acidified with 4N HCl in 1,4-dioxane (100 uL) to make it into HCl salt form before submitting it to biological assay.

Yield= 41 mg (90%), LCMS [$M+H^+$] = 653.4.

Preparation 47

Preparation of 2-Chloro-1-(5,8-dichloro-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethanone

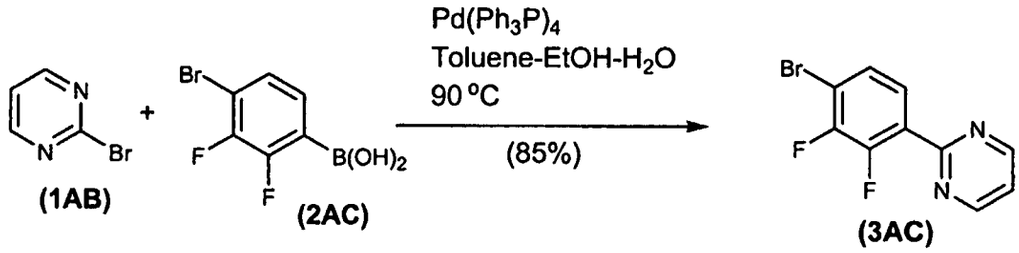


(1AC)

To a stirred suspension of 5, 8-di-fluoro-1,2,3,4-tetrahydroisoquinoline hydrochloride (0. 69g, 3.36 mmol) in dichloromethane (20 ml) at 0 °C under nitrogen, diisopropylethylamine (1.40 ml, 8.05 mmol) followed by chloroacetyl chloride (0.32 ml, 4.03 mmol) were added. The mixture was stirred at 0 °C for 2 hr. After being quenched with saturated sodium carbonate solution, water and dichloromethane were added. Layers were separated and the separated aqueous layer was extracted with dichloromethane. The combined organic layers were dried ($MgSO_4$), filtered and solvents were removed in vacuum. Column purification [Hexanes – Ethyl acetate, 4:1 (v/v)] gave chloride **1AC** (619 mg, 75%) as colourless oil.

Preparation 48

STEP 1: Preparation of 2-(4-Bromo-2,3-difluoro-phenyl)-pyrimidine

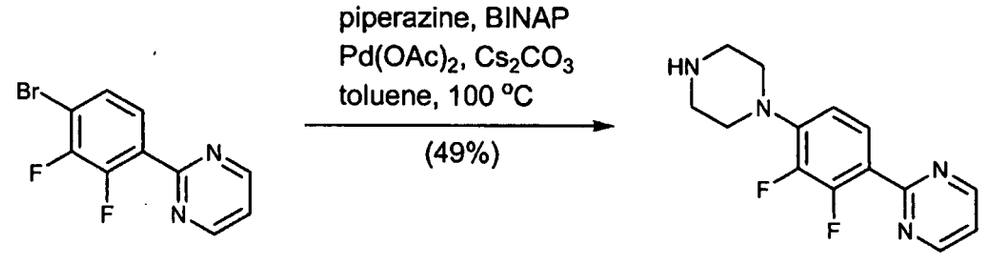


(1AB) **(2AC)** **(3AC)**

A mixture of 2-bromopyrimidine (2.0 g, 12.7 mmol) , 4-bromo-2,3-difluorobenzeneboronic acid (1.0g, 4.22 mmol), potassium carbonate (2.93 g, 21.1 mmol) in a mixture of toluene (30 ml) /ethanol (30 ml) /water (15 ml) were purged with nitrogen for 15 min. Tetrakis(triphenylphosphine)palladium(0) (488 mg, 0.42 mmol) was added and the mixture was stirred at 90 °C in a sealed-tube for overnight. The

mixture was cooled to r.t. and was diluted with water and ethyl acetate. Layers were separated. The separated organic layer was dried ($MgSO_4$), filtered and solvents were removed in vacuum. Column purification [Hexanes – Ethyl acetate, 2:1 (v/v)] gave bromide **3AC** (0.97 g, 85%) as white solid.

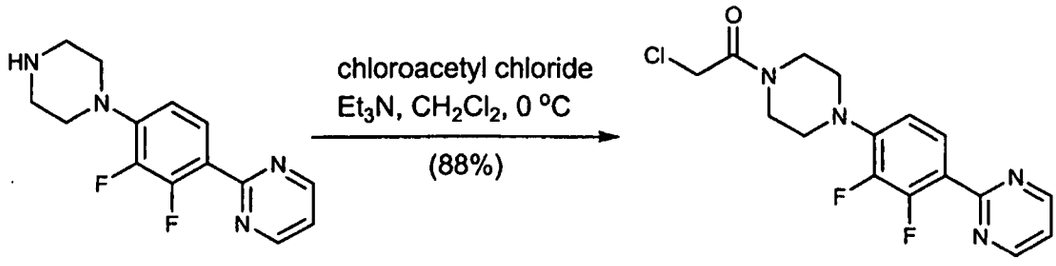
Step 2: Preparation of 2-(2,3-Difluoro-4-piperazin-1-yl-phenyl)-pyrimidine



(3AC) **(5AC)**

A mixture of bromide **3AC** (300 mg, 1.11 mmol), piperazine (286 mg, 3.32 mmol), BINAP (69 mg, 0.11 mmol), cesium carbonate (721 mg, 2.21 mmol) in toluene (10 ml) were purged with nitrogen for 15 min. Palladium (II) acetate (13 mg, 0.055 mmol) was added and the mixture was stirred at 100 °C in a sealed-tube for overnight. The mixture was cooled to r.t. and was diluted with water and ethyl acetate. Layers were separated. The separated organic layer was dried ($MgSO_4$), filtered and solvents were removed in vacuum. Column purification [Methanol – Ethyl acetate, 1:1 (v/v)] gave piperazine **5AC** (150 mg, 49%) as white solid.

Step 3: Preparation of 2-Chloro-1-[4-(2,3-Difluoro-4-pyrimidin-2-yl-phenyl)-piperazin-1-yl]-ethanone

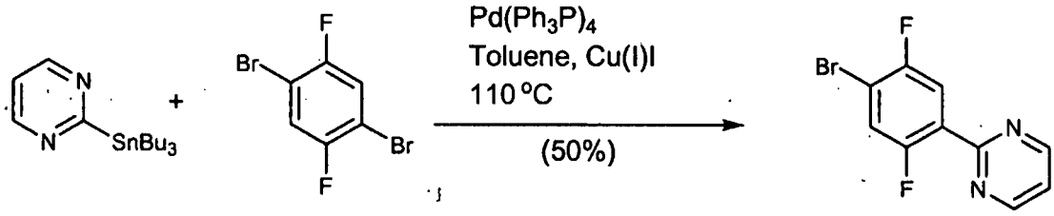


(5AC) **(7AC)**

To a stirred solution of piperazine **5AC** (150 mg, 0.54 mmol) in dichloromethane (5 ml) at 0 °C under nitrogen, triethylamine (0.076 ml, 0.54 mmol) followed by chloroacetyl chloride (0.043 ml, 0.54 mmol) were added. The mixture was stirred at 0 °C for 2 hr. After being quenched with saturated sodium carbonate solution, water and dichloromethane were added. Layers were separated and the separated aqueous layer was extracted with dichloromethane. The combined organic layers were dried ($MgSO_4$), filtered and solvents were removed in vacuum. Column purification [Hexanes – Ethyl acetate, 1:1 (v/v)] gave chloride **7AC** (169 mg, 88%) white solid.

Preparation 49

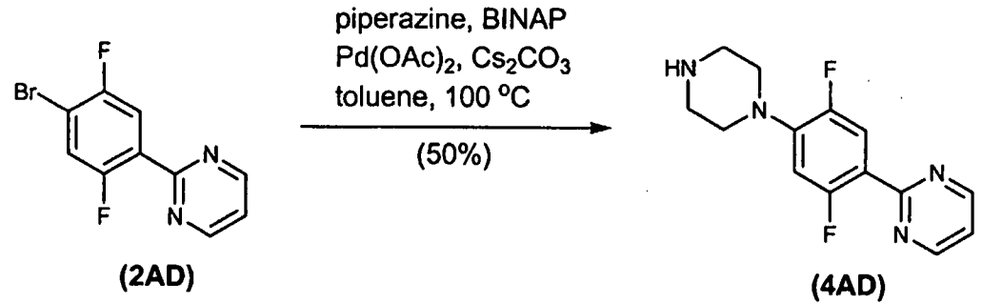
Step 1: Preparation of 2-(4-Bromo-2,5-difluoro-phenyl)-pyrimidine



(2AD)

A mixture of 1, 4-dibromobenzene (4.4 g, 16.3 mmol) , 2-(tributylstannyl)pyrimidine (3.0 g, 8.13 mmol), copper (I) iodide (154 mg, 0.81 mmol) in toluene (50 ml) were purged with nitrogen for 15 min. Tetrakis(triphenylphosphine)palladium(0) (939 mg, 0.81 mmol) was added and the mixture was stirred at 110 °C in a sealed-tube for 1 day. The mixture was cooled to r.t. and was diluted with water and ethyl acetate. Layers were separated. The separated organic layer was dried ($MgSO_4$), filtered and solvents were removed in vacuum. Column purification [Hexanes – Ethyl acetate, 2:1 (v/v)] gave bromide **2AD** (1.09 g, 50%) as white solid.

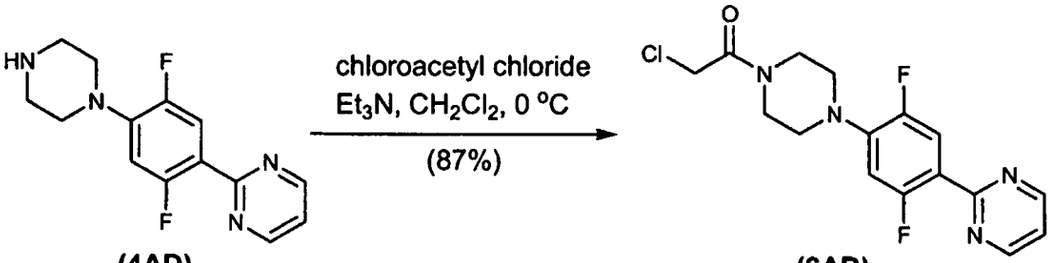
Step 2: Preparation of 2-(2,5-Difluoro-4-piperazin-1-yl-phenyl)-pyrimidine



(2AD) **(4AD)**

A mixture of bromide **2AD** (850 mg, 3.14 mmol), piperazine (810 mg, 9.41 mmol), BINAP (196 mg, 0.31 mmol), cesium carbonate (2.0 g, 6.27 mmol) in toluene (30 ml) were purged with nitrogen for 15 min. Palladium (II) acetate (35 mg, 0.16 mmol) was added and the mixture was stirred at 100 °C in a sealed-tube for overnight. The mixture was cooled to r.t. and was diluted with water and ethyl acetate. Layers were separated. The separated organic layer was dried ($MgSO_4$), filtered and solvents were removed in vacuum. Column purification [Methanol – Ethyl acetate, 1:1 (v/v)] gave piperazine **4AD** (393 mg, 43%) as white solid.

Step 3: Preparation of 2-Chloro-1-[4-(2,5-Difluoro-4-pyrimidin-2-yl-phenyl)-piperazin-1-yl]-ethanone



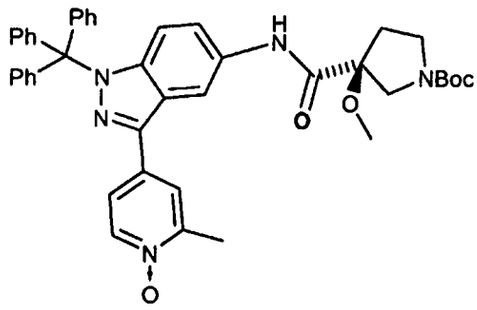
(4AD) **(6AD)**

To a stirred solution of piperazine **4AD** (255 mg, 0.92 mmol) in dichloromethane (5 ml) at 0 °C under nitrogen, triethylamine (0.13 ml, 0.92 mmol) followed by chloroacetyl chloride (0.074 ml, 0.92 mmol) were added. The mixture was stirred at 0 °C for 2 hr. After being quenched with saturated sodium carbonate solution, water and dichloromethane were added. Layers were separated and the separated aqueous layer was extracted with dichloromethane. The combined organic layers were dried ($MgSO_4$), filtered and solvents were removed in vacuum. Column

purification [Hexanes – Ethyl acetate, 1:1 (v/v)] gave chloride **6AD** (283 mg, 87%) white solid.

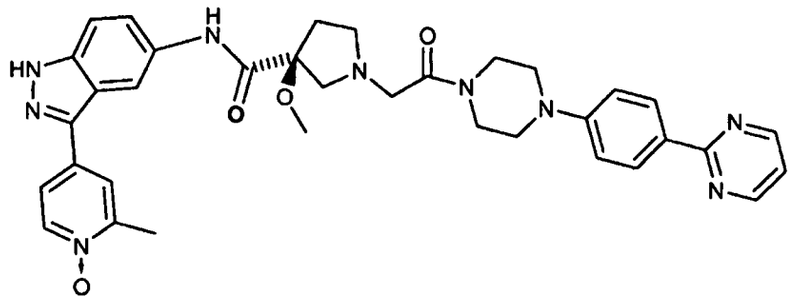
Example 620

STEP 1: Preparation of 3-Methoxy-3-[3-(2-methyl-1-oxy-pyridin-4-yl)-1-trityl-1H-indazol-5-ylcarbamoyl]-pyrrolidine-1-carboxylic acid tert-butyl ester



3-Methoxy-3-[3-(2-methyl-pyridin-4-yl)-1-trityl-1H-indazol-5-ylcarbamoyl]-pyrrolidine-1-carboxylic acid tert-butyl ester (2.9 g, 4.2 mmol) was dissolved in CH_2Cl_2 (80 mL) at rt followed by addition of mCPBA (2.0 g, max. 77%). After stirring for 24 hrs, the reaction solution was conc. to a small volume *in vacuo* and purified using silica gel column eluting with 2%, 5% and 10% methanol in CH_2Cl_2 to yield a brown solid (1.94 g).

STEP 2: Preparation of 3-Methoxy-1-{2-oxo-2-[4-(4-pyrimidin-2-yl-phenyl)-piperazin-1-yl]-ethyl}-pyrrolidine-3-carboxylic acid [3-(2-methyl-1-oxy-pyridin-4-yl)-1H-indazol-5-yl]-amide

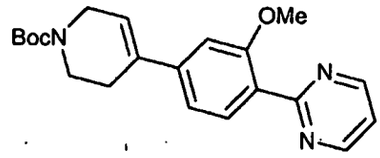


3-Methoxy-3-[3-(2-methyl-1-oxy-pyridin-4-yl)-1-trityl-1H-indazol-5-ylcarbamoyl]-pyrrolidine-1-carboxylic acid tert-butyl ester (170 mg) and triethylsilane (0.1 mL) were

dissolved in CH_2Cl_2 (5 mL) at rt followed by addition of TFA (1 mL). After 2 hrs, the reaction mixture was conc. to dryness *in vacuo*. To this, DMF (5 mL), triethyl amine (0.1 mL) and 2-chloro-1-[4-(4-pyrimidin-2-yl-phenyl)-piperazin-1-yl]-ethanone (170 mg) were added. The resulting mixture was heated at 70 °C for 16 hrs. After cooling to rt, the reaction mixture was conc. to dryness. The resulting crude was purified via reverse phase HPLC (ACN/H2O/0.1% HCOOH) to yield a yellow solid (70.0 mg). LCMS (M+1) 648.4 (rt 2.12)

Preparation 50

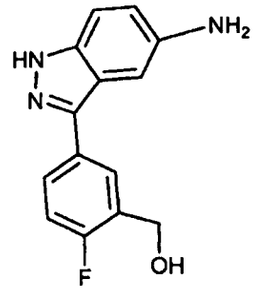
Preparation of 4-(3-Methoxy-4-pyrimidin-2-yl-phenyl)-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester



4-(3-Methoxy-4-pyrimidin-2-yl-phenyl)-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester was prepared using essentially the same scheme for Preparation 38 starting from 1-bromo-4-iodo-2-methoxy-benzene.

Preparation 51

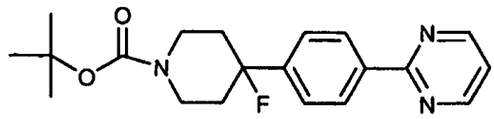
Preparation of [5-(5-Amino-1H-indazol-3-yl)-2-fluoro-phenyl]-methanol



[5-(5-Amino-1H-indazol-3-yl)-2-fluoro-phenyl]-methanol was prepared using essentially the same scheme for preparing 10H (see Preparation 17 Step 3). The boronic acid for the first step was 4-fluoro-3-hydroxylmethylphenylboronic acid.

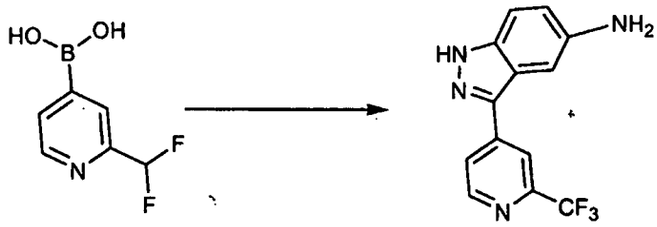
Preparation 52

Preparation of 4-Fluoro-4-(4-pyrimidin-2-yl-phenyl)-piperidine-1-carboxylic acid tert-butyl ester



The above compound was prepared using a procedure similar to that of Preparation 54 Step 4 by using 4-(4-Bromo-phenyl)-4-fluoro-piperidine-1-carboxylic acid tert-butyl ester in place of **3AE**.

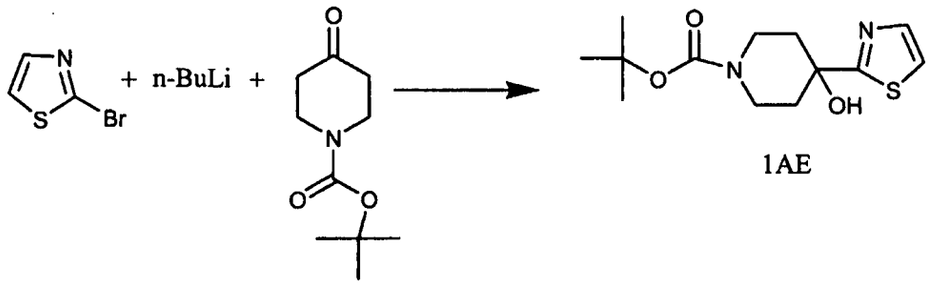
Preparation 53



3-(2-Trifluoromethyl-pyridin-4-yl)-1H-indazol-5-ylamine was prepared by a procedure similar to that of Preparation 25 by substituting CF_3CO_2Et with CF_2CO_2Et in Preparation 25 (Chem. Het. Cpds, 1997, p995) and utilizing the procedure similar to that of Example 98 Steps 2 & 3,

Preparation 54

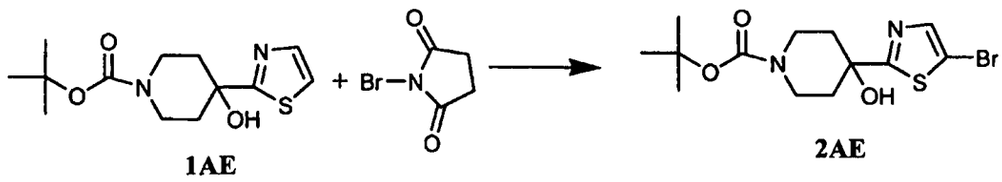
Step 1



1AE

Compound 1AE was prepared following a procedure similar to that of Example 132.

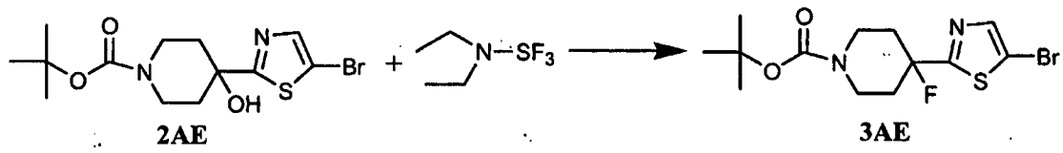
Step 2



1AE 2AE

4.03 g (14.18 m.mole) **1AE** was dissolved in 50 ml anhy. CH_3CN at r.t. under dry N2 gas this 2.524 g (14.18 m.mole) of N-Bromosuccinimde was added at r.t. and mixture was heated a 50°C under dry N2 gas for 3 hrs.. The mixture was evaporated to dryness. The residue was partitioned between 100 ml EtOAc and 100 ml saturated $NaHCO_3$ solution. The organic phase dried over $MgSO_4$ and evaporated to dryness. The resulting brown gum was purified on silica g (Hexane-30% EtOAc/ Hexane) gave 1.3 g (25%) yellow solid.

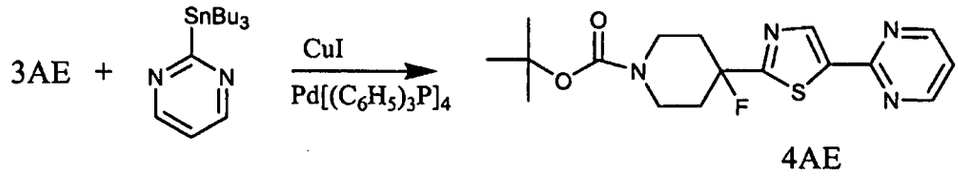
Step 3



2AE 3AE

2.38 g (6.55 m.mole) of 3 was dissolved in 30 ml anhy. Dichloromethane at r.t. under dry N_2 gas. The mixture was cooled to 0°C in ice-bath and 2.112g (13.1 m. mole) of DAST was added dropwise at 0°C under dry N_2. The mixture was stirred at 0° C for 1 hr. The reaction mixture was cautiously (CO_2 gas evolution) basified with saturated $NaHCO_3$ solution at 0°C. The mixture was tranfered to separatory funnel and shaken well. The organic phase was removed and aqueous phase was extracted with 2X50 ml Dichloromethane. The combine organic phases were dried over $MgSO_4$ and evaporated to dryness, gave 2.368 (99%) off-white low melting solid .

Step 4

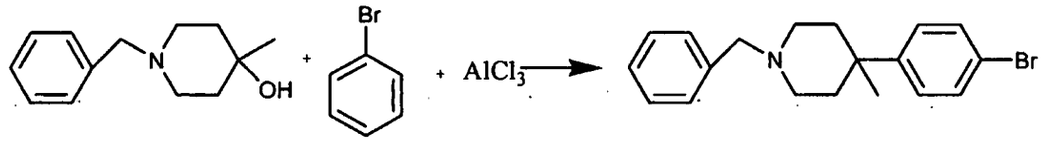


4AE

1.7g (4.65 m. mole) of **4AE** was dissolved in 15 ml anhy DMF at r.t. under dry N_2 gas. To this mixture CuI 0.93g (4.88 m.mole), Tetrakis(triphenylphosphine) palladium 0.537g (0.465 m.mole) and 2-Tributylstannylpyrimidine 1.762g (5.2 m.mole) were added and the mixture was stirred at 60°C under dry N_2 gas for 24 hrs. The mixture was concentrated to small volume, diluted with 50ml EtOAc and filtered through pad of celite. The filtrate was washed with brine and dried over $MgSO_4$. The evaporation of the solvent gave dark brown gum which was purified on silica gel (Hexane-25% EtOAc/ Hexane) gave 0.300g (17%) of brown solid.

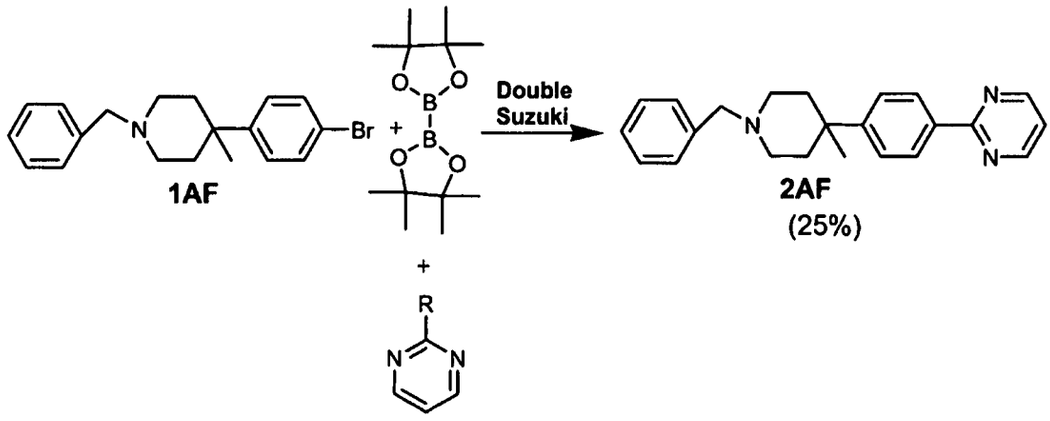
Preparation 55

Step 1



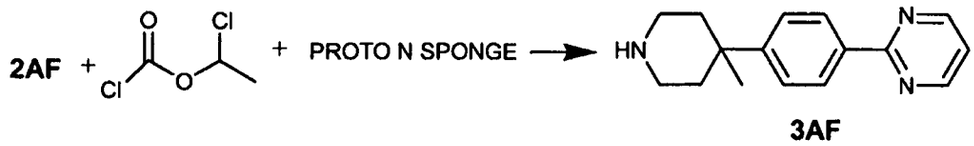
1-Benzyl-4-hydroxy-4-methyl piperidine (4.927g, 24m.mole) was dissolved in Bromobenzene(12ml, 114m.mole) at r.t.under dry N_2 gas. $AlCl_3$ (4.81g,36 m.mole) as solid was added to the above mixture at r.t. under dry N_2 gas. There was slightly exothermic reaction. The resulting dark brown solution was heated at 100°C over the week-end. The reaction was allowed to cool to r.t and was poured into ice-water. Saturated aqueous $NaHCO_3$ was added till pH 7. The mixture was extracted with 3X100 ml EtOAc. The combined organic extract dried over $MgSO_4$ and evaporated to dryness. The resulting dark brown gum was purified on silica and was eluted with (Hexane-25%EtOAc/Hexane), gave 4.43g (53%) as violet clear thick oil.

Step 2



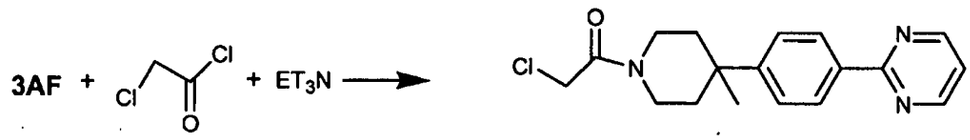
To a solution of 4.43 g (12.87 m.mole) of **1AF** in 100 ml anhy. DMSO were added 4.903 g (19.31 m.mole) of Bis(pinacolato)diboron, 3.784 g (38.61 m.mole) of Potassium acetate and 1.051 g (1.287 m.mole) of $Pd(dppf)Cl_2$ at r.t. under dry N_2 gas. The contents were degassed couple of times with N_2 gas and stirred at 100°C for 2 hrs. The mixture was allowed to cool to r.t. and 50 ml of water was added followed by 2.455 g (15.44 m.mole) of 2-Bromopyrimidine, 8.894 g (64.35 m.mole) of Potassium carbonate and 1.49 g (1.29 m.mole) of Tetrakis(triphenylphosphine)palladium. The contents were degassed couple of times with N2 gas and stirred at 100 C for 2 hrs. The mixture was allowed to cool to r.t.. 100 ml of water and 100 ml of EtOAc were added to the reaction mixture and filtered through pad of celite and washed with EtOAc. The contents were transfered to separatory funnel and the organic phase was separated and the aqueous phase was extracted with EtOAC . The organic phases were combined and washed with water and dried over MgSO4. The solvent was evaporated to dryness and dark brown gum was purified on silica gel (Hexane-25% EtOAC/Hexane), gave 1.00 off white solid.

Step 3



1.00 g(2.9 m.mole) of **2AF** was in 20 ml anhy. dichloromethane at r.t. under dry N_2 gas. To this solution 0.178g (0.83 m.mole) Proton Sponge was added at r.t. followed by dropwise addition of 0.713g (4.99 m.mole) of 2-Chloroethyl chloroformate. The reaction mixture was stirred at r.t. under dry N_2 gas for 4 hrs. The mixture was evaporated to dryness and dried under high vacuum for 15 minutes. The resulting residue was dissolved in 20 ml anhy. MeOH under dry N_2 gas and was stirred under reflux under dry N_2 gas for 4 hrs. The mixture was allowed to cool to r.t. and evaporated to dryness. The crude was purified on silica gel (CH_2Cl_2-25%MeOH/CH_2Cl_2) and gave 0.606g (82%) white solid.

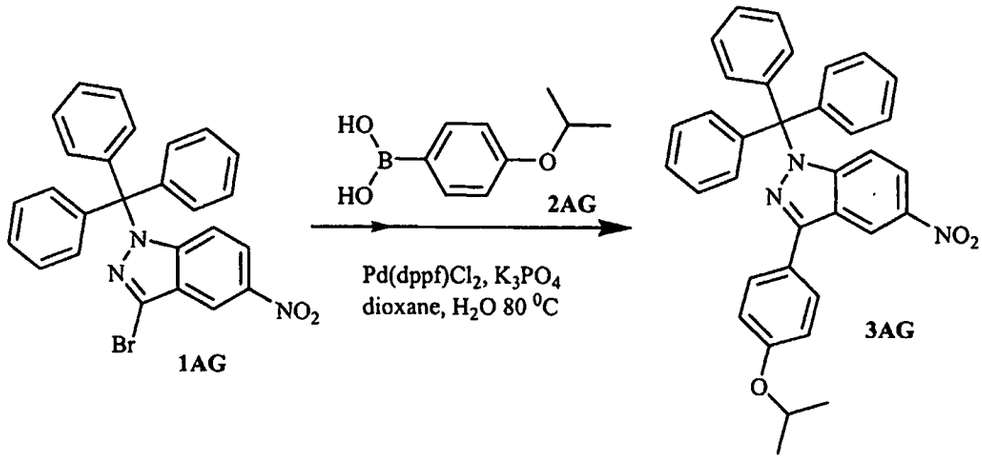
Step 4



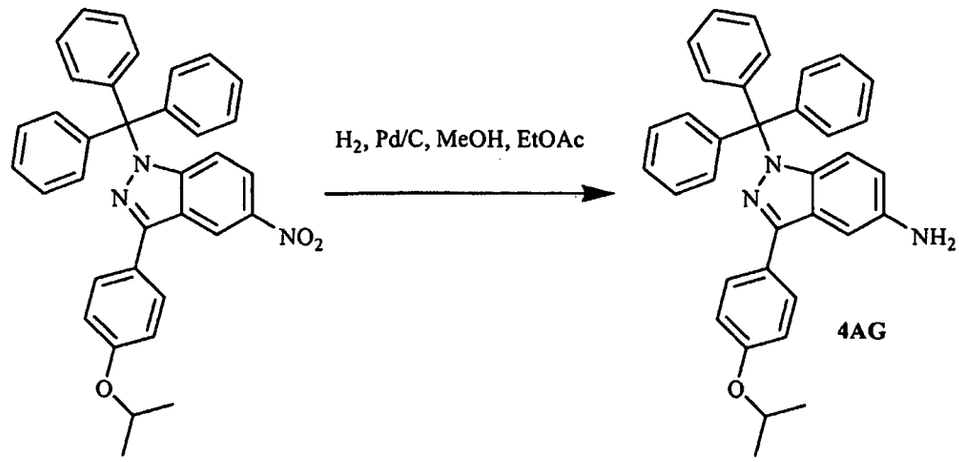
To a stirred solution of 0.60 g (2.37 m.mole) of **3AF** in 15 ml anhy. Dichloromethane 1.2((11.85 m.mole) of Triethylamine was added at r.t. under dry N_2 gas. The mixture was cooled to ice- water bath and 0.321 g (2.84 m.mole) of Chloroacetylchloride was added dropwise at 0°C dry N_2 gas. the mixture was stirred at 0°C for half an hr. 25 ml of CH_2Cl_2 and aqueous saturate $NaHCO_3$ solution were added at 0°C. The contents were transferred to separatory funnel and s well. The oranic phase was separated, dried over $MgSO_4$ and evaporated to dryness, gave bro solid. This solid was used without purification for subsequent reaction.

Preparation 56

Preparation of 3-(4-isopropoxyphenyl)-1-trityl-1*H*-indazol-5-amine



In a Sealed tube containing **1AG** (1.21 g, 2.50 mmol), **2AG** (0.67 g, 3.75 mmol), $Pd(dppf)Cl_2$ (0.21g, 0.25 mmol) and K_3PO_4 (1.31 g, 6.25 mmol) was added dioxane (25 mL) and water (12 mL) and degassed under nitrogen atmosphere three times. This reaction mixture was stirred at 80 °C for 18 hours. The reaction mixture was diluted with water and EtOAc, then filtered through Celite. The organic layer was washed with water, dried over $MgSO_4$, filtered and rotovap to dryness. The crude was chromat. (Biotage, 40L, 5%EtOAc/hexane) to give **3AG** (0.68 g, 50.4%), PMR ($CDCl_3$)

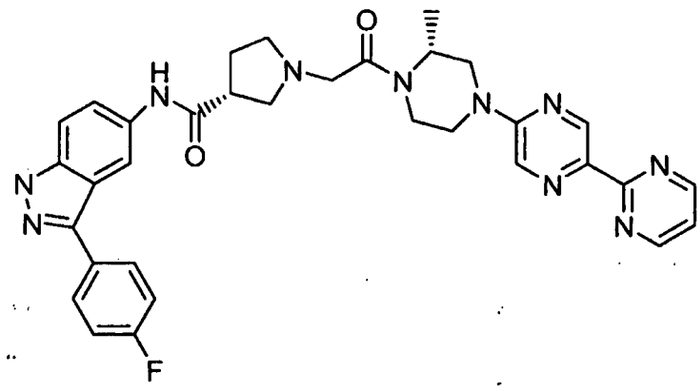


In a RB compound **3AG** (0.6 g, 1.11 mmol) stirred in a mixture of MeOH and EtOAc (10 mL each) was added 0.2 g of Pd/C (10%, 50% water). The reaction

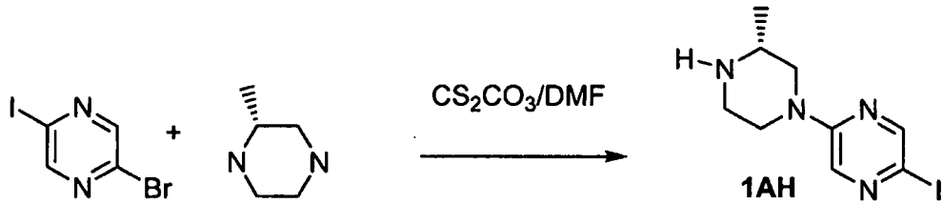
mixture was degassed under hydrogen atmosphere (balloon) and stirred overnight. MS of the reaction mixture showed (M+H) at 510. The reaction mixture was filtered (Celite) and rotovap. to dryness to give a crude **4AG**, used as is for next reaction.

Example 621

1-[2-(3-Methyl-5'-pyrimidin-2-yl-2,3,5,6-tetrahydro-[1,2']bipyrazinyl-4-yl)-2-oxo-ethyl]-pyrrolidine-3-carboxylic acid [3-(4-fluoro-phenyl)-1H-indazol-5-yl]-amide

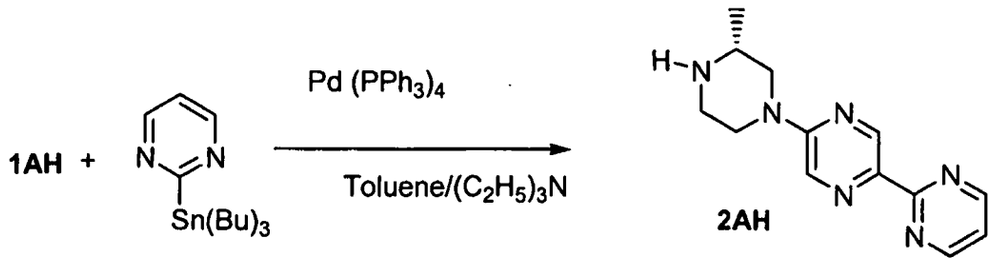


Step 1: 5'-Iodo-3-methyl-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl (1)



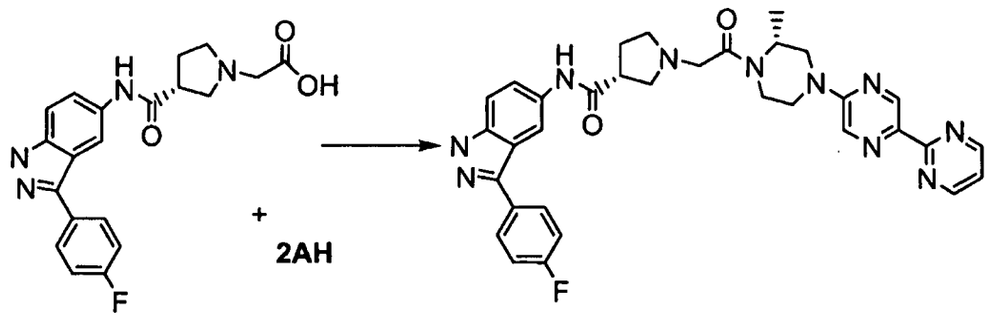
A mixture of 2-bromo-5-iodopyrazine (200mg, 0.704mmol), cesium carbonate (400mg, 1.23mmol) and 2R methyl piperazine (85mg, 0.85mmol) in DMF (10ml) was stirred at 100^{0}C overnight. The reaction was cooled and solvent evaporated.Water (100ml) was added and insoluble solid was filtered, then dissolved in $MeCl_2$ (100ml), dried over Na_2SO_4, filtered and solvent evaporated yielding product (205mg, 95%) Mass Spec (MH, 305)

Step 2: 3-Methyl-5'-pyrimidin-2-yl-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl (2)



Added $Pd(PPh_3)_4$ (30mg,0.025mmol) to a mixture of **5'-Iodo-3-methyl-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl (1AH) (** 50mg, 0.164mmol), 2-tributyl stannyl pyrimidine (0.2ml), triethylamine (0.2ml, 1.43mmol) in toluene (3ml) at room temperature then stirred at 100°C for 5 hours. The reaction was cooled, diluted with EtOAc (50ml) and water (20ml). The organic layer was separated, dried (Na_2SO_4) filtered and solvent evaporated. The residue was purified on Prep TLC eluting with 10% MeOH:$MeCl_2$:NH_4OH yielding product (10mg,24%) Mass Spec MH 256

Step 3: 1-[2-(3-Methyl-5'-pyrimidin-2-yl-2,3,5,6-tetrahydro-[1,2']bipyrazinyl-4-yl)-2-oxo-ethyl]-pyrrolidine-3-carboxylic acid [3-(4-fluoro-phenyl)-1H-indazol-5-yl]-amide

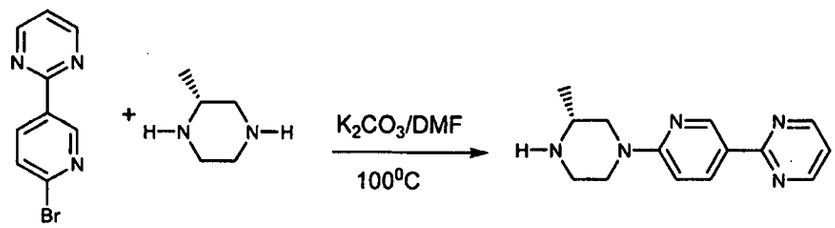


A mixture of the acid (20mg, 0.044mmol); **3-Methyl-5'-pyrimidin-2-yl-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl (2AH)** (10mg,0.039mmol) EDCI (10mg, 0.052mmol);HOBT (7mg, 0.052mmol) and NMM (0.1ml) was stirred in DMF (3ml) at room temperature overnight. The reaction was diluted with EtOAc (20ml) and water (10ml) and organic layer separated. The organics were washed with brine (10ml) dried over Na_2SO_4 filtered and solvent evaporated yielding a residue which purified on

silica gel eluting with 10% MeOH; $MeCl_2$;NH_4OH yielding title product as a solid (10mg,31%) Mass Spec (MH, 621)

Preparation 57

2-[6-(3-R-Methyl-piperazin-1-yl)-pyridin-3-yl]-pyrimidine

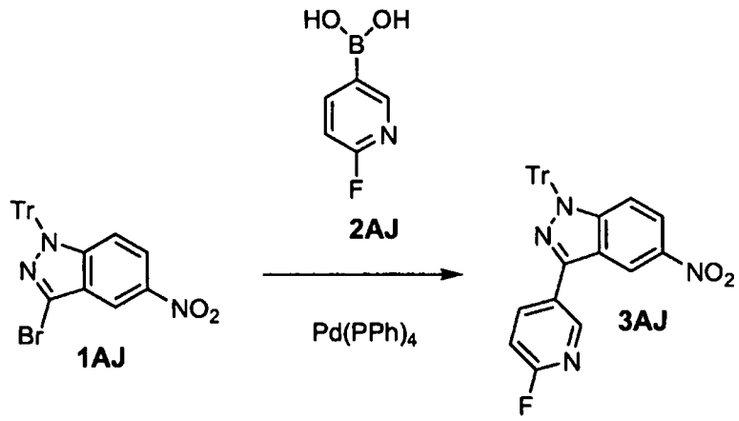


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Following the procedure described in Example 98 Step 7, but substituting an equivalent quantity of 2-R-Methyl piperazine for piperazine, the title compound is obtained as a white solid (ESMS MH,256) 95% Yield.

Preparation 58

Step 1: Preparation of 1-N-Trityl-3-(6-Fluoro-pyridin-3-yl)-1-methyl-5-nitro-1H-indazole

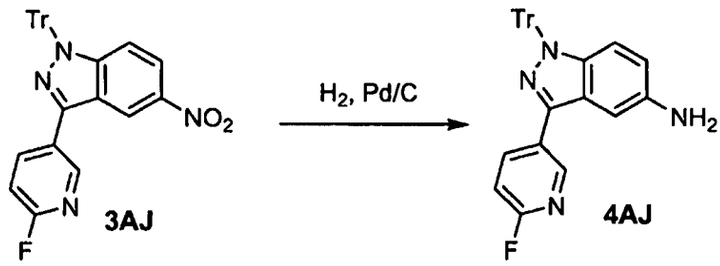


1AJ **2AJ** **3AJ**

A mixture of compound **1AJ** (8 g, 16.53 mmol), compound **2AJ** (2.33 g, 16.53 mmol), $Pd(PPh_3)_4$ (1.9 g, 1.653 mmol) and 1:1 dioxane/Na_2CO_3 (2M) (60 ml) was degassed for 15 min. Then it was heated at 120 °C for overnight. Cooled down to room temperature and diluted with DCM (300 ml). The organic layer was washed with

water (200 ml), dried over Na_2SO_4, filtered and concentrated. The residue was purified by Biotage to give the desired product **3AJ** (6 g, 58%).

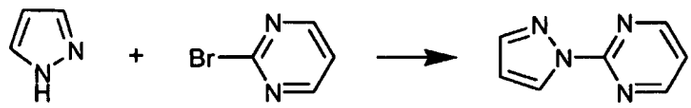
Step 2: Preparation of 1-N-Trityl-3-(6-Fluoro-pyridin-3-yl)-1-methyl-5-amino-1H-indazole



A mixture of compound **3AJ** (6 g) and Pd/C (10%, 200 mg) in EtOAc (200 ml) was stirred for overnight. Filtered and concentrated. The residue was purified by Biotage to give the desired product **4AJ** (5 g, 83%).

Preparation 59

Step 1: 2-Pyrazol-1-yl-pyrimidine



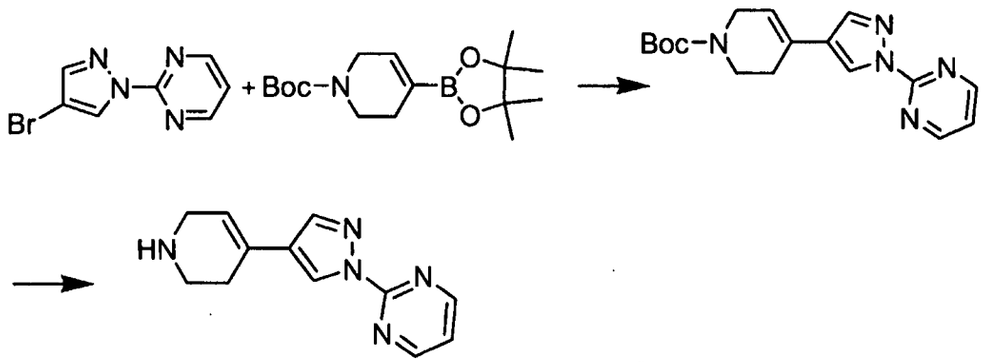
A reaction mixture containing pyrazole (2 g, 29 mmol), 2-bromopyrimidine (3.8 g, 24 mmol), copper (I) iodide (0.91 g, 4.8 mmol) and 1,10-phenanthroline (1.7 g, 9.6 mmol) in DMA was heated at 140 °C in a sealed tube for 6 hours. After the reaction, ethyl acetate (30 mL) was added, followed by water. The aqueous layer was extract three times (20 mL) and the organic layer was collected, dry over sodium sulfate. After concentration under vacuum, the crude product was purified using column chromatography (10% ethyl acetate in dichloromethane) to give 0.55 g of pure product. 15 % yield. MS (ESMS, M+H 146).

Step 2: 2-(4-Bromo-pyrazol-1-yl)-pyrimidine



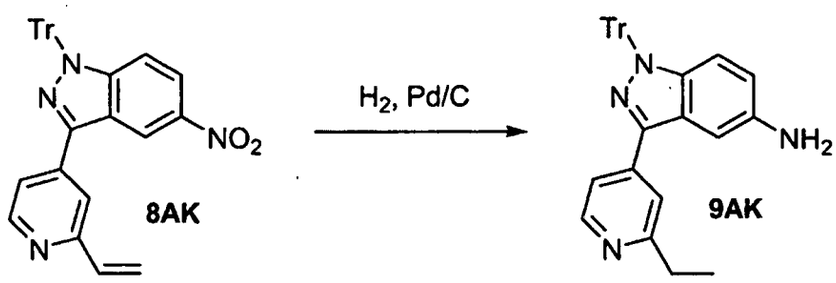
To a solution of 2-pyrazol-1-yl-pyrimidine (0.55 g, 3.7 mmol) in acetic acid (5 mL) was added bromine (1.2 g, 7.5 mmol) in acetic acid (3 mL) dropwisely. After addition, the reaction mixture was stirred at room temperature overnight. After removed the acetic acid, the crude product was purified using column chromatography (2% methanol in dichloromethane) to give 0.7 g of pure product in 85 % yield. MS (ESMS, M+H 225).

Step 3: 2-[4-(1,2,3,6-Tetrahydro-pyridin-4-yl)-pyrazol-1-yl]-pyrimidine



A solution containing 2-(4-bromo-pyrazol-1-yl)-pyrimidine (300 mg, 1.34 mmol), 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester (280 mg, 1.34 mmol), $PdCl_2(dppf)$ (95 mg, 0.13 mmol) and potassium phosphate (800 mg, 4 mmol) in dioxane was heated at 80 °C under argon for overnight. After removed the solvent, ethylacetate was added and the mixture was filtered, washed with water. After concentration under vacuum, it was found the product was hard to separated from impurity and the crude product was treated with 90% of TFA for 20 min and TFA was removed under vacuum. The crude product was then purified using prep HPLC to give desired product as TFA salt (120 mg, 0.37 mmol) in 27 % overall yield. MS (ESMS, M+H 228)

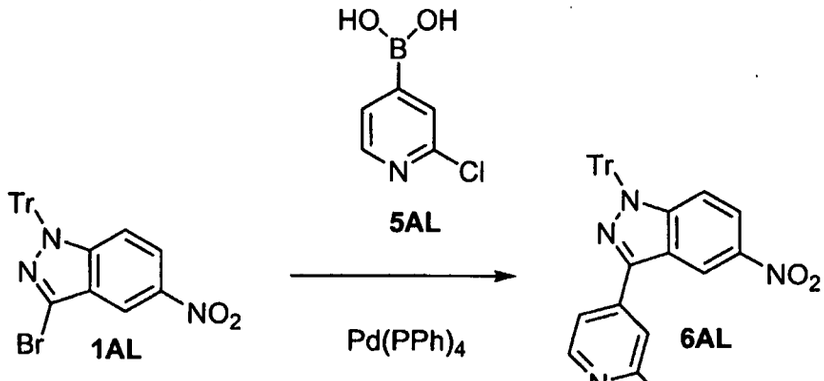
Preparation 60

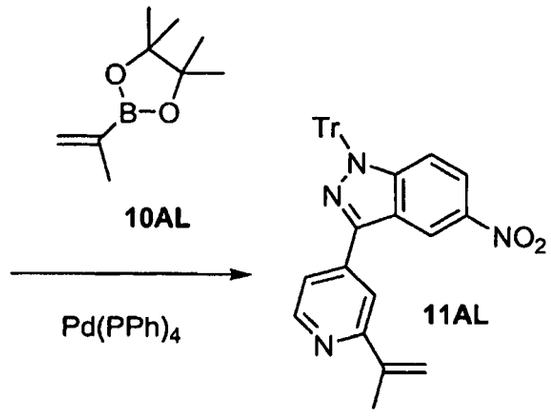


A mixture of compound **8AK** (5 g) and Pd/C (10%, 200 mg) in EtOAc (200 ml) was stirred for overnight. Filtered and concentrated. The residue was purified by Biotage to give the desired product **9AK** (4.6 g, 92%).

Preparation 61

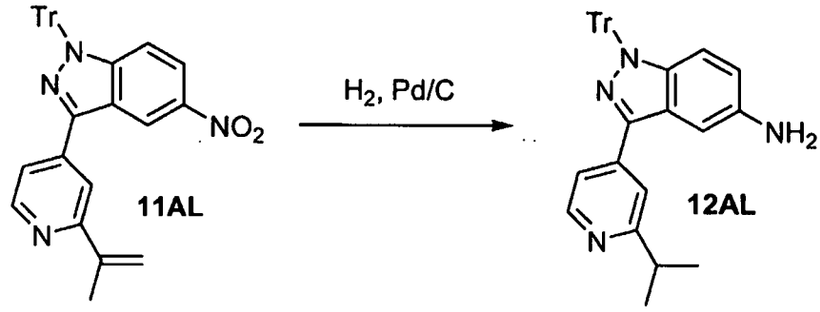
Step 1





A mixture of compound **1AL** (10 g, 20.66 mmol), compound **5AL** (3.23 g, 20.66 mmol), $Pd(PPh_3)_4$ (2.3 g, 2 mmol) and 1:1 dioxane/Na_2CO_3 (2M) (70 ml) was degassed for 15 min. Then it was heated at 120 °C for overnight. Cooled down to room temperature and added compound **10AL** (3.47 g, 20.66 mmol), then heated at 120 °C for overnight. Cooled down to room temperature and diluted with DCM (400 ml). The organic layer was washed with water (250 ml), dried over Na_2SO_4, filtered and concentrated. The residue was purified by Biotage to give the desired product **11AL** (6 g, 50%).

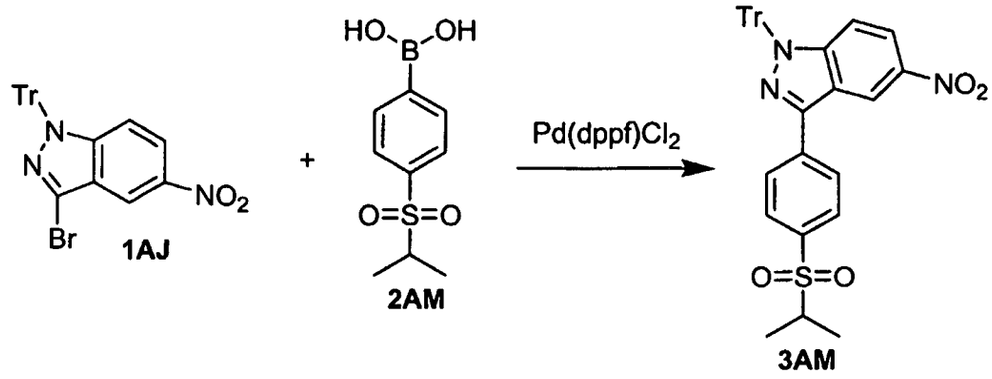
Step 2



A mixture of compound **11AL** (6 g) and Pd/C (10%, 200 mg) in EtOAc (200 ml) was stirred for overnight. Filtered and concentrated. The residue was purified by Biotage to give the desired product **12AL** (5 g, 83%).

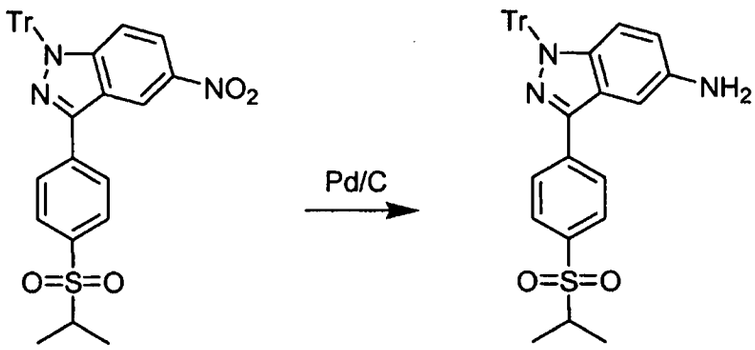
Preparation 62

Step 1



A mixture of 3-bromo-5-nitro-1-trityl-1*H*-indazole **1AJ** (0.43g, 0.9mmol), 4-(propane-2-sulfonyl)-phenyl boronic acid **2AM** (0.3 g, 1.35mmol), potassium carbonate (0.38g, 2.7mmol), $Pd(dppf)Cl_2$ (0.07g, 0.09mmol) and 4/1 /dioxane/water (5ml) was degassed for 5 minutes. Then it was heated at 80°C for overnight. Cooled to room temperature and diluted with EtOAc (60ml). The organic layer was washed with water (20ml), dried over $MgSO_4$, filtered and concentrated. The residue was purified on silica gel eluting with 1/2 EtOAc/Hexane to give the desired product **3AM** (0.4g, 76%).

Step 2

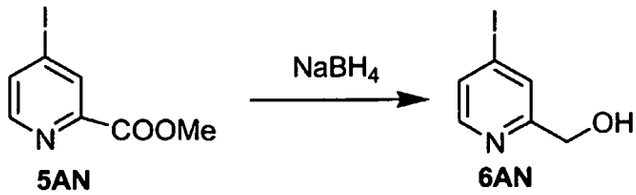


3AM **4AM**

A solution of 5-nitro-3-[4-(propane -2-sulfonyl)-phenyl]-1-trityl-1*H*-indazole **3AM** (0.4g, 0.68mmol) in EtOAc (18ml) and MeOH (9ml) was degassed for 5 minutes. To this solution 10% Pd/C (38mg) was added. After stirring for overnight at 40°C, it was cooled and filtered on a celite pad. The filtrate was concentrated to give the desired product **4AM** (0.36g, 99%).

Preparation 63

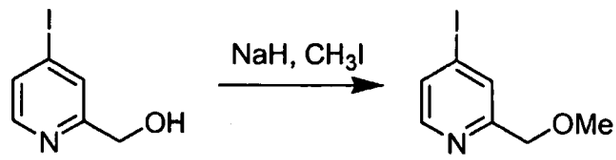
Step 1



5AN **6AN**

To a solution of methyl 4-iodopicolinate **5AN** (2.83g, 10.78mmol) in MeOH (30ml) was added $NaBH_4$ (1.59g, 43.12mmol) portion wise at 0°C. Reaction mixture was allowed to warm up to r.t. After stirring for 3 days at r.t, it was quenched with 14ml of 1N NaOH. Reaction mixture was diluted with DCM (200ml). The organic layer was washed with water (2 x 30ml), dried over $MgSO_4$, filtered and concentrated. The residue was purified on silica gel eluting with 3/1 EtOAc/Hexane to give the desired product (4-iodo-pyridin-2-yl)-methanol **6AN** (2.27g, 90%).

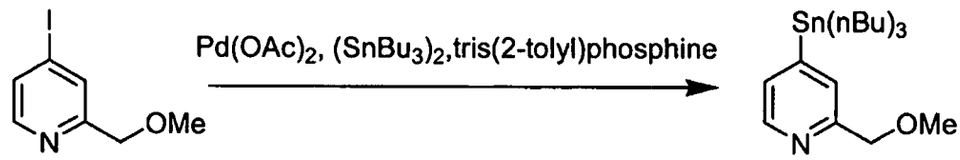
Step 2



6AN **7AN**

A solution of (4-iodo-pyridin-2-yl)-methanol **6AN** (0.51g, 2.16mmol) in THF (7.5ml) was added in a dry NaH (0.17g, 4.32mmol). Reaction mixture was stirred for 20 min at r.t. It was cooled to 0°C and CH_3I 0.16ml, 2.59mmol) was added drop wise. After 30 mins at 0°C, it was warmed up to r.t. and stirred further for 2 hr. Then it was diluted with EtOAc (50ml) and washed with water (2 x 10ml) and brine (1 x 15ml). Organic extracts were dried over $MgSO_4$, filtered and concentrated. The residue was purified on silica gel eluting with 1/2 EtOAc/Hexane to give the desired product 4-Iodo-2-methoxymethyl-pyridine **7AN** (0.39, 72%).

Step 3

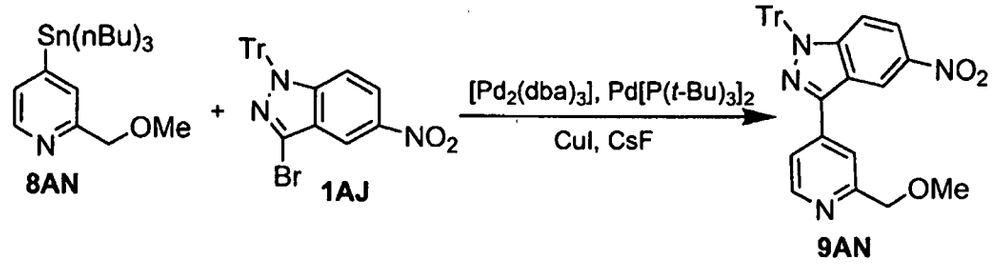


7AN **8AN**

To a mixture of 4-iodo-2-methoxymethyl-pyridine **7AN** (0.22g, 0.89mmol), $Pd(OAc)_2$ (9mg, 0.04mmol) and tris (2-tolyl)phosphine (72mg, 0.23mmol) in ACN (7ml) was added TEA (0.27ml, 1.78mmol) and bis(tributyltin) (0.53ml, 1.07mmol). It was degassed for 5 minutes. Then it was heated at 85°C for 2hr. Cooled to room temperature and diluted with EtOAc (50ml). The organic layer was washed with water

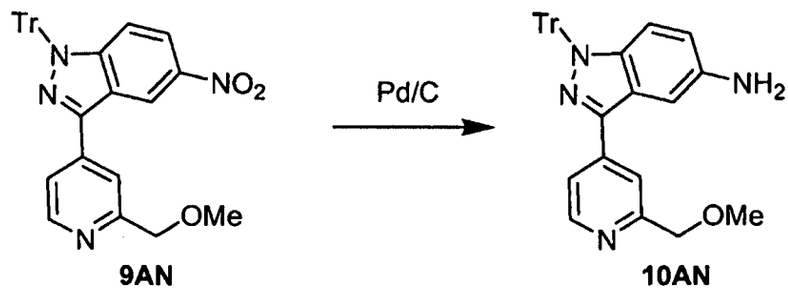
(15ml), dried over $MgSO_4$, filtered on a celite pad and concentrated. The residue was purified on silica gel eluting with 1/2 EtOAc/Hexane to give the desired product 2-methoxymethyl-4-tributylstannanyl-pyridine **8AN** (0.36g, 80%).

Step 4



A mixture of 2-methoxymethyl-4-tributylstannanyl-pyridine **8AN** (0.1g, 0.24mmol), 3-bromo-5-nitro-1-trityl-1*H*-indazole **1AJ** (0.12g, 0.24mmol), CsF (0.08g, 0.53mmol), $[Pd_2(dba)_3]$ (5mg, 0.005mmol), $Pd[P(t\text{-}Bu)_3)_2$, and CuI (4mg, 0.024mmol) in DMF (2ml) was degassed for 5 minutes. Then it was heated at 120°C for two hours. Cooled to room temperature and diluted with EtOAc (10ml). It was then filtered on a celite pad. Filtrate was washed with water (3ml) and the organic extracts were dried over $MgSO_4$. It was filtered again on a celite pad and concentrated. The residue was purified on silica gel eluting with 2/1 EtOAc/Hexane to give the desired product 3-(2-methoxymethyl-pyridin-4-yl)-5-nitro-1-trityl-1*H*-indazole **9AN** (0.095g, 76%).

Step 5

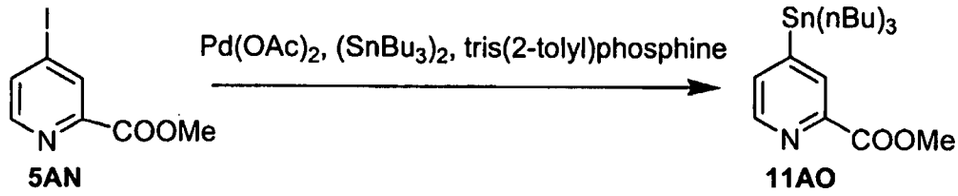


A solution of 3-(2-methoxymethyl-pyridin-4-yl)-5-nitro-1-trityl-1*H*-indazole **9AN** (0.095g 0.18mmol) in EtOAc (5ml) was degassed for 5 minutes. To this solution 10% Pd/C (20mg) was added. After stirring for overnight at r.t, it was cooled and filtered on

a celite pad. The filtrate was concentrated to give the desired product 3-(2-methoxymethyl-pyridin-4-yl)-1-trityl-1*H*-indazol-5-ylamine **10AN** (0.086g, 96%).

Preparation 64

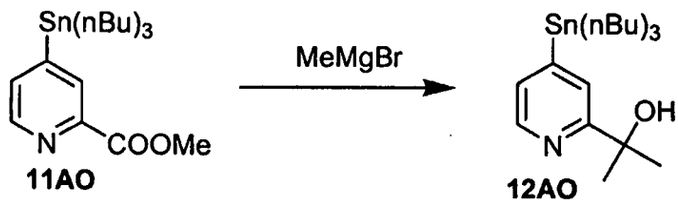
Step 1



5AN **11AO**

To a mixture of methyl 4-iodopicolinate **5AN** (2.6g, 9.89mmol), $Pd(OAc)_2$ (0.1g, 0.45mmol) and tris (2-tolyl)phosphine (0.79g, 2.58mmol) in ACN (20ml) was added TEA (2.8ml, 19.89mmol) and bis(tributyltin) (6ml, 11.93mmol). It was degassed for 5 minutes. Then it was heated at 85°C for 2hr. Cooled to room temperature and diluted with EtOAc (200ml). The organic layer was washed with water (50ml), dried over $MgSO_4$, filtered on a celite pad and concentrated. The residue was purified on silica gel eluting with 1/2 EtOAc/Hexane to give the desired product 4-tributylstannanyl-pyridine-2-carboxylic acid methyl ester **11AO** (3.48g, 82%).

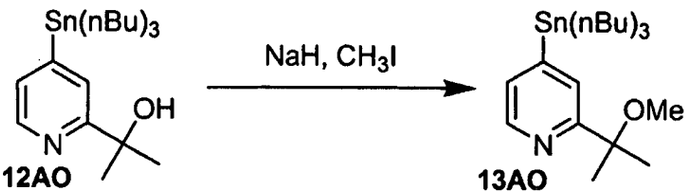
Step 2



11AO **12AO**

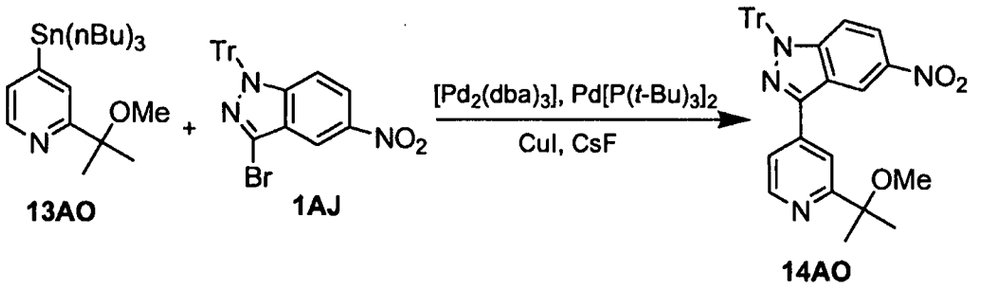
In a solution of 4-tributylstannanyl-pyridine-2-carboxylic acid methyl ester **11AO** (0.34g, 0.8mmol) in THF (7ml) at -78°C was added MeMgBr (1.15ml, 1.6mmol, 1.4M in toluene/THF) drop wise. It was stirred at -78 ^{0}C for 30 mins. Reaction mixture was warmed up to r.t. After 1.5hr, it was cooled again to 0°C and quenched with 5ml of saturated. NH_4Cl. Organic extracts were washed with water (3ml) and brine (3ml) and dried over $MgSO_4$. The residue was purified on silica gel eluting with 1/2 EtOAc/Hexane to give the desired product 2-(4-tributylstannanyl-pyridin-2-yl)-propan-2-ol **12AO** (012g, 77%).

Step 3



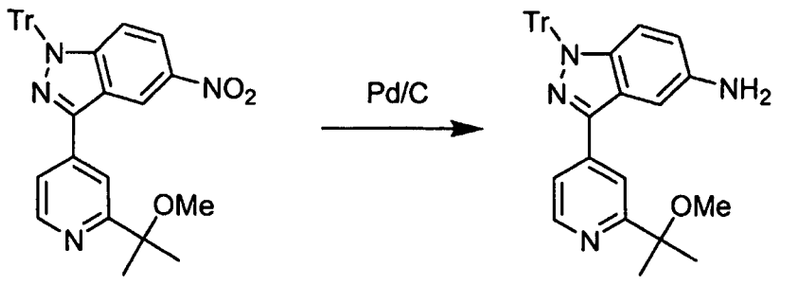
A solution of 2-(4-tributylstannanyl-pyridin-2-yl)-propan-2-ol **12AO** (0.12g, 0.27mmol) in THF (2ml) was added in a dry NaH (0.02g, 0.54mmol). Reaction mixture was stirred for 20 min at r.t. It was cooled to 0 ^{0}C and CH_3I (0.02ml, 0.32mmol) was added drop wise. After 30 mins at 0°C, reaction mixture was warmed up to r.t. It was diluted with EtOAc (15ml) after 2 hr and washed with water (2 x 3ml) and brine (5ml). Organic extracts were dried over $MgSO_4$, filtered and concentrated. The residue was purified on silica gel eluting with 1/4 EtOAc/Hexane to give the desired product 2-(1-methoxy-1-methyl-ethyl)-4-tributylstannanyl-pyridine **13AO** (0.1g, 88%).

Step 4



2-(1-methoxy-1-methyl-ethyl)-4-tributylstannanyl-pyridine **13AO** (0.1g,, 0.24mmol), 3-bromo-5-nitro-1-trityl-1*H*-indazole **1AJ** (0.12g, 0.24mmol), CsF (0.08g, 0.53mmol), $[Pd_2(dba)_3]$ (5mg, 0.005mmol), $Pd[P(t\text{-}Bu)_3)_2$, and CuI (4mg, 0.024mmol) in DMF (2ml) was degassed for 5 minutes. Then it was heated at 120°C for two hours. Cooled to room temperature and diluted with EtOAc (10ml). It was then filtered on a celite pad. Filtrate was washed with water (3ml) and the organic extracts were dried over $MgSO_4$. It was filtered again on a celite pad and concentrated. The residue was purified on silica gel eluting with 1/3 EtOAc/Hexane to give the desired product 3-[2-(1-methoxy-1-methyl-ethyl)-pyridin-4-yl]-5-nitro-1-trityl-1*H*-indazole **14AO** (0.05g, 39%).

Step 5

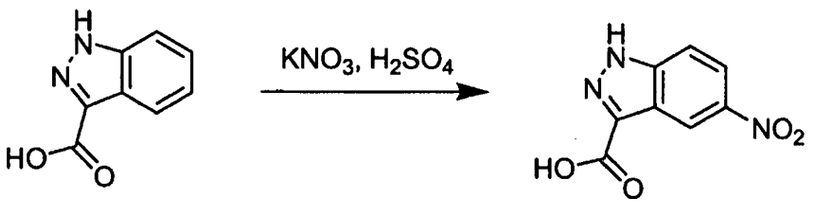


14AO **15AO**

A solution of 33-[2-(1-methoxy-1-methyl-ethyl)-pyridin-4-yl]-5-nitro-1-trityl-1*H*-indazole **14AO** (0.05g, 0.09mmol) in EtOAc (5ml) was degassed for 5 minutes. To this solution 10% Pd/C (10mg) was added. After stirring for overnight at r.t, it was cooled and filtered on a celite pad. The filtrate was concentrated to give the desired product 3-[2-(1-methoxy-1-methyl-ethyl)-pyridin-4-yl]-1-trityl-1*H*-indazole-5-ylamine **15AO** (0.046g, 97%).

Procedure 65

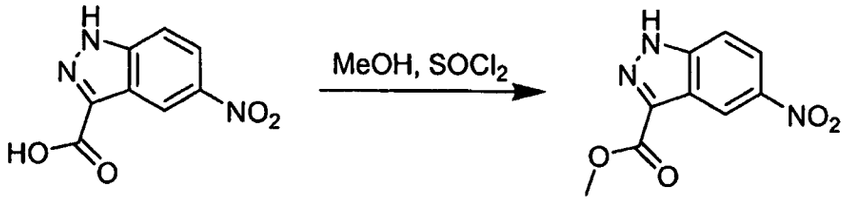
Step 1



16AP **17AP**

To a suspension of indazole-3-carboxylic acid **16AP** (10.5g, 64.8mmol) in concentrated sulfuric acid (125ml) at 0°C was added KNO_3 (64.8mmol, 6.55g). The reaction mixture was warmed up to r.t. After stirring for 4hr at r.t, it was poured into a 525ml of ice/water. Solid was collected by filtration and washed with water to give desired 5-nitro-1*H*-indazole-3-carboxylic acid **17AP** (10.74g, 80%).

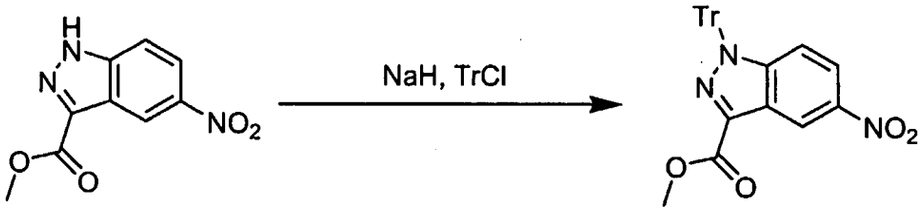
Step 2



17AP **18AP**

To a suspension of 5-nitro-1*H*-indazole-3-carboxylic acid **17AP** (10.74g, 51.88mmol) in MeOH (145ml) at 0°C was added $SOCl_2$ (35ml) dropwise. After stirring for 10 min at 0°C, the reaction mixture was refluxed overnight. HCl gas was evolved (Condenser was equipped with empty balloon to trap HCl). It was then cooled to room temperature, solid was collected by filtration and washed with MeOH to give desired 5-nitro-1*H*-indazole-3-carboxylic acid methyl ester **18AP** (7g, 61%).

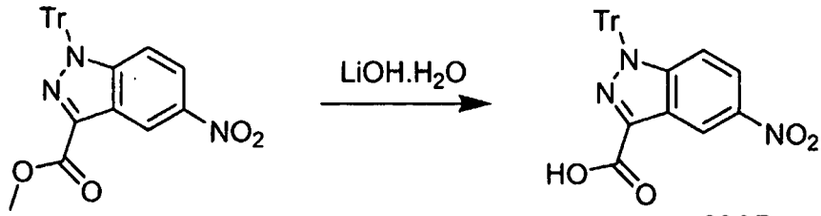
Step 3



18AP **19AP**

Suspension of 5-nitro-1*H*-indazole-3-carboxylic acid methyl ester **18AP** (7g, 31.67mmol) in THF (130ml) and DCM (15ml) was added to a NaH (60% in Mineral Oil, 1.61g, 41.17mmol) at 0°C. H_2 gas was evolved. Chlorotriphenyl methane (8.83g, 31.67mmol) was added after stirring for 20 min at 0°C. Reaction mixture was subjected to heat at 60°C for overnight. It was then cooled to room temperature and concentrated under reduced pressure. Solid was redissolved in DCM and filtered. Filtrate was concentrated under reduced pressure to give desired 5-nitro-1-trityl-1*H*-indazole-3-carboxylic acid methyl ester **19AP** (12.95g, 88%).

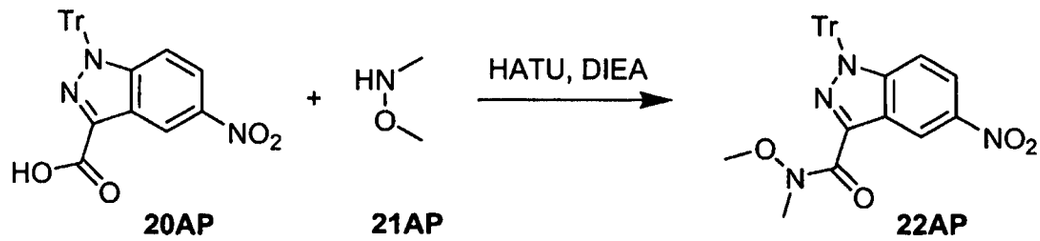
Step 4



19AP **20AP**

To a solution of 5-nitro-1-trityl-1*H*-indazole-3-carboxylic acid methyl ester **19AP** (12.95g, 27.96mmol) in THF (270ml) and H_2O (135ml) was added $LiOH{\cdot}H_2O$ (2.34g, 55.92mmol) at room temperature. After stirring for overnight at room temperature, it was cooled to 0°C and acidified with slow addition of 1N HCl (55.9ml, 55.92mmol). Reaction mixture was concentrated under reduced pressure. Solid was collected by filtration and washed with water to give desired 5-nitro-1-trityl-1*H*-indazole-3-carboxylic acid **20AP** (12.06g, 96%).

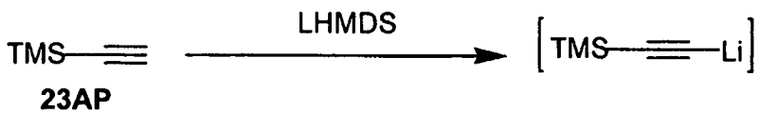
Step 5



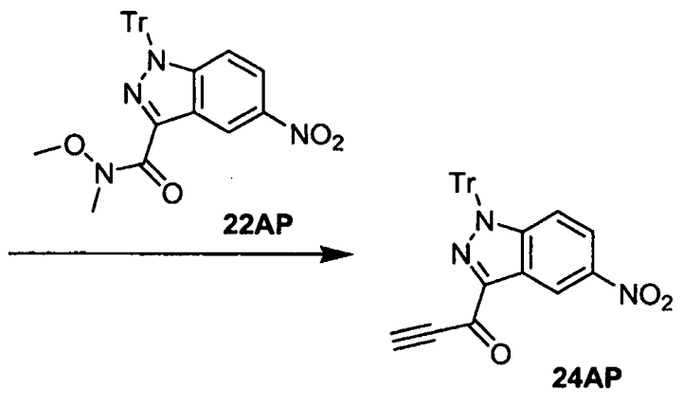
20AP **21AP** **22AP**

5-nitro-1-trityl-1*H*-indazole-3-carboxylic acid **20AP** (12.06g, 26.85mmol) and HATU (10.2g, 26.85mmol) was dissolved in DMF (100ml). After stirring for 10 min at room temperature, *N,O*-dimethylhydroxyl amine hydrochloride **21AP** (2.62g, 26.85mmol) and DIEA (14.1ml, 80.55mmol) was added. It was stirred further for 1 hr at room temperature. Reaction mixture was poured into 300ml of water. Solid was collected by filtration. This solid was redissolved in EtOAc (300ml) and 75ml of sat. $NaHCO_3$ was added. Organic fraction was washed with water (2 X 75ml), brine (75ml) and dried over $MgSO_4$. Solvent was removed under reduced pressure to give desired 5-nitro-1-trityl-1*H*-indazole-3-carboxylic acid methoxy-methyl-amide **22AP** (12.56g, 95%).

Step 6



23AP

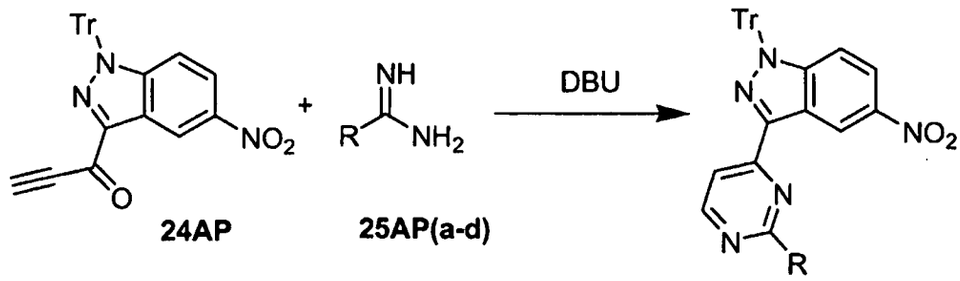


22AP

24AP

To a cold (-20°C) solution of TMS-acetylene **23AP** (5.5ml, 38.28mmol) in toluene (23ml) was added LHMDS (33.2ml, 1M in THF, 33.2mmol) dropwise over 5 min keeping T < -5°C. The mixture was stirred at 0°C for 30 min, then transferred to the cold (-10°C) reaction mixture that contains 5-nitro-1-trityl-1*H*-indazole-3-carboxylic acid methoxy-methyl-amide **22AP** (12.56g, 25.52mmol) in THF (120ml) at a rate that kept T < -5°C. The resulting mixture was stirred for 20 min at -5°C then 1.5hr at room temperature. Reaction mixture was cooled to 0°C and quenched by a slow addition of 1N HCl (40ml) under N_2. It was stirred further for 5 min. Reaction mixture was diluted with EtOAc (500ml). The organic fraction was separated and washed with water (2 x 100ml) and brine (1 x 125ml). It was dried over $MgSO_4$, filtered and concentrated. The residue was purified on silica gel eluting with 2/1 EtOAc/Hexane to give the desired 1-(5-nitro-1-trityl-1*H*-indazol-3-yl-)-propynone **24AP** (6.99g, 60%).

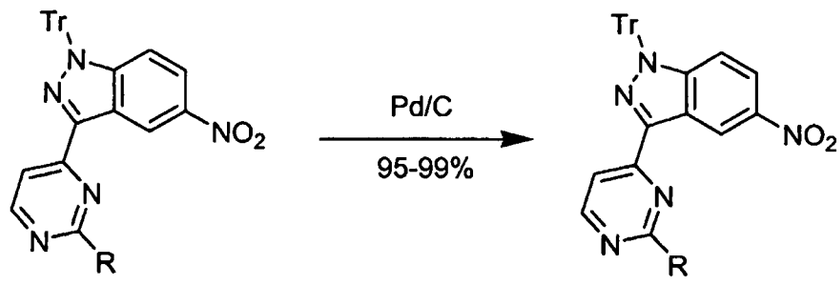
Step 7



a. R = methyl(60%)
b. R = ethyl(58%)
c. R = Isopropyl(54%)
d. R = *t*-butyl(43%)

A mixture of 1-(5-nitro-1-trityl-1*H*-indazol-3-yl-)-propynone **24AP** (0.5g, 1.09mmol), amidine hydrochloride **25AP** (1.75mmol) and DBU (1.6ml, 10.9mmol) in acetonitrile (10ml) was heated at 120°C for 50 minutes under microwave. It was then cooled to room temperature and diluted with DCM (60ml). The organic layer was washed with water (10ml), dried over $MgSO_4$, filtered and concentrated. The residue was purified on silica gel eluting with 1/1 EtOAc/Hexane to give the desired product **26AP**.

Step 8



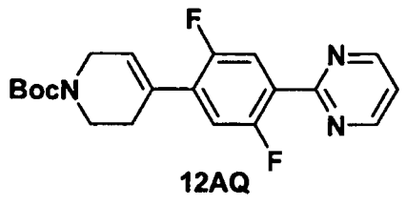
a. R = methyl
b. R = ethyl
c. R = Isopropyl
d. R = *t*-butyl

A solution of **26AP** (0.96mmol) in EtOAc (20ml) and MeOH (5ml) was degassed for 5 minutes. To this solution 10% Pd/C (0.08g) was added. After stirring

for overnight at 40°C, it was cooled and filtered on a celite pad. The filtrate was concentrated to give the desired **27AP**.

Preparation 66

Preparation of 4-(2,5-Difluoro-4-pyrimidin-2-yl-phenyl)-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (Compound 12AQ)

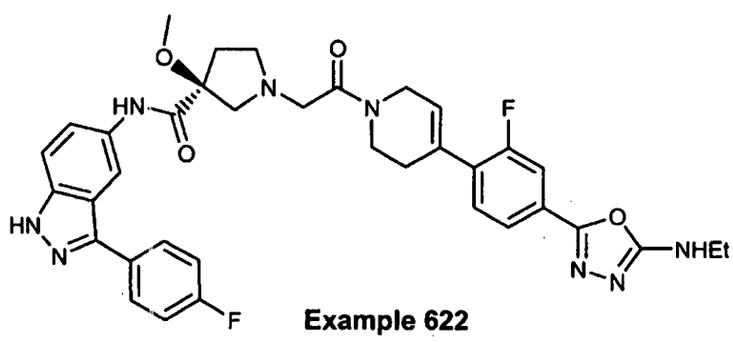


12AQ

The Compound **12AQ** was prepared from 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester using the procedure as described for the preparation of Compound 4-(2-fluoro-4-pyrimidin-2-yl-phenyl)-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester but using 1,4-dibromo-2,5-difluoro-benzene in place of 4-bromo-2-fluoro-1-iodobenzene.

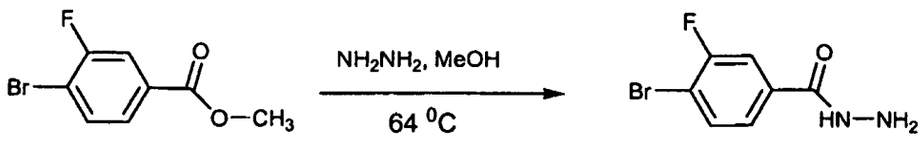
Example 622

Preparation of 1-(2-{4-[4-(5-Ethylamino-[1,3,4]oxadiazol-2-yl)-2-fluoro-phenyl]-3,6-dihydro-2*H*-pyridin-1-yl}-2-oxo-ethyl)-3-methoxy-pyrrolidine-3-carboxylic acid [3-(4-fluoro-phenyl)-1*H*-indazol-5-yl]-amide



Example 622

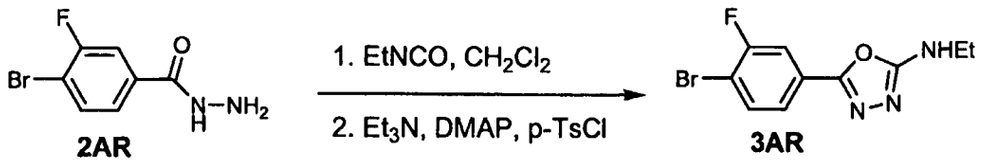
Step 1: Preparation of 4-Bromo-3-fluoro-benzoic acid hydrazide



1AR **2AR**

A mixture of compound 4-bromo-3-fluoro-benzoic acid methyl ester (1 g, 4.29 mmol), hydrazine hydrate (2.2 mL, 42.9 mmol) and MeOH (20 mL) was heated at 70 °C for overnight. Concentrated, diluted with EtOAc (300 mL) and washed with water (100 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated give the desired product **2AR** (0.9 g, 90%).

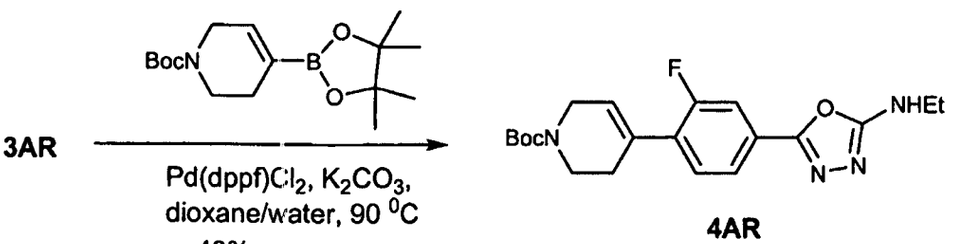
Step 2: Preparation of [5-(4-Bromo-3-fluoro-phenyl)-[1,3,4]oxadiazol-2-yl]-ethyl-amine



2AR **3AR**

A mixture of Compound **2AR** (0.9 g, 2.53 mmol), CH_2Cl_2 (5 mL) and ethyl isocyanate (0.34 mL, 4.35 mmol) was stirred at room temperature for 3 hours. To the reaction mixture was added triethylamine (0.94 mL, 6.7 mmol), DMAP (0.205 g, 1.675 mmol) and a solution of p-toluenesulfonyl chloride (0.83 g, 4.36 mmol) in CH_2Cl_2 (10 mL). Reaction mixture was stirred at room temperature for 18 hours. Diluted with CH_2Cl_2 (200 mL) and washed with water (100 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified on silica gel eluting with 3% MeOH/ CH_2Cl_2 to give the desired product **3AR** (0.56 g, 58%).

Step 3: Preparation of 4-[4-(5-Ethylamino-[1,3,4]oxadiazol-2-yl)-2-fluoro-phenyl]-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester

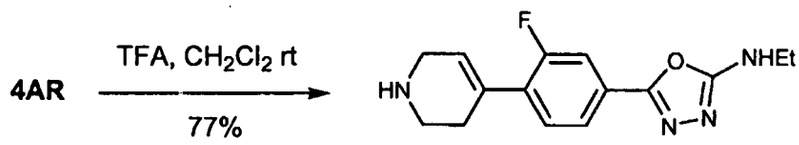


4AR

A mixture of Compound **3AR** (0.56 g, 1.96 mmol), 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester (0.73 g, 2.35 mmol), potassium carbonate (0.81 g, 5.88 mmol), $Pd(dppf)Cl_2$ (0.192 g, 0.235 mmol) and 4/1 /dioxane/water (10 ml) was degassed for 15 minutes. Then it

was heated at 80 °C for overnight. Cooled to room temperature and diluted with EtOAc (200 ml). The organic layer was washed with water (100 ml), dried over Na_2SO_4, filtered and concentrated. The residue was purified on silica gel eluting with 5% MeOH/CH_2Cl_2 to give the desired product **4AR** (0.44 g, 48%).

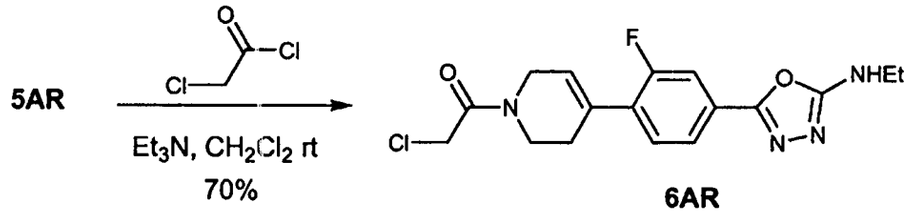
Step 4: Preparation of Ethyl-{5-[3-fluoro-4-(1,2,3,6-tetrahydro-pyridin-4-yl]-[1,3,4]oxadiazol-2yl}-amine



5AR

A mixture of Compound **4AR** (0.44 g, 1.13 mmol), CH_2Cl_2 (20 mL) and TFA (2 mL) was stirred at room temperature for 18 hours. Concentrated and purified on silica gel eluting with 5% MeOH (NH_3)/ CH_2Cl_2 to give the desired product **5AR** (0.25 g, 77%).

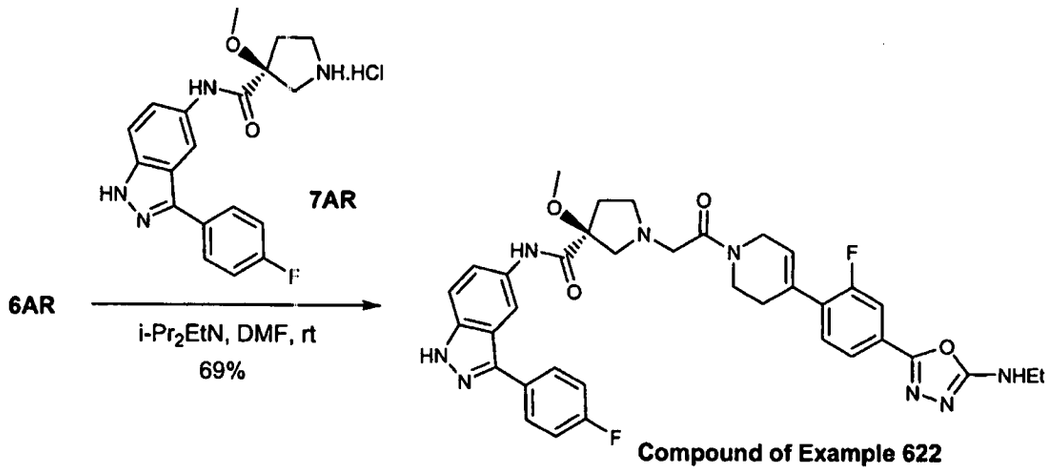
Step 5: Preparation of 2-Chloro-1-{4-[4-(5-ethylamino-[1,3,4]oxadiazol-2-yl)-2-fluoro-phenyl]-3,6-dihydro-2*H*-pyridin-1-yl}-ethanone



6AR

To a mixture of Compound **5AR** (0.1 g, 0.35 mmol), CH_2Cl_2 (5 mL), MeOH (1 mL) and triethyl amine (0.041 mL, 0.29 mmol) at -78 °C was added chloroacetyl chloride (0.021 mL, 0.264 mmol). Reaction mixture was stirred at -78 °C for 10 minutes then warm to 0 °C and stirred for 1 hour. Diluted with CH_2Cl_2 (100 mL) and washed with saturated aq. $NaHCO_3$ (100 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified on silica gel eluting with 2% MeOH/ CH_2Cl_2 to give the desired product **6AR** (0.09 g, 70%).

Step 6

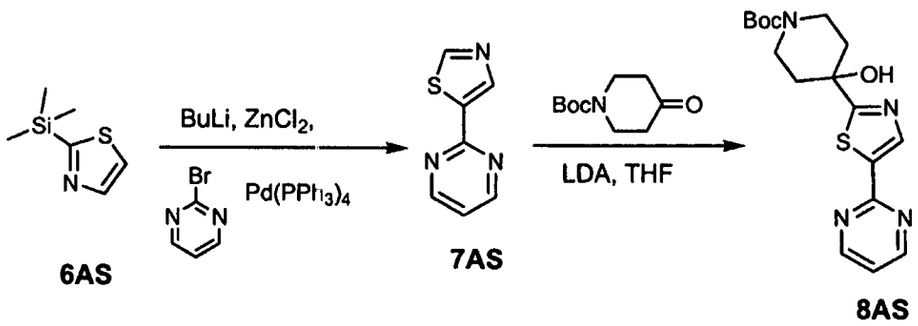


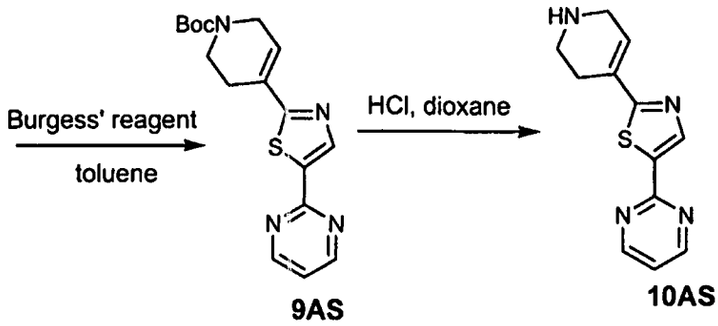
Compound of Example 622

A mixture of Compound **6AR** (0.09 g, 0.247 mmol), compound **7AR** (0.073 g, 0.2 mmol), DMF (2 mL) and N,N-diisopropylethylamine (0.131 mL, 0.74 mmol) was stirred at room temperature for 18 hours. Diluted with EtOAc (100 mL) and washed with water (2 x 100 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified on silica gel eluting with 5% MeOH (NH_3)/ CH_2Cl_2 to give the desired compound of **Example 622** (0.11 g, 69%).

Preparation 67

Step 1





9AS **10AS**

In a 250 round bottom flask was placed butyl lithium (6.1 mL, 2.5 M in hexanes, 15.2 mmol) in THF at -78 °C under Ar. To this was added 6 (2.0 g, 12.7 mmol), stirred for 15 min and added Zinc chloride (38.1 mL, 0.5 M in THF, 19.1 mmol). The mixture was warmed up to room temperature and stirred for 1 hr. To this was added 2-bromopyrimidine (2.4 g, 15.2 mmol) and $Pd(PPh_3)_4$ (293 mg, 0.252 mmol). The reaction was heated to reflux overnight, cooled to room temperature and filtered. The filtrate was partitioned between brine and ethyl acetate. The organic layer was dried over sodium sulfate and concentrated. The resulting mixture was purified by biotage column chromatography to afford **7AS** (936 mg, 54.2%)

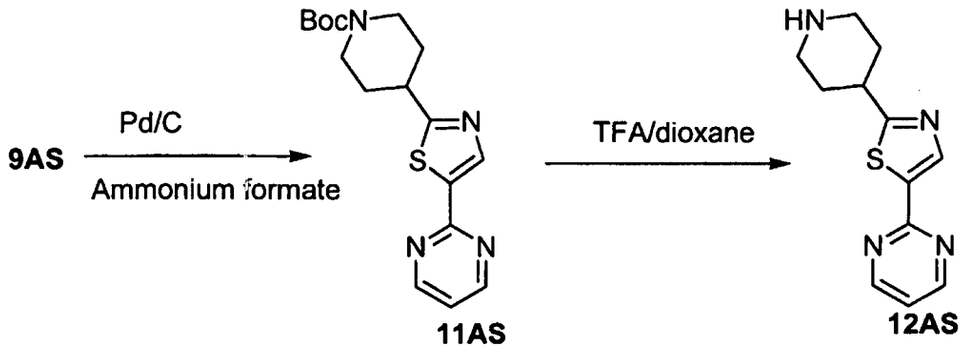
To a solution of **7AS** (710 mg, 4.35 mmol) in THF at -78 °C was added LDA (2.61 mL, 2.0 M, 5.22 mmol), and then Boc-4-piperidone (1.04 g, 5.22 mmol). The reaction was stirred at -78 °C for 1 hr, warmed up to room temperature and quenched with ammonium chloride solution. The mixture was extracted with ethyl acetate. The combined organic layer was dried over sodium sulfate and concentrated. The resulting oil was purified by biotage column chromatography to afford **8AS** (1.08 g, 68%)

To a solution of **8AS** (800 mg, 2.21 mmol) in toluene was added Burgess reagent (1.09 g, 4.58 mmol). The mixture was heated to 100 °C, stirred for 2 hrs, cooled to room temperature and concentrated. The residue was purified biotage column chromatography to afford **9AS** (562 mg, 74%)

Step 2

To **9AS** (560 mg, 1.63 mmol) in a 20 mL vial was added 4 mL of HCl in dioxane (4 M). The reaction was stirred at room temperature for 4 hrs and the precipitate was filtered. The resulting solid was pump dried to afford **10** (350 mg, 88%)

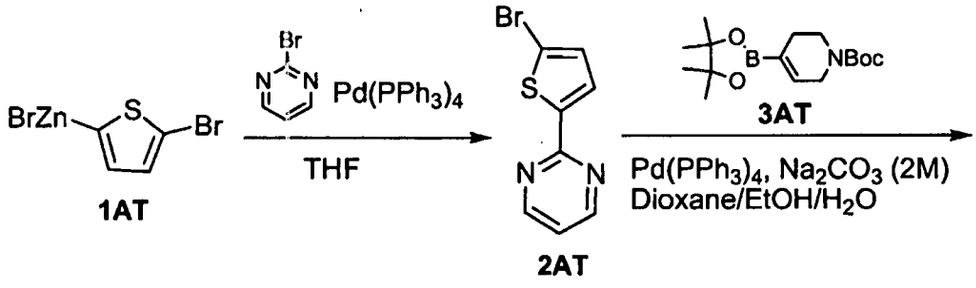
Step 3

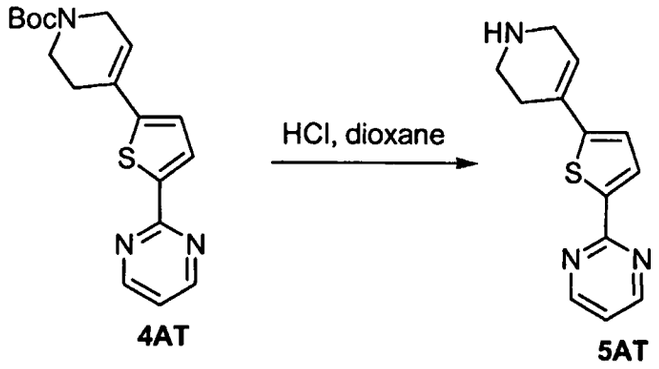


To a solution of **9AS** (100 mg, 0.291 mmol) and ammonium formate (183 mg, 2.91 mmol) in methanol was added catalytic amount of 10 % Palladium on carbon. The mixture was heated to reflux overnight, cooled to room temperature and filtrated. The filtrate was concentrated and the residue was purified biotage column chromatography to afford **11AS** (52 mg, 52%) and recovered 9 (18 mg, 18%)

To **11AS** (52 mg, 0.15 mmol) in 1 mL of DCM was added 1 mL of TFA. The reaction was stirred at room temperature for 2 hrs and concentrated to afford crude **12AS**.

Preparation 68





4AT **5AT**

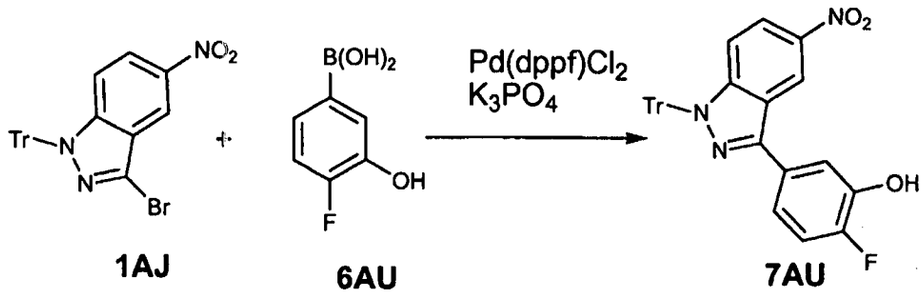
In a 250 mL of round bottom flask was placed **1AT** (0.5 M in THF, 20.0 mL, 10.0 mol). To this was added 2-bromopyrimidine (2.00 g, 12.6 mol) and $Pd(PPh_3)_4$ (346 mg, 0.3 mmol). The mixture was heated to reflux under Ar overnight and cooled down to room temperature. The reaction was quenched with ammonium chloride solution and extracted with ethyl acetate. The combined organic layer was dried over sodium sulfate and concentrated. The resulting oil was purified by biotage column chromatography to afford **2AT** (1.62 g, 69%)

In a 5 mL of biotage microwave vessel was placed **2AT** (136 mg, 0.568 mmol), pinacol ester **3AT** (193 mg, 0.625 mmol), $Pd(PPh_3)_4$ (32.8 mg, 0.0284 mmol) and sodium carbonate solution (0.85 mL, 2 M) in dioxane/EtOH/H2O (7:3:2, 2.5 mL) under Ar. The vessel was sealed and heated in microwave reactor at 150 °C for 10 minutes. The reaction was partitioned between ethyl acetate and water. The organic layer was dried over sodium sulfate and concentrated. The resulting oil was purified by biotage column chromatography to afford **4AT** (149 mg, 76%).

To **4AT** (144 mg, 0.420 mmol) in a 20 mL vial was added 2 mL of HCl in dioxane (4 M). The reaction was stirred at room temperature for 4 hrs and the precipitate was filtered. The resulting solid was pump dried to afford **5AT** (83 mg, 82%)

Preparation 69

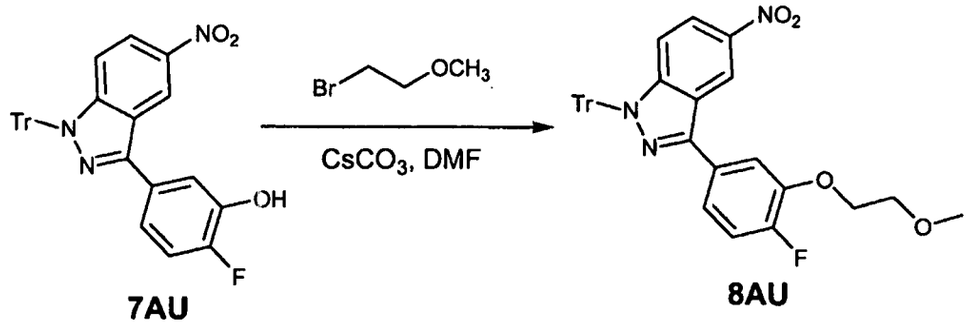
Step 1: Preparation of 3-(4-Fluoro-3-hydroxyphenyl)-5-nitro-1-trityl-1H-indazole



1AJ **6AU** **7AU**

A suspension of 3-bromo-5-nitro-1-trityl-1H-indazole **1AJ** (10.0 g, 20.68 mmol), 4-fluoro-3-hydroxyphenylboronic acid **6AU** (3.55 g, 22.78 mmol), $Pd(dppf)Cl_2$ (1.6 mg, 1.96 mmol) and K_3PO_4 (10.6 g, 4.99 mmol) in 200 mL of dioxane/H_2O (4/1) was heated to 75°C for overnight. After removal of most of the solvent, the black residue was diluted with EtOAc (250 mL) and H2O (60 mL). The resulting mixture was filtered through a pad of Celite. Additional 150 mL of EtOAc was used to wash the Celite cake. The filtrates were combined. The aqueous layer was separated and the organic layer was washed with brine, dried ($MgSO_4$) and concentrated to give a green solid, which was recrystallized from CH_2Cl_2/hexane to give 3-(4-fluoro-3-hydroxyphenyl)-5-nitro-1-trityl-1H-indazole **7AU** (8.1 g).

Step 2: Preparation of 3-[4-Fluoro-3-(2-methoxy-ethoxy)-phenyl]-1-trityl-5-nitro-1H-indazole

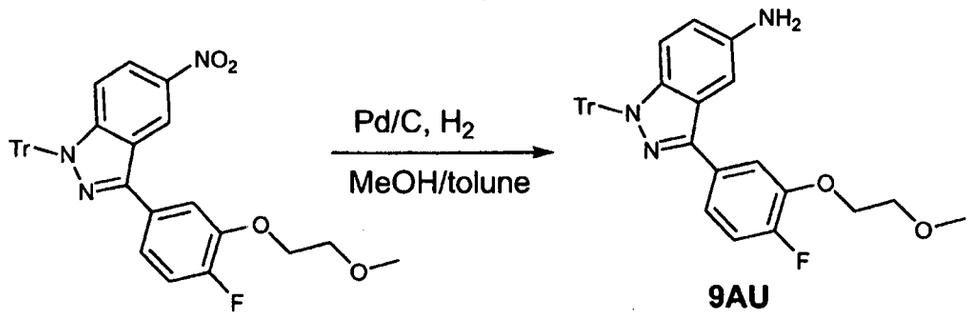


7AU **8AU**

To a stirred mixture of 3-(4-fluoro-3-hydroxyphenyl)-5-nitro-1-trityl-1H-indazole **7AU** (2 g, 3.88 mmol) in DMF (25 mL) was added $CsCO_3$ 1.9 g, 5.82 mmol) and bromoethylmethyl ether (474 µL, 5.04 mmol). The resulting mixture was stirred at rt for overnight then diluted with EtOAc (300 mL), which was washed with brine, dried

($MgSO_4$) and concentrated. Chromatograph on silica gel (2:1, hexanes/EtOAc) gave 3-[4-fluoro-3-(2-methoxy-ethoxy)-phenyl]-1-trityl-5-nitro-1H-indazole **8AU** (1.8 g) as a yellow solid.

Step 3: Preparation of 3-[4-Fluoro-3-(2-methoxy-ethoxy)-phenyl]-1-trityl-1H-indazol-5-ylamine

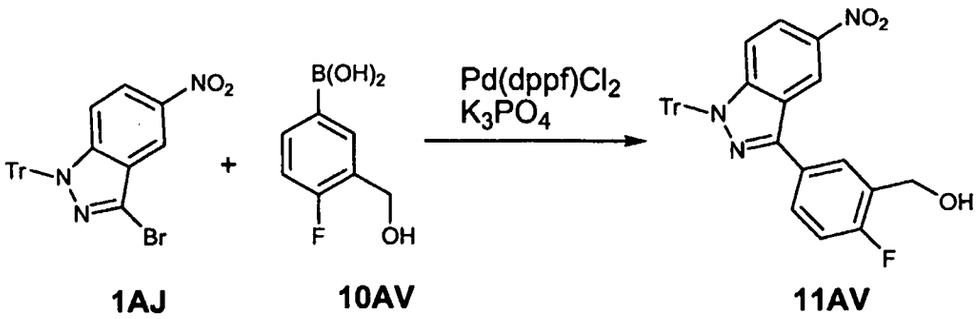


8AU **9AU**

A suspension of **8AU** (890 mg, 1.55 mmol) and catalytic amount of Pd on carbon (5 wt%, 180 mg) in 45 mL of methanol/tolune/CH_2Cl_2 (4:4:1) was stirred under a hydrogen atmosphere for 2 d and filtered through Celite. The filtrate was concentrated and purified on silica gel column (1:1, hexanes/EtOAc) provide 3-[4-fluoro-3-(2-methoxy-ethoxy)-phenyl]-1-trityl-1H-indazol-5-ylamine **9AU** (680 mg) as a white solid.

Preparation 70

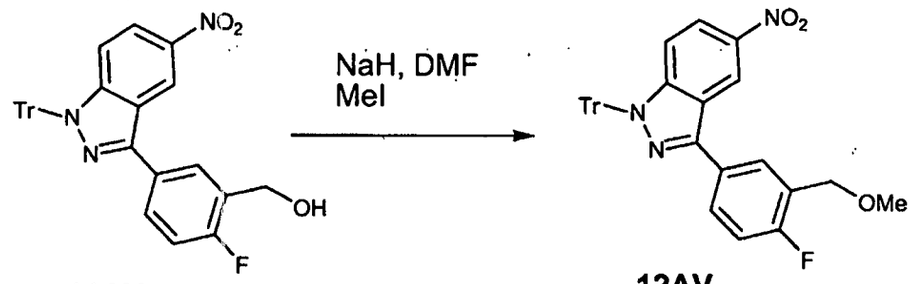
Step 1: Preparation of 3-(4-Fluoro-3-hydroxymethylphenyl)-5-nitro-1-trityl-1H-indazole



1AJ **10AV** **11AV**

A suspension of 3-bromo-5-nitro-1-trityl-1H-indazole **1** (6 g, 12.41 mmol), 4-fluoro-3-hydroxymethylphenylboronic acid **10AV** (2 g, 12.87 mmol), $Pd(dppf)Cl_2$ (800 mg, 0.98 mmol) and K_3PO_4 (6 g, 28.30 mmol) in 124 mL of dioxane/H_2O (25:6) was heated to 80°C for overnight. After removal of most of the solvent, the black residue was diluted with EtOAc (250 mL) and H_2O (60 mL). The resulting mixture was filtered through a pad of Celite. Additional 150 mL of EtOAc was used to wash the Celite cake. The filtrates were combined. The aqueous layer was separated and the organic layer was washed with brine, dried ($MgSO_4$) and concentrated to give crude 3-(4-fluoro-3-hydroxymethylphenyl)-5-nitro-1-trityl-1H-indazole **11AV** (8.2 g) as a greenish yellow solid.

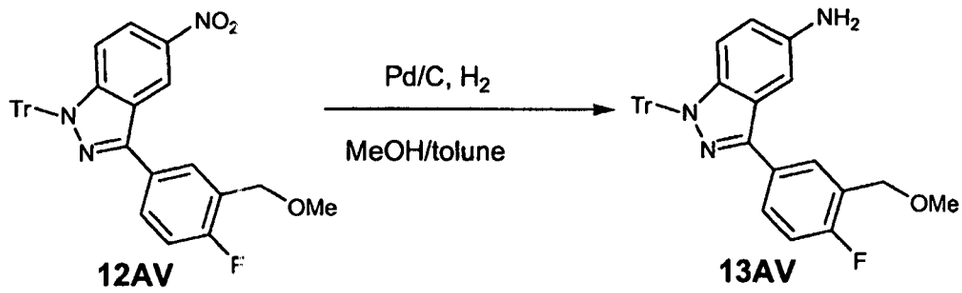
Step 2: Preparation of 3-[4-Fluoro-3-(2-methoxymethyl)-phenyl]-1-trityl-5-nitro-1H-indazole



11AV **12AV**

To a stirred solution of 3-(4-fluoro-3-hydroxymethylphenyl)-5-nitro-1-trityl-1H-indazole **11AV** (5.5 g, 10.4 mmol) in DMF (120 mL) at 0°C under N_2 was added NaH (60% in mineral oil, 500 mg, 12.5 mmol) in portions over 10 min. After 15 min, MeI (1 mL, 16.06 mmol) was added dropwise. The reaction mixture was stirred at 0°C to rt for overnight and quenched with H_2O. The resulting mixture was extracted with EtOAc, washed with brine, dried ($MgSO_4$) and concentrated to give the crude 3-[4-fluoro-3-(2-methoxymethyl)-phenyl]-1-trityl-5-nitro-1H-indazole **12AV** (7.2 g) as a yellow solid.

Step 3: Preparation of 3-[4-Fluoro-3-(2-methoxymethyl)-phenyl]-1-trityl-1H-indazol-5-ylamine

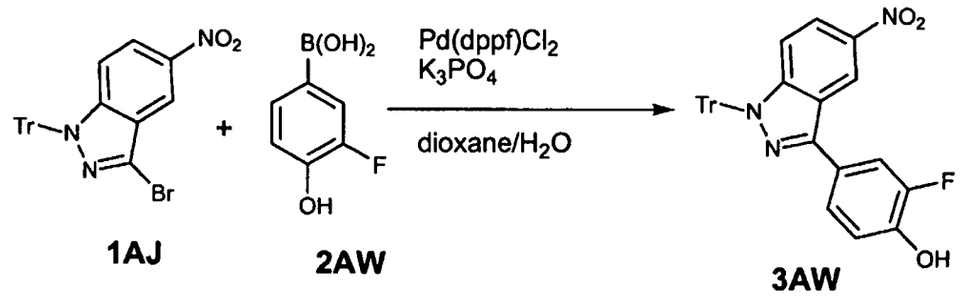


12AV **13AV**

A suspension of the crude 3-[4-fluoro-3-(2-methoxymethyl)-phenyl]-1-trityl-5-nitro-1H-indazole **12AV** (7.2 g) from step 2 and catalytic amount of Pd on carbon (5 wt%, 1.3 g) in 150 mL of methanol/toluene (1:1) was stirred under a hydrogen atmosphere for overnight and filtered through Celite. The filtrate was concentrated and purified on silica gel column (4:1, hexanes/EtOAc) provide 3-[4-fluoro-3-(2-methoxymethyl)-phenyl]-1-trityl-1H-indazol-5-ylamine **13AV** (5 g) as a white solid.

Preparation 71

Step 1: Preparation of 3-(3-Fluoro-4-hydroxyphenyl)-5-nitro-1-trityl-1H-indazole

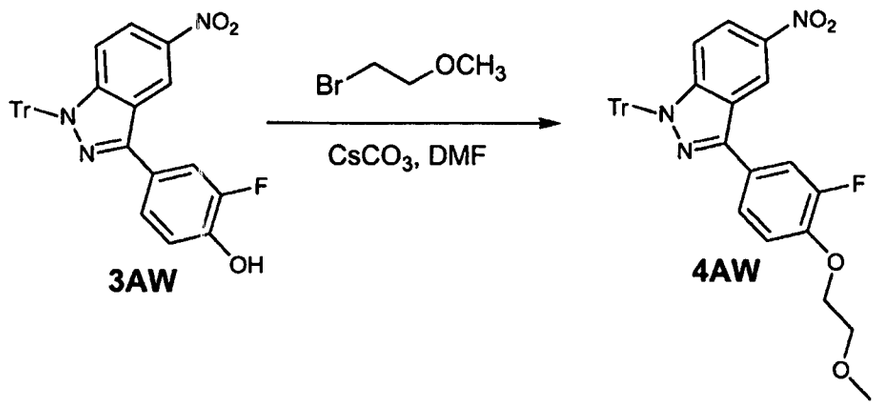


1AJ **2AW** **3AW**

A suspension of 3-bromo-5-nitro-1-trityl-1H-indazole **1AJ** (10.0 g, 20.68 mmol), 3-fluoro-4-hydroxyphenylboronic acid **2AW** (3.55 g, 22.78 mmol), $Pd(dppf)Cl_2$ (1.6 g, 1.96 mmol) and K_3PO_4 (10.6 g, 4.99 mmol) in 200 mL of dioxane/H_2O (4/1) was heated to 75°C for overnight. After removal of most of the solvent, the black residue was diluted with EtOAc (250 mL) and H_2O (60 mL). The resulting mixture was filtered through a pad of Celite. Additional 150 mL of EtOAc was used to wash the Celite cake. The filtrates were combined. The aqueous layer was separated and the organic layer was washed with brine, dried ($MgSO_4$) and concentrated to give a green solid,

which was recrystalized from CH_2Cl_2/hexane to give 3-(3-fluoro-4-hydroxyphenyl)-5-nitro-1-trityl-1H-indazole **3AW** (8.1 g).

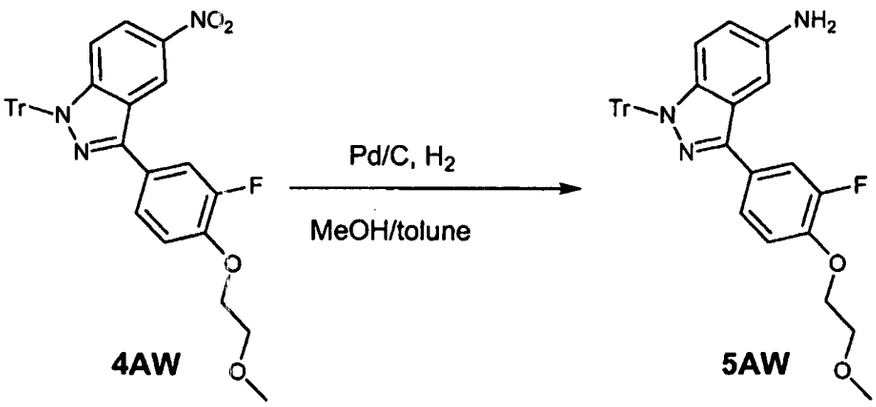
Step 2: Preparation of 3-[3-Fluoro-4-(2-methoxy-ethoxy)-phenyl]-1-trityl-5-nitro-1H-indazole



3AW 4AW

To a stirred mixture of 3-(3-fluoro-4-hydroxyphenyl)-5-nitro-1-trityl-1H-indazole **3AW** (3 g, 5.82 mmol) in DMF (40 mL) was added $CsCO_3$ (2.85 g, 8.75 mmol) and bromoethylmethyl ether (711 µL, 7.57 mmol). The resulting mixture was stirred at rt for overnight then diluted with EtOAc (300 mL), which was washed with brine, dried ($MgSO_4$) and concentrated. Chromatograph on silica gel (2:1, hexanes/EtOAc) gave 3-[3-fluoro-4-(2-methoxy-ethoxy)-phenyl]-1-trityl-5-nitro-1H-indazole **4AW** (2.8 g).

Step 3: Preparation of 3-[3-Fluoro-4-(2-methoxy-ethoxy)-phenyl]-1-trityl-1H-indazol-5-ylamine

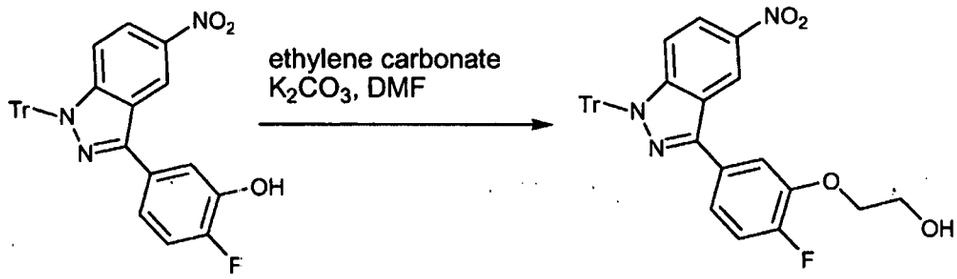


4AW 5AW

A suspension of 3-[3-fluoro-4-(2-methoxy-ethoxy)-phenyl]-1-trityl-5-nitro-1H-indazole **4** (2.8 g, 4.88 mmol) and catalytic amount of Pd on carbon (5 wt%, 0.5 g) in 120 mL of methanol/toluene (1:1) was stirred under a hydrogen atmosphere for 6 h and filtered through Celite. The filtrate was concentrated to provide 3-[3-fluoro-4-(2-methoxy-ethoxy)-phenyl]-1-trityl-1H-indazol-5-ylamine **5** (2.6 g) as an off-white solid.

Preparation 72

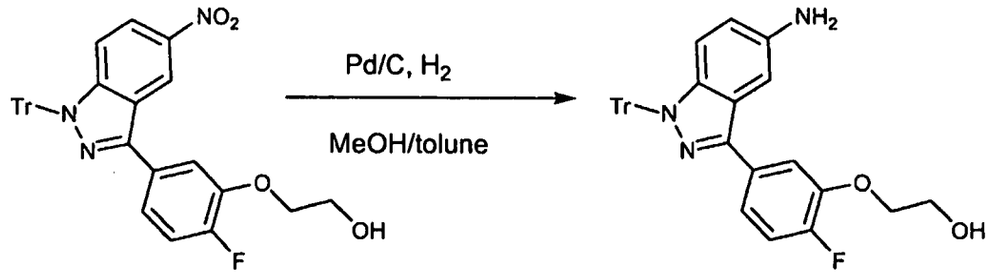
Step 1: Preparation of 3-[4-Fluoro-3-(2-hydroxy-ethoxy)-phenyl]-1-trityl-5-nitro-1H-indazole



7AU **14AX**

A mixture of 3-(4-fluoro-3-hydroxyphenyl)-5-nitro-1-trityl-1H-indazole **7AU** (1.25 g, 2.42 mmol), K_2CO_3 (402 mg, 2.91 mmol) and ethylene carbonate (2.6 mL, 24.00 mmol) in DMF (10 mL) was stirred in a sealed tube at 160°C for 4 h and cooled to rt. H_2O was added to quench the reaction. The resulting mixture was extracted with EtOAc, which was washed with H_2O, brine, dried ($MgSO_4$) and concentrated to give a yellow oil. Chromatograph on silica gel (4:1, hexanes/EtOAc) gave 3-[4-fluoro-3-(2-hydroxy-ethoxy)-phenyl]-1-trityl-5-nitro-1H-indazole **14AX** (1.4 g) as a yellow oil.

Step 2: Preparation of 3-[4-Fluoro-3-(2-hydroxy-ethoxy)-phenyl]-1-trityl-1H-indazol-5-ylamine

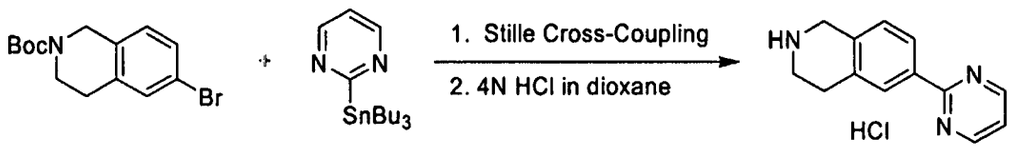


14AX **15AX**

A suspension of 3-[4-fluoro-3-(2-hydroxy-ethoxy)-phenyl]-1-trityl-5-nitro-1H-indazole **14AX** (1.5 g) and catalytic amount of Pd on carbon (5 wt%, 300 mg) in 40 mL of methanol/toluene (1:1) was stirred under a hydrogen atmosphere for 1 d and filtered through Celite. The filtrate was concentrated to provide 3-[4-fluoro-3-(2-hydroxy-ethoxy)-phenyl]-1-trityl-1H-indazol-5-ylamine **15AX** (1.4 g) as an off-white solid.

Preparation 73

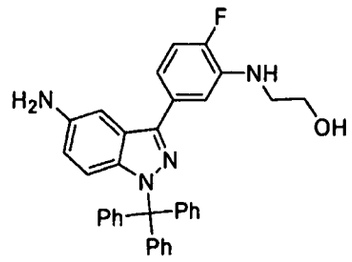
Synthesis of 6-Pyrimidin-2-yl-1,2,3,4-tetrahydro-isoquinoline



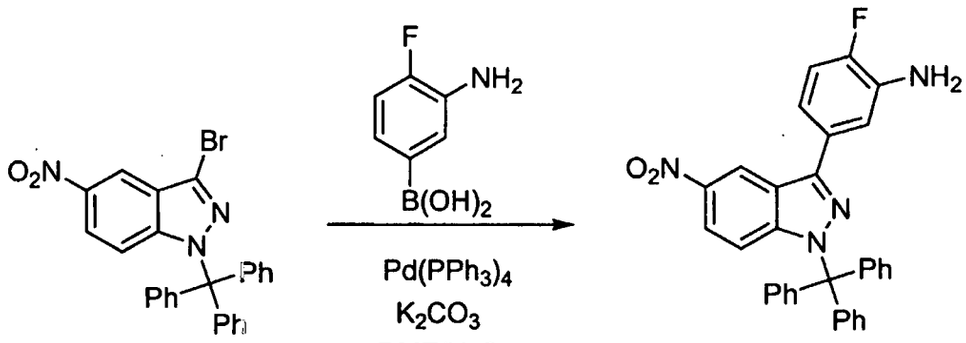
To a Schlenk tube were charged $Pd_2(dba)_3$ (10 mg, 0.01 mmol), bis(tri-*tert*-butylphosphine)palladium (20 mg, 0.04 mmol), CuI (16 mg, 0.08 mmol) and CsF (334 mg, 2.2 mmol). The tube was evacuated under high vacuum and back-filled with nitrogen for three cycles. DMF (2 ml) was introduced, followed by 2-tributylstannylpyrimidine (537 mg, 1.4 mmol). The tube was sealed with a Teflon cap and the reaction mixture was heated with stirring at 120°C for 2 hours. After cooling, the mixture was filtered through Celite, washed with ethyl acetate. Filtrate was washed with water three times, brine and dried ($MgSO_4$). After concentration the residue was purified on silica gel eluting with ethyl acetate in hexanes (0-100%) to give 6-pyrimidin-2-yl-3, 4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester (28 mg). The compound was treated with 4N HCl in dioxane for 30 minutes. After concentration title compound was obtained as hydrochloride salt.

Preparation 74

Preparation of 2-[5-(5-amino-1-trityl-1*H*-indazol-3-yl)-2-fluoro-phenylamino]-ethanol



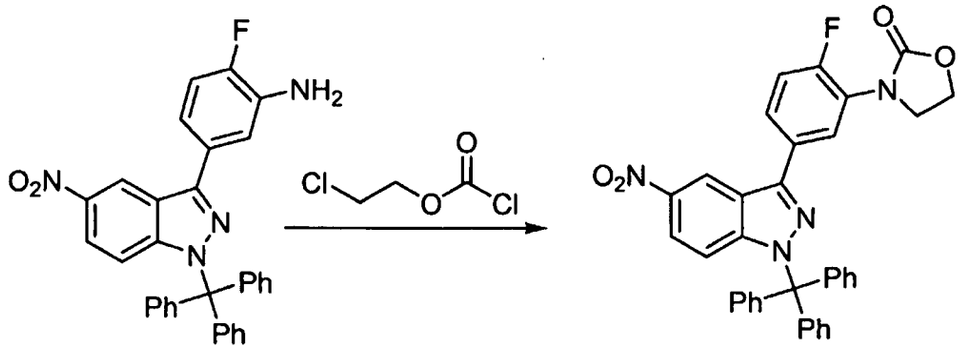
Step 1: Preparation of 2-fluoro-5-(5-nitro-1-trityl-1*H*-indazol-3-yl)-phenylamine



1AJ **2AY**

To a pressure tube were charged compound **1AJ** (1g, 2.1 mmol), 3-amino-4-fluoro-phenylboronic acid (448 mg, 2.89 mmol), $Pd(PPh_3)_4$ (120 mg, 0.1 mmol), K_2CO_3 (1.4 g, 10.1 mmol), DME (8 ml) and water (2 ml). The resulting mixture was degassed with nitrogen for 20 seconds and the tube was sealed with a Teflon cap, and heated at 100 C with stirring overnight. After cooling the reaction mixture was diluted with ethyl acetate, organic layer was isolated, washed with brine. After concentration, the residue was purified on silica gel. Elution with ethyl acetate in hexanes (0-70%) gave compound **2AJ** (1g).

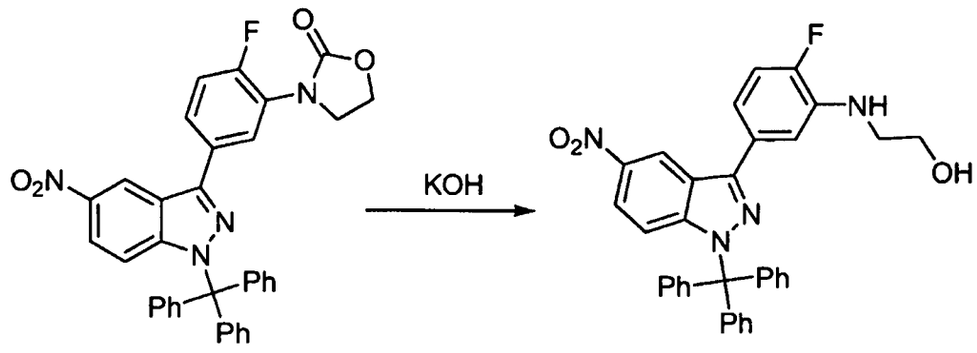
Step 2: Synthesis of 3-[2-fluoro-5-(5-nitro-1-trityl-1*H*-indazol-3-yl)-phenyl]-oxazolidin-2-one



2AY **3AY**

To a mixture of compound **2AY** (1g, 1.95 mmol), Cs_2CO_3 (1.2 g, 3.68 mmol) in acetonitrile (20 ml) was added 2-chloroethyl chloroformate (200 µl, 1.94 mmol) and the resulting mixture was refluxed for 20 minutes. After addition of 2-chloroethyl chloroformate (150 µl) the reaction mixture was allowed to reflux overnight. A solution of 40% KOH was added and the mixture was further refluxed for 2 hours. After cooling the reaction mixture was diluted with ethyl acetate and water, and aqueous layer was separated and extracted with ethyl acetate twice. Combined organic layers were washed with brine and dried ($MgSO_4$). After concentration the residue was purified on silica gel eluting with ethyl acetate in hexanes (0-40%) to give compound **3AY** (1g).

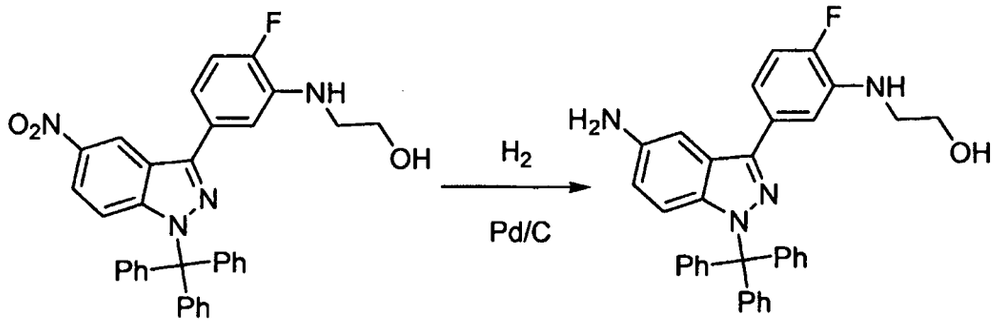
Step 3: Preparation of 2-[2-fluoro-5-(5-nitro-1-trityl-1*H*-indazol-3-yl)-phenylamino]-ethanol



3AY **4AY**

A mixture of compound **3AY** (658 mg) in DME (15 ml), MeOH (6 ml) and 40% KOH (4 ml) was refluxed overnight. After cooling, the mixture was diluted with ethyl acetate, organic layer was separated, washed with brine and dried ($MgSO_4$). After concentration the residue was purified on silica gel eluting with ethyl acetate in hexanes (0-100%) to give compound **4AY** (559 mg).

Step 4: Preparation of 2-[5-(5-amino-1-trityl-1*H*-indazol-3-yl)-2-fluoro-phenylamino]-ethanol

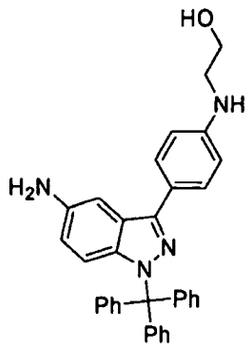


4AY **5AY**

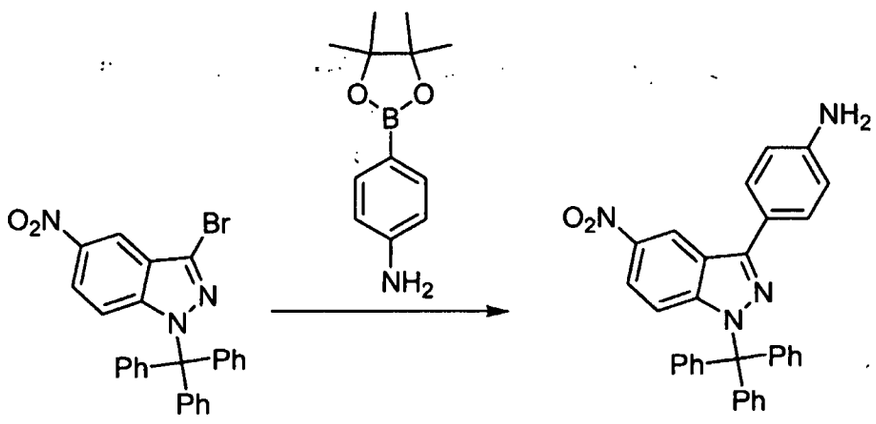
A mixture of compound **4AY** (173 mg), 10% Pd/C (50 mg) in ethyl acetate (10 ml) was stirred under hydrogen (balloon pressure) overnight. After filtration and concentration, the residue was purified on silica eluting with ethyl acetate to provide compound **5AY** (81 mg).

Preparation 75

Synthesis of 2-[4-(5-amino-1-trityl-1*H*-indazol-3-yl)-phenylamino]-ethanol



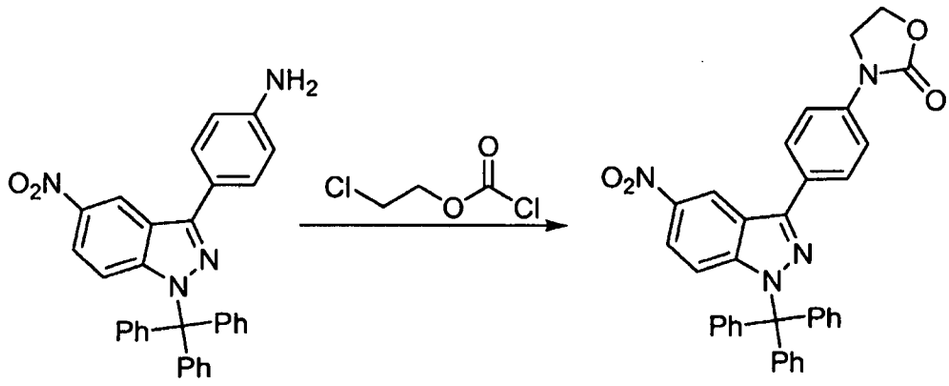
Step 1: Preparation of 4-(5-nitro-1-trityl-1*H*-indazol-3-yl)-phenylamine



1AJ **2AZ**

To a pressure tube were charged with compound **1AJ** (1g, 2.1 mmol), 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenylamine (0.635 g, 2.9 mmol), $Pd(PPh_3)_4$ (0.12 g, 0.1 mmol), K_2CO_3 (1.4 g, 10.1 mmol), DME (8 ml) and water (2 ml). The resulting mixture was degassed with nitrogen briefly and the tube was sealed with a Teflon cap, and heated at 100 C with stirring overnight. After cooling, the reaction mixture was diluted with ethyl acetate, organic layer was isolated, washed with brine. After concentration, the residue was purified on silica gel. Elution with ethyl acetate in hexanes (0-70%) gave compound **2AZ** (0.956 g).

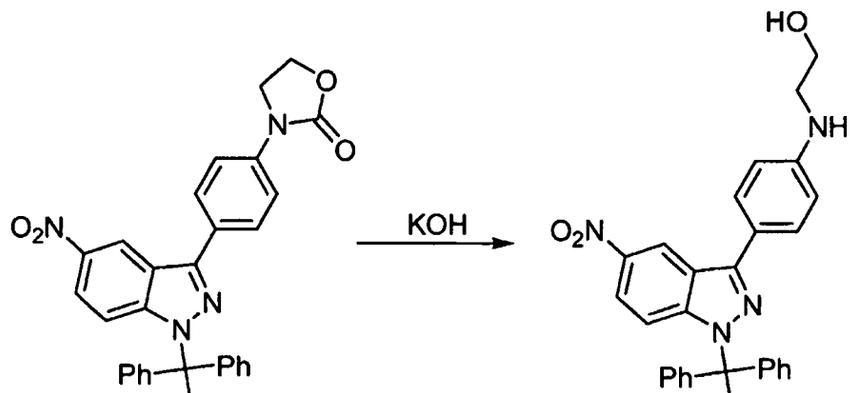
Step 2: Preparation of 3-[4-(5-nitro-1-trityl-1*H*-indazol-3-yl)-phenyl]-oxazolidin-2-one



2AZ **3AZ**

To a mixture of compound **2AZ** (409 mg, 0.82 mmol), 10% NaOH (2 ml) in DME (8 ml) was added 2-chloroethyl chloroformate (102 µl, 1 mmol) and the resulting mixture was stirred at rt for overnight. The mixture was diluted with ethyl acetate and water, and aqueous layer was separated and extracted with ethyl acetate twice. Combined organic layers were washed with brine and dried ($MgSO_4$). After concentration the residue was purified on silica gel eluting with ethyl acetate in hexanes (0-80%) to give compound **3AZ** (340 mg).

Step 3: Preparation of 2-[4-(5-nitro-1-trityl-1*H*-indazol-3-yl)-phenylamino]-ethanol

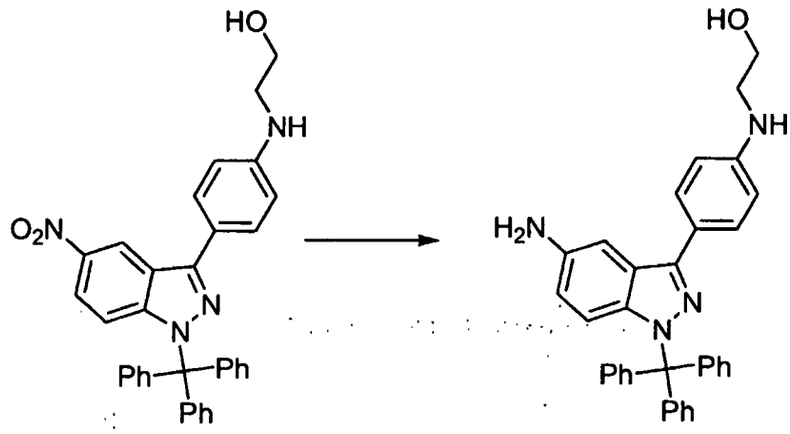


3AZ **4AZ**

A mixture of compound **3AZ** (340 mg) in DME (6 ml), MeOH (4 ml) and 40% KOH (2 ml) was refluxed for two hours. After cooling, solvents were removed, diluted

with water, extracted with dichloromethane three times, combined organic layers were washed with brine and dried ($MgSO_4$). After concentration the residue was purified on silica gel eluting with ethyl acetate in hexanes (0-100%) to give compound **4AZ** (280 mg).

Step 4: Preparation of 2-[4-(5-amino-1-trityl-1*H*-indazol-3-yl)-phenylamino]-ethanol

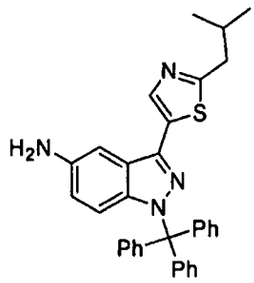


4AZ **5AZ**

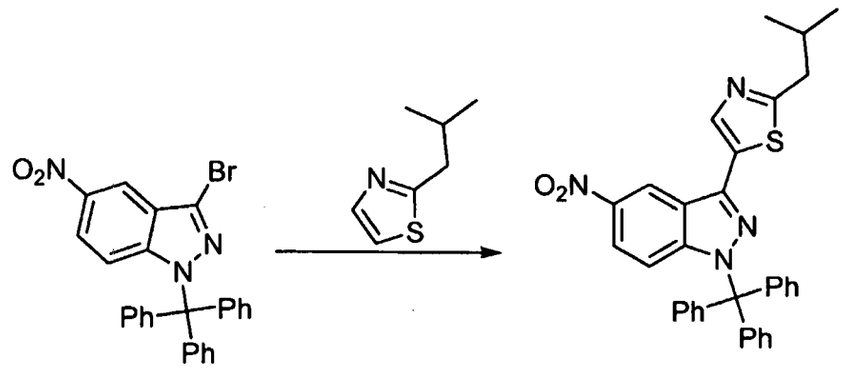
A mixture of compound **4AZ** (280 mg), 10% Pd/C (70 mg) in ethanol (10 ml) was stirred at 45^{0}C under hydrogen (balloon pressure) overnight. After filtration and concentration, the residue was purified on silica eluting with ethyl acetate to provide compound **5AZ** (224 mg).

Preparation 76

Synthesis of 3-(2-Isobutyl-thiazol-5-yl)-1-trityl-1*H*-indazol-5-ylamine



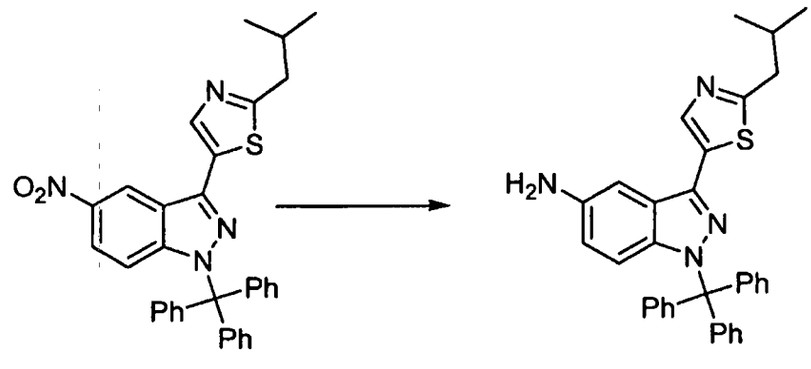
Step 1: Preparation of 3-(2-Isobutyl-thiazol-5-yl)-5-nitro-1-trityl-1*H*-indazole



1AJ **2BA**

To a pressure tube were charged compound **1AJ** (194 mg, 0.4 mmol), $Pd(OAc)_2$ (90 mg, 0.4 mmol), (2-biphenyl)-di-*tert*-butylphospine (12 mg, 0.1 mmol), C_2CO_3 (313 mg, 0.96 mmol) and the tube was evacuated under vacuum and back-filled with nitrogen. Dioxane (4 ml) was introduced, followed by 2-isobutylthiazole (114 µl, 0.8 mmol). The tube was sealed and heated at 100 ^{0}C with stirring overnight. After cooling the reaction mixture was filtered through Celite, washed with ethyl acetate several times. Filtrate was concentrated and the residue was purified on silica gel. Elution with ethyl acetate in hexanes (0-30%) gave compound **2BA** (124 mg).

Step 2: Preparation of 3-(2-Isobutyl-thiazol-5-yl)-1-trityl-1*H*-indazol-5-ylamine



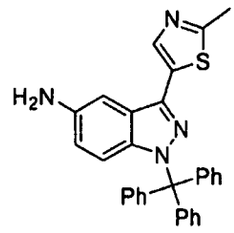
2BA **3BA**

A mixture of compound **2BA** (180 mg), 10% Pd/C (50 mg) in ethyl acetate (8 ml) was stirred at 45^{0}C under hydrogen (balloon pressure) overnight. After filtration

and concentration, the residue was purified on silica eluting with ethyl acetate to provide compound **3BA** (75 mg).

Preparation 77

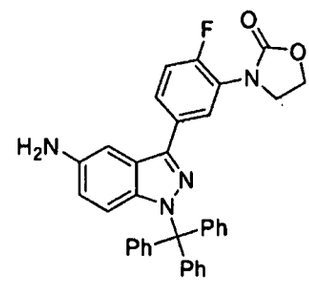
Synthesis of 3-(2-methyl-thiazol-5-yl)-1-trityl-1*H*-indazol-5-ylamine

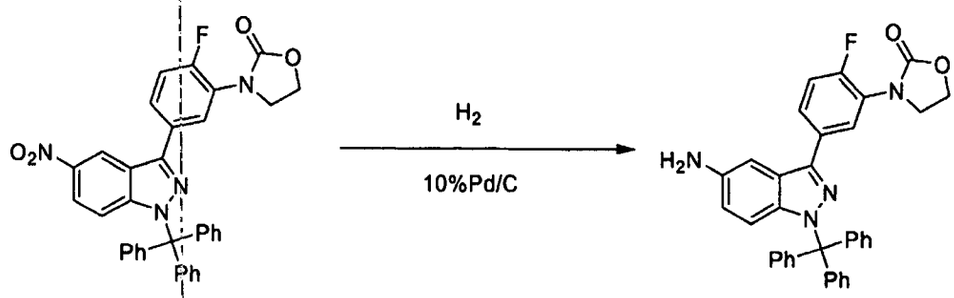


Preparation of 3-(2-methyl-thiazol-5-yl)-1-trityl-1*H*-indazol-5-ylamine was similar to that of 3-(2-isobutyl-thiazol-5-yl)-1-trityl-1*H*-indazol-5-ylamine as illustrated above except using 2-methylthiazole in the cross-coupling reaction.

Preparation 78

Synthesis of 3-[5-(5-amino-1-trityl-1H-indazol-3-yl)-2-fluoro-phenyl]-oxazolidin-2-one

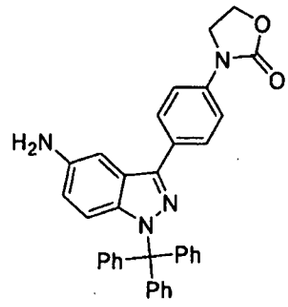


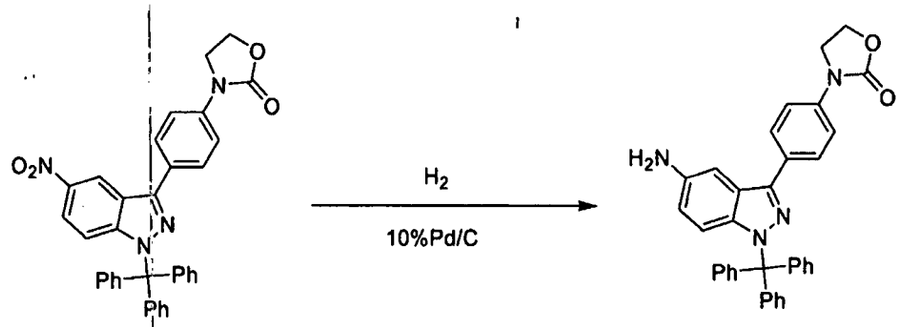


The hydrogenation of 3-[2-fluoro-5-(5-nitro-1-trityl-1*H*-indazol-3-yl)-phenyl]-oxazolidin-2-one was conducted in similar way to the other examples as illustrated above.

Preparation 79

Synthesis of 3-[4-(5-amino-1-trityl-1*H*-indazol-3-yl)-phenyl]-oxazolidin-2-one

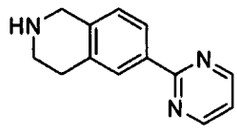


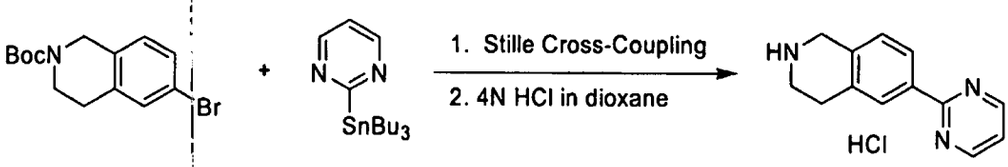


The hydrogenation of 3-[4-(5-nitro-1-trityl-1*H*-indazol-3-yl)-phenyl]-oxazolidin-2-one was conducted in similar way to the other examples as illustrated above.

Preparation 80

Synthesis of 6-Pyrimidin-2-yl-1,2,3,4-tetrahydro-isoquinoline

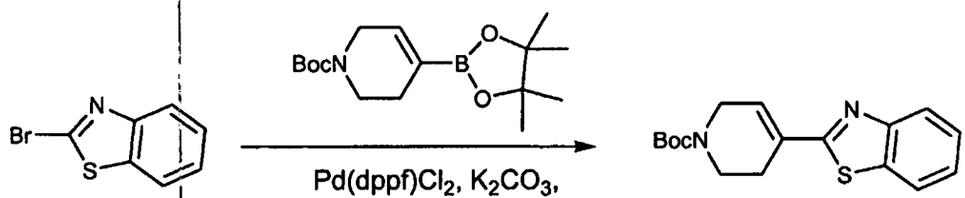




To a Schlenk tube were charged $Pd_2(dba)_3$ (10 mg, 0.01 mmol), bis(tri-*tert*-butylphosphine)palladium (20 mg, 0.04 mmol), CuI (16 mg, 0.08 mmol) and CsF (334 mg, 2.2 mmol). The tube was evacuated under high vacuum and back-filled with nitrogen for three cycles. DMF (2 ml) was introduced, followed by 2-tributylstannylpyrimidine (537 mg, 1.4 mmol). The tube was sealed with a Teflon cap and the reaction mixture was heated with stirring at 120°C for 2 hours. After cooling, the mixture was filtered through Celite, washed with ethyl acetate. Filtrate was washed with water three times, brine and dried ($MgSO_4$). After concentration the residue was purified on silica gel eluting with ethyl acetate in hexanes (0-100%) to give 6-pyrimidin-2-yl-3, 4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester (28 mg). The compound was treated with 4N HCl in dioxane for 30 minutes. After concentration title compound was obtained as hydrochloride salt.

Preparation 81

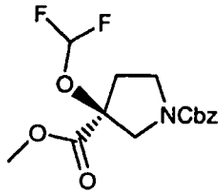
Preparation of 4-Benzothiazol-2-yl-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester (Compound 21BB)



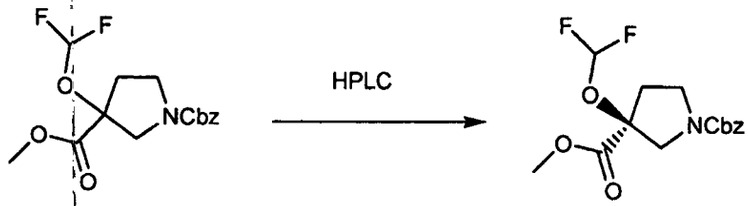
22BB **21BB**

A mixture of 2-bromo-benzothiazole (0.38 g, 1.1 mmol), 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester (0.5 g, 1.62 mmol), potassium carbonate (0.67 g, 4.85 mmol), $Pd(dppf)Cl_2$ (0.132 g, 0.16 mmol) and 4/1 /dioxane/water (10 ml) was degassed for 15 minutes. Then it was heated at 90 °C for overnight. Cooled to room temperature and diluted with EtOAc (200 mL). The organic layer was washed with water (100 ml), dried over Na_2SO_4, filtered and concentrated. The residue was purified on silica gel to give the desired product **21BB** (0.4 g, 78%).

Preparation 82



16BC

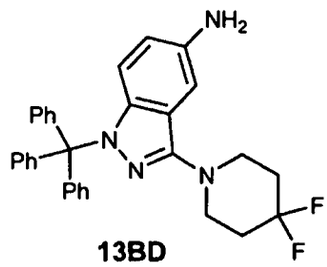


17BC **16BC**

The Compound **17BC** is prepared following a procedure similar to that of Preparation 37 Steps 1 to 4 by substituting 3-oxo-pyrrolidine-1-carboxylic acid benzyl ester for 3-oxo-pyrrolidine-1-carboxylic acid tert-butyl ester in Step 1 of Ppreparation 37. Compound **17BC** was separated on HPLC using ChiralCel AS column eluting with 25% isopropanol/ 75% hexane. The first peak (retention time 46 minutes) was the desired product **16BC**.

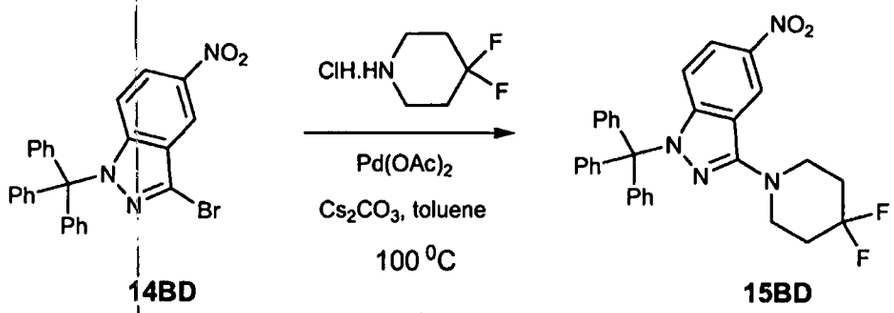
Preparation 83

Preparation of 3-(4,4-Difluoro-piperidin-1-yl)-1-trityl-1*H*-indazol-5-ylamine (Compound 13BD)



13BD

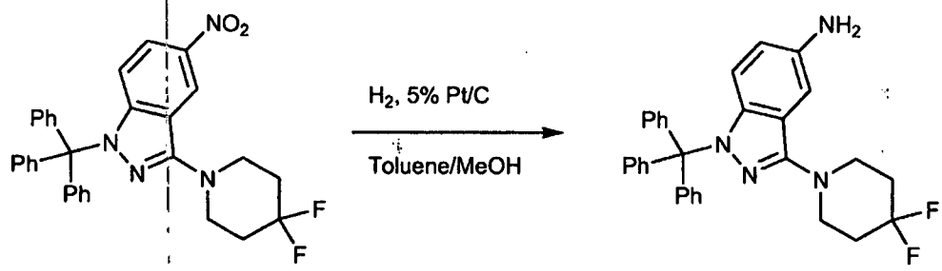
Step 1: Preparation of 3-(4,4-Difluoro-piperidin-1-yl)-5-nitro-1-trityl-1*H*-indazole



14BD **15BD**

The Compound 14BD was converted to Compound 15BD using the procedure as described for the preparation of Compound 4AD (Preparation 49 Step 2) from Compound 2AD (Preparation 49 Step 2).

Step 2

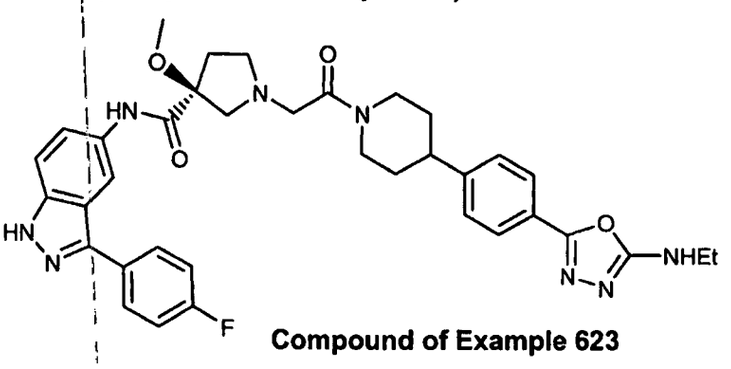


15BD **13BD**

A mixture of Compound **15BD** (1.6 g, 3.1 mmol), 1/1 toluene/MeOH (25 mL) and 5% Pt/C (0.726 mg) was stirred under hydrogen at room temperature for 18 hours. Reaction mixture was filtered over celite and the filtrate was concentrated. The residue was purified on silica gel eluting with 5% MeOH/CH_2Cl_2 to give the desired product **13BD** (1.38 g, 91%).

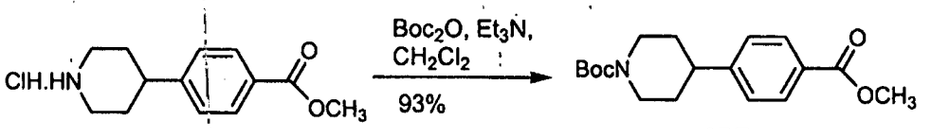
Example 623

Preparation of 1-(2-{4-[4-(5-Ethylamino-[1,3,4]oxadiazol-2-yl)-phenyl]-piperidin-1-yl}-2-oxo-ethyl)-3-methoxy-pyrrolidine-3-carboxylic acid [3-(4-fluoro-phenyl)-1*H*-indazol-5-yl]-amide (Compound of Example 623)



Compound of Example 623

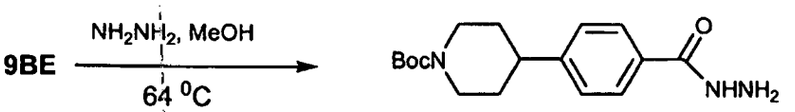
Step 1: Preparation of 4-(4-Methoxycarbonyl-phenyl)-piperidine-1-carboxylic acid *tert*-butyl ester



8BE **9BE**

A mixture of Compound **8BE** (3 g, 11.73 mmol), CH_2Cl_2 (30 mL), triethyl amine (4.9 mL, 35.19 mmol) and di-*tert*-butyl dicarbonate (3.83 g, 17.55 mmol) was stirred at room temperature for 3 hours. Diluted with CH_2Cl_2 (100 mL) and washed with water (100 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified on silica gel eluting with 100% EtOAc to give the desired product **9BE** (3.5 g, 93%).

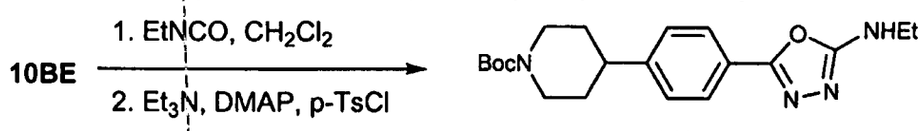
Step 2: Preparation of 4-(4-Hydrazinocarbonyl-phenyl)-piperidine-1-carboxylic acid *tert*-butyl ester



10BE

The Compound **9BE** was converted to Compound **10BE** using the procedure as described for the preparation of Compound **2AR** from Compound **1AR** (Example 622 Step 1).

Step 3: Preparation of 4-[4-(5-Ethylamino-[1,3,4]oxadiazol-2-yl)-phenyl]-piperidine-1-carboxylic acid *tert*-butyl ester (Compound 11BE)



11BE

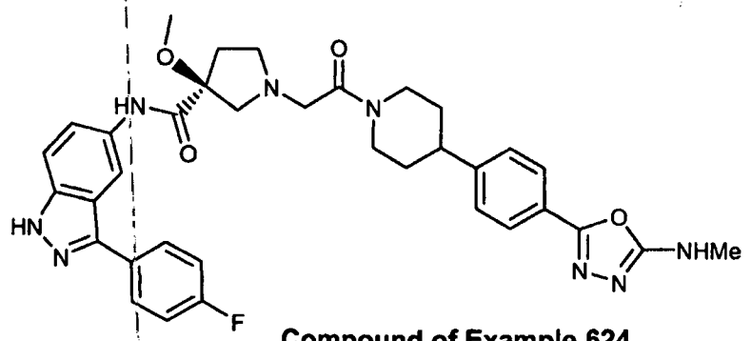
The Compound **10BE** was converted to Compound **11BE** using the procedure as described for the preparation of Compound **3AR** from Compound **2AR** (Example 622 Step 2).

Step 4:

The Compound **11BE** was converted to the compound of Example **623** using the procedure as described for the preparation of the compound of Example **622** from Compound **4AR**.

Example 624

Preparation of 1-(2-{4-[4-(5-methylamino-[1,3,4]oxadiazol-2-yl)-phenyl]-piperidin-1-yl}-2-oxo-ethyl)-3-methoxy-pyrrolidine-3-carboxylic acid [3-(4-fluoro-phenyl)-1*H*-indazol-5-yl]-amide (Compound of Example 624)



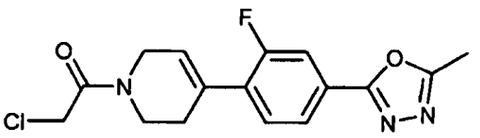
Compound of Example 624

The compound of Example **624** was prepared from Compound **10BE** (Example 623 Step 3) using the procedure as described for the preparation of the compound of

Example **623** from Compound **10BE** but using methyl isocyanate in place of ethyl isocyanate.

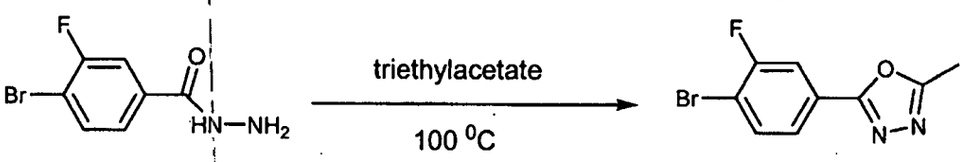
Preparation 84

Preparation of of 2-Chloro-1-{4-[2-Fluoro-4-(5-methyl-[1,3,4]oxadiazol-2-yl)-phenyl]-3,6-dihydro-2*H*-pyridin-1-yl}-ethanone (Compound 20BF)



Compound 20BF

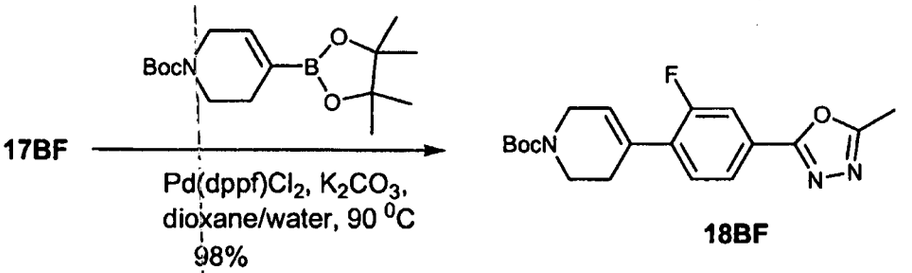
Step 1: Preparation of of 2-(4-Bromo-3-fluoro-phenyl)-5-methyl-[1,3,4]oxadiazole



2BF 32% **17BF**

A mixture of Compound **2BF** (0.9 g, 2.53 mmol) and triethylacetate (5 mL) was heated at 100 °C for 18 hours. Cooled to room temperature and poured into water (100 mL). Extracted with EtOAc (100 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated. The residue was purified on silica gel eluting with 20% EtOAc/ hexane to give the desired product **17BF** (0.36 g, 32%).

Step 2: Preparation of of 4-[2-Fluoro-4-(5-methyl-[1,3,4]oxadiazol-2-yl)-phenyl]-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl

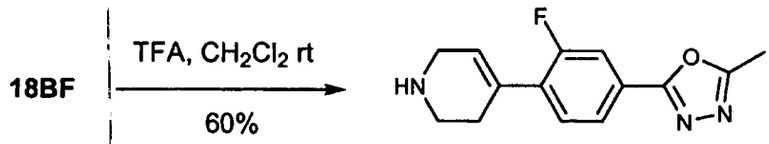


18BF

A mixture of Compound **17BF** (0.34 g, 0.99 mmol), 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester (0.37 g, 1.19 mmol), potassium carbonate (0.41 g, 2.97 mmol), $Pd(dppf)Cl_2$ (0.081 g,

0.099 mmol) and 4/1 /dioxane/water (10 ml) was degassed for 15 minutes. Then it was heated at 90 °C for overnight. Cooled to room temperature and diluted with EtOAc (200 ml). The organic layer was washed with water (100 ml), dried over Na_2SO_4, filtered and concentrated. The residue was purified on silica gel to give the desired product **18BF** (0.35 g, 98%).

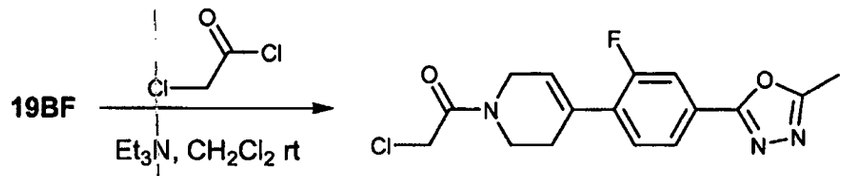
Step 3: Preparation of 4-[2-Fluoro-4-(5-methyl-[1,3,4]oxadiazol-2-yl)-phenyl]-1,2,3,6-tetrahydro-pyridine



19BF

The Compound **18BF** (0.44 g, 1.13 mmol) was converted to Compound **19BF** using the procedure as described for the preparation of Compound **5AR** from Compound **4AR** (Example 622 Step 4).

Step 4:

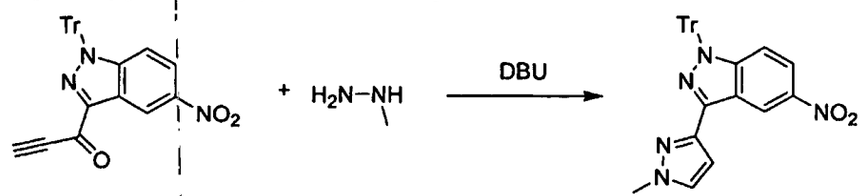


20BF

The Compound **19BF** (0.44 g, 1.13 mmol) was converted to Compound **20BF** using the procedure as described for the preparation of Compound **6AR** from Compound **5AR** (Example 622 Step 5).

Preparation 85

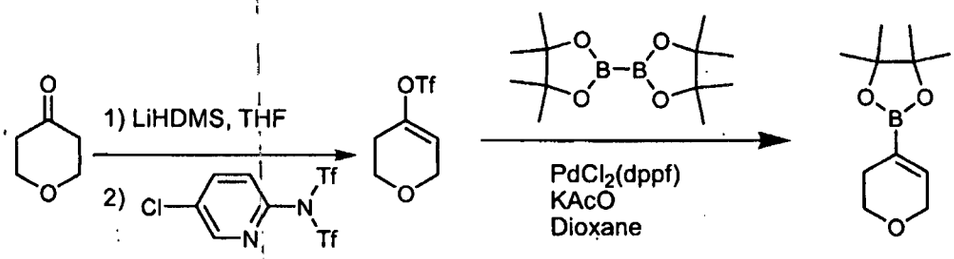
3-(1-Methyl-1H-pyrazol-3-yl)-5-nitro-1-trityl-1H-indazole

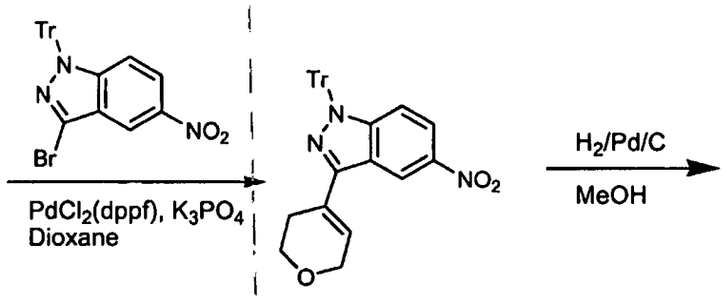


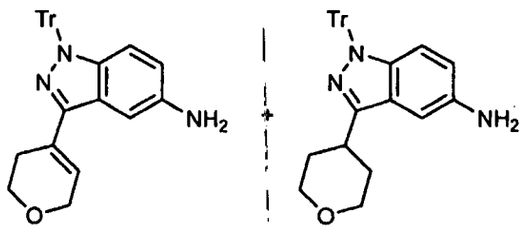
A mixture of 1-(5-nitro-1-trityl-1*H*-indazol-3-yl-)-propynone (0.5g, 1.09mmol), methyl hydrazine hydrochloride (1.75mmol) and DBU (1.6ml, 10.9mmol) in acetonitrile (10ml) was heated at 120°C for 50 minutes under microwave. It was then cooled to room temperature and diluted with DCM (60ml). The organic layer was washed with water (10ml), dried over $MgSO_4$, filtered and concentrated. The residue was purified on silica gel eluting with 1/1 EtOAc/Hexane to give the desired product (0.42 g, 79%). MS (ESMS, M+H 486)

Reduction of the 5-nitro compound was achieved by hydrogenation as stated previously

Preparation 63







Step 1: **Preparation of Trifluoro-methanesulfonic acid 3,6-dihydro-2H-pyran-4-yl ester**

To a solution of 4-tetrahydropyranone (2g, 0.02 mol) in THF (10 mL) at -78 °C, LiHMDS (1 M, 11 ml) was added dropwise through a syringe. The formed solution was then stirred at -78 °C for about 1 hour. The reaction was warmed up to room temperature briefly and was cooled back to -78 °C. Then 2-[N, N-bis(trifluoromethylsulfonyl)amino]-5-chloropyrine (7.85 g, 0.02 mol) was added in four portions. The resulted reaction mixture was gradually warmed up to room temperature and was stirred for overnight. After removal of solvent, the residue was purified using chromatography (eluted with DCM/Hexane = 80/20) to give product as a colorless oil (3g).

Step 2: **Preparation of 4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-3,6-dihydro-2H-pyran**

A 250 mL round bottom flask containing trifluoro-methanesulfonic acid 3, 6-dihydro-2H-pyran-4-yl ester (2.7 g, 11.6 mmol), $PdCl_2$(dppf) (440 mg, 0.6 mmol) and potassium acetate (3g, 36 mmol) in dioxane (20 mL) was flushed with Ar three times. The reaction mixture was heated at 80 °C for overnight. After the reaction was cooled to room temperature, the reaction mixture was filter through a column packed with celite and the filtrate was concentrated. The residue was purified using column chromatography (10 % hexane in dichloromethane) and product was obtained as white solid (2g, 81% yield).

Step 3: **Preparation of 3-(3,6-Dihydro-2H-pyran-4-yl)-5-nitro-1-trityl-1H-indazole**

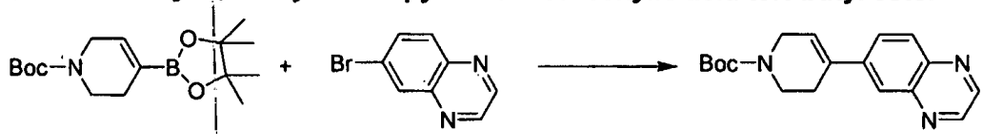
A mixture containing 4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-3,6-dihydro-2H-pyran (0.8 g, 3.8 mmol), 3-Bromo-5-nitro-1-trityl-1H-indazole (2g, 4.0 mmol), $PdCl_2$(dppf) (150 mg, 0.2 mmol) and potassium phosphate (2.6 g, 12 mmol) in dioxane (10 mL) was flushed with Ar and was heated at 80 °C for overnight under Ar. LC-MS indicated the completion of reaction and the mixture was filter through celite. The filtrate was concentrated and was purified on a column (10 hexane in dichloromethane) to give 1.2 g of product (64 % yield).

Step 4: Preparation of 3-(3,6-Dihydro-2H-pyran-4-yl)-1-trityl-1H-indazol-5-ylamine and 3-(Tetrahydro-pyran-4-yl)-1-trityl-1H-indazol-5-ylamine

To a solution of 3-(3,6-Dihydro-2H-pyran-4-yl)-5-nitro-1-trityl-1H-indazole (100 mg, 0.2 mmol) in methanol was added and Pd/C (10%, 20 mg). The reaction mixture was evacuated under vacuum and hydrogen gas was filled. After repeated three times the reaction was kept under hydrogen atmosphere overnight at room temperature. LCMS showed the starting material was consumed completely and both 3-(3,6-dihydro-2H-pyran-4-yl)-1-trityl-1H-indazol-5-ylamine and 3-(tetrahydro-pyran-4-yl)-1-trityl-1H-indazol-5-ylamine were obtained. The two products were separated using prep-HPLC to give both product in 60 % and 40 % yield respectively.

Preparation 87

4-Quinoxalin-6-yl-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester

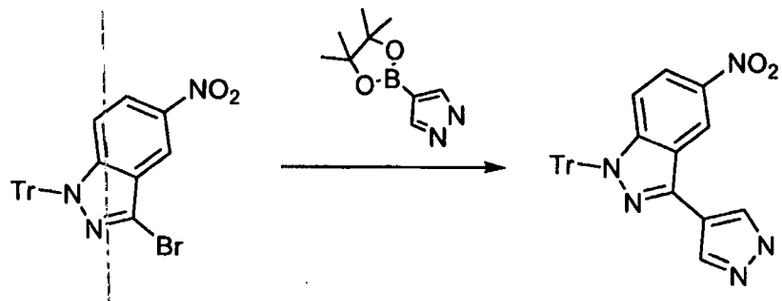


A solution containing 6-bromo-quinoxaline (417 mg, 2.0 mmol), 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester (600 mg, 1.94 mmol), tetrakis [triphenylphosphine] palladium (108 mg, 0.1 mmol) and sodium carbonate (2 M solution, 3 mL) in 5 mL of dioxane/ethanol/water (7:3:1) was heated at 160 °C using microwave reactor for 15 minutes. After the reaction, ethylacetate was added and the mixture was filtered, washed with water. After concentration under vacuum, the product was purified using column chromatography (5% methanol in dichloromethane)

Preparation 88

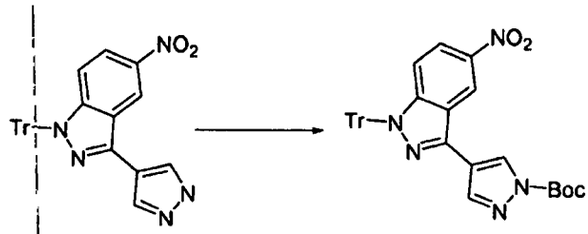
1-N Trityl-4-(5-Amino-1-methyl-1H-indazol-3-yl)-pyrazole-1-carboxylic acid tert-butyl ester

Step 1



To a vial containing 3-bromo-5-nitro-1-trityl-1H-indazole (1.45 g, 3.00 mmol), 4-(4,4,5,5-TETRAMETHYL-1,3,2-DIOXABOROLAN-2-YL)-1H-PYRAZOLE (0.873 g, 4.50 mmol) [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II),complex with dichloromethane (1:1) (0.245 g, 0.300 mmol) and Potassium phosphate (1.59 g, 7.50 mmol) in a mixture of 1,4-Dioxane (25 mL, 320 mmol) Water (12 mL, 670 mmol) was degassed under an atmosphere of Nitrogen. This rxn mixture was was heated at 80 °C overnight under an atmosphere of Nitrogen. TLC (20%EtOAc/hexane) showed starting material. MS showed (M+H) at 472. The rxn was diluted with EtOAc and Water (50/50 mL) and filtered through Celite. The org. layer was washed with water, dried over Magnesium sulfate (2 g, 20 mmol) and rotavap to give a crude, 2.2g. The crude was chrom. (30%EtOAc/Hexane) on Biotage (40L) to obtain the product (fraction 2), M+H at 472, 5-nitro-3-(1H-pyrazol-4-yl)-1-trityl-1H-indazole (0.54 g; Yield = 38%)

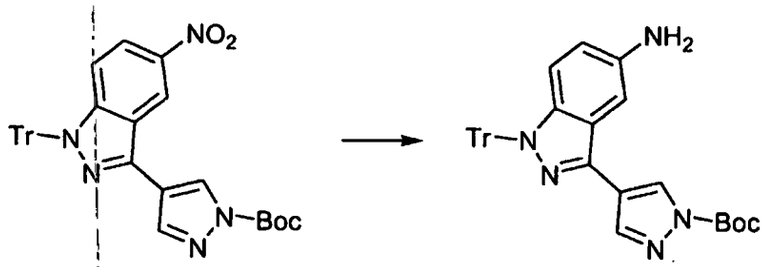
Step 2



Into a Round bottom flask was added 5-nitro-3-(1H-pyrazol-4-yl)-1-trityl-1H-indazole (0.390 g, 0.827 mmol, recovered unreacted starting material, Methylene

chloride (5.00 mL, 78.0 mmol), Di-tert-Butyldicarbonate (0.228 g, 1.04 mmol) 4-Dimethylaminopyridine (0.127 g, 1.04 mmol) The rxn was stirred for 2 days under an atmosphere of Nitrogen. TLC (20%EtOAc/Hexane) showed rxn complete. The rxn was loaded onto Biotage 40S and eluted with 20%EtOAc/hexane to give tert-butyl 4-(5-nitro-1-trityl-1H-indazol-3-yl)-1H-pyrazole-1-carboxylate (0.44 g; Yield = 93%)

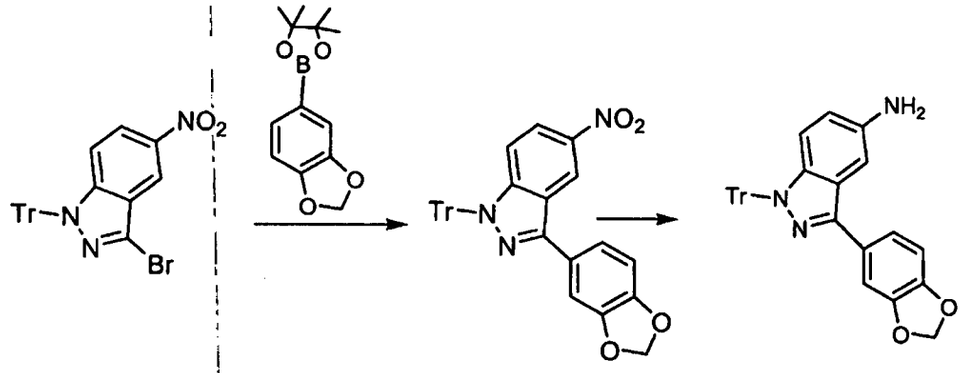
Step 3



Into a Round bottom flask was added tert-butyl 4-(5-nitro-1-trityl-1H-indazol-3-yl)-1H-pyrazole-1-carboxylate (0.440 g, 0.770 mmol) and 10 mL of MeOH and 5 mL of EtOAc followed by Palladium (0.100 g, 0.000470 mmol). The rxn was degassed under Hydrogen (2000 mL, 90 mmol) in ballon, was stirred overnight. TLC (20%EtOAc/Hexane) and MS showed rxn complete. The rxn was filtered through Celite and was rotovaped to dryness to give tert-butyl 4-(5-amino-1-trityl-1H-indazol-3-yl)-1H-pyrazole-1-carboxylate (0.400 g; Yield = 95.9%)

Preparation 89

Preparation of 1-N-Trityl-3-Benzo[1,3]dioxol-5-yl-1-methyl-1H-indazol-5-ylamine

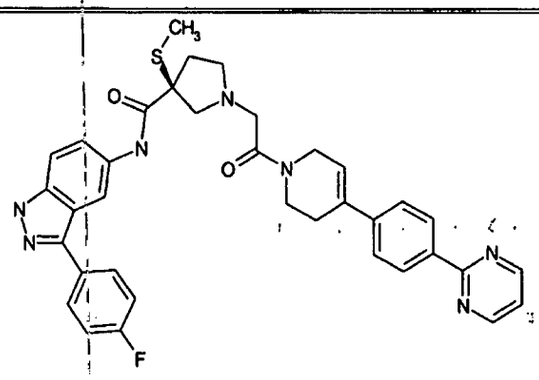
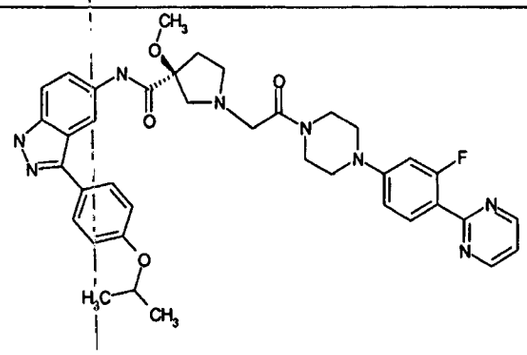
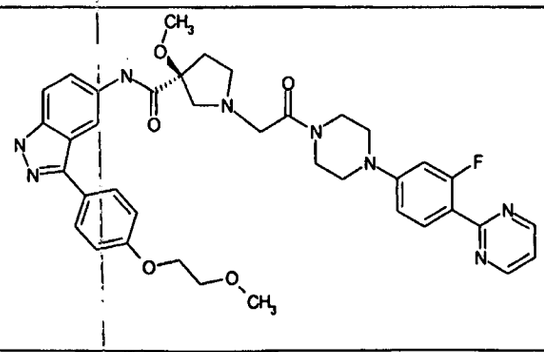


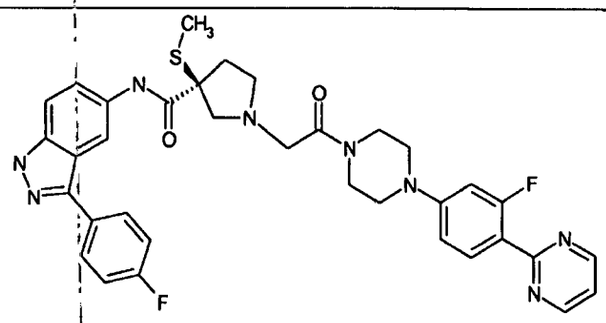
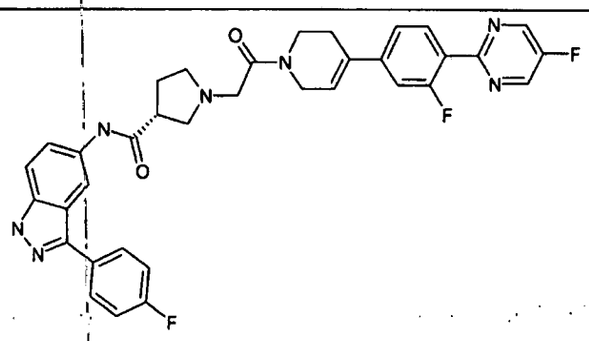
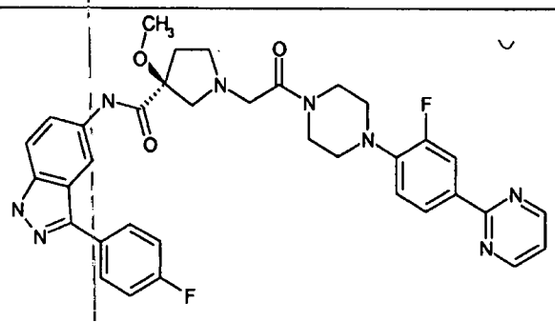
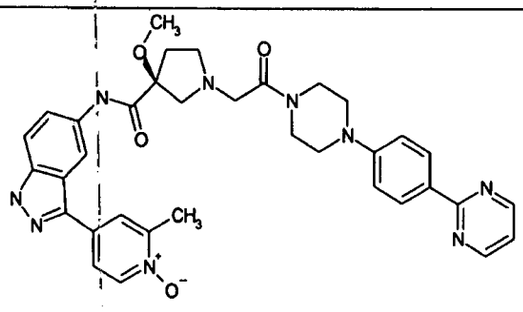
1-N-Trityl-3-Benzo[1,3]dioxol-5-yl-1-methyl-1H-indazol-5-ylamine was prepared by substituting 5-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzo[1,3]dioxole for

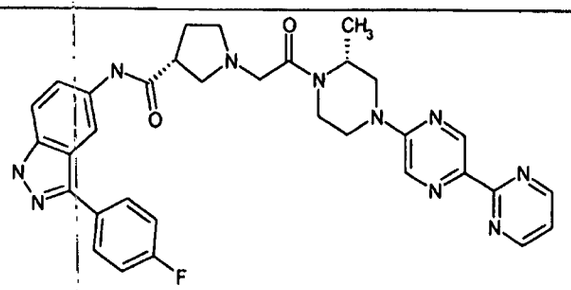
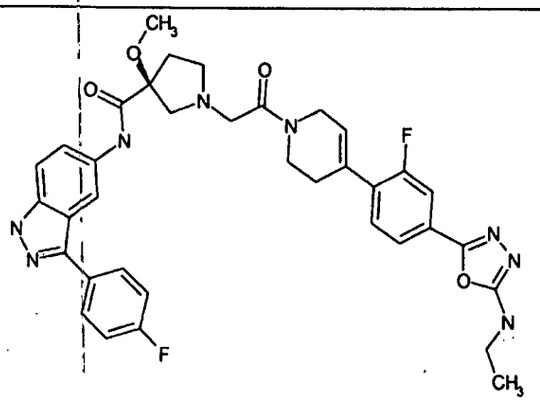
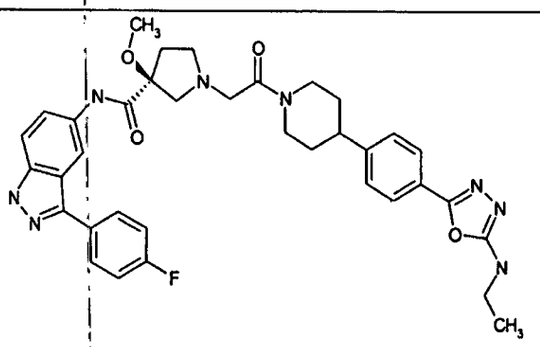
4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-pyrazole in Preparation 88 in Steps 1 & 3.

Table 27 provides data for the compounds of Examples 613 to 623.

Table 27

Ex No.	COMPOUND	M+1	Retention Time (min)
613 (16AA)		648.4	2.8
614 (9AB)		693.4	2.84
615 11AB		709.4	2.54

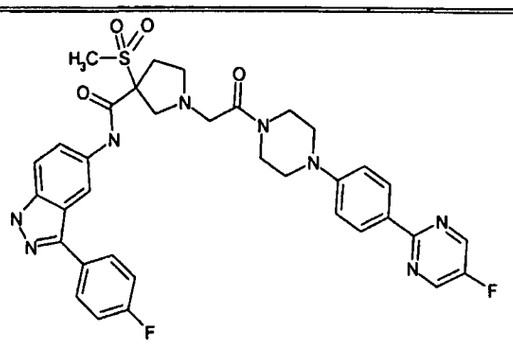
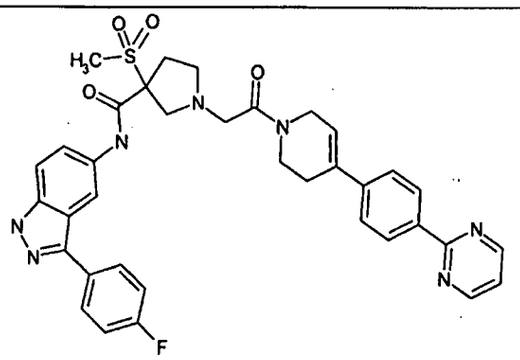
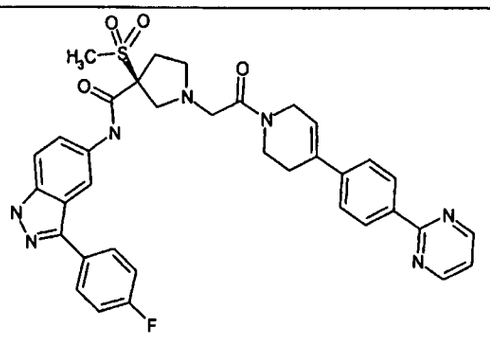
616 (13AB)		669.4	2.75
617 (25AB)		638.4	3.33
619 (33AB)		653.4	2.89
620		648.4	2.12

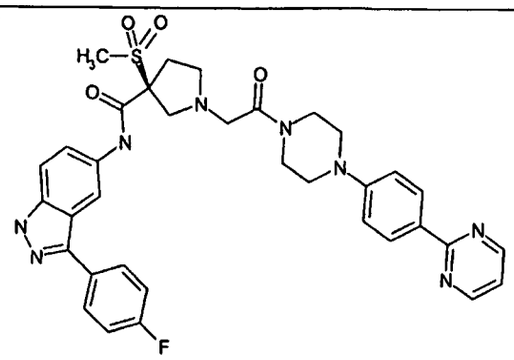
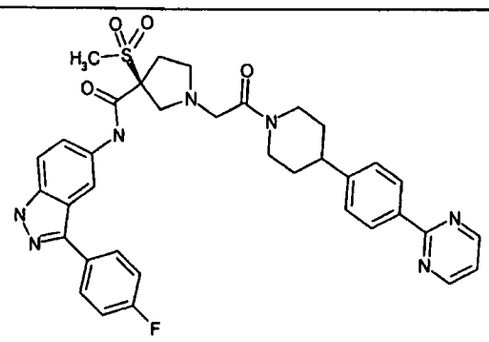
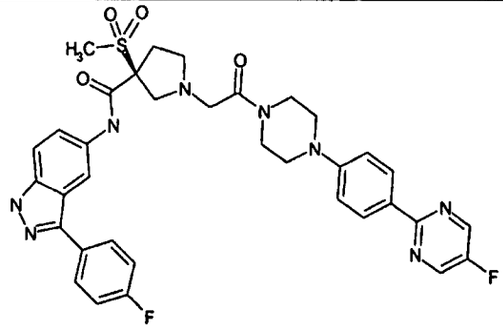
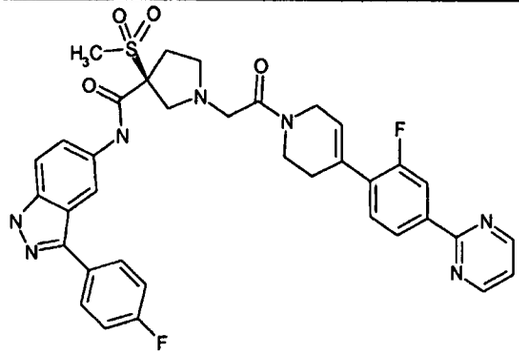
621		623	2.42
622		683.4	2.98
623		667.4	2.69

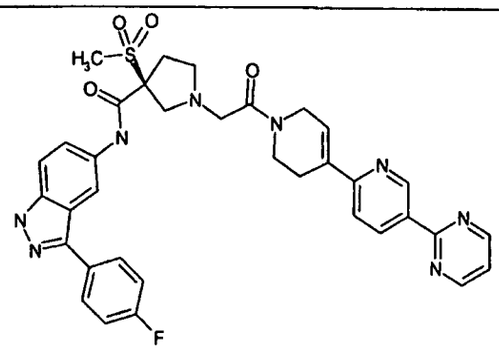
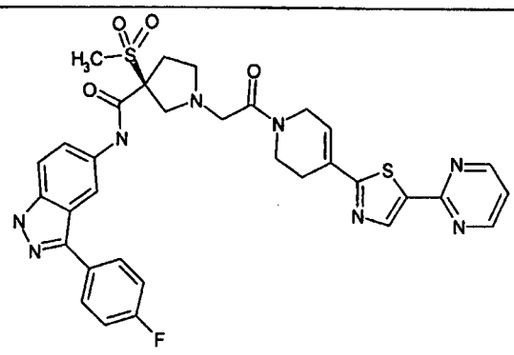
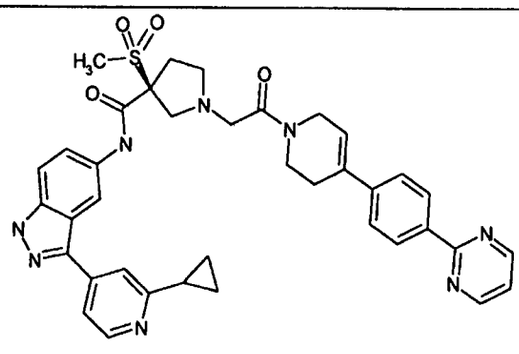
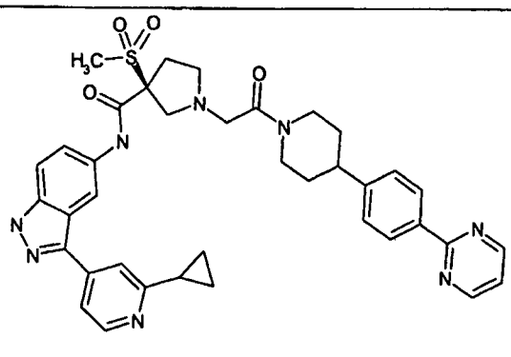
Examples 625 to 825

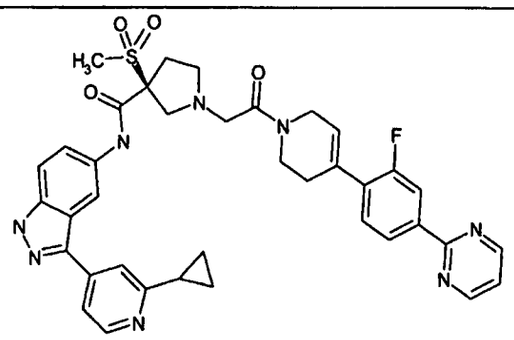
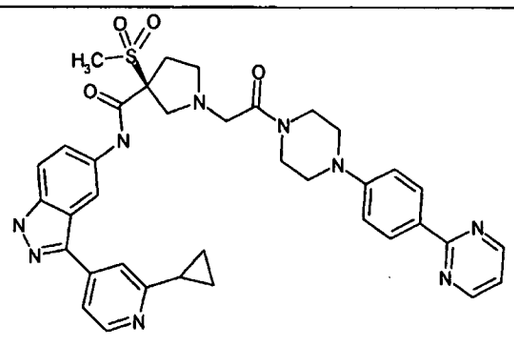
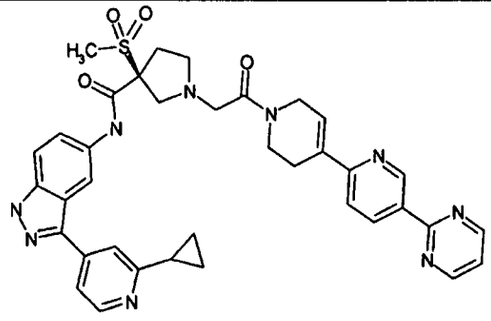
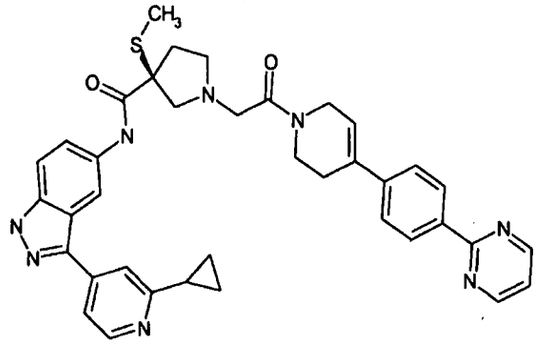
Following the procedures described above, as well as those indicated in Table 28, the compounds in Table 28 were prepared.

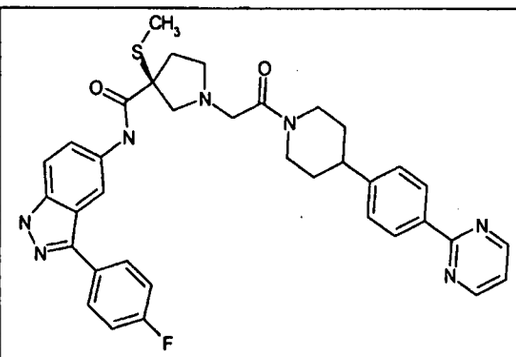
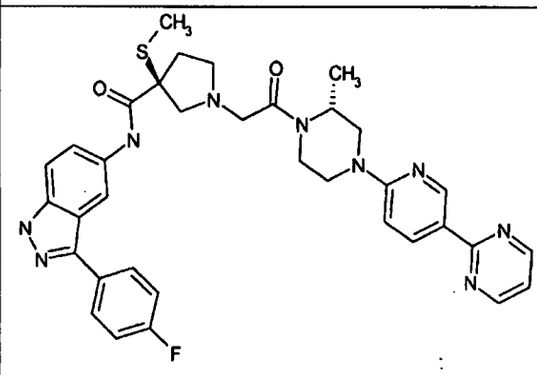
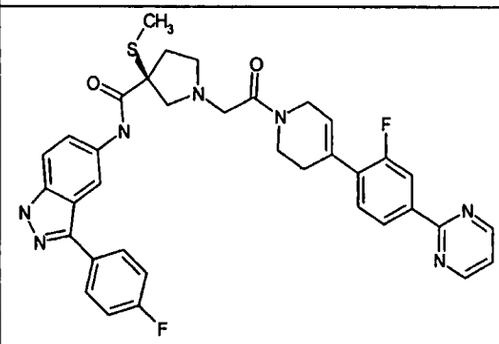
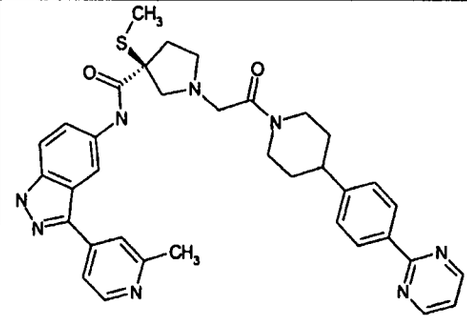
Table 28

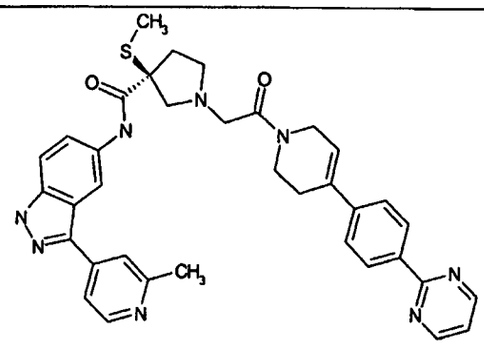
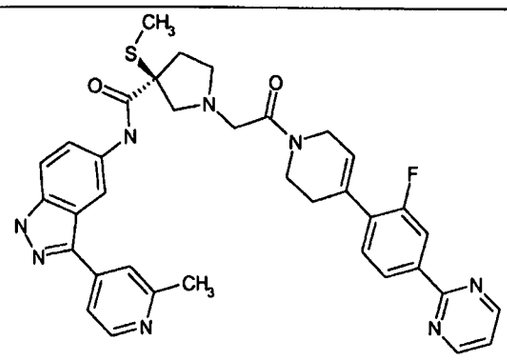
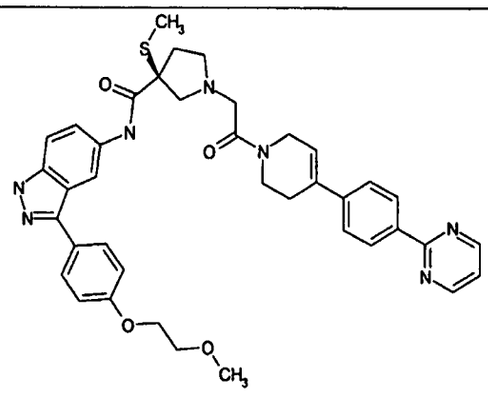
Ex No.	COMPOUND	M+1	Retention Time (min)
625		701.4	3.05
626		680.4	2.99
627	 (see also Example 619)	680.4	2.8

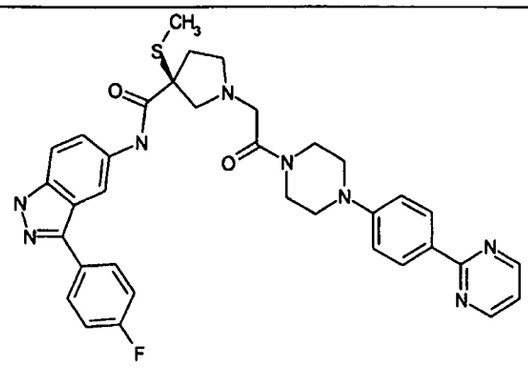
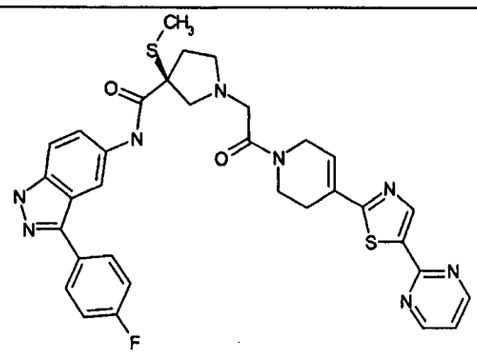
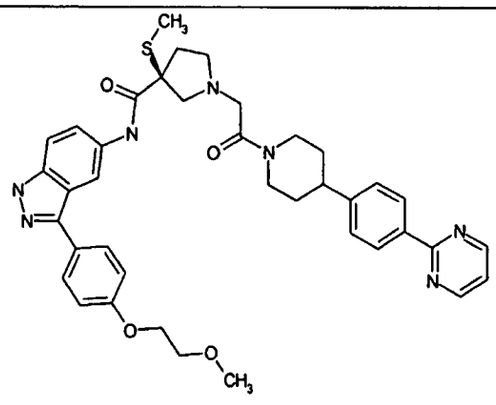
628		683.4	2.93
629		682.4	2.83
630		701.4	3.04
631		698.4	3.1

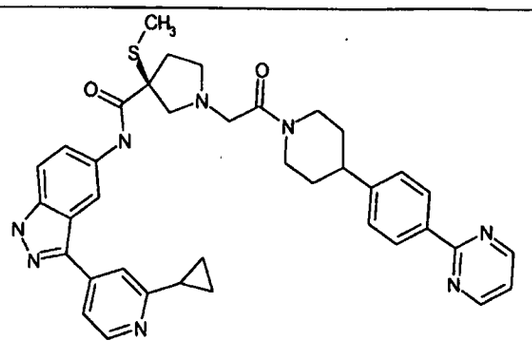
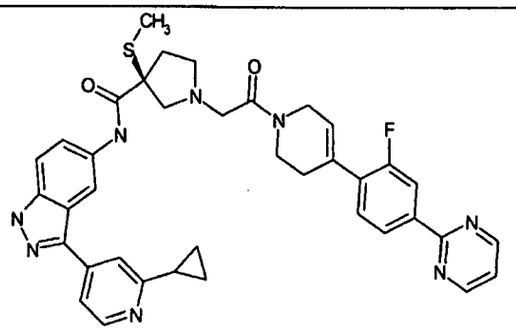
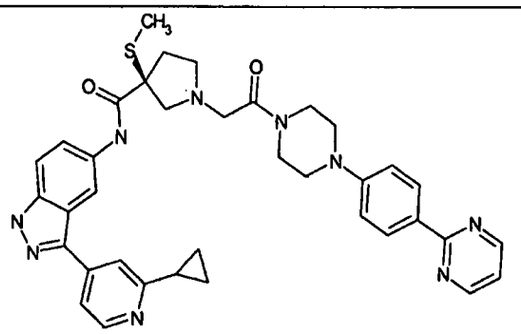
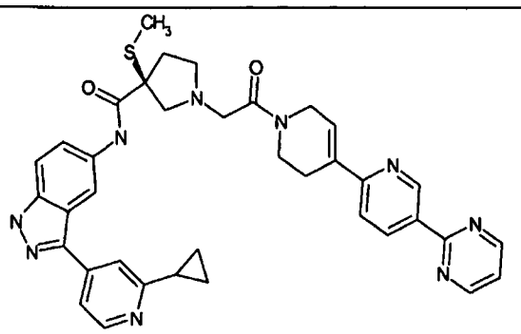
632		681.4	2.5
633		687.4	2.54
634		703.4	2.33
635		705.4	2.25

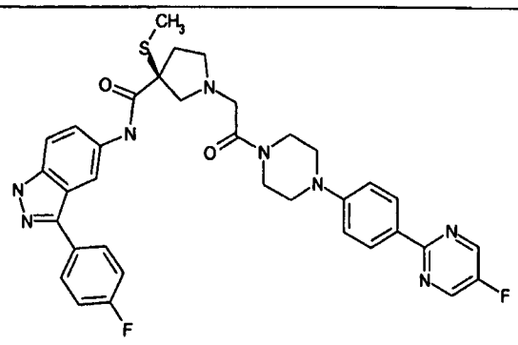
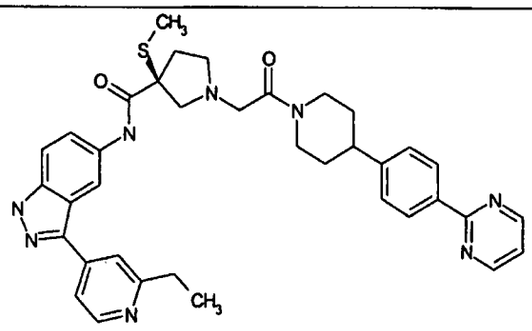
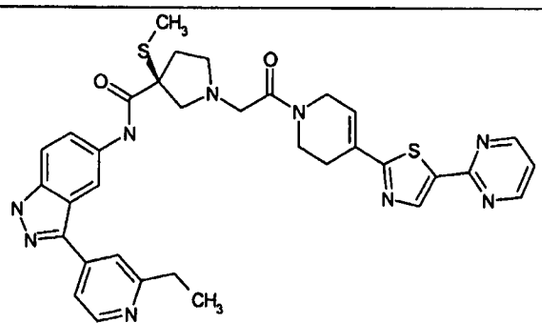
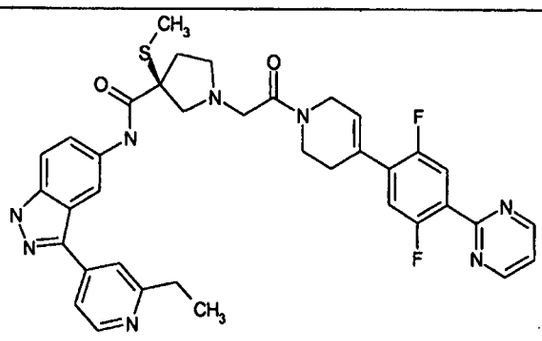
636		721.4	2.38
637		706.4	2.14
638		704.4	1.93
639		671.4	2.31

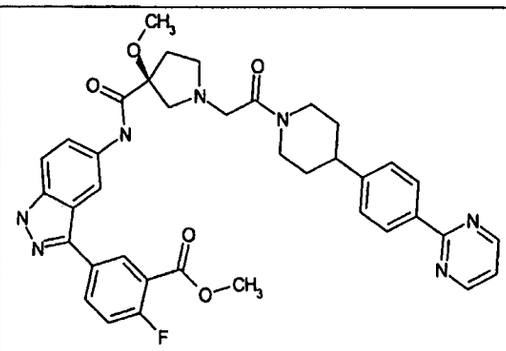
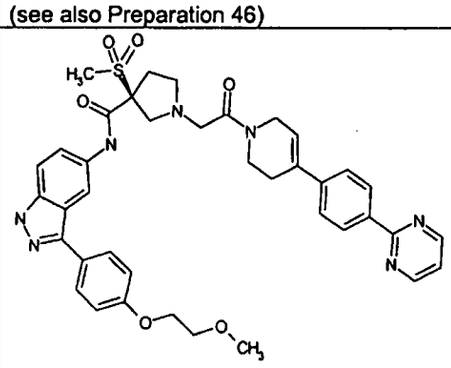
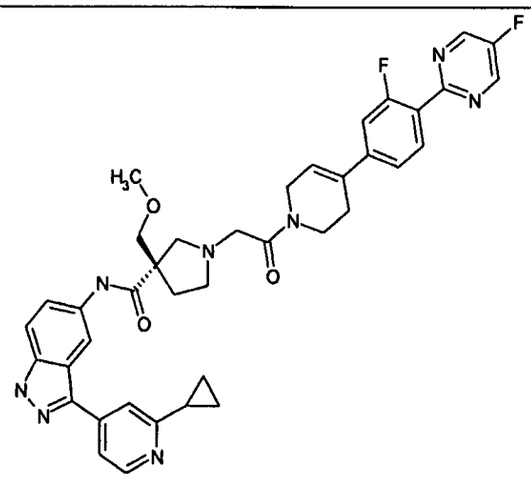
640		650.4	2.8
641		666.4	2.37
642		666.4	3.14
643		647.4	2.16

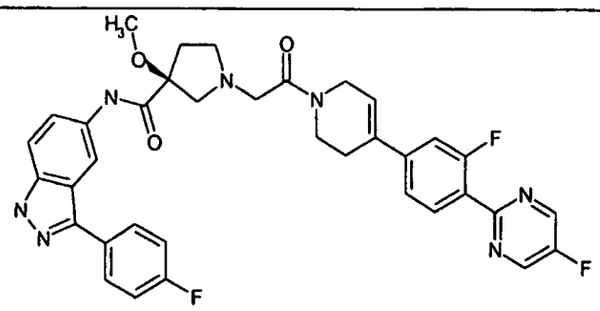
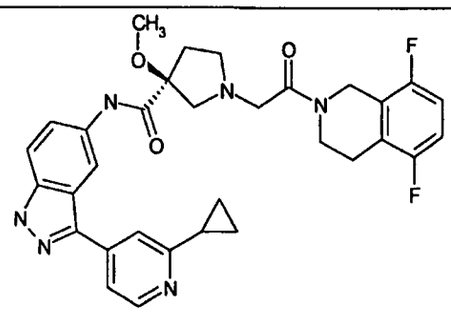
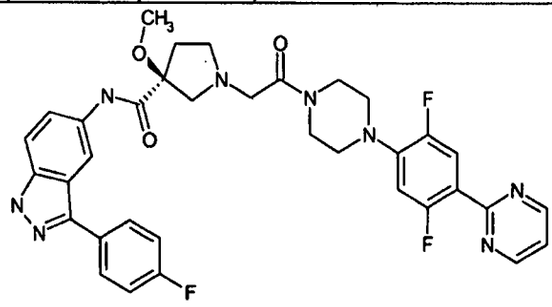
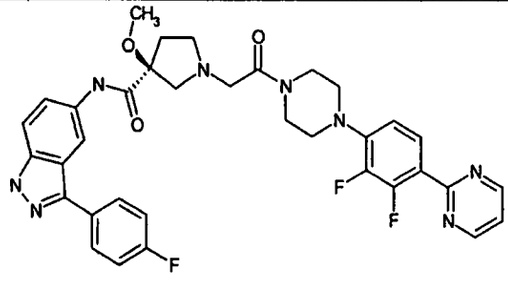
644		645.4	2.03
645		663.4	2.14
646		704.4	2.72

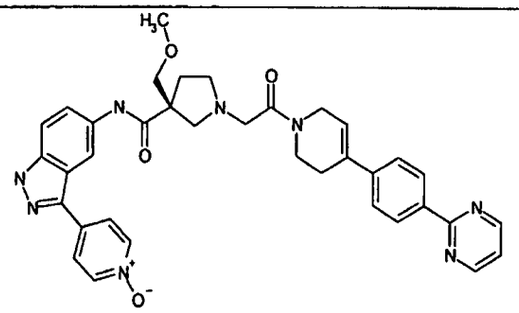
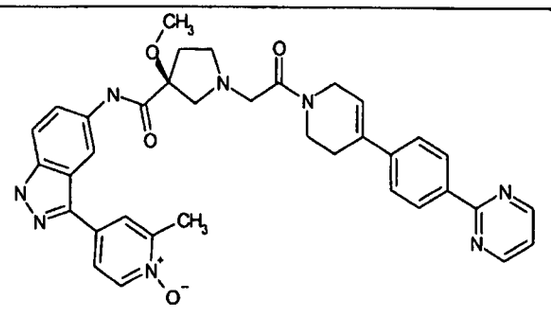
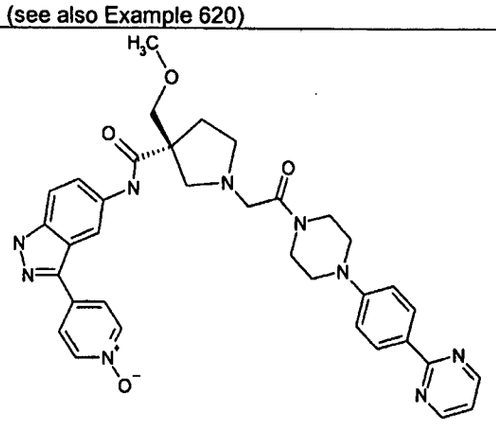
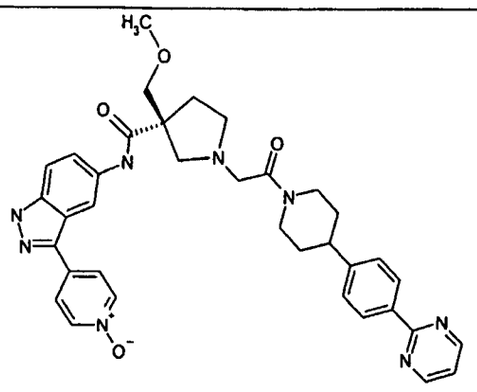
647		651.4	2.74
648		655.4	2.72
649		706.4	2.8

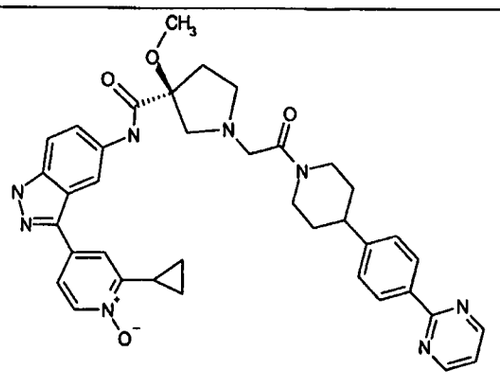
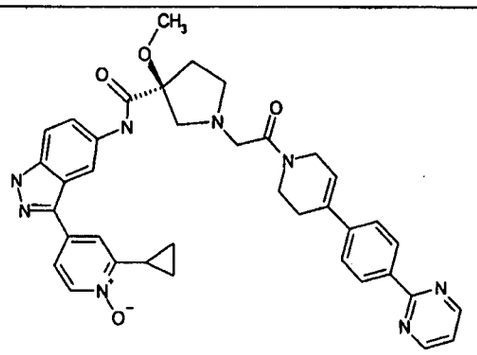
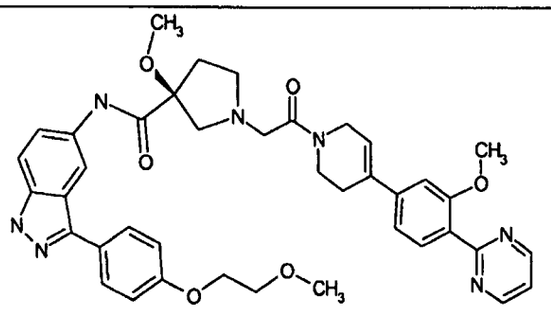
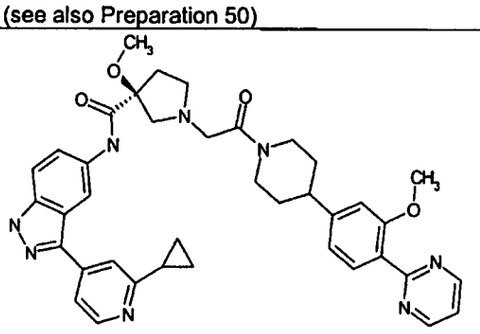
650		673.4	2.29
651		689.4	2.4
652		674.4	2.17
653		672.4	2.01

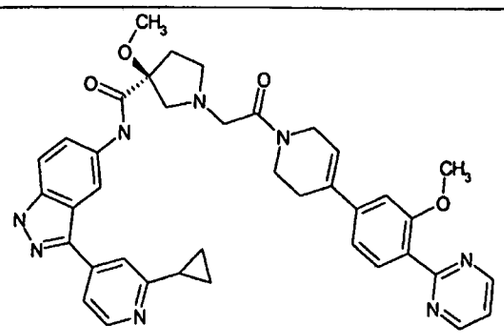
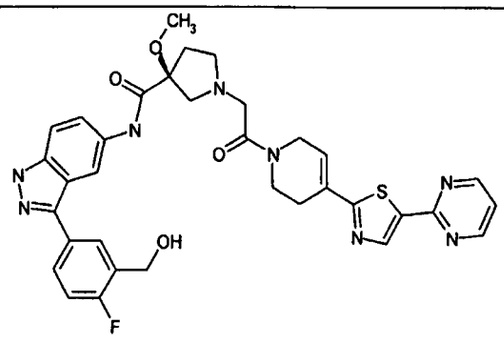
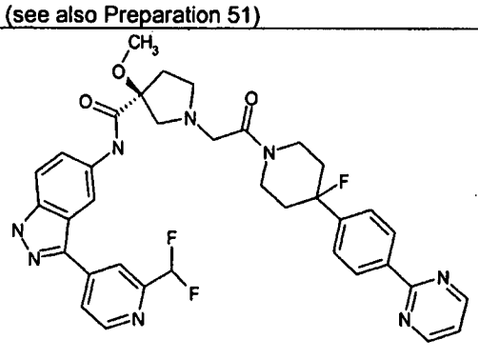
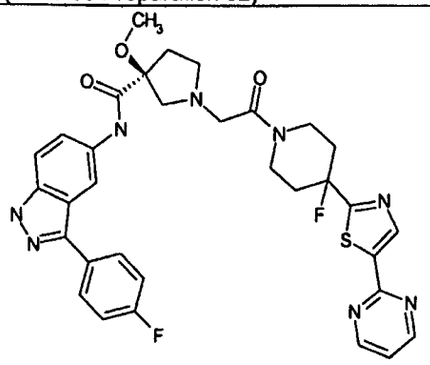
654		669.4	3.16
655		661.4	2.82
656		666.3	2.66
657		695.3	2.83

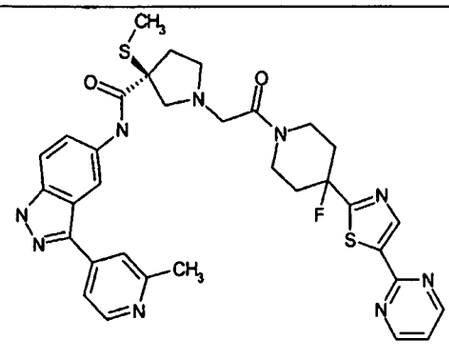
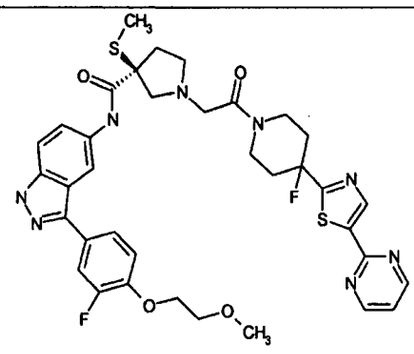
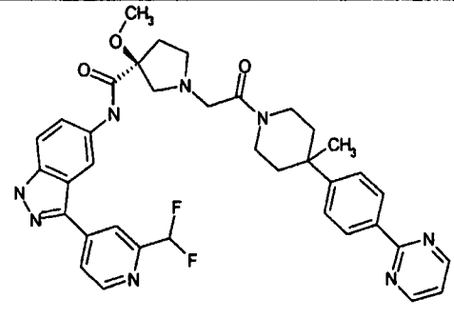
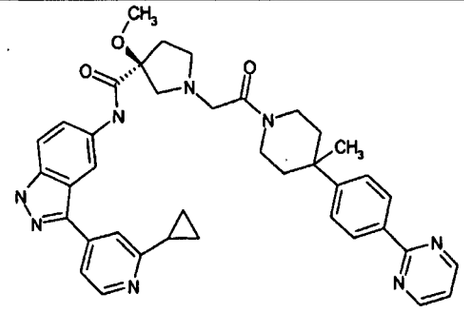
658	 (see also Preparation 46)	692.4	2.92
659		736.4	2.8
660	 (see also Example 618)	705.4	2.51

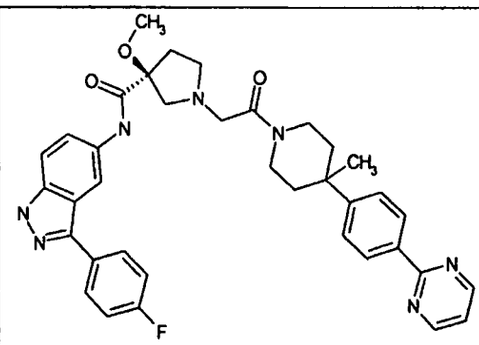
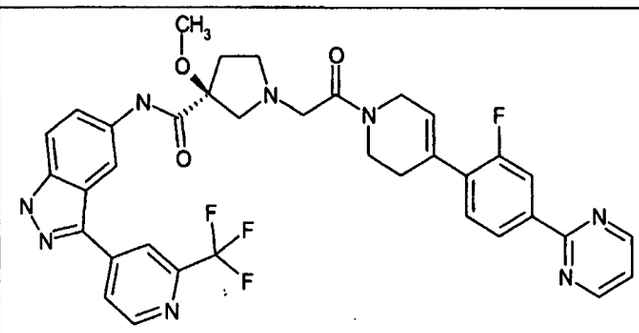
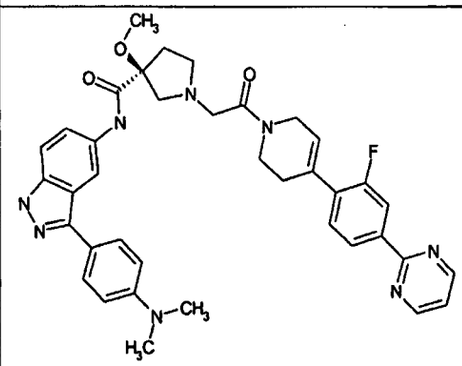
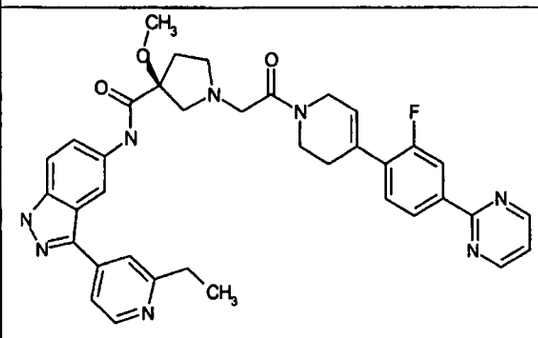
661		668.4	3.06
662	 (see also Preparation 47)	587.3	2.46
663	 (see also Preparation 49)	671.4	2.8
664	 (see also Preparation 48)	671.4	2.78

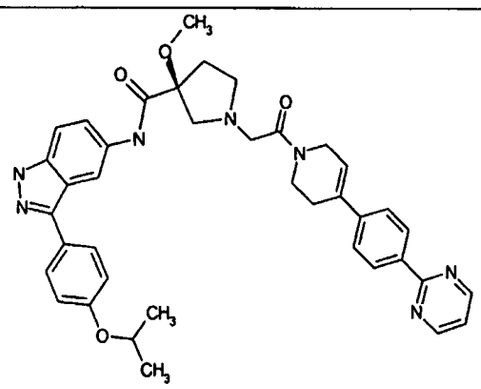
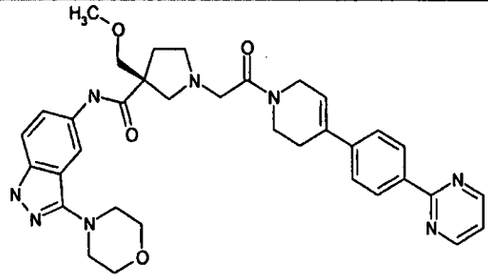
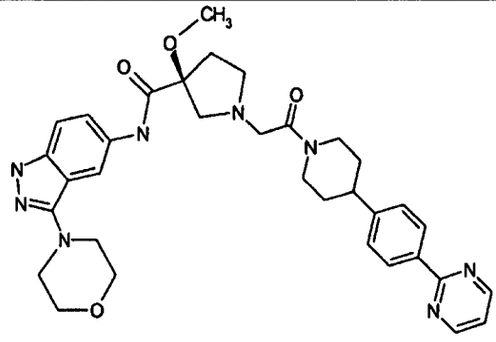
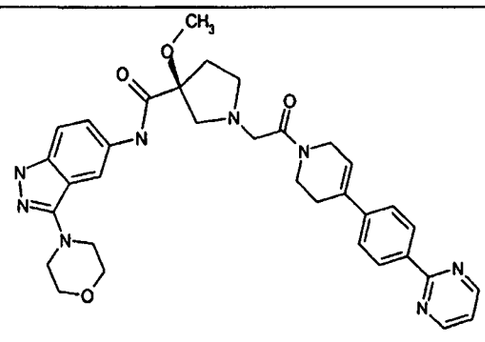
665		645.4	2.48
666	 (see also Example 620)	645.4	2.31
667		648.4	2.15
668		647.4	2.28

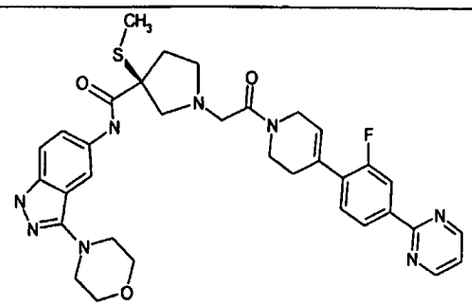
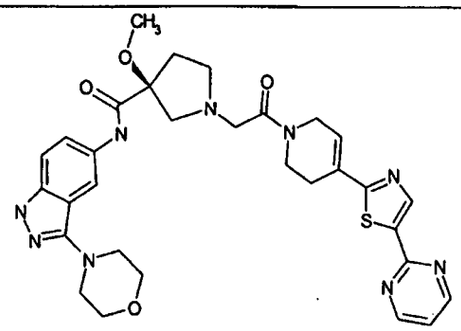
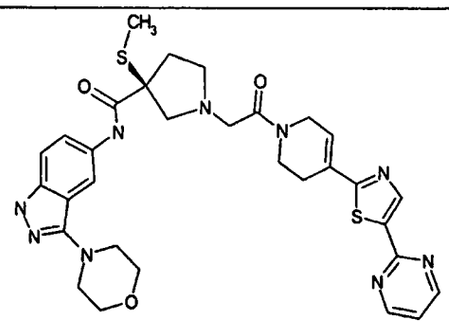
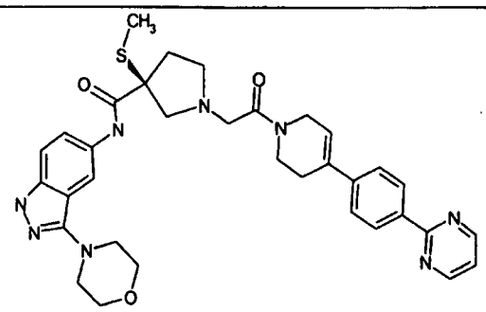
669		673.4	2.56
670		671.4	2.58
671	 (see also Preparation 50)	718.4	2.67
672		687.4	2.18

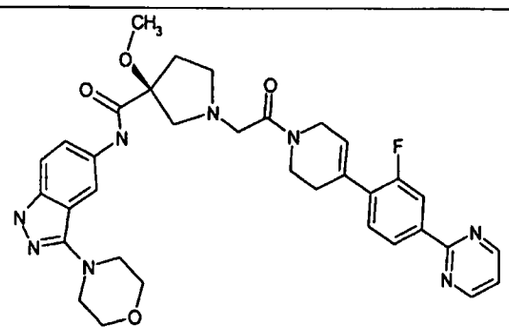
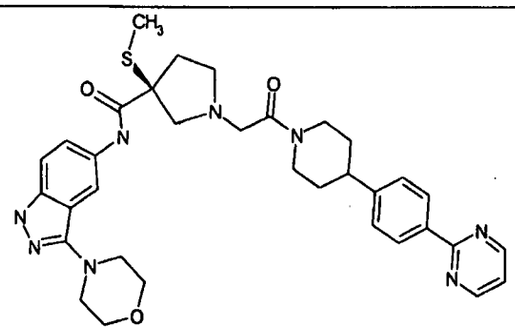
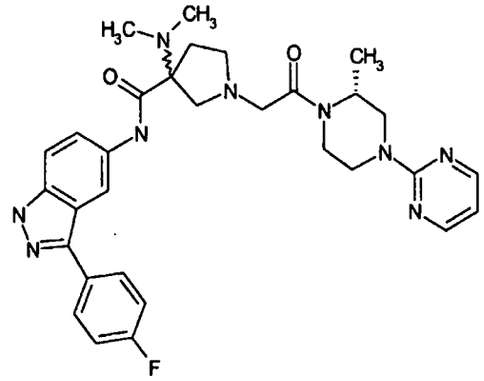
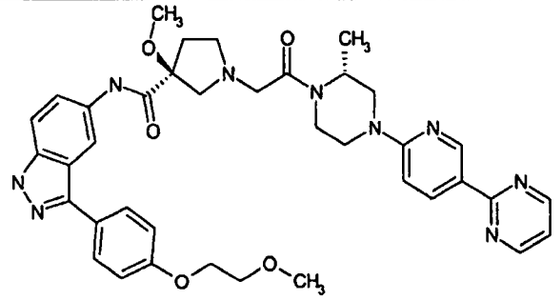
673		685.4	2.13
674	 (see also Preparation 51)	669.4	2.45
675	 (see also Preparation 52)	685.4	2.98
676	 (see also Preparation 54)	659.4	2.86

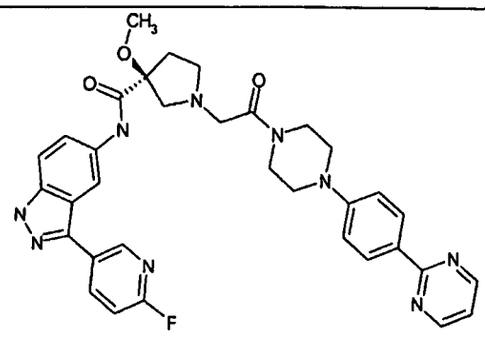
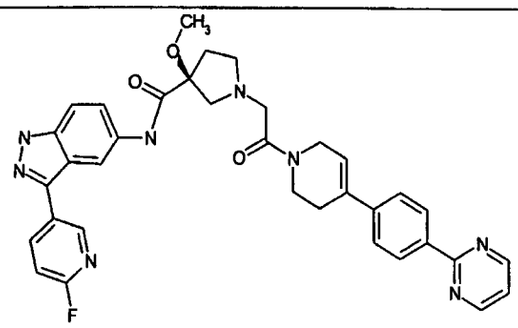
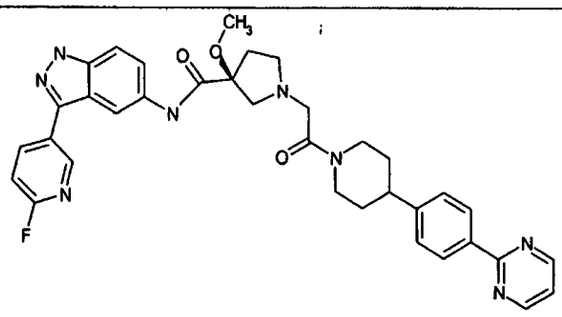
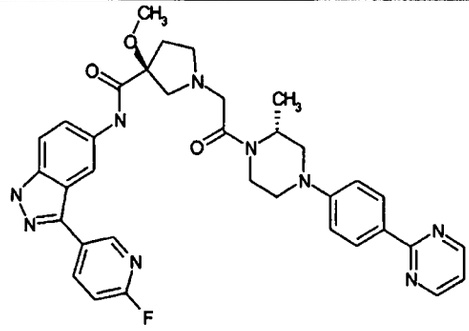
677		672.4	2.01
678		749.4	2.9
679		681.4	2.85
680	 (see also Preparation 55)	671.4	2.47

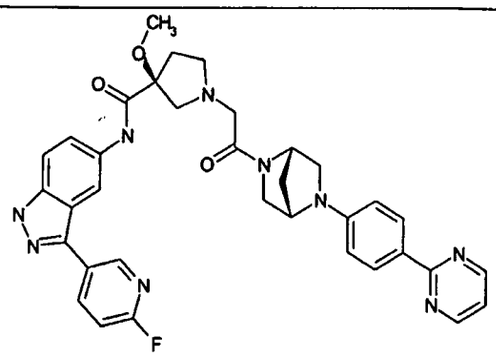
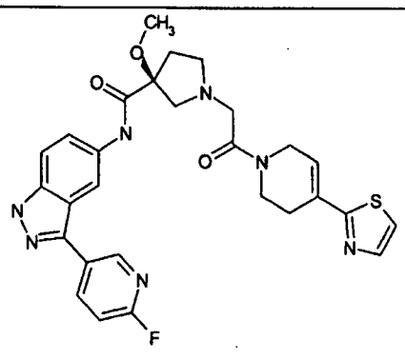
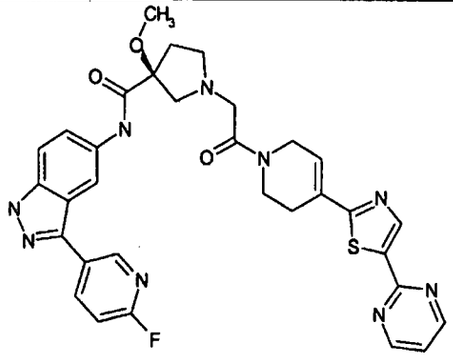
681		648.4	2.87
682		701.4	3.36
683		675.4	2.33
684		661.7	3.21

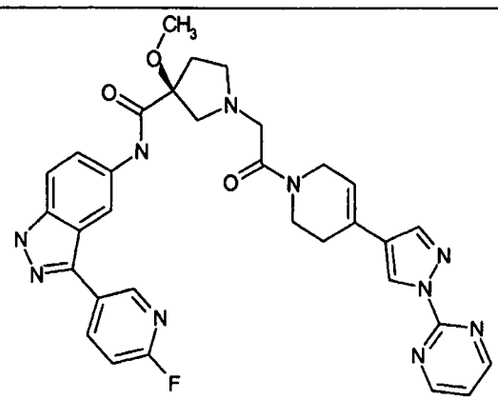
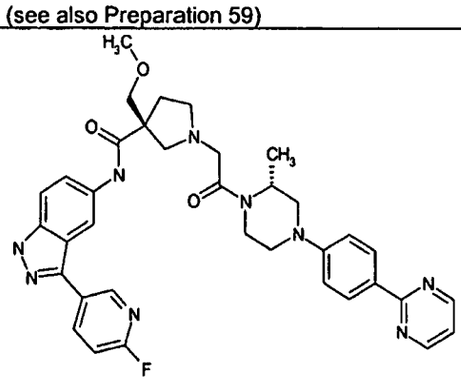
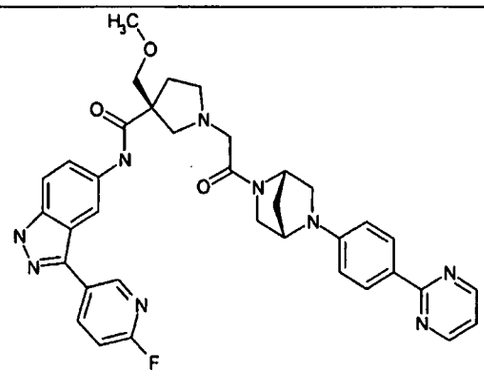
685	 (see also Preparation 56)	623	2.41
686		637	2.65
687		625	2.47
688		672	3.08

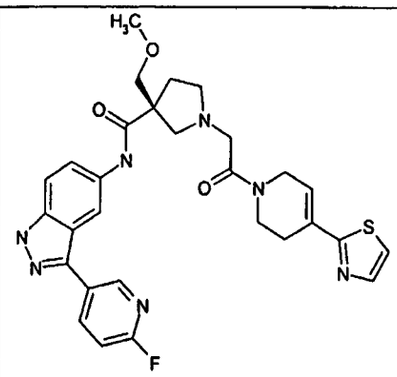
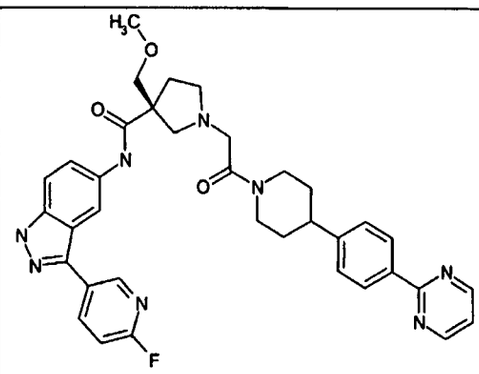
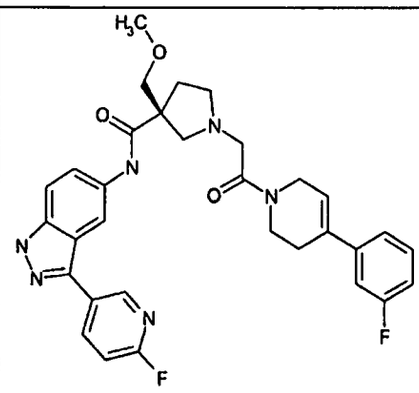
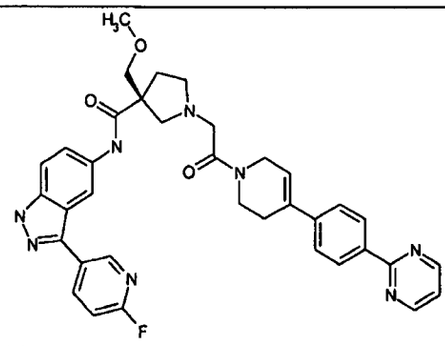
689		657	2.63
690		630	2.18
691		646	2.29
692		639	2.46

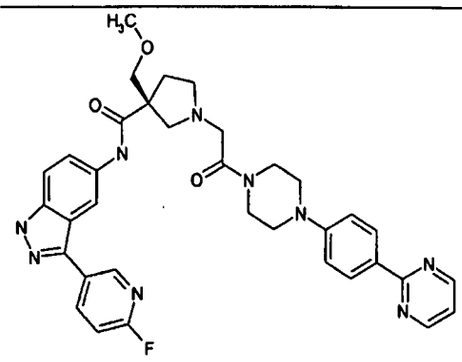
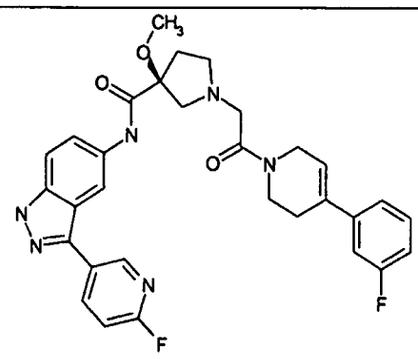
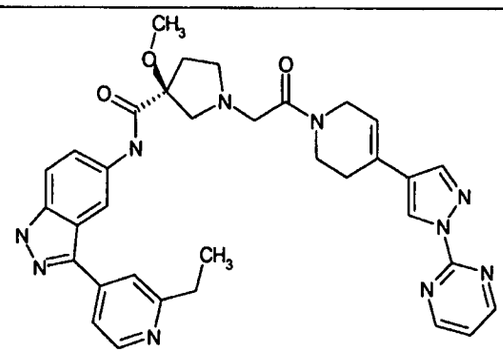
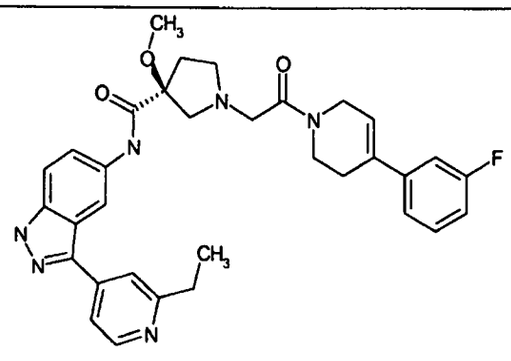
693		641	2.51
694		641	2.49
695		586	2.62
696	 (see also Preparation 57)	706	2.46

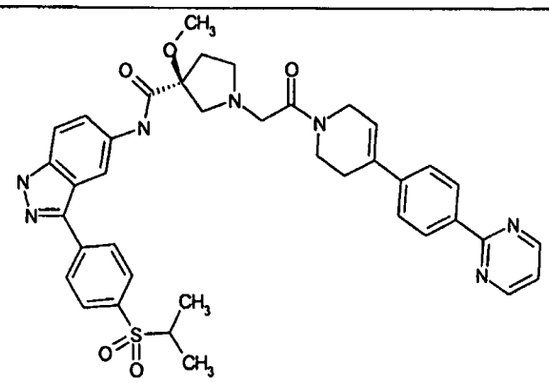
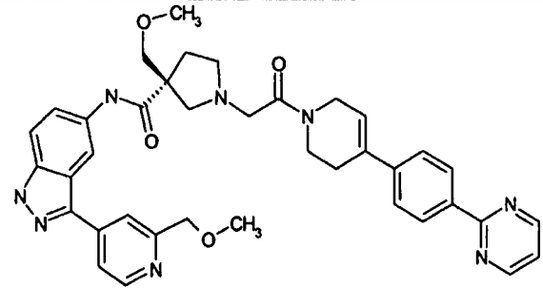
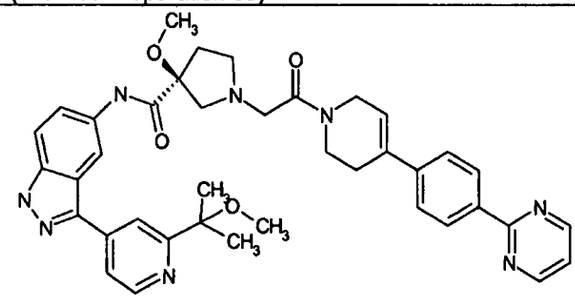
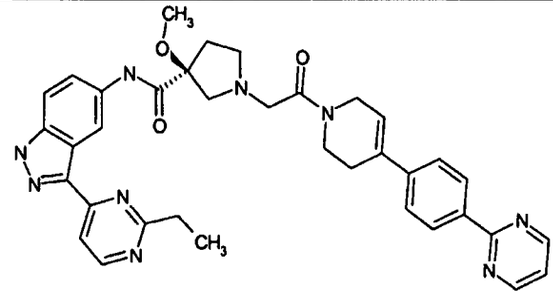
697		636.7	3.12
698		633.7	3.46
699		635.7	3.33
700	 (see also Preparation 58)	650.7	3.24

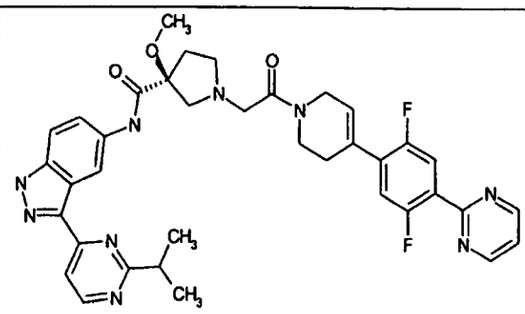
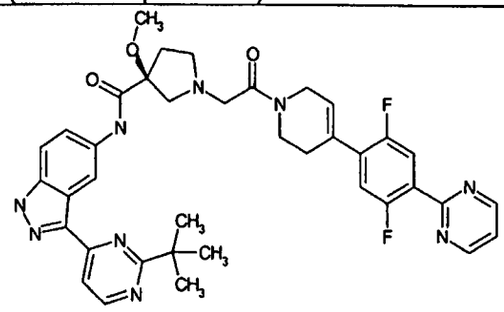
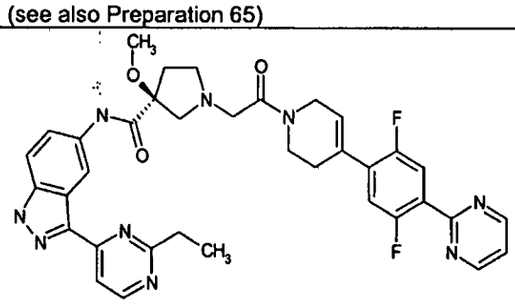
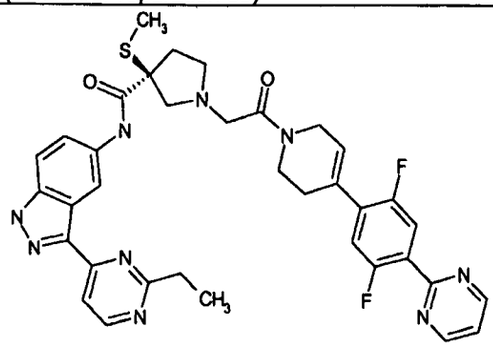
701		648.7	3.05
702		562.6	2.83
703		640.7	3.12

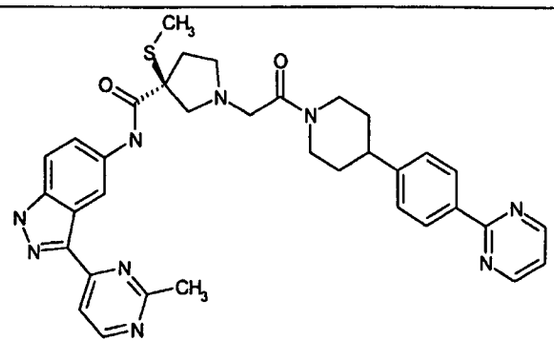
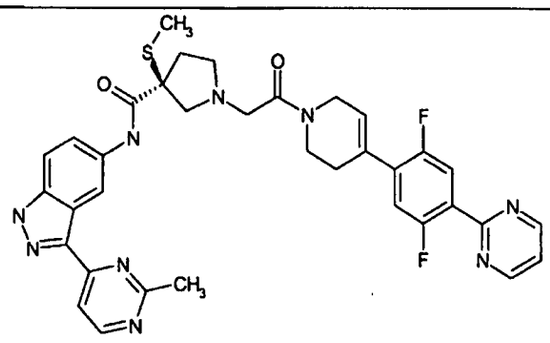
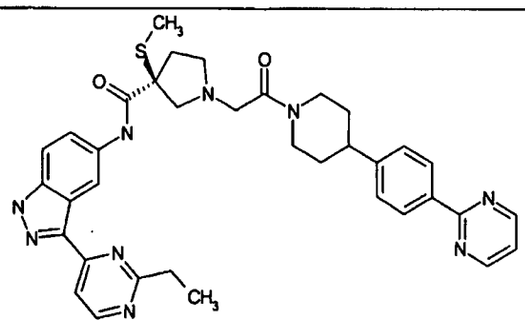
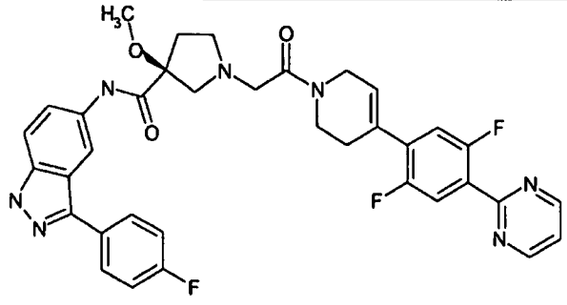
704	 (see also Preparation 59)	623.7	2.88
705		664.7	3.4
706		662.7	3.16

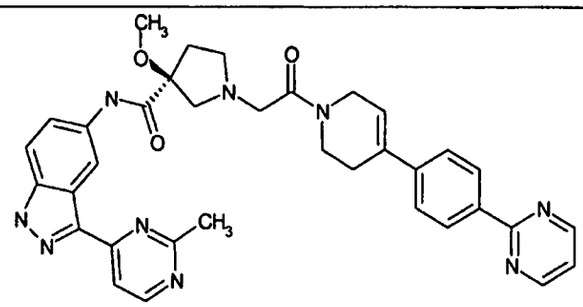
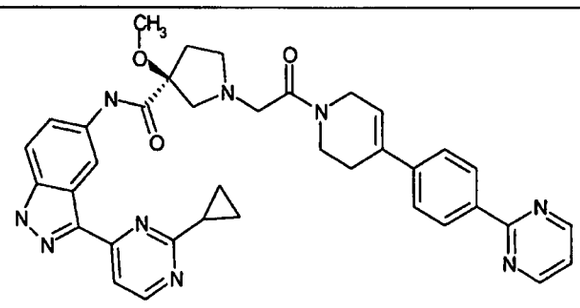
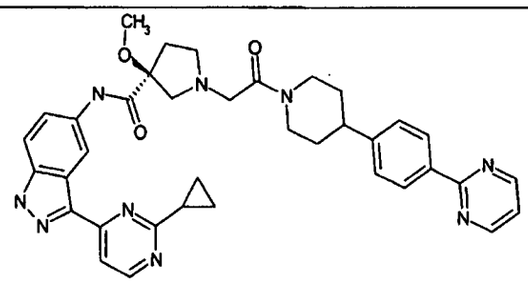
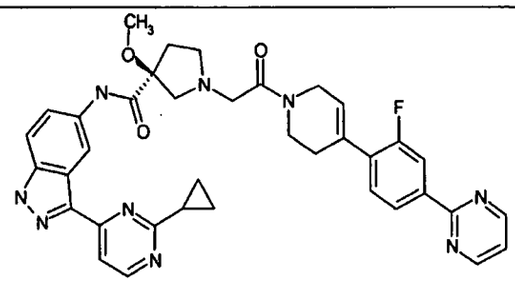
707		576.7	2.97
708		649.7	3.45
709		587.6	3.58
710		647.7	3.49

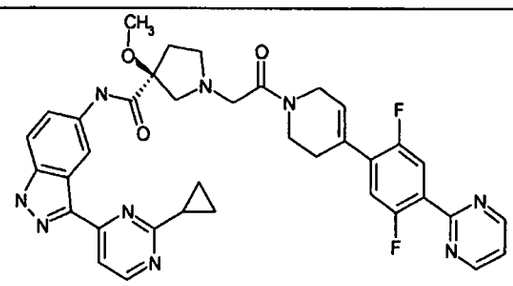
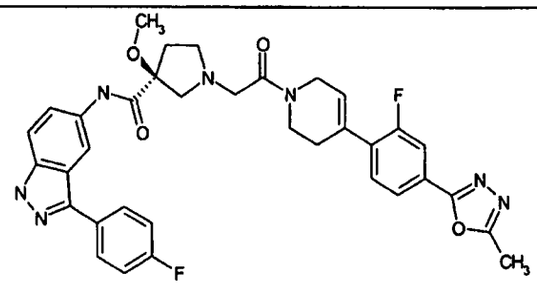
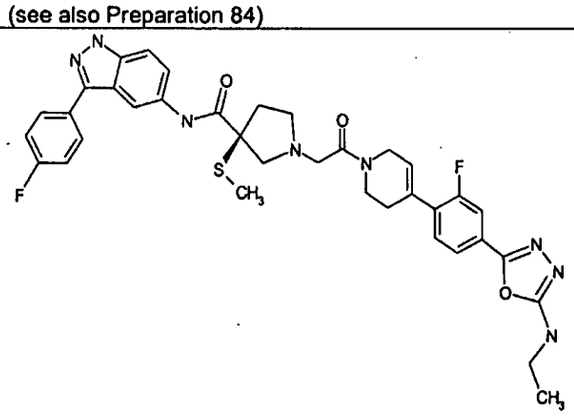
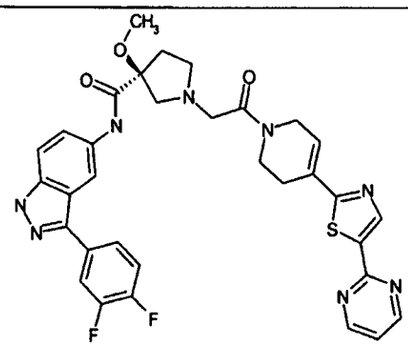
711		650.7	3.23
712		573.6	3.45
713		633.7	2.34
714	 (see also Preparation 60)	583.7	2.81

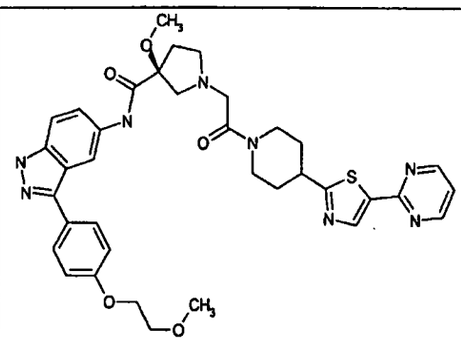
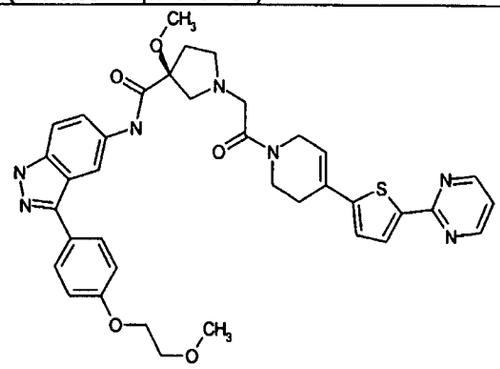
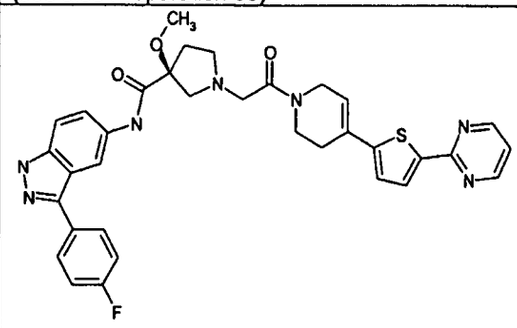
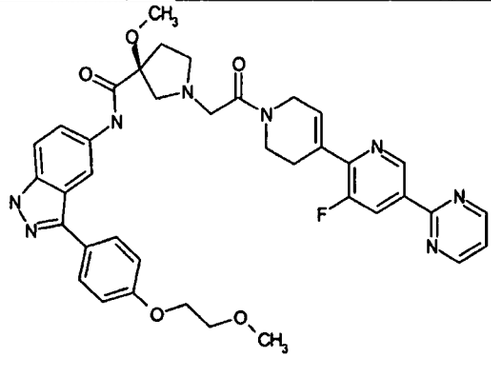
715	 (see also Preparation 62)	602.8	3.65
716	 (see also Preparation 63)	709.8	2.62
717	 (see also Preparation 64)	683.9	3
718	 (see also Preparation 65)	676.8	3.09

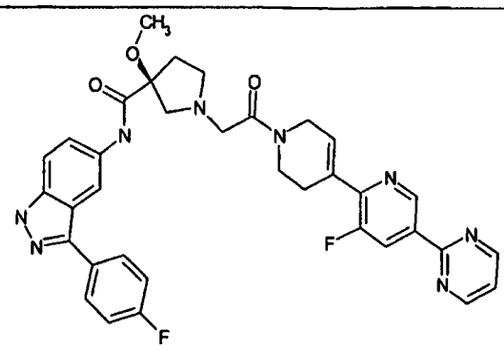
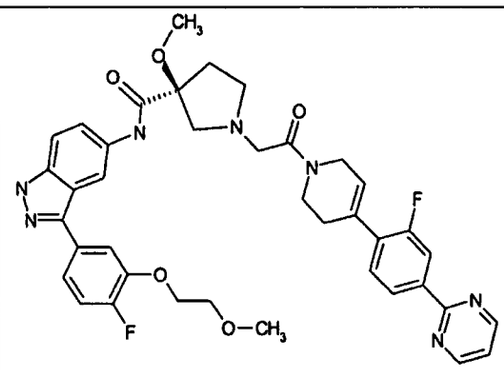
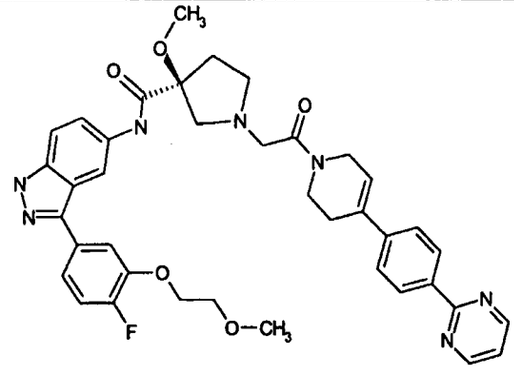
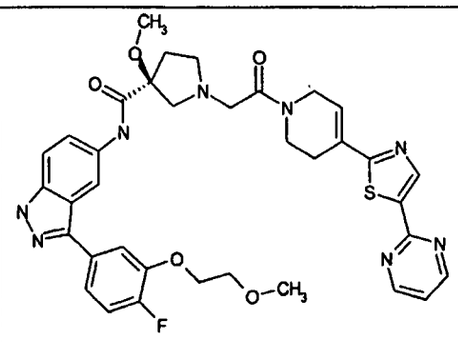
719	 (see also Preparation 65)	694.3	3.71
720	 (see also Preparation 65)	708.4	4.08
721	 (see also Preparation 65)	680.3	3.09
722		696.2	3.52

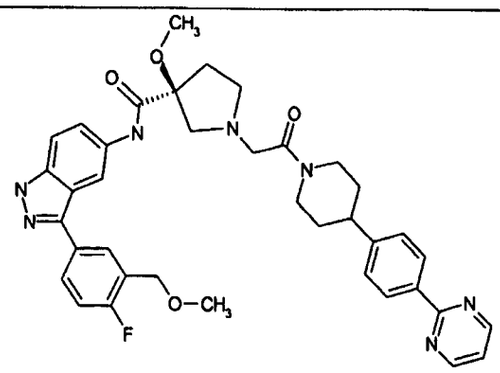
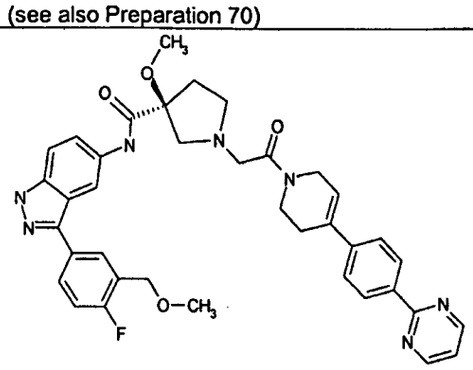
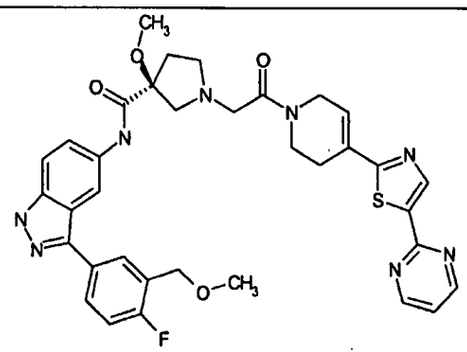
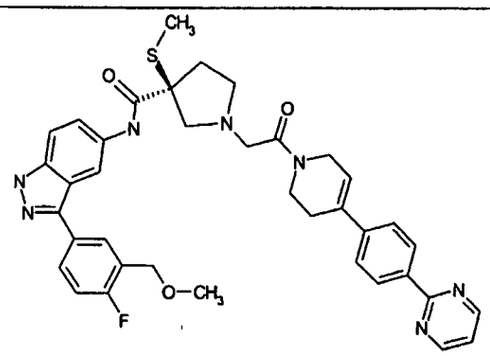
723		648.3	2.98
724		682.2	3.01
725		667.3	3.12
726	 (see also Preparation 66)	668.4	3.21

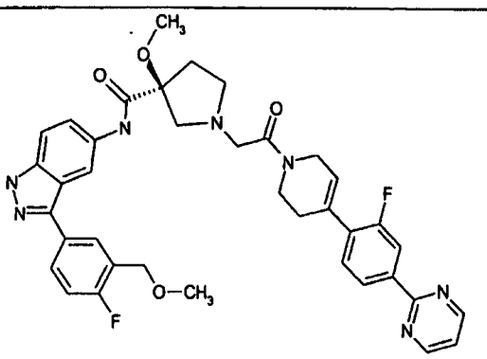
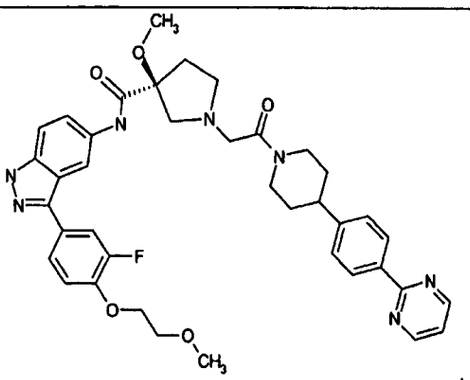
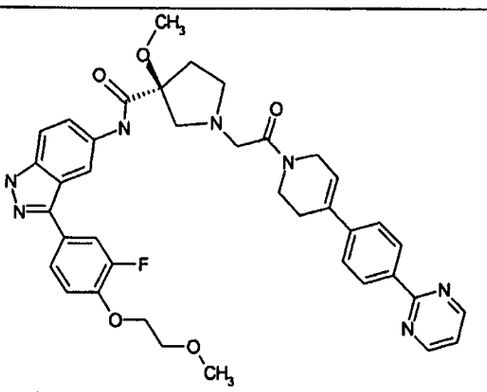
727		630.3	3.29
728		656	3.22
729		658.3	3.38
730		674	3.84

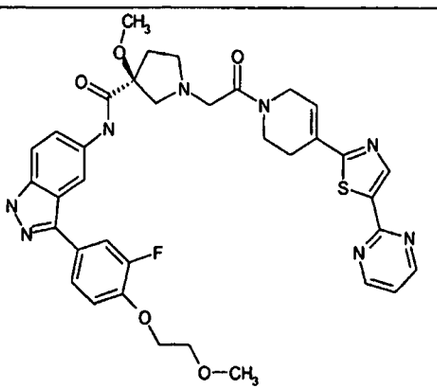
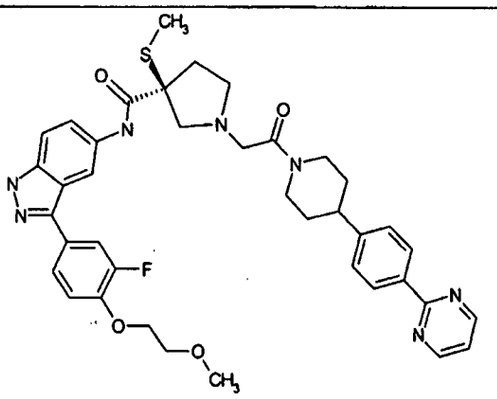
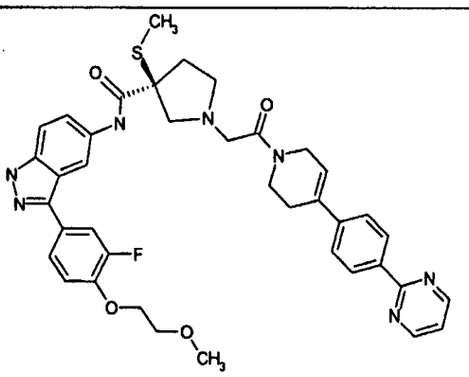
731		692	3.41
732	 (see also Preparation 84)	654.4	3.02
733		699.4	2.9
734	 (see also Preparation 67)	657.4	2.73

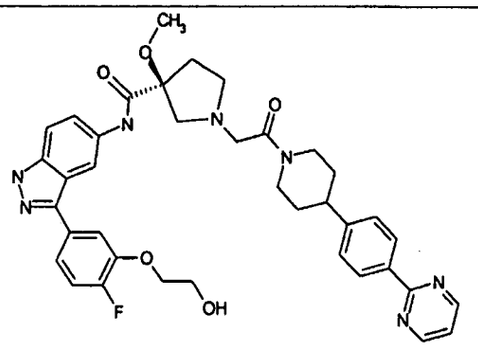
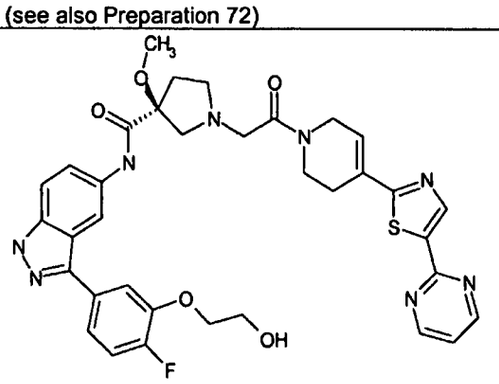
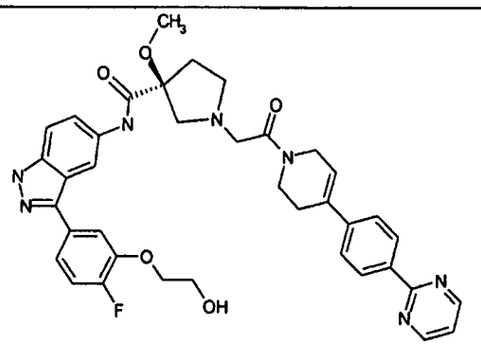
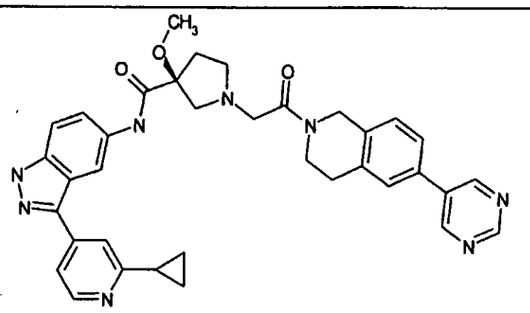
735	 (see also Preparation 67)	697.3	3.31
736	 (see also Preparation 68)	694.2	4.07
737		638.3	3.56
738		707.3	3.57

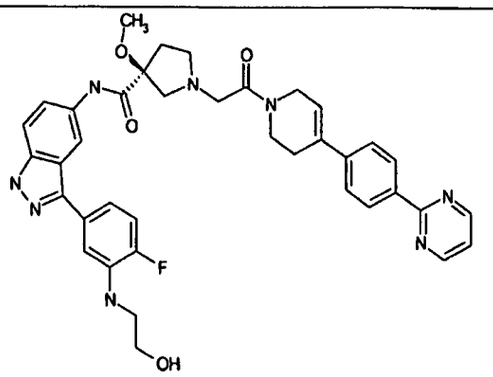
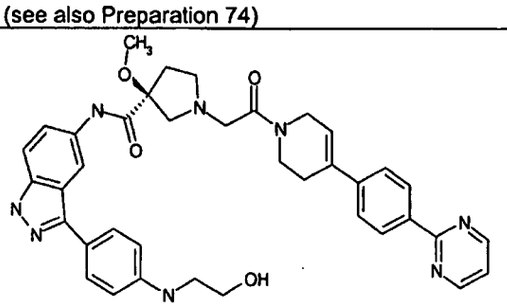
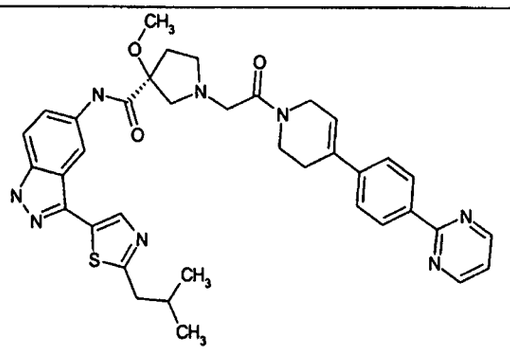
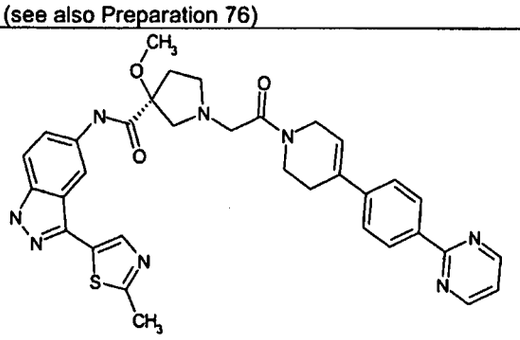
739		651.3	3.69
740	 (see also Preparation 69)	724.4	3.16
741		706.4	3.24
742		713.4	2.7

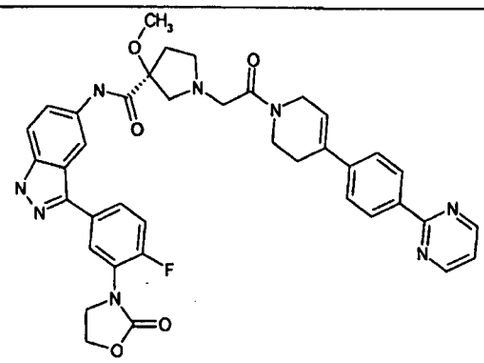
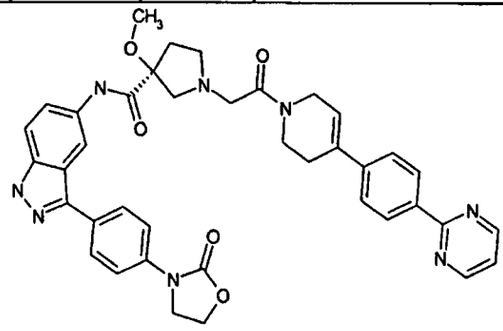
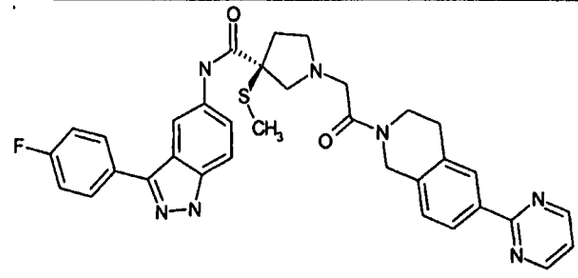
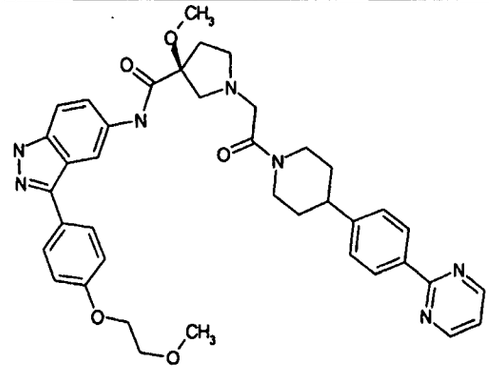
743	 (see also Preparation 70)	678.4	3.2
744		676.4	3.18
745		683.4	2.71
746		692.4	2.91

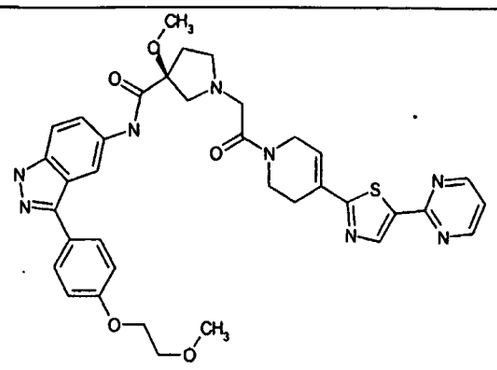
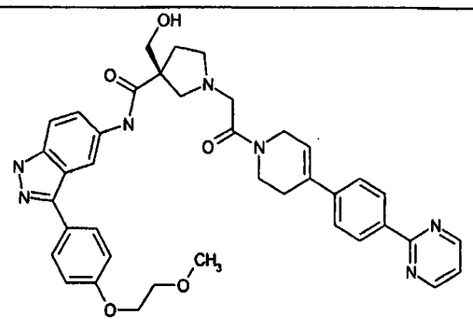
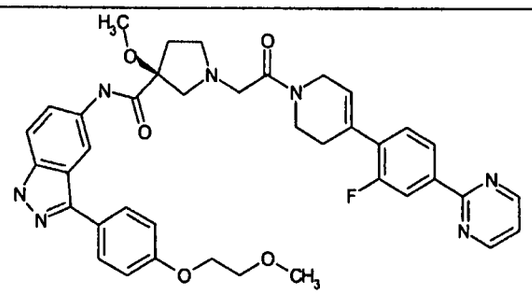
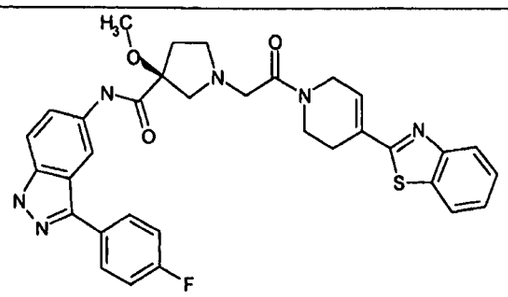
747		694.4	2.91
748		708.4	2.81
749	 (see also Preparation 71)	706.4	2.85

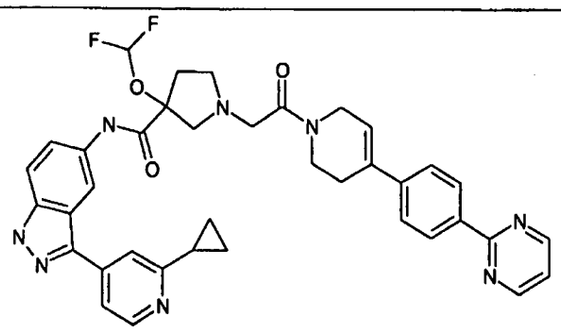
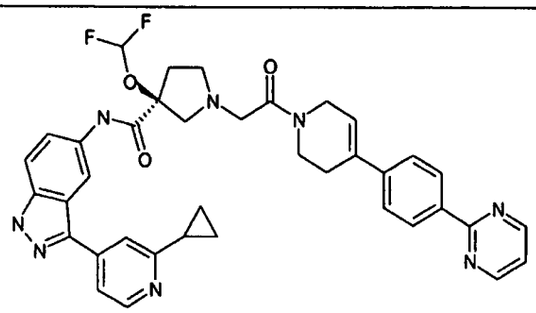
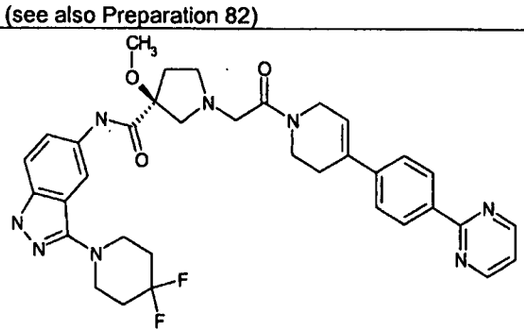
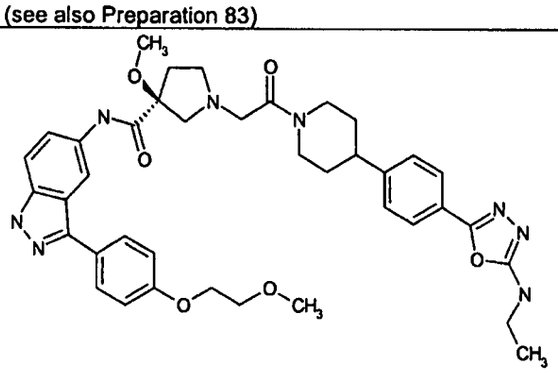
750		713.4	2.68
751		724.4	2.94
752		722.4	2.97

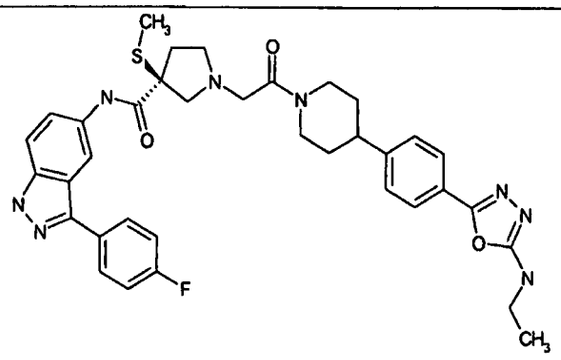
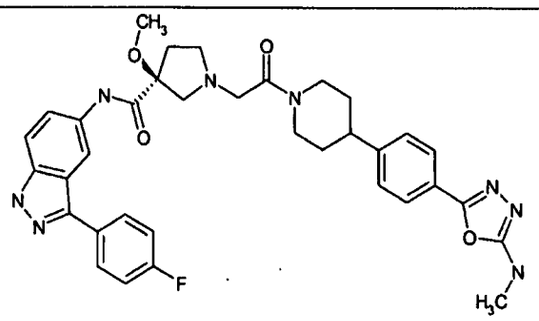
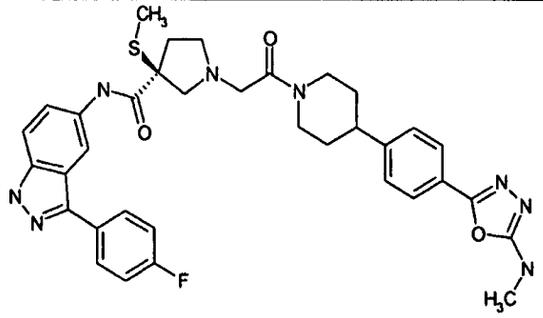
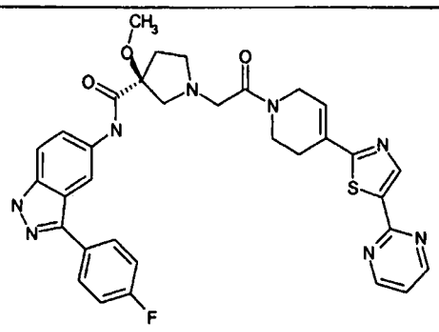
753	 (see also Preparation 72)	694.4	2.62
754		699.4	2.44
755		692.4	2.65
756	 (see also Preparation 73)	629.7	2.57

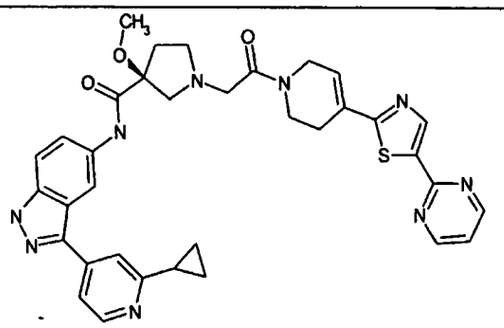
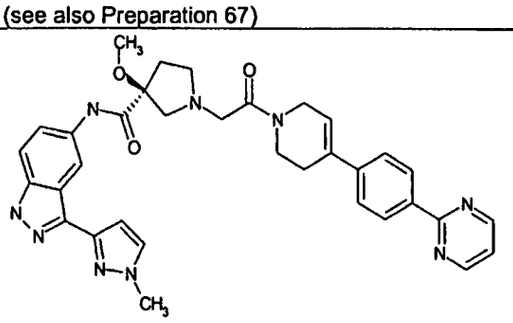
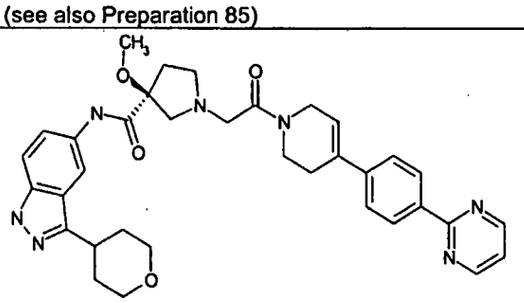
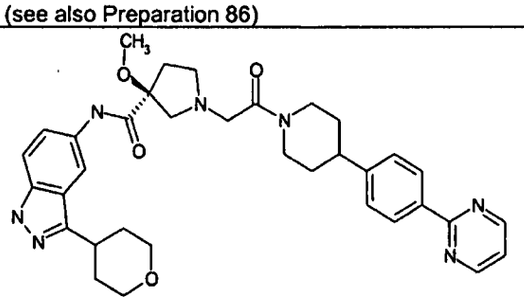
757	 (see also Preparation 74)	691.2	3.54
758		673.2	2.92
759	 (see also Preparation 76)	677.2	3.93
760	 (see also Preparation 77)	635.2	3.33

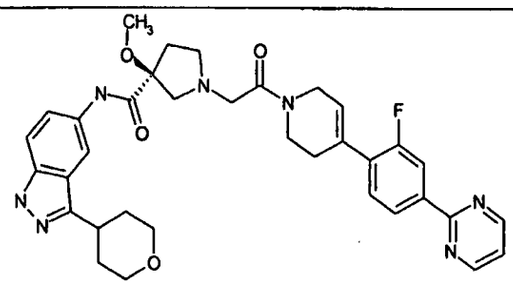
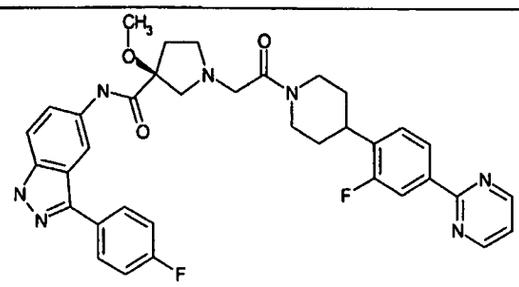
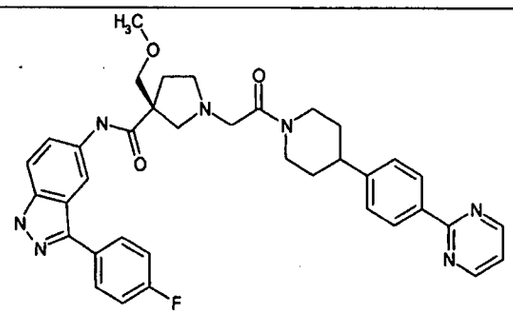
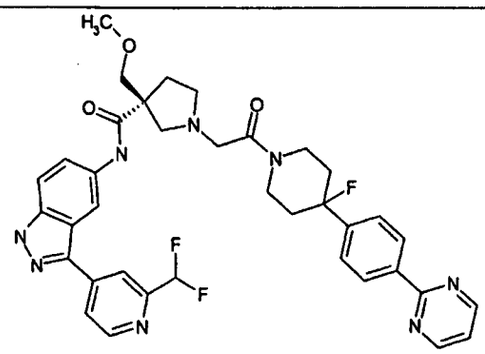
761	 (see also Preparation 78)	717.2	3.8
762	 (see also Preparation 79)	699.7	3.31
763	 (see also Preparation 80)	622.3	3.52
764		690.3	3.8

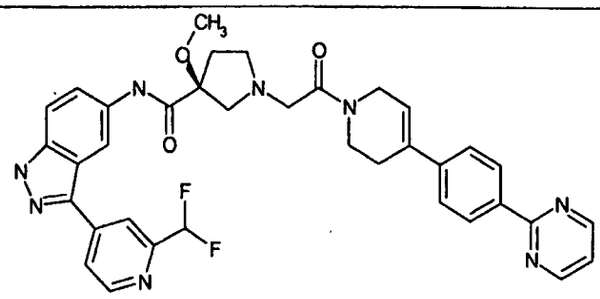
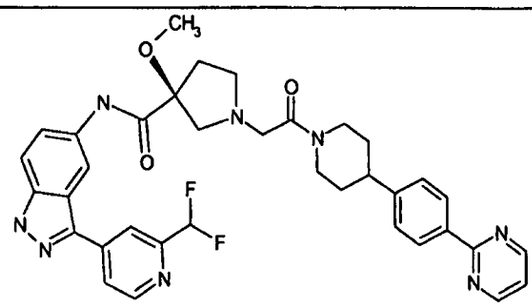
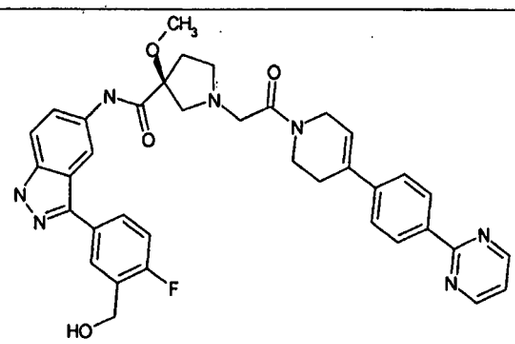
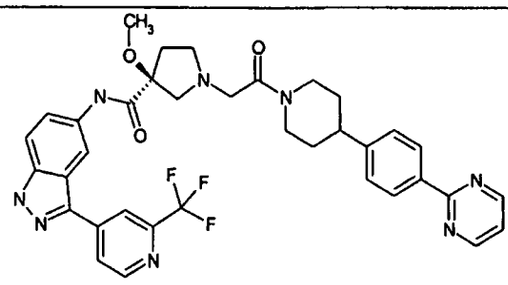
765		695.3	3.56
766		688.4	3.43
767		706.4	3.05
768	 (see also Preparation 81)	611.3	3.17

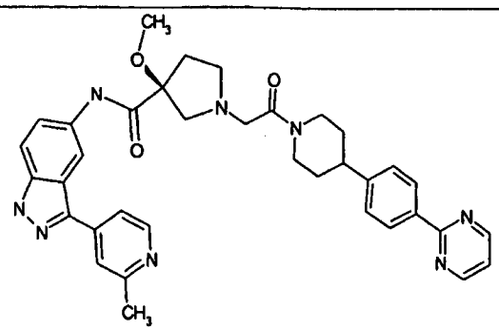
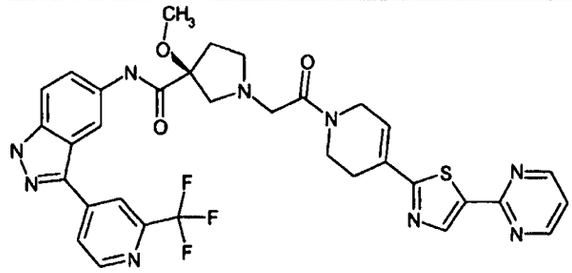
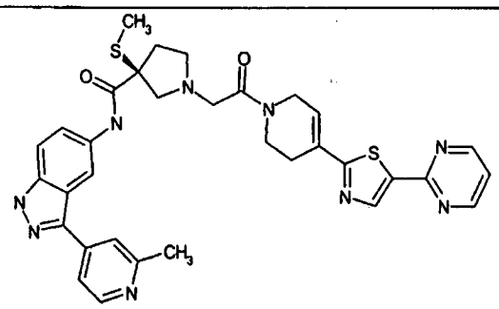
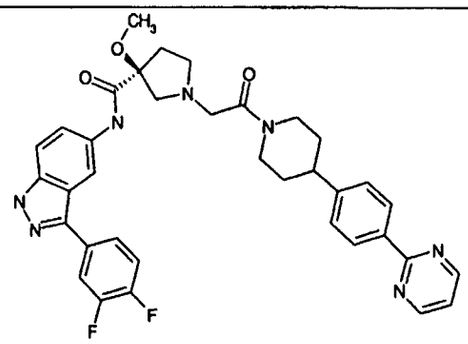
769		691.4	2.44
770	 (see also Preparation 82)	691.4	2.31
771	 (see also Preparation 83)	657.4	2.78
772		723.4	2.64

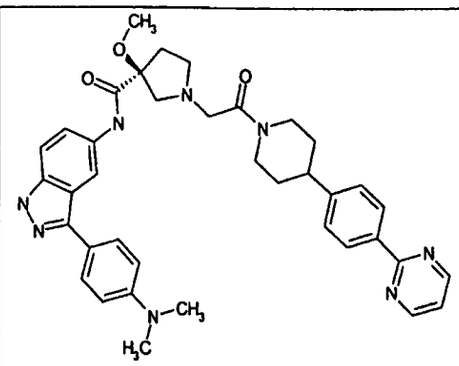
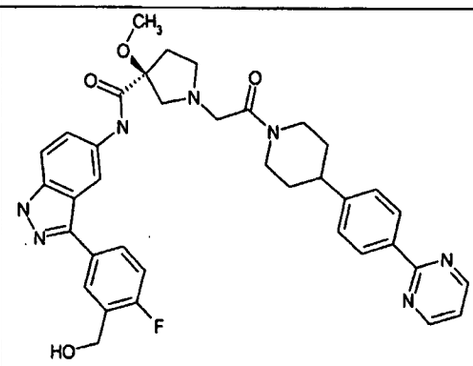
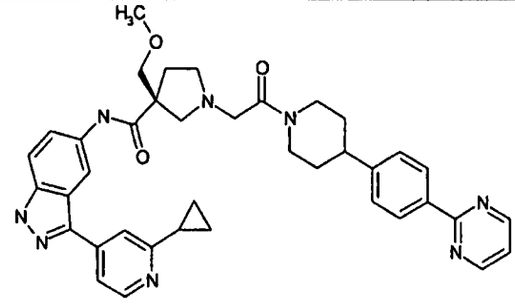
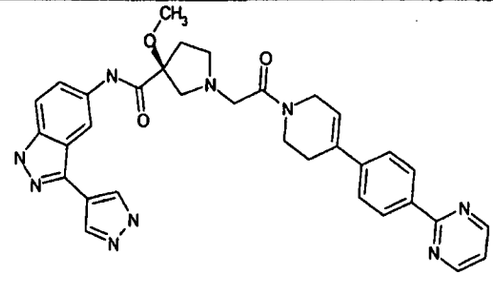
773		683.4	2.67
774	 (see also Example 624)	653.4	2.54
775		669.4	2.58
776		639.7	3.41

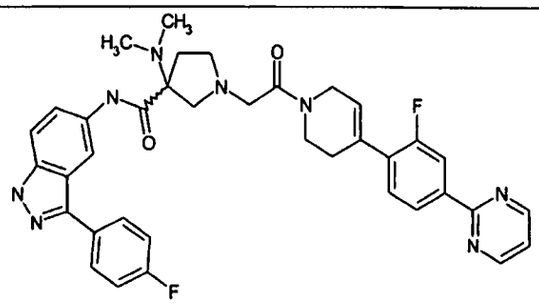
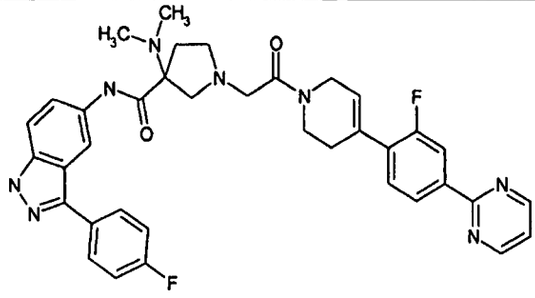
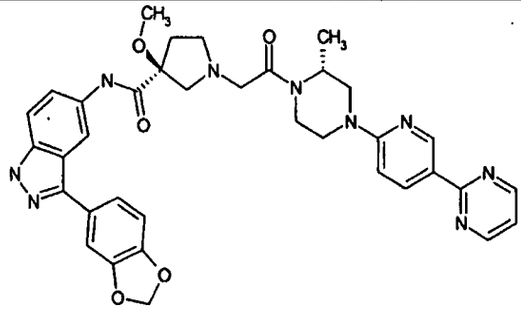
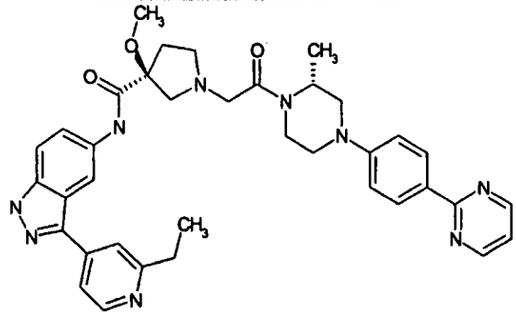
777	 (see also Preparation 67)	662	2.72
778	 (see also Preparation 85)	618	3.19
779	 (see also Preparation 86)	622	3.16
780		624	3.13

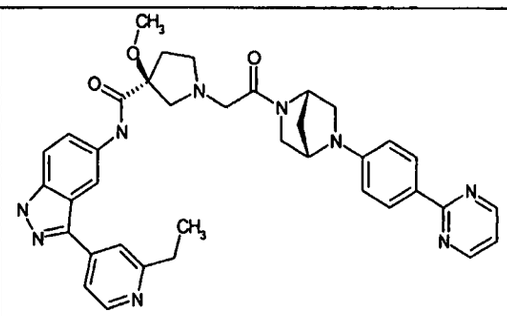
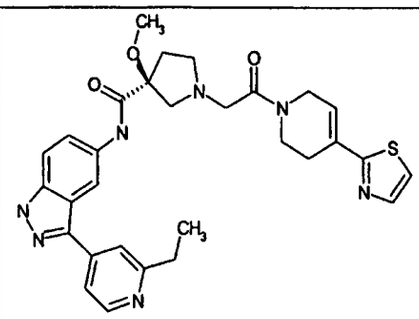
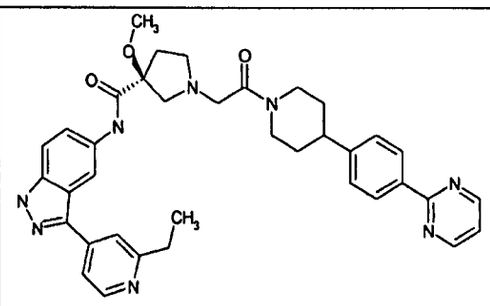
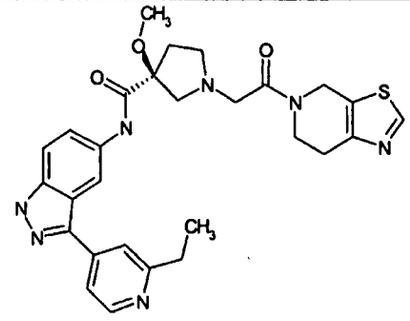
781		640	3.37
782		652.4	3.35
783		648.4	3.11
784		699.4	3

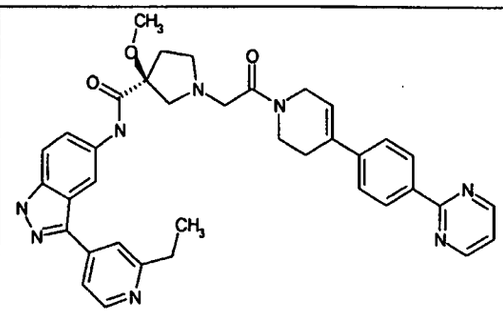
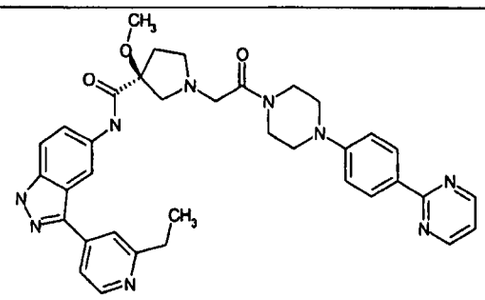
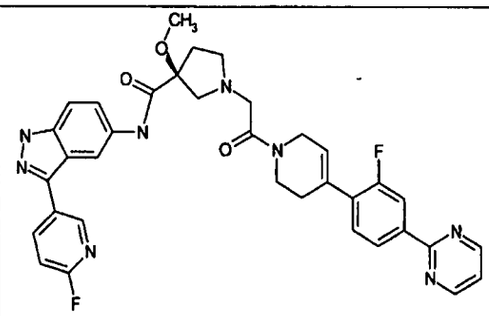
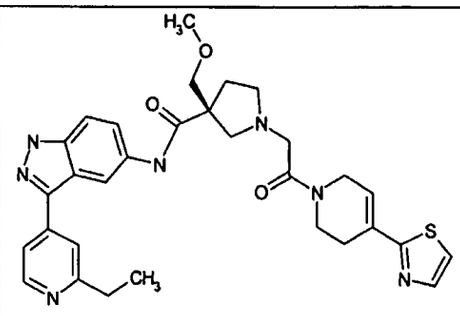
785		665.4	2.97
786		667.4	2.89
787		662.4	2.84
788		685.4	2.92

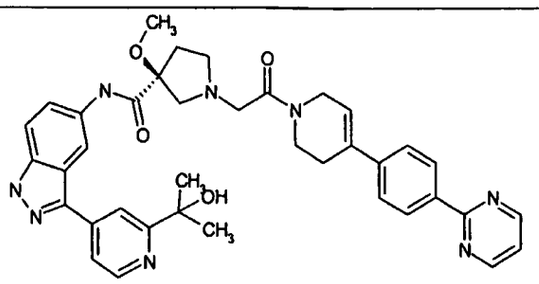
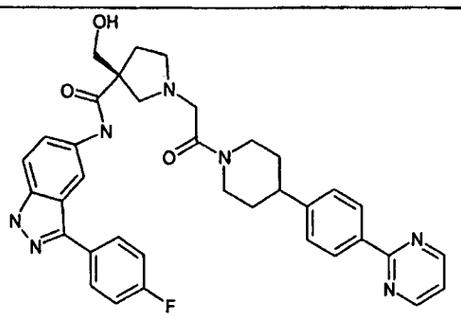
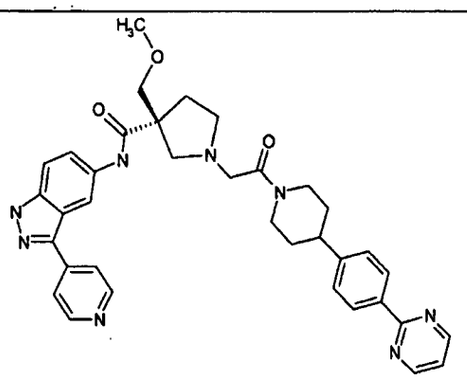
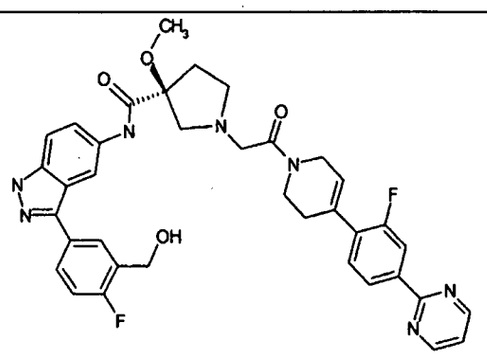
789		631.3	2.07
790		690.4	2.75
791		652.4	1.83
792		652.4	2.94

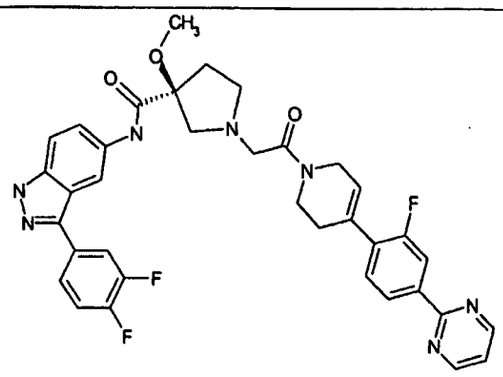
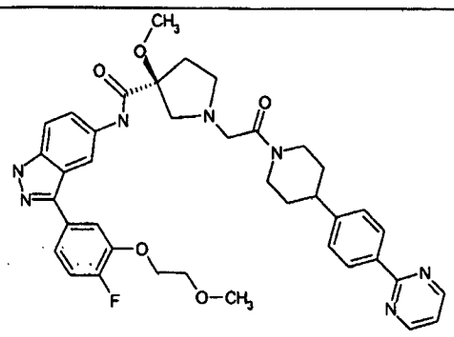
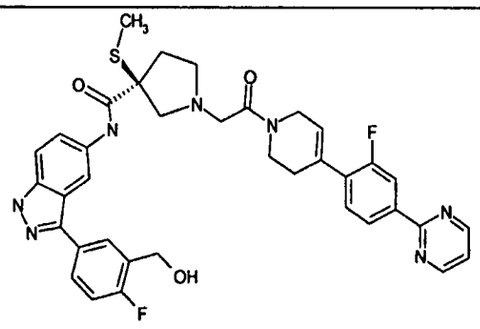
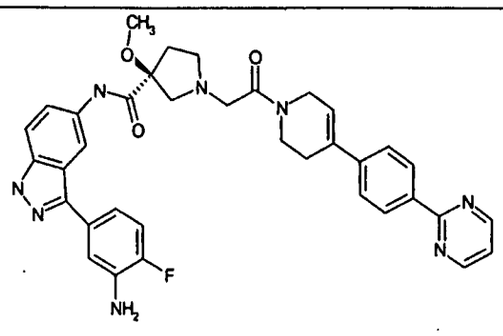
793		659.4	2.41
794		664.4	2.76
795		671	2.59
796		604	2.33

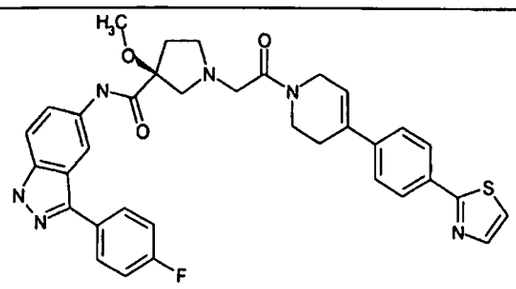
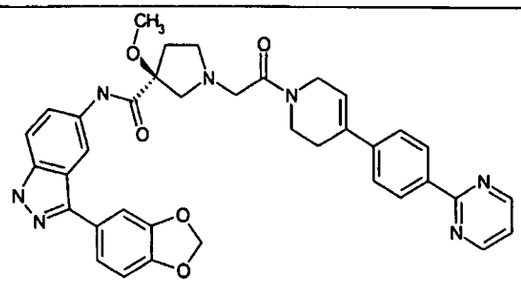
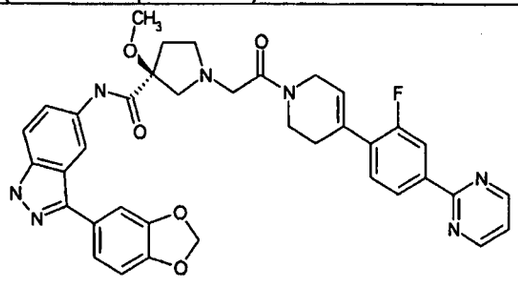
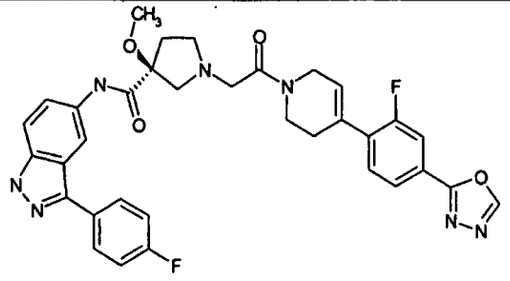
797		663	3.26
798		663	3.26
799		676	2.49
800		660.8	2.71

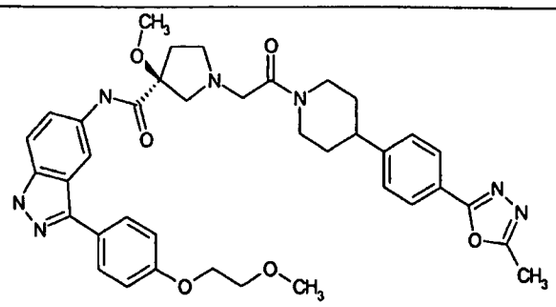
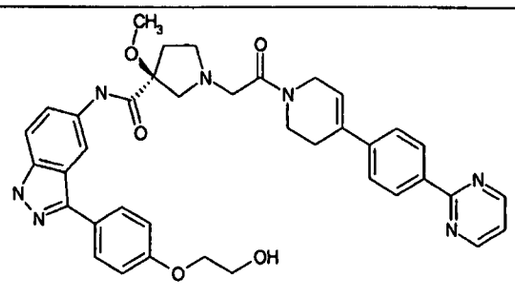
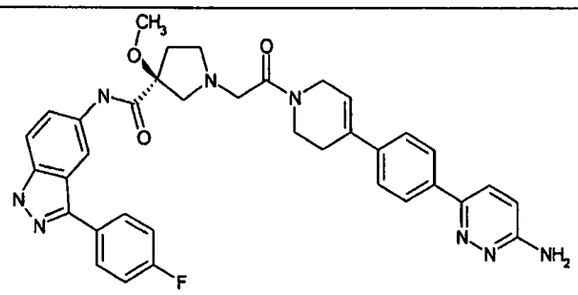
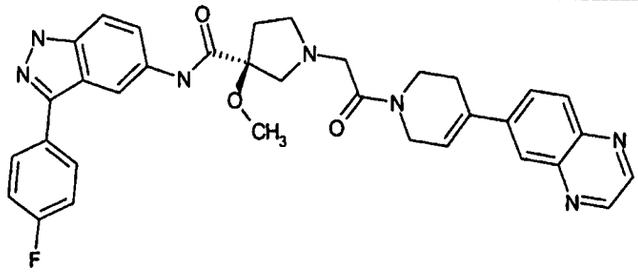
801		658.8	2.5
802		572.7	2.27
803		645.8	2.73
804		546.7	2.02

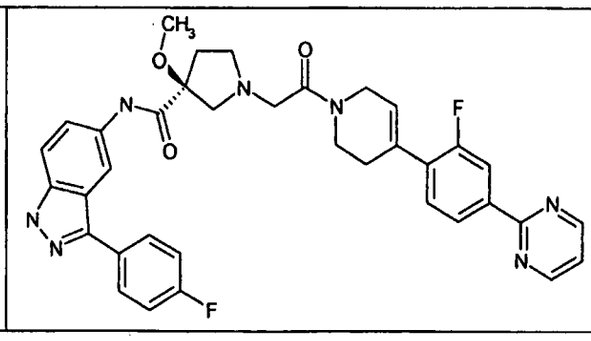
805		643.7	2.76
806		646.8	2.55
807		651.7	3.99
808		586.7	2.28

809		576.7	2.75
810		634.3	3.52
811		631.3	2.25
812		680.4	2.91

813		668.4	3.31
814		708.4	3.07
815		696.4	2.84
816		647.2	3.34

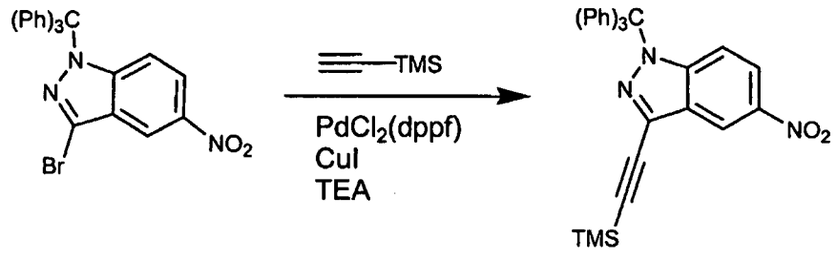
817		637.4	3.34
818	 (see also Preparation 89)	658.4	3.13
819		676.4	3.11
820		640.4	2.78

821		694.4	2.64
822		674.4	2.53
823		647.4	2.38
824	 (see also Preparation 87)	606	3.32

825		650.4	3.28

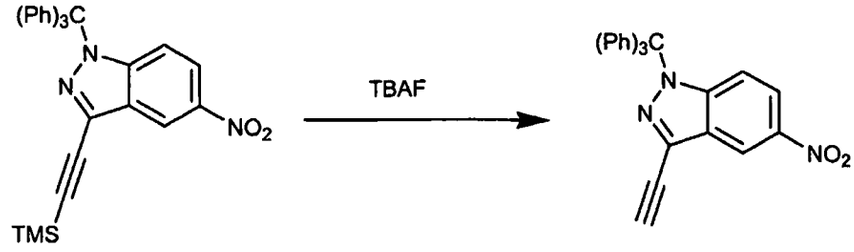
Examples 826 and 827

Synthesis of 5-Nitro-3-trimethylsilanylethynyl-1-trityl-1H-indazole:



A mixture of 3-bromo-5-nitro-1-trityl-1H-indazole (4.83 g, 10 mmol), ethynyl-trimethyl-silane (1g, 10 mmol), copper (I) iodide (91 mg, 0.5 mmol), $PdCl_2(dppf)$ (337 mg, 0.5 mmol) and triethylamine (1.2 g, 12 mmol) in DMF (50 mL) was stirred overnight at 80 °C under argon. Then ethyl acetate (100 mL) was added, followed by water. The organic layer was collected and aqueous layer was extracted three times with ethyl acetate. The combined organic fraction was washed with water and then brine. The solvent was removed under vacuum and the product was purified using chromatography (20% hexane in dichloromethane) to give desired product (3.4 g) in 67% yield.

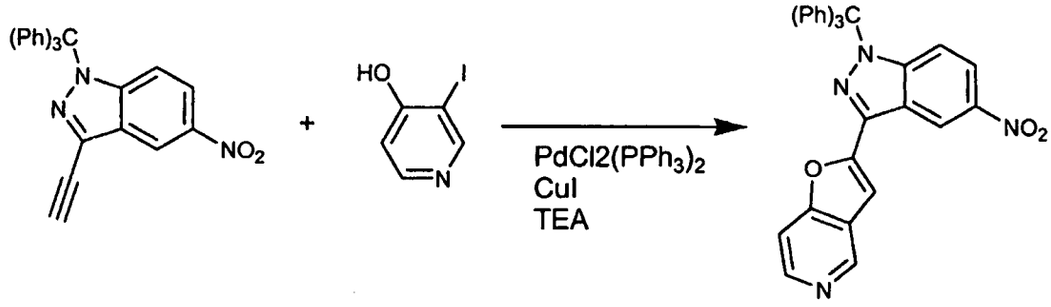
Synthesis of 3-ethynyl-5-nitro-1-trityl-1H-indazole:



To a solution of 5-nitro-3-trimethylsilanylethynyl-1-trityl-1H-indazole (700 mg, 1.4 mmol) in THF (5 mL) was added tributylammonium fluoride (1M, 2.8 mL, 2.8

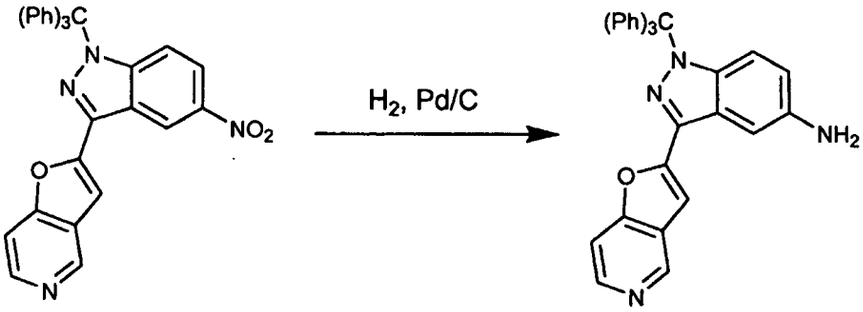
mmol). The resulted solution was stirred at room temperature for 2 hours. TLC showed the completion of reaction. After removal the solvent under vacuum, the product was purified using silica (20 hexane in dichloromethane) to give 560 mg of titled product (93% yield).

Synthesis of 2-(5-Nitro-1-trityl-1H-indazol-3-yl)-furo[3,2-c]pyridine



A reaction mixture containing 3-ethynyl-5-nitro-1-trityl-1H-indazole (215 mg, 0.5 mmol), 3-iodo-pyridin-4-ol (132 mg, 0.6 mmol), copper (I) iodide (4.5 mg, 0.025 mmol), $PdCl_2(PPh_3)_2$ and triethylamine (120 mg, 1.2 mmol) in DMF (3 mL) was heated at 100 °C overnight under argon. After the completion of reaction (shown by TLC), ethyl acetate (50 mL)was added and the reaction mixture was added to water. The organic layer was collected, washed with water, brine and concentrated under vacuum. After purification using silica (7% methanol in dichloromethane), the desired product was obtained (210 mg, 0.4 mmol) in 80% yield.

Synthesis of 2-(5-amino-1-trityl-1H-indazol-3-yl)-furo[3,2-c]pyridine

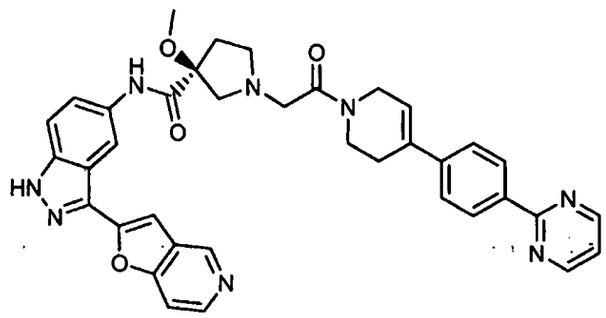
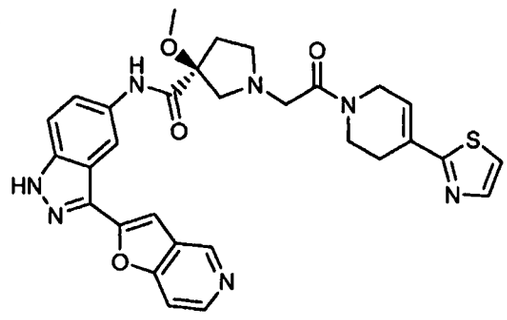


In a round-bottom flask equipped with a balloon, a mixture 2-(5-Nitro-1-trityl-1H-indazol-3-yl)-furo[3,2-c]pyridine (210 mg, 0.4 mmol) and 5% Pd on carbon (21 mg)

in ethyl acetate and methanol (10 mL, 1:1) was hydrogenated overnight at room temperature to give 157 mg desired product (80% yield).

Following procedures described above the compounds in Table 29 were prepared.

Table 29

Compound	Retention Time (min)	M+1
 (Example 826)	2.67	655
 (Example 827)	2.18	584

ASSAYS

Coupled ERK2 Assay:

Activity of compounds against inactive ERK2 was tested in a coupled MEK1/ERK2 IMAP assay as follows: Compounds were diluted to 25x final test concentration in 100% DMSO. 14µl of kinase buffer (10mM Tris.HCl pH 7.2, 10mM $MgCl_2$, 0.01% Tween-20, 1mM DTT) containing 0.4ng unphosphorylated Mouse

ERK2 protein was added to each well of a black 384-well assay plate. 1µl of 25x compound was added to each well and incubated at room temperature for 30 minutes to allow an opportunity for the compound to bind to the inactive enzyme. DMSO concentration during initial incubation is 6.7%. ERK2 activity was determined to be insensitive to DMSO concentrations up to 20%. ERK2 was then activated and it's kinase activity measured by the addition of 10µl kinase buffer with the following components (final concentration per reaction): 2ng active (phosphorylated) human MEK1 protein and 4µM (total) ERK2 IMAP substrate peptides (3.9µM unlabeled IPTTPITTTYFFFK-$CONH_2$ and 100nM IPTTPITTTYFFFK(5-carboxyfluorescein)-$CONH_2$) and 30µM ATP. DMSO concentration during ERK activation was 4%. After one hour, reactions were terminated by addition of 60µl IMAP detections beads in binding buffer (Molecular Devices). Binding was allowed to equilibrate for 30 minutes before reading the plate on an LJL Analyst Fluorescence Polarization plate reader. Compound inhibition was calculated relative to DMSO and fully inhibited standards. Active compounds were reconfirmed in an independent assay.

Active ERK2 Assay:

Activated ERK2 activity was also determined in the IMAP assay format using the procedure outlined above. 1µl of 25x compound was added to 14µl of kinase buffer containing 0.25ng fully phosphorylated, active Mouse ERK2 protein. Following a 30 minute incubation, the reactions were initiated by addition of 10µl of kinase buffer containing 1µM ERK2 IMAP substrate peptide (0.9µM unlabeled IPTTPITTTYFFFK-$CONH_2$ and 100nM IPTTPITTTYFFFK(5-carboxyfluorescein)-$CONH_2$) and 30µM ATP. Reactions proceeded for 30 minutes before termination by addition of 60µl IMAP detection beads in binding buffer. Plates were read as above after 30 minute binding equilibration. Active compounds were reconfirmed in an independent assay.

Soft Agar Assay:

Anchorage-independent growth is a characteristic of tumorigenic cell lines. Human tumor cells can be suspended in growth medium containing 0.3% agarose and an indicated concentration of a farnesyl transferase inhibitor. The solution can be overlayed onto growth medium solidified with 0.6% agarose containing the same concentration of ERK1 and ERK2 inhibitor as the top layer. After the top layer is

solidified, plates can be incubated for 10-16 days at 37°C under 5% CO_2 to allow colony outgrowth. After incubation, the colonies can be stained by overlaying the agar with a solution of MTT (3-[4,5-dimethyl-thiazol-2-yl]-2,5-diphenyltetrazolium bromide, Thiazolyl blue) (1 mg/mL in PBS). Colonies can be counted and the IC_{50}'s can be determined.

The AUC (area under the concentration-time curve during the first 6 hours (AUC_{6hr}) in Table 30 below was determined using the Protocol of Cassette Accelerating Rapid Rat screen (CARRS)

Animal dosing and sample collection

Male Sprague-Dawley rats (Charles River, Co.) were pre-cannulated (femoral artery) in order to facilitate precise blood sampling times, and to reduce the stress on the animals caused by serial bleedings. Following an overnight fast, two rats were dosed orally with one compound at a dose of 10 mg/kg in a 5-mL/kg dose volume. Blood was collected into heparin-containing tubes serially from each animal at 0.5, 1, 2, 3, 4 and 6 h post-dosing and centrifuged to generate plasma. Approximately 100 µL of plasma were collected at the individual time points. The plasma samples were stored at -20 °C until analysis.

Plasma sample and standard curve preparation

A set of 12 rat plasma samples was generated for each NCE (i.e. 6 timepoints and n = 2 rats). These 12 samples were pooled across the two rats at each timepoint to provide 6 pooled samples (one sample per time point) for each NCE. The pooled samples were assayed as cassettes of six (36 samples total) to provide data on the six compounds. The50-µL aliquots of the 36 plasma samples were placed into individual wells of a 96-well plate. An additional compound (often a structural analog of the test compounds) was selected as the internal standard. A mini-calibration curve was prepared (three points plus a zero) for each compound assayed. Drug-free rat plasma was measured into 1-mL aliquots and each aliquot was spiked with known concentrations of the compounds to generate standards of the desired concentrations. The concentrations of the standards were chosen to bracket the expected concentration of the pooled samples based on historical data from previous studies on other compounds. For this work, the standards were set to contain

concentrations of 25, 250 and 2500 ng NCE/mL plasma. The plasma standards were precipitated in duplicate along with the samples. Protein precipitation occurred after addition of 150 µL of acetonitrile containing the internal standard at a concentration of 1 ng/mL into each sample well using the Tomtec Quadra 96 system. The precipitated samples and standards were vortexed and centrifuged in the 96-well plate. Approximately 50-100 µL of the supernatant were removed and placed into a fresh 96-well plate using the Tomtec Quadra 96 system. A volume of 5-10 µL of the supernatant was used for analysis by HPLC-MS/MS. The mini-standard curve was run in duplicate, once before and once after the samples. Thus, a total of 14 study samples plus standards were analyzed per compound. In addition, solvent blanks were injected before and after each set of 14 and after the highest calibration standard for each compound; therefore, a total of 103 injections were made into each HPLC system for each set of six compounds. Multiple solvent blank injections could be made from a single well. Twelve solvent blank wells were designated in each 96-well plate. Thus, one batch (cassette) of six NCEs was prepared and assayed using one 96-well plate format.

HPLC-MS/MS analysis

All the compounds were analyzed using selected reaction monitoring (SRM) methods with LC/MS/MS instruments. Once the method development had been completed, the assay was quickly set up using a standard injection sequence template for the CARRS assay.

The final compounds of Examples 1, 2, 4-61, 65-73, 77-84, 86, 88-98, 100, 102-114, 116-118, 120, 121, 124, 125, 151-155, 159-179, 183, 184, 186, 188-193, 196-199, 202-205, 250, 253-259, 260-299, 301-318, 320-323, 332-347, 356 (Isomer Z), 356 (Isomer E), 357-360, 362, 362 (compound 9P), 364, 368-436, 440-509, 511-602, 606, 607, 609-623, and 625 to 824 had an AERK2 IC50 in the range of 0.16 to 20,000 nM. The final compounds of Examples 1 to 611 are disclosed in WO2007/070398 (published on June 21, 2007).

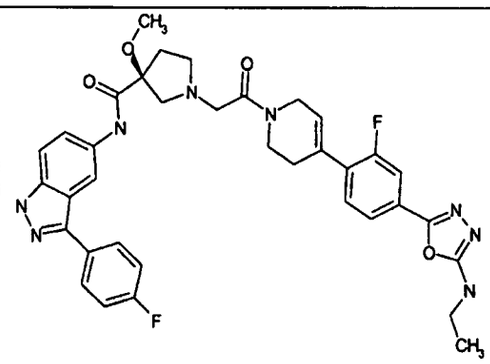
The final compounds of Examples 1, 2, 4-28, 61, 86, 88, 89, 92, 95, 98, 100, 120, 125, 132, 142, 152, 154, 168, 176, 183, 184, 186, 188-193, 196-199, 202-205, 250, 251, 253-259, 261, 264, 269, 271, 274-276, 282, 286, 289, 290, 292, 294, 302, 303, 304, 306, 314-316, 332, 333, 335, 338, 343, 358, 362, 368-370, 384-390, 440-

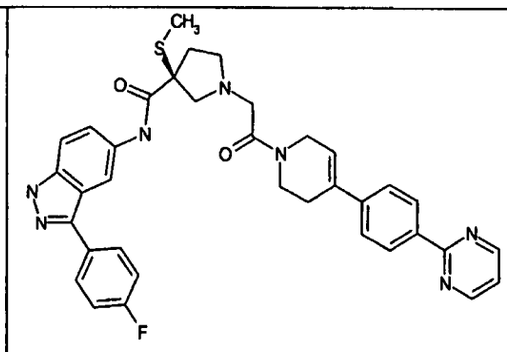
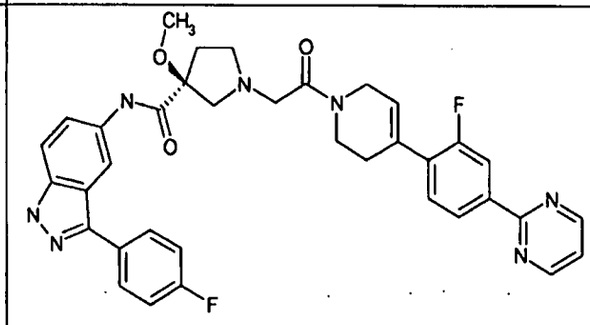
493, 510-558, 606, 611, 613-617, 620, 622, 623, 627-630, 634, 635, 639, 641, 643-645, 647, 651, 654-658, 661, 663, 666, 669, 670, 672, 673, 675-677, 679, 680, 682, 685, 688-694, 696-703, 705-707, 710-735, 737, 738, 740, 741, 743-745, 747, 749, 751-753, 755, 757, 758, 760-762, 764, 765, 767, 770-772, 776, 777, 779, 785, 786, 788, 789, 792, 793, 794, 796, 799, 802, 803-805, 807-809, 811-812, 814-816, 818-820, 822, and 823 had an AERK2 IC_{50} in the range of 0.16 to 18 nM. The final compounds of Examples 1 to 611 are disclosed in WO2007/070398 (published on June 21, 2007).

The final compounds of Examples 6, 100, 183, 184, 186, 188-192, 261, 440-450, 510-517 and 787 had an AERK2 IC_{50} in the range of 0.16 to 1.5 nM. The final compounds of 6, 100, 183, 184, 186, 188-192, 261, 440-450, 510-517 are disclosed in WO2007/070398 (published on June 21, 2007).

Table 30 provides AERK2 IC_{50} data and Rat Auc data for compounds of this invention.

Table 30

Ex.	Compound	AERK2 IC50 (nM)	Rat AUC PO (nM.h)
622		5	1128

613		10	25914
825		20	1101

For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. The powders and tablets may be comprised of from about 5 to about 95 percent active ingredient. Suitable solid carriers are known in the art, e.g. magnesium carbonate, magnesium stearate, talc, sugar or lactose. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration. Examples of pharmaceutically acceptable carriers and methods of manufacture for various compositions may be found in A. Gennaro (ed.), Remington: The Science and Practice of Pharmacy, 20th Edition, (2000), Lippincott Williams & Wilkins, Baltimore, MD.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection or addition of sweeteners and opacifiers for oral solutions, suspensions and emulsions. Liquid form preparations may also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas, e.g. nitrogen.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

The compounds of the invention may also be deliverable transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

Preferably the compound is administered orally.

Preferably, the pharmaceutical preparation is in a unit dosage form. In such form, the preparations subdivided into suitably sized unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose.

The quantity of active compound in a unit dose of preparation may be varied or adjusted from about 0.01 mg to about 1000 mg, preferably from about 0.01 mg to about 750 mg, more preferably from about 0.01 mg to about 500 mg, and most preferably from about 0.01 mg to about 250 mg according to the particular application.

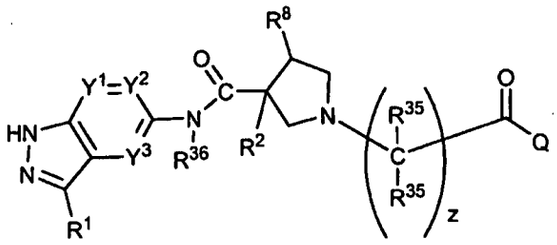
The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage regimen for a particular situation is within the skill in the art. For convenience, the total daily dosage may be divided and administered in portions during the day as required.

The amount and frequency of administration of the compounds of the invention and/or the pharmaceutically acceptable salts thereof will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. A typical recommended daily dosage regimen for oral administration can range from about 0.04 mg/day to about 4000 mg/day, in two to four divided doses.

While the present invention has been described in conjunction with the specific embodiments set forth above, many alternatives, modifications and variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

WHAT IS CLAIMED IS:

1. A compound of formula 1.0:



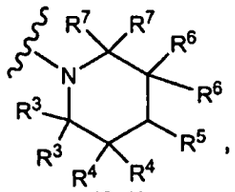
(1.0)

or the pharmaceutically acceptable salts, esters and solvates thereof, wherein:

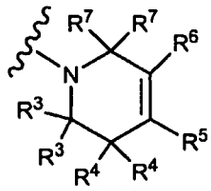
Y^1, Y^2, and Y^3 are each independently selected from the group consisting of: -CH=, -N= and $-CR^9$=;

z is 1 to 3;

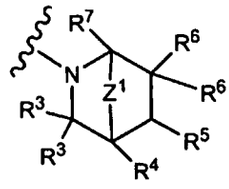
Q is a substituent selected from the group consisting of:



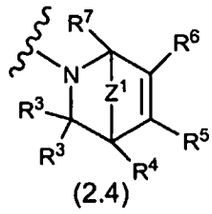
(2.1)



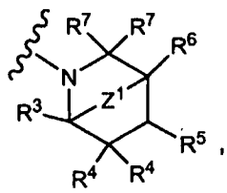
(2.2)



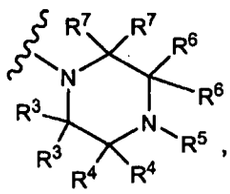
(2.3)



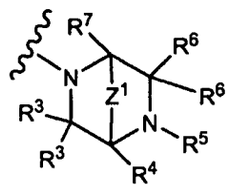
(2.4)



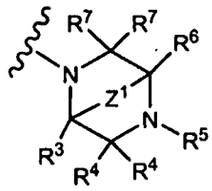
(2.5)



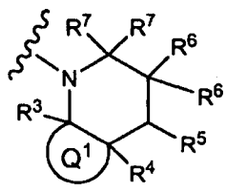
(2.6)



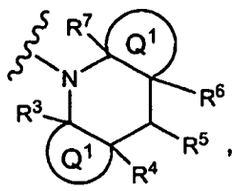
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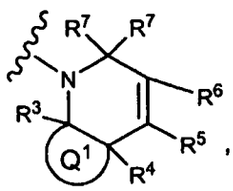
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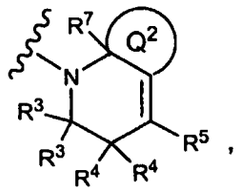
(2.9)



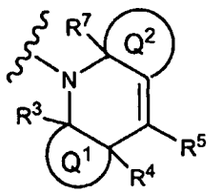
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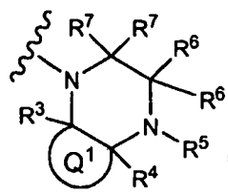


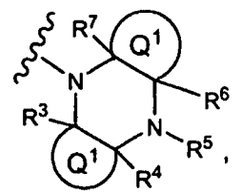
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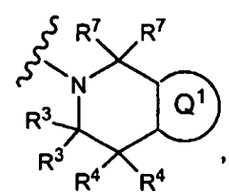


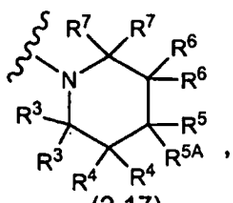
(2.12)

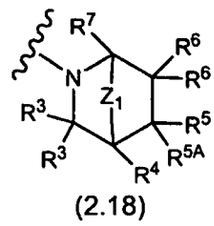

(2.13),

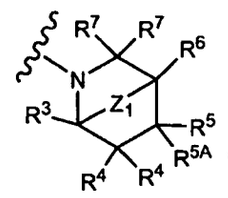

(2.14),

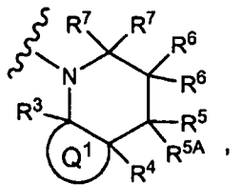

(2.15),

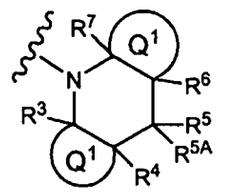

(2.16),

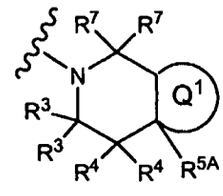

(2.17),


(2.18),


(2.19),


(2.20),


(2.21), and


(2.22);

Each Q^1 represents a ring independently selected from the group consisting of: cycloalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl, wherein said substituted rings are substituted with 1 to 3 substituents independently selected from the group consisting of: halo and the R^{10} moieties; provided that when Q^1 is aryl, heteroaryl, substituted aryl or substituted heteroaryl then the carbon atoms at the ring junction are not substituted;

Q^2 represents a ring selected from the group consisting of: cycloalkyl, substituted cycloalkyl, heterocycloalkyl, and substituted heterocycloalkyl, wherein said substituted rings are substituted with 1 to 3 substituents independently selected from the group consisting of: the R^{10} moieties;

Z^1 represents $-(C(R^{24})_2)_w-$ wherein each R^{24} is independently selected from the group consisting of: H, alkyl and F, and wherein w is 1, 2 or 3;

Z^2 is selected from the group consisting of: $-N(R^{44})-$, -O- and $-C(R^{46})_2-$;

m is 1 to 6;

n is 1 to 6;

p is 0 to 6;

t is 0, 1, or 2;

R^1 is selected from the group consisting of:

(1) –CN,

(2) $-NO_2$,

(3) $-OR^{10}$,

(4) $-SR^{10}$,

(5) $-N(R^{10})_2$,

(6) R^{10},

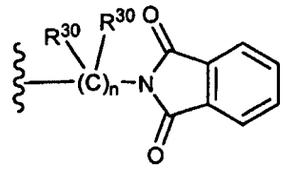
(7) $-C(O)R^{10}$,

(8) $-(C(R^{30})_2)_n-NR^{32}-C(O)-R^{10}$,

(9) $-(C(R^{30})_2)_n-NR^{32}-S(O)_t-R^{10}$,

(10) $-(C(R^{30})_2)_n-NR^{32}-C(O)-N(R^{32})-R^{10}$,

(11)



(12) $-CF_3$,

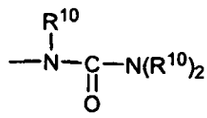
(13) $-C(O)OR^{10}$,

(14) $-(C(R^{30})_2)_nR^{13}$ (e.g., $-(CH_2)_nR^{13}$),

(15) alkenyl,

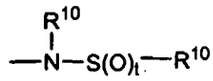
(16) $-NR^{32}-C(O)-R^{14}$,

(17)



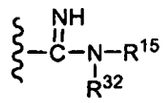
wherein each R^{10} is independently selected,

(18)



wherein each R^{10} is independently selected,

(19)



,

(20) $-C(O)-NR^{32}-(C(R^{30})_2)_p-OR^{10}$,

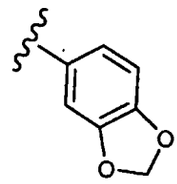
(21) $-C(O)N(R^{10})_2$ wherein each R^{10} is independently selected,

(22) $-C(O)-NR^{32}-C(R^{18})_3$,

(23) $-C(O)-NR^{32}-(C(R^{30})_2)_n-C(O)-N(R^{10})_2$,

(24) heterocycloalkenyl,

(25)



, and

(26) arylalkenyl-;

R^2 is selected from the group consisting of:

(1) H,

(2) -CN,

(3) halo,

(4) alkyl,

(5) substituted alkyl wherein said substituted alkyl is substituted with 1 to 3 substitutents selected from the group consisting of: (a) -OH, (b) -O-alkyl (e.g., -O-(C_1-C_3alkyl), (c) -O-alkyl substituted with 1 to 3 F atoms, and (d) $-N(R^{40})_2$ wherein each R^{40} is independently selected from the group consisting of: (i) H, (ii) C_1-C_3 alkyl, (iii) $-CF_3$, and (e) halo,

(6) alkynyl,

(7) alkenyl,

(8) $-(CH_2)_mR^{11}$,

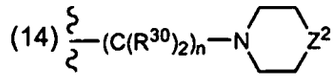
(9) $-N(R^{26})_2$,

(10) $-OR^{23}$,

(11) $-N(R^{26})C(O)R^{42}$,

(12) cycloalkyl,

(13) cycloalkylalkyl,

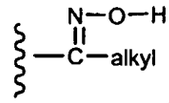
(14)  ,

(15) –O-(substituted alkyl) wherein said substituted alkyl is substituted with 1 to 3 F atoms,

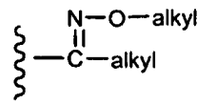
(16) $-S(O)_t$-alkyl,

(17) –C(O)-alkyl,

(18)

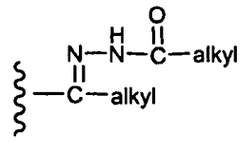
 ,

(19)



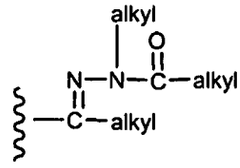
wherein each alkyl is independently selected,

(20)



which each alkyl is independently selected,

(21)



wherein each alkyl is independently selected,

(22) $-N(R^{48})$-C(O)-R^{48} wherein each R^{48} is independently selected from the group consisting of: H and alkyl, and

(23) –C(O)-alkyl, such as, for example, -C(O)-(C_1-C_6 alkyl), such as, for example, $-C(O)CH_3$;

each R^3, R^4, R^5, R^6 and R^7 is independently selected from the group consisting of:

(1) H,
(2) alkenyl,
(3) substituted alkenyl,
(4) alkyl,
(5) substituted alkyl,
(6) cycloalkyl,
(7) substituted cycloalkyl,
(8) cycloalkylalkyl-,
(9) substituted cycloalkylalkyl-,
(10) heterocycloalkyl,
(11) substituted heterocycloalkyl,
(12) heterocycloalkylalkyl-,
(13) substituted heterocycloalkylalkyl-,
(14) $-C(O)R^{10}$,
(15) arylheteroaryl-,
(16) substituted arylheteroaryl-,
(17) heteroarylaryl-,
(18) substituted heteroarylaryl-,
(19) aryl,
(20) substituted aryl,
(21) heteroaryl,
(22) substituted heteroaryl,
(23) heteroarylheteroaryl-,
(24) substituted heteroarylheteroaryl-,
(25) arylaminoheteroaryl-,
(26) substituted arylaminoheteroaryl-,
(27) arylalkynyl-,
(28) substituted arylalkynyl-,
(29) heteroarylalkynyl-,
(30) substituted heteroarylalkynyl-, and
(31) benzoheteroaryl,

wherein said R^3, R^4, R^5, R^6 and R^7 substituted groups (7), (9), (11), (13), (16), (18), (20), (22), (24), (26), (28) and (30) are substituted with 1 to 3 substituents independently selected from the group consisting of: $-NH_2$, $-NHR^{20}$, $-N(R^{20})_2$ wherein each R^{20} is independently selected, alkyl, alkenyl, halo, $-C(O)-NH-R^{28}$, $-C(O)OR^{28}$, $-C(O)R^{28}$, and $-OR^{20}$, and

wherein said R^3, R^4, R^5, R^6 and R^7 substituted groups (3) and (5) are substituted with 1 to 3 substituents independently selected from the group consisting of: $-NH_2$, halo (e.g., F, Cl and Br, and in another example F), $-C(O)-NH-R^{28}$ (e.g., $-C(O)-NH-CH_3$), $-C(O)OR^{28}$ (e.g., $-C(O)OC_2H_5$), and $-C(O)R^{28}$ (e.g., $-C(O)CH_3$);

R^{5A} is selected from the group consisting of: halo, -OH, alkyl, and –O-alkyl;

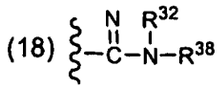
R^8 is selected from the group consisting of: H, -OH, $-N(R^{10})_2$, $-NR^{10}C(O)R^{12}$, and alkyl;

each R^9 is independently selected from the group consisting of:halogen, -CN, $-NO_2$, $-OR^{10}$, $-SR^{10}$, $-N(R^{10})_2$, and R^{10};

each R^{10} is independently selected from the group consisting of: H, alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, alkylheteroaryl-, alkylaryl-, substituted alkyl, substituted aryl, substituted arylalkyl, substituted heteroaryl, substituted heteroarylalkyl, substituted cycloalkyl, substituted cycloalkylalkyl, substituted heterocycloalkyl, substituted heterocycloalkylalkyl, substituted alkylheteroaryl-, substituted alkylaryl-, heterocycloalkenyl, and substituted heterocycloalkenyl, and wherein:

said R^{10} substituted alkyl is substituted with 1 to 3 substituents independently selected from the group consisting of: $-NH_2$, $-NHR^{20}$, $-NO_2$, -CN, $-OR^{26}$, halo, $-C(O)-NH-R^{26}$, $-C(O)OR^{26}$, and $-C(O)R^{26}$, and

said R^{10} substituted aryl, substituted arylalkyl, substituted heteroaryl, substituted heteroarylalkyl, substituted cycloalkyl, substituted cycloalkylalkyl, substituted heterocycloalkyl, substituted heterocycloalkylalkyl, substituted alkylheteroaryl- and substituted alkylaryl- are substituted with 1 to 3 substituents independently selected from the group consisting of: (1) $-NH_2$, (2) $-NO_2$, (3) -CN, (4) -OH, (5) $-OR^{20}$, (6) $-OCF_3$, (7) alkyl substituted with 1 to 3 independently selected halo atoms, (8) $-C(O)R^{38}$, (9) alkyl, (10) alkenyl, (11) halo, (12) $-C(O)-NH-R^{26}$, (13) $-C(O)OR^{38}$, (14) $-C(O)-NR^{32}-(C(R^{30})_2)_n-N(R^{38})_2$, (15) $-S(O)_tR^{38}$, (16) $-C(O)-NR^{32}-R^{38}$, (17) $-NR^{32}-C(O)-R^{38}$,

(18) 

(19) $-NHR^{20}$, (20) cycloalkyl, (21) –O-alkyl-O-R^{20}, (22) hydroxyalkyl, (23) $-N(R^{20})_2$ wherein each R^{20} is independently selected, (24) –alkyl-OR^{20}, (25) –O-alkyl-OH, (26) –NH(hydroxyalkyl), and (27) oxazolidinone;

R^{11} is selected from the group consisting of: F, -OH, -CN, $-OR^{10}$, $-NHNR^1R^{10}$, $-SR^{10}$ and heteroaryl;

R^{12} is selected from the group consisting of: alkyl, aryl, heteroaryl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl and heterocycloalkylalkyl;

R^{14} is selected from the group consisting of: alkyl, aryl, heteroaryl, cycloalkyl, cycloalkylalkyl-, heterocycloalkyl, alkylheterocycloalkyl, heterocycloalkylalkyl-, alkylheteroaryl- and alkylaryl-;

R^{15} is selected from the group consisting of: H, -OH, alkyl, aryl, heteroaryl, cycloalkyl, cycloalkylalkyl-, heterocycloalkyl and heterocycloalkylalkyl-, alkylheteroaryl- and alkylaryl-;

R^{20} represents alkyl;

R^{23} is selected from the group consisting of: H, alkyl, aryl, cycloalkyl, and cycloalkylalkyl-;

each R^{26} is independently selected from the group consisting of: H and alkyl;

R^{28} is alkyl;

each R^{30} is independently selected from the group consisting of: H, alkyl, and F;

each R^{32} is independently selected from the group consisting of: H and alkyl, and wherein each R^{32} is generally H;

each R^{35} is independently selected from the group consisting of: H and C_1 to C_6 alkyl;

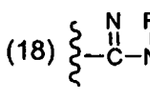
R^{36} is selected from the group consisting of: H, alkyl, and –O-alkyl;

each R^{38} is independently selected from the group consisting of: H, alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, alkylheteroaryl-, alkylaryl-, substituted alkyl, substituted aryl, substituted arylalkyl, substituted heteroaryl, substituted heteroarylalkyl, substituted cycloalkyl, substituted cycloalkylalkyl, substituted heterocycloalkyl, substituted

heterocycloalkylalkyl, substituted alkylheteroaryl- and substituted alkylaryl-, and wherein:

said R^{38} substituted alkyl is substituted with 1 to 3 substituents independently selected from the group consisting of: $-NH_2$, $-NO_2$, -CN, $-OR^{26}$, halo, $-C(O)-NH-R^{28}$, $-C(O)OR^{28}$, and $-C(O)R^{28}$, and

said R^{38} substituted aryl, substituted arylalkyl, substituted heteroaryl, substituted heteroarylalkyl, substituted cycloalkyl, substituted cycloalkylalkyl, substituted heterocycloalkyl, substituted heterocycloalkylalkyl, substituted alkylheteroaryl- and substituted alkylaryl- are substituted with 1 to 3 substituents independently selected from the group consisting of: (1) $-NH_2$, (2) $-NO_2$, (3) -CN, (4) -OH, (5) $-OR^{20}$, (6) $-OCF_3$, (7) $-CF_3$, (8) $-C(O)R^{26}$, (9) alkyl, (10) alkenyl, (11) halo, (12) $-C(O)-NH-R^{26}$, (13) $-C(O)OR^{26}$, (14) $-C(O)-NR^{32}-(C(R^{30})_2)_n-N(R^{26})_2$, (15) $-S(O)_tR^{26}$, (16) $-C(O)N(R^{32})(R^{26})$, (17) $-NR^{32}C(O)R^{26}$,

(18)  ; and

(19) $-NHR^{20}$;

R^{42} is selected from the group consisting of: alkyl, aryl, heteroaryl, and cycloalkyl;

R^{44} is selected from the group consisting of: H, alkyl, cycloalkyl, and cycloalkylalkyl;

Each R^{46} is independently selected from the group consisting of: H, alkyl, cycloalkyl, and cycloalkylalkyl; and

provided that:

(1) Q^1 is a substituted ring wherein at least one substitutent is halo; and/or

(2) R^2 is substituted alkyl wherein said substituent is $-OCH_3$, or R^2 is selected from the group consisting of: $-CH_2OH$ and $-CH_2OCH_3$; and/or

(3) at least one of R^3, R^4, R^5, R^6, and R^7 is:

(i) selected from the group consisting of: oxadiazolylphenyl-, pyridazinylphenyl-, pyrimidinylpyrazinyl-, substituted oxadiazolylphenyl-, substituted pyridazinylphenyl-, substituted pyrimidinylpyrazinyl-, and benzoheteroaryl; or

(ii) selected from the group consisting of:

(a) substituted cycloalkyl,

(b) substituted cycloalkylalkyl-,

(c) substituted heterocycloalkyl,

(d) substituted heterocycloalkylalkyl-,

(e) substituted arylheteroaryl-,

(f) substituted heteroarylaryl-,

(g) substituted aryl,

(h) substituted heteroaryl,

(i) substituted heteroarylheteroaryl-,

(j) substituted arylaminoheteroaryl-,

(k) substituted arylalkynyl-, and

(l) substituted heteroarylalkynyl-, and

wherein at least one substitutent on at least one at least one of said (ii)(a) to (ii)(l) R^3, R^4, R^5, R^6, or R^7 group is selected from the group consisting of: $-NHR^{20}$, $-N(R^{20})_2$ (wherein each R^{20} is independently selected), and $-OR^{20}$; and/or

(4) R^{5A} is alkyl; and/or

(5) R^{10} is a substituted aryl, and at least one substitutent is selected from the group consisting of:

(a) $-S(O)_tR^{38}$ wherein R^{38} is isopropyl,

(b) –O-alkyl-O-R^{20},

(c) hydroxyalkyl,

(d) $-N(R^{20})_2$,

(e) –alkyl-OR^{20},

(f) –O-alkyl-OH,

(g) –NH(hydroxyalkyl), and

(h) oxazolidinone; and/or

(6) R^{20} is isopropyl.

2. The compound of Claim 1 wherein the proviso is that:

(1) Q^1 is a substituted ring wherein at least one substitutent is halo; and/or

(2) R^2 is substituted alkyl wherein said substituent is $-OCH_3$, or R^2 is selected from the group consisting of: $-CH_2OH$ and $-CH_2OCH_3$; and/or

(3) R^5 is:

(i) selected from the group consisting of: oxadiazolylphenyl-, pyridazinylphenyl-, pyrimidinylpyrazinyl-, substituted oxadiazolylphenyl-, substituted pyridazinylphenyl-, substituted pyrimidinylpyrazinyl-, and benzoheteroaryl; or

(ii) selected from the group consisting of:

(a) substituted cycloalkyl,

(b) substituted cycloalkylalkyl-,

(c) substituted heterocycloalkyl,

(d) substituted heterocycloalkylalkyl-,

(e) substituted arylheteroaryl-,

(f) substituted heteroarylaryl-,

(g) substituted aryl,

(h) substituted heteroaryl,

(i) substituted heteroarylheteroaryl-,

(j) substituted arylaminoheteroaryl-,

(k) substituted arylalkynyl-, and

(l) substituted heteroarylalkynyl-, and

wherein at least one substitutent on at least one at least one of said (ii)(a) to (ii)(l) R^3, R^4, R^5, R^6, or R^7 group is selected from the group consisting of: $-NHR^{20}$ (e.g., $-NHCH_2CH_3$ and $-NHCH_3$), $-N(R^{20})_2$ (wherein each R^{20} is independently selected), and $-OR^{20}$ (e.g., $-OCH_3$); and/or

(4) R^{5A} is alkyl (e.g., C_1 to C_6 alkyl, such as, for example, $-CH_3$); and/or

(5) R^{10} is a substituted aryl, and at least one substitutent is selected from the group consisting of:

(a) $-O$-alkyl-O-R^{20},

(b) hydroxyalkyl,

(c) $-N(R^{20})_2$,

(d) -alkyl-OR^{20},

(e) $-O$-alkyl-OH,

(f) –NH(hydroxyalkyl), and

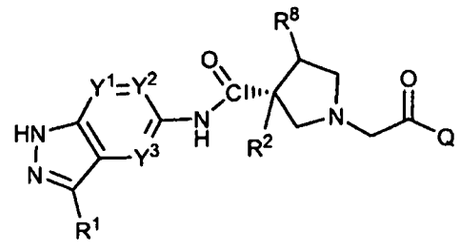
(g) oxazolidinone; and/or

(6) R^{20} is isopropyl.

3. The compound of Claim 1 wherein R^2 is substituted alkyl wherein said substituent is $-OCH_3$.

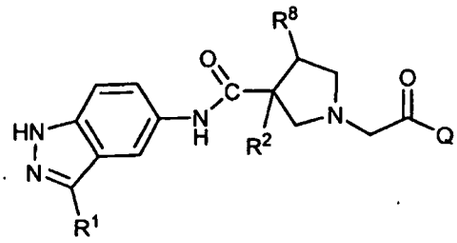
4. The compound of Claim 1 wherein R^2 is selected from the group consisting of: $-CH_2OH$ and $-CH_2OCH_3$.

5. The compound of Claim 1 having the formula:



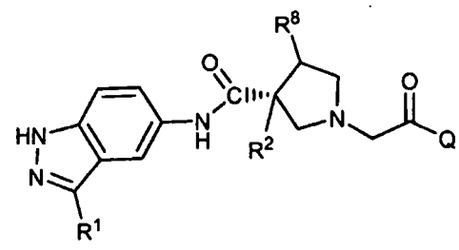
(1.1)

6. The compound of Claim 1 having the formula:



(1.2)

; or

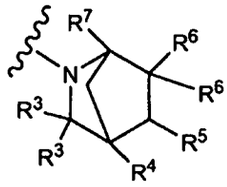


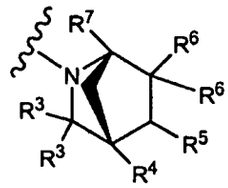
(1.3)

7. The compound of Claim 3 wherein Q is selected from the group consisting of: 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.17, 2.18, 2.19, 2.20, 2.21, and 2.22.

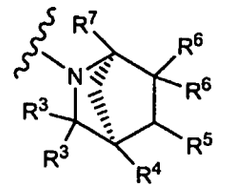
8. The compound of Claim 1 wherein Z^1 is $-CH_2-$, and each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and methyl.

9. The compound of Claim 7 wherein Q is selected from the group consisting of: moieties 2.1, 2.2, and 2.3, and 2.3 is selected from the group consisting of:


(2.3A)


(2.3B)

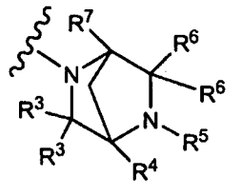
and

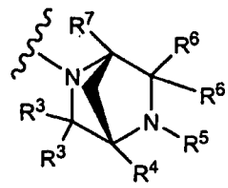

(2.3C)

, and each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and methyl.

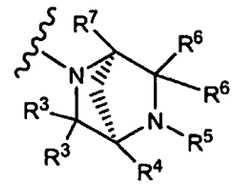
10. The compound of Claim 9 wherein each R^3, R^4, R^6, and R^7 is H, and Q is selected from the group consisting of: 2.1 and 2.3B.

11. The compound of Claim 7 wherein Q is selected from the group consisting of: moieties 2.6 and 2.7, and 2.7 is selected from the group consisting of:


(2.7A)


(2.7B)

and


(2.7C)

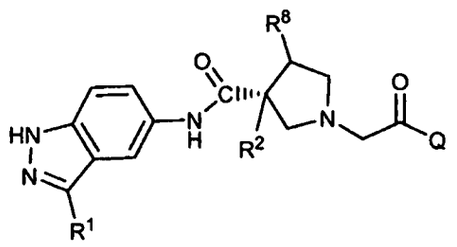
, and each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and methyl.

12. The compound of Claim 11 wherein each R^3, R^4, R^6, and R^7 is H, and Q is selected from the group consisting of: 2.6, 2.7A, and 2.7B.

13. The compound of Claim 1 wherein Q is 2.17, and each R^3, R^4, R^6, and R^7 is independently selected from the group consisting of: H and methyl.

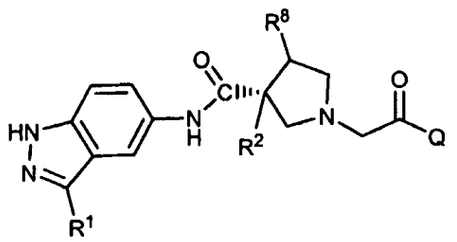
14. The compound of Claim 13 wherein each R^3, R^4, R^6, and R^7 is H.

15. The compound of Claim 10 wherein the compound of formula 1.0 is:



(1.3)

16. The compound of Claim 12 wherein the compound of formula 1.0 is:



(1.3)

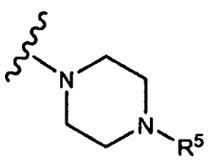
17. The compound of Claim 10 wherein Q is 2.1, and R^3, R^4, R^6, and R^7 are each H.

18. The compound of Claim 12 wherein Q is 2.6.

19. The compound of Claim 12 wherein Q is selected from the group consisting of: 2.7A and 2.7B.

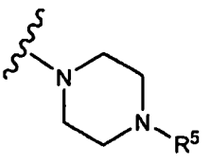
20. The compound of Claim 1 wherein Q is selected from the group consisting of:

(1)



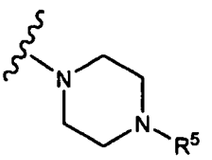
(2.6A) ;

(2)



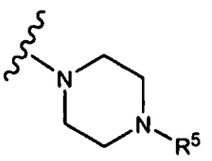
substituted with one or two substituents independently selected from the group consisting of R^3 groups, provided that said one or two substitutents are not H;

(3)



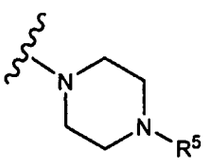
substituted with one or two alkyl groups;

(4)



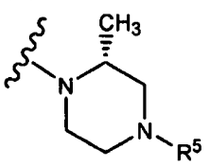
substituted with one or two methyl groups;

(5)



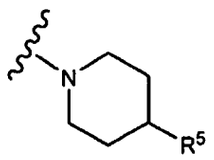
substituted with one methyl group; and

(6)



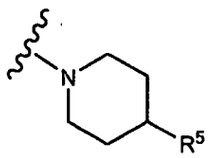
21. The compound of Claim 1 wherein Q is selected from the group consisting of:

(1)



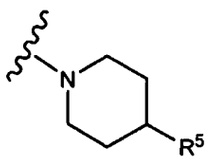
substituted with one or two substituents independently selected from the group consisting of R^3 groups, provided that said one or two substitutents are not H;

(2)



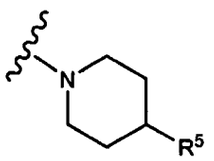
substituted with one or two alkyl groups;

(3)



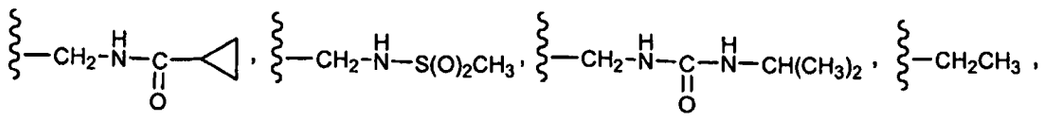
substituted with one or two methyl groups; and

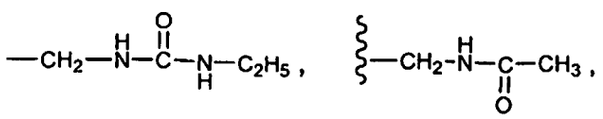
(4)

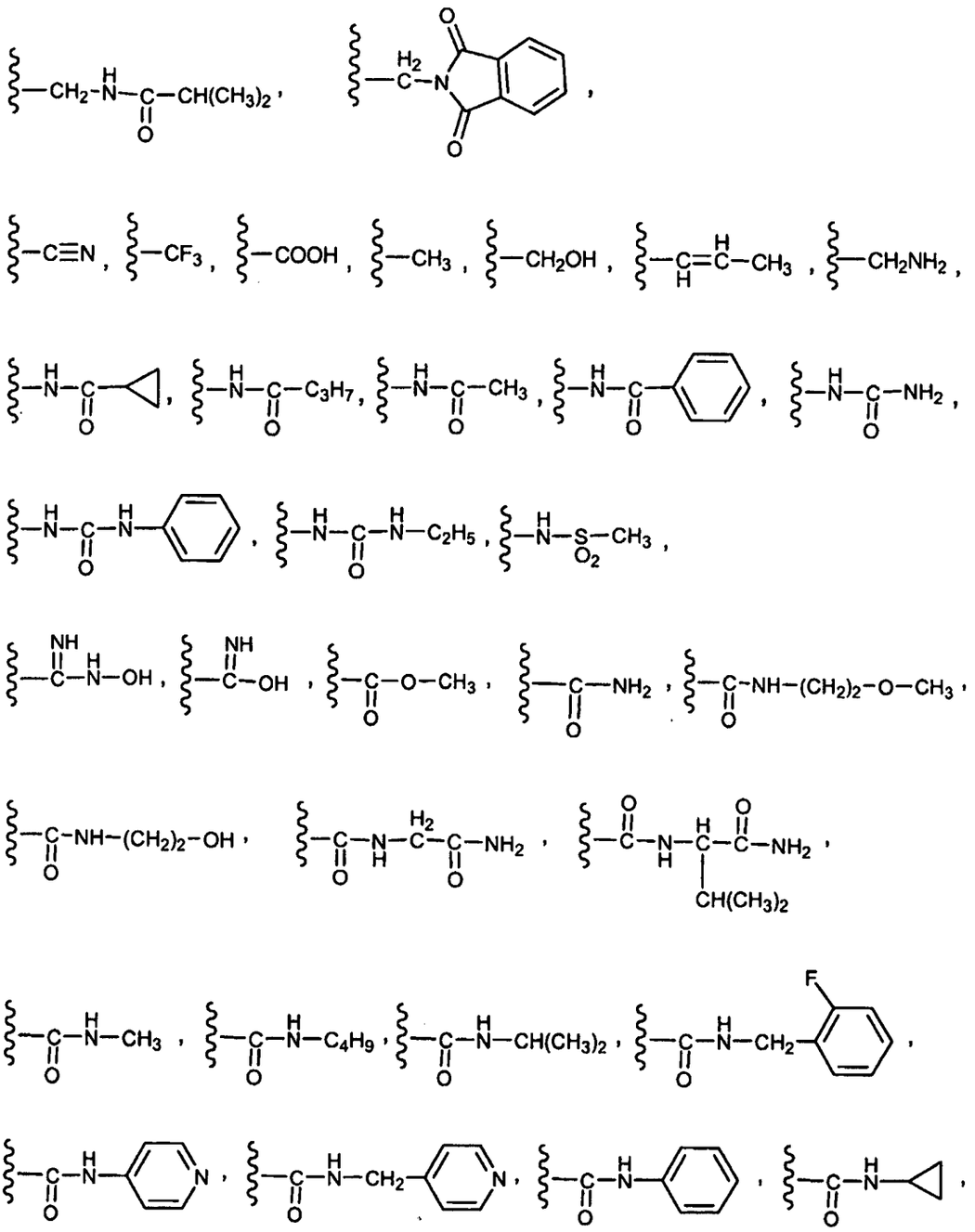


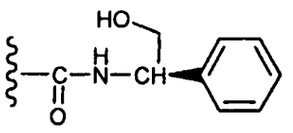
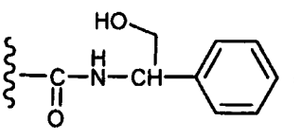
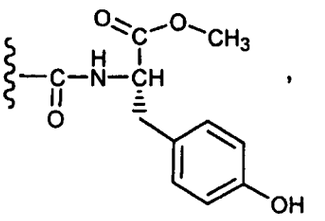
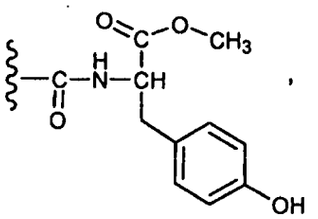
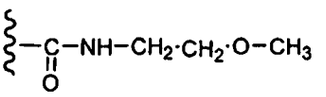
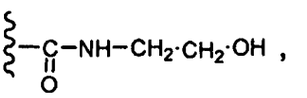
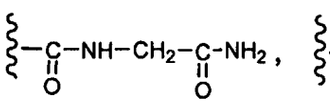
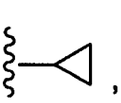
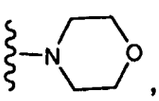
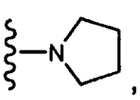
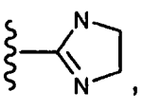
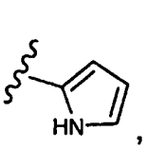
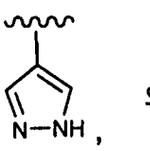
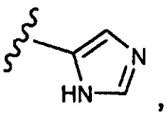
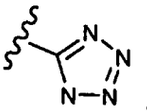
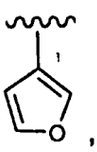
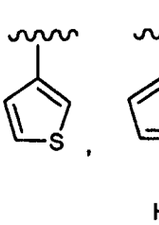
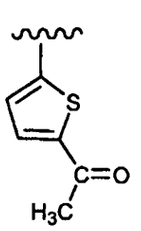
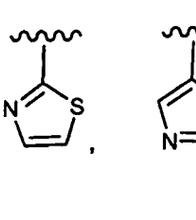
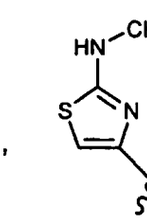
substituted with one methyl group.

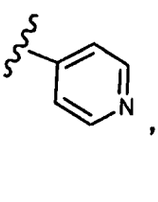
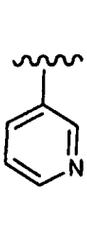
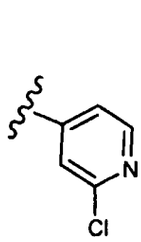
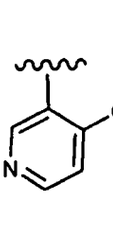
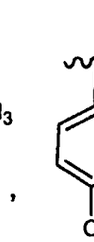
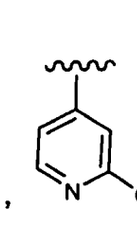
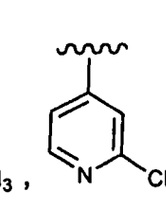
22. The compound of Claim 1 wherein R^1 is selected from the group consisting of:

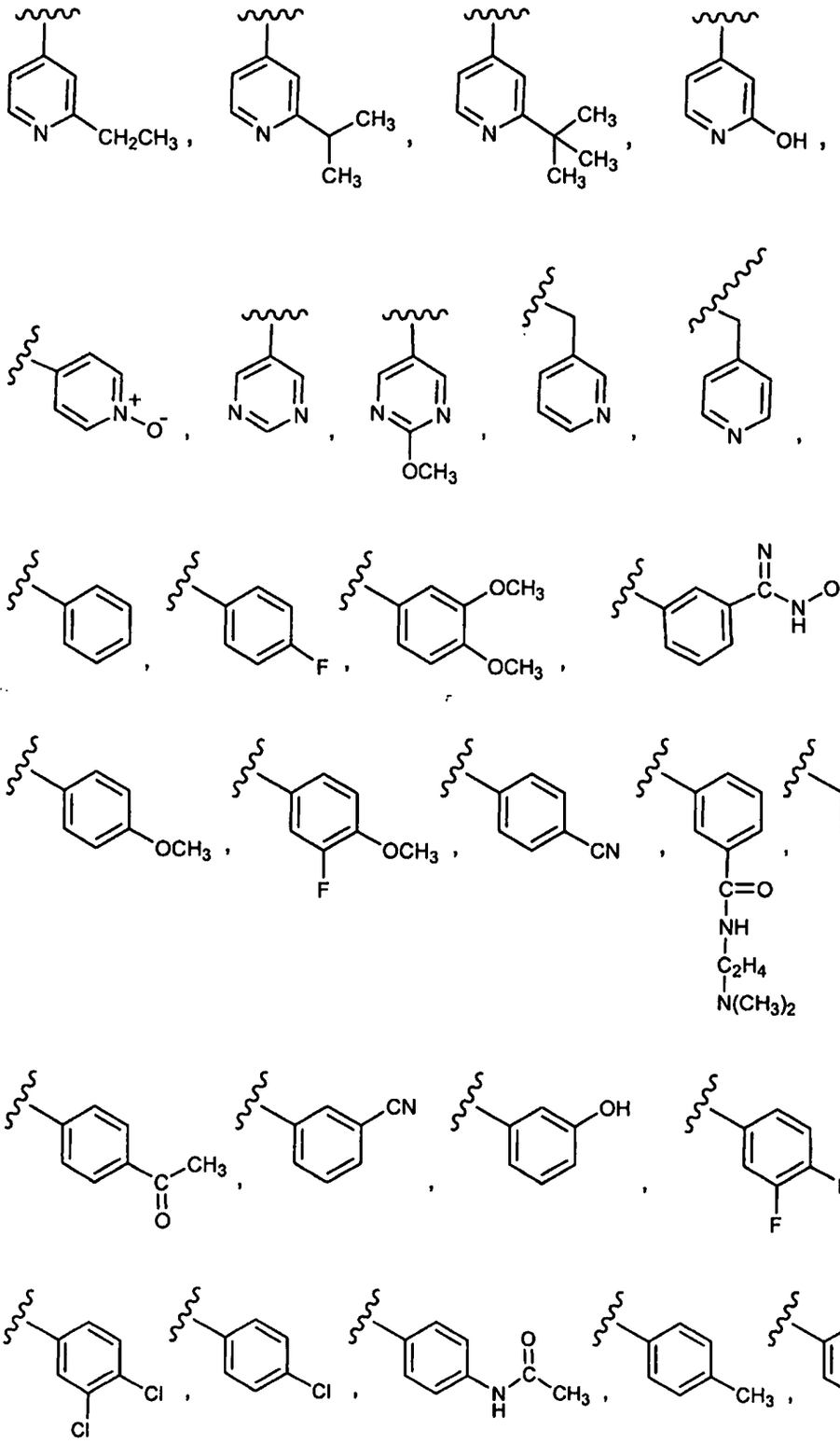


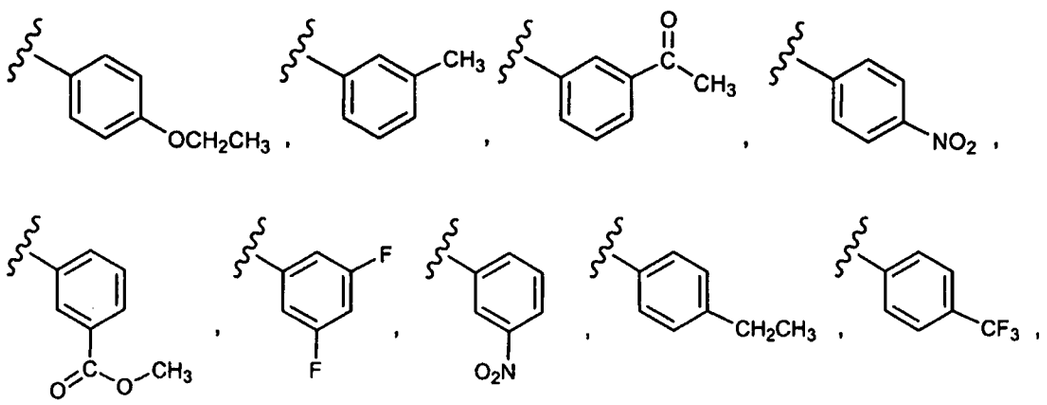


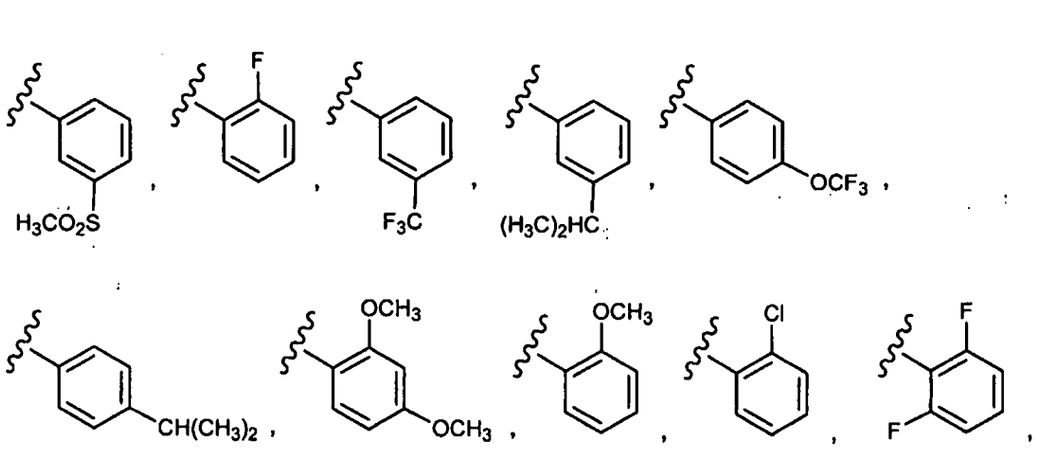


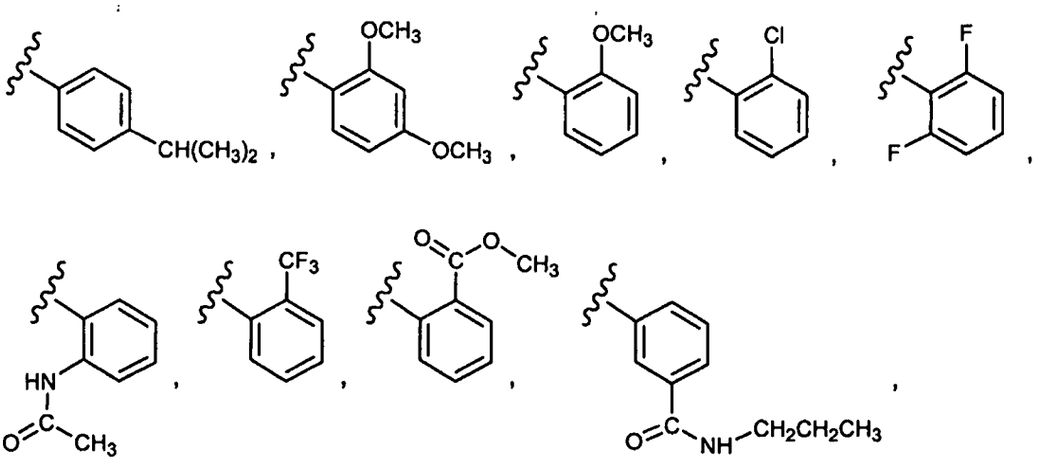





















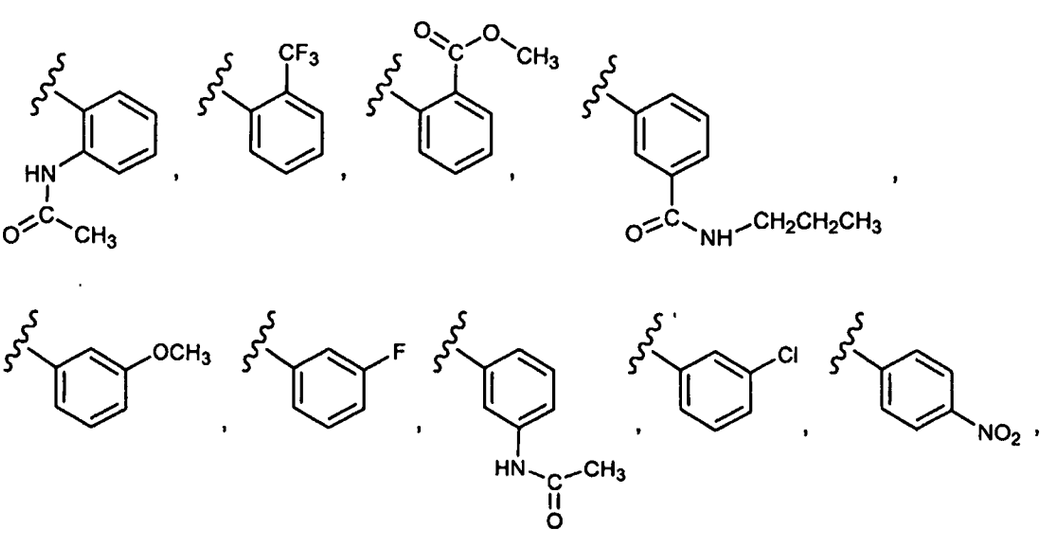








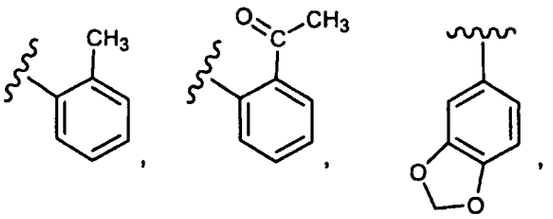


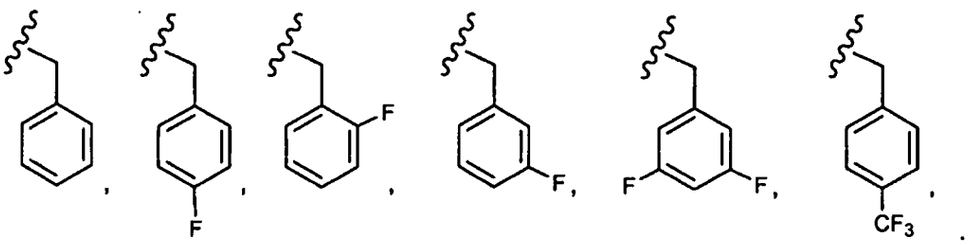


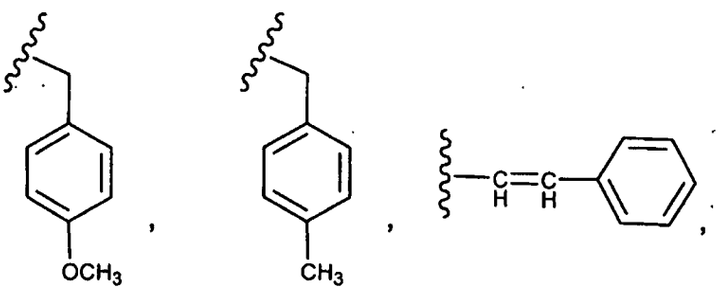


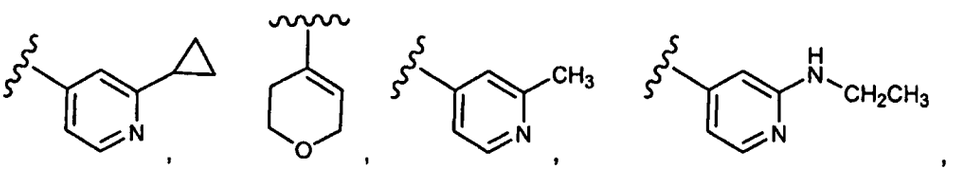


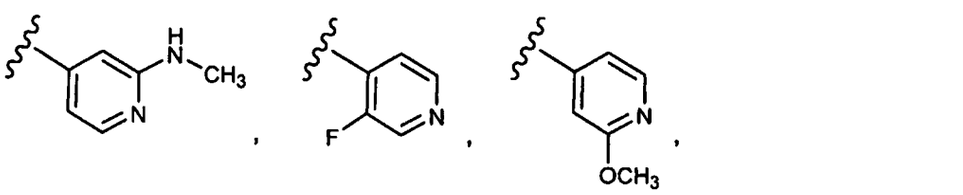


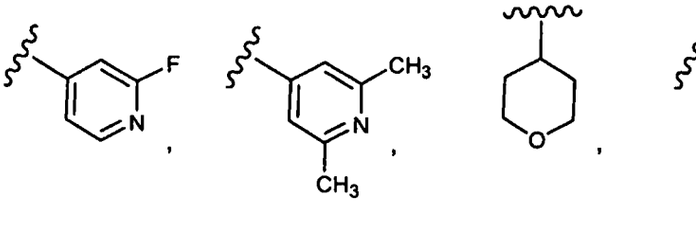


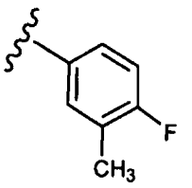
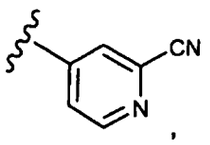
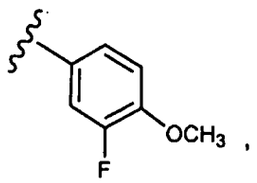
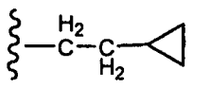
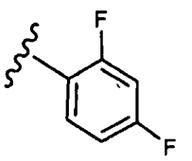
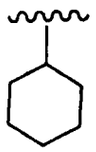
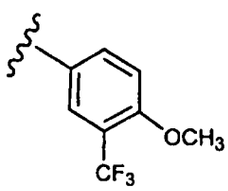
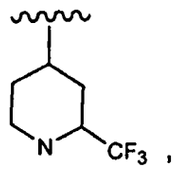




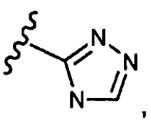
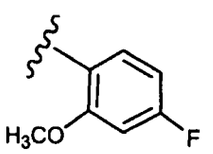
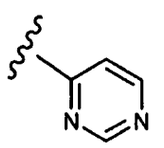
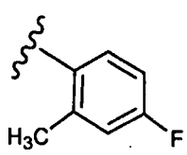


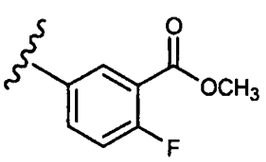
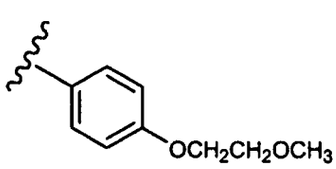
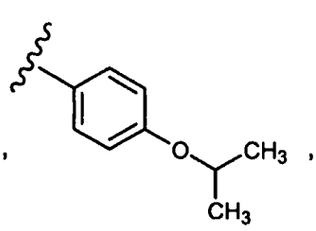




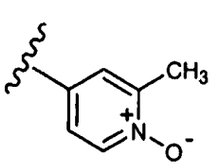
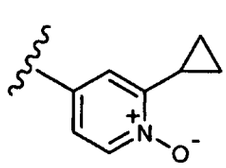
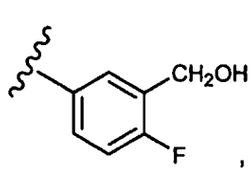









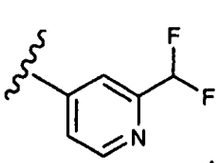
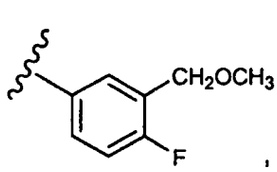
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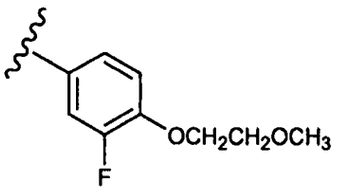
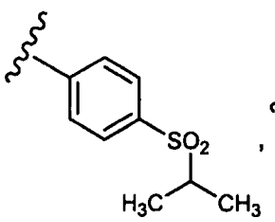
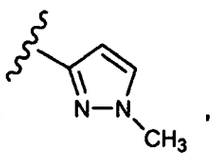
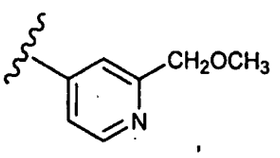
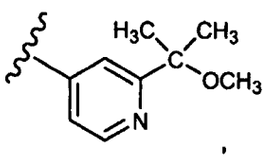
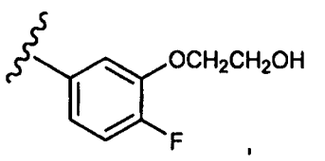
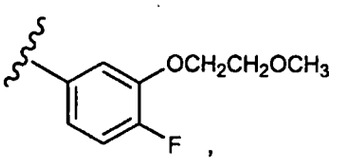





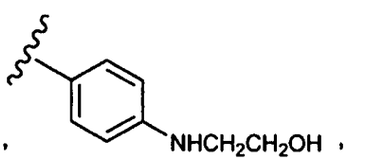
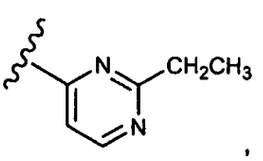
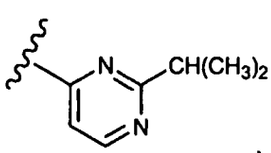
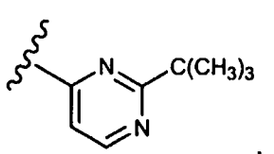
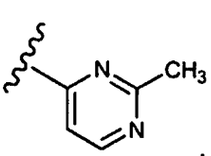
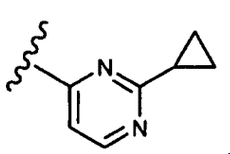
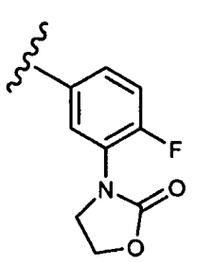
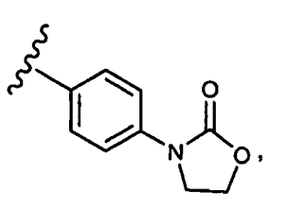
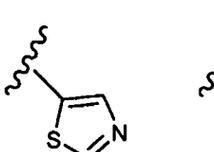
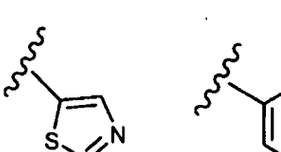




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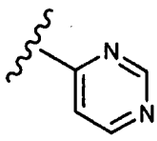
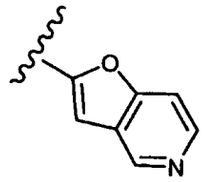



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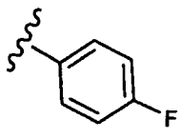
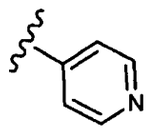
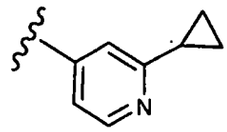
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 and 

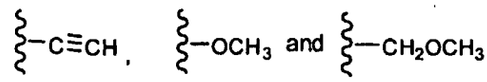
23. The compound of Claim 1 wherein R^1 is aryl.

24. The compound of Claim 1 wherein R^1 is heteroaryl or substituted heteroaryl.

25. The compound of Claim 64 wherein R^1 is selected from the group consisting of:

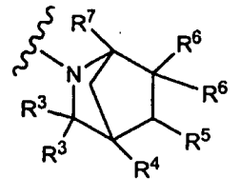
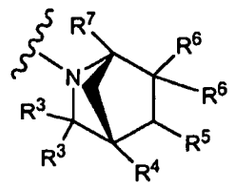
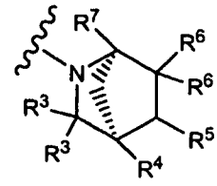
 ,  and 

26. The compound of Claim 1 wherein R^2 is selected from the group consisting of:



27. The compound of Claim 1 wherein R^2 is selected from the group consisting of: (1) substituted alkyl wherein said substituent is $-OCH_3$, (2) $-CH_2OH$ and (3) $-CH_2OCH_3$.

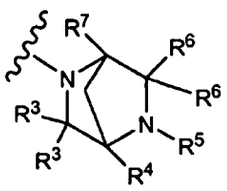
28. The compound of Claim 22 wherein Q is selected from the group consisting of: 2.1, 2.2, and 2.3, and 2.3 is selected from the group consisting of:

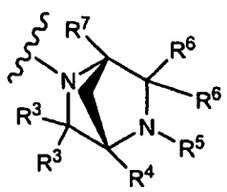

(2.3A) ,

(2.3B) and

(2.3C) ,

and R^3, R^4, R^6, and R^7 are each independently selected from the group consisting of: H and alkyl.

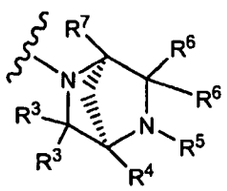
29. The compound of Claim 28 wherein R^3, R^4, R^6, and R^7 are each H, and Q is 21.

30. The compound of Claim 22 wherein Q is selected from the group consisting of: 2.6 and 2.7, and 2.7 is selected from the group consisting of:


(2.7A)


(2.7B)

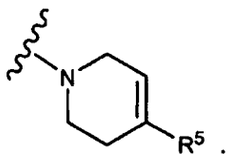
and


(2.7C)

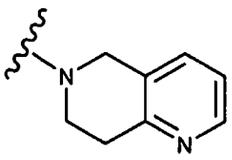
and R^3, R^4, R^6, and R^7 are each independently selected from the group consisting of: H and alkyl.

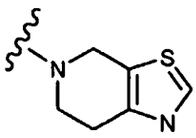
31. The compound of Claim 30 wherein R^3, R^4, R^6, and R^7 are each H, and Q is selected from the group consisting of; 2.6 and 2.7B.

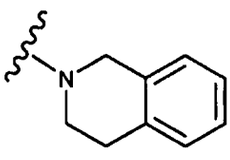
32. The compound of Claim 1 wherein Q is

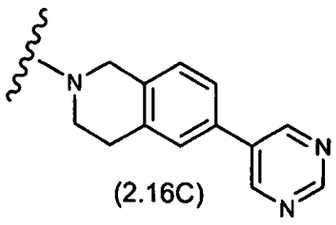


33. The compound of Claim 1 wherein Q is selected from the group consisting of:

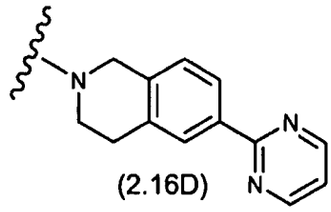

(2.16A)


(2.16A1)

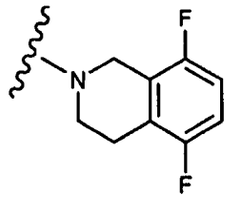

(2.16B)



(2.16C) ,

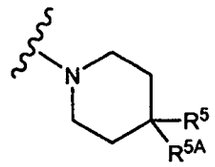


(2.16D) and



(2.16E) .

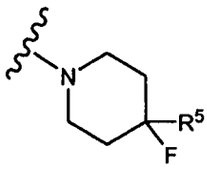
34. The compound of Claim 1 wherein Q is:



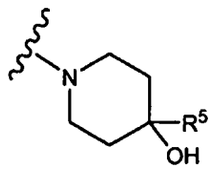
(2.17A)

and R^{5A} is selected from the group consisting of: halo, -OH, alkoxy, and alkyl.

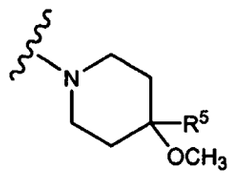
35. The compound of Claim 1 wherein Q is selected from the group consisting of:



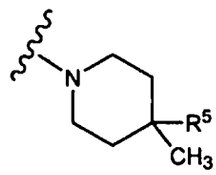
(2.17B) ,



(2.17C) ;

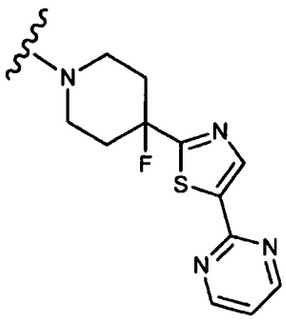


(2.17E) and

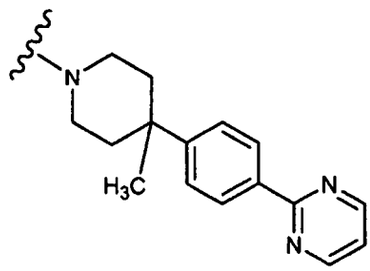


(2.17G) .

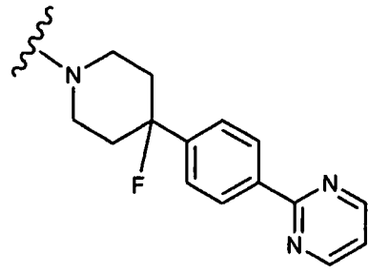
36. The compound of Claim 1 wherein Q is selected from the group consisting of:

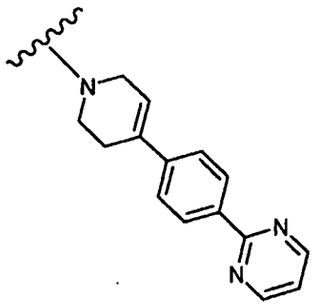


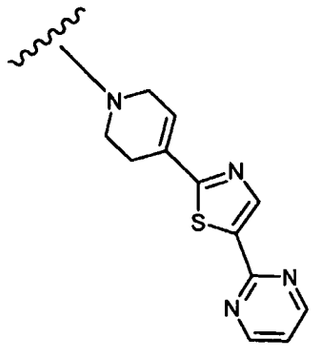
,

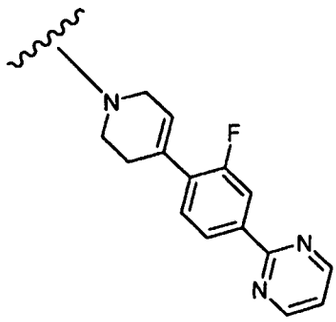


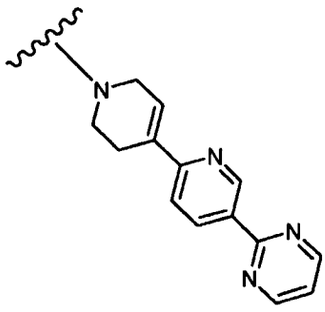
,

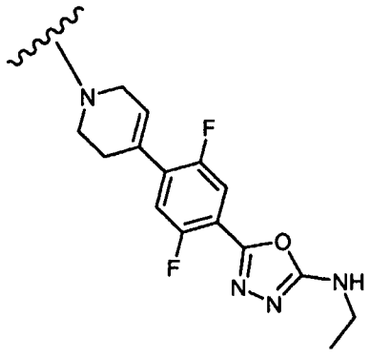


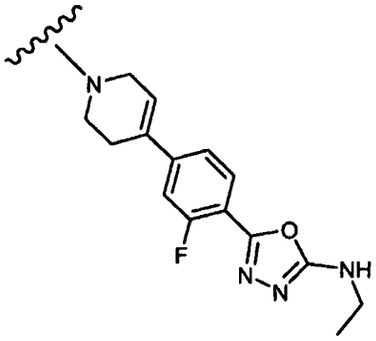


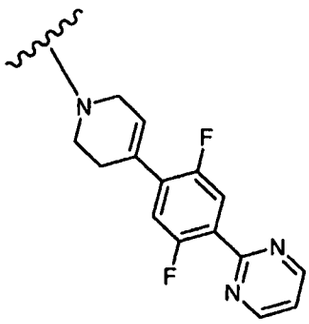


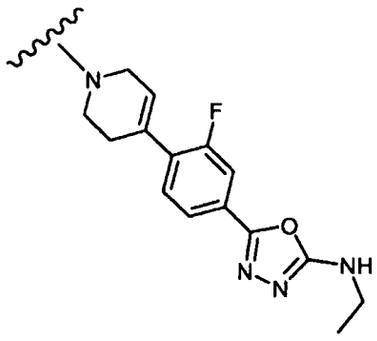




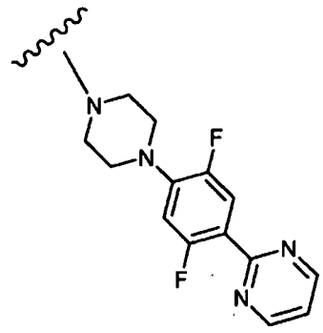








and



37. The compound of Claim 1 wherein said compound is a compound of formula 1.0.

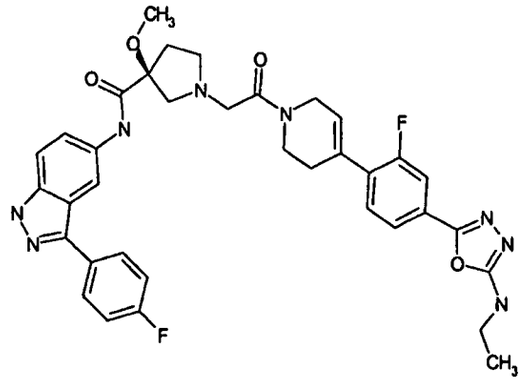
38. The compound of Claim 1 wherein said compound is a salt of the compound of formula 1.0.

39. The compound of Claim 1 wherein said compound is an ester of the compound of formula 1.0.

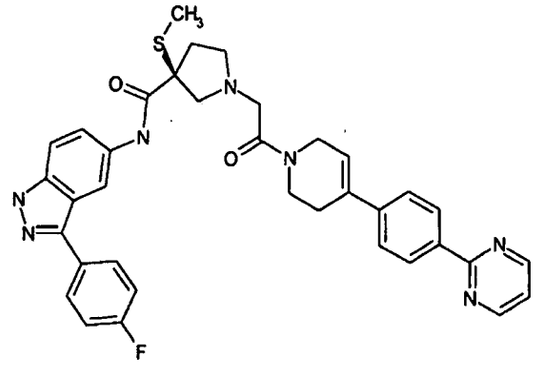
40. The compound of Claim 1 wherein said compound is a solvate of the compound of formula 1.0.

41. A compound selected from the group consisting of the final compounds of Examples 612 to 827.

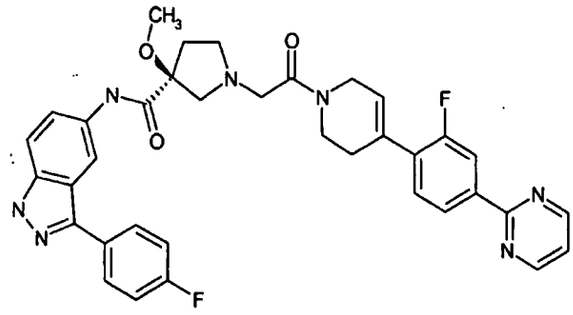
42. The compound of Claim 1 having the formula;



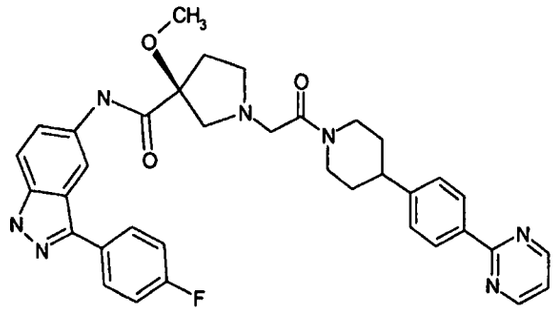
43. The compound of Claim 1 having the formula



44. The compound of Claim 1 having the formula



45. The compound of Claim 1 having the formula



46. A pharmaceutical composition comprising at least one compound of any of Claims 1 to 45 and a pharmaceutically acceptable carrier.

47. A use of at least one compound of any of Claims 1 to 45:

(1) for the manufacture of a medicament for treating cancer; or

(2) for the manufacture of a medicament for treating cancer, said medicament being used in combination with at least one chemotherapeutic agent; or

(3) for the manufacture of a medicament for treating treating cancer, said medicament being used in combination with at least one chemotherapeutic agent, and radiation therapy; or

(4) for the manufacture of a medicament for treating cancer, said medicament being used in combination with at least one chemotherapeutic agent selected from the group consisting of: (1) taxanes, (2) platinum coordinator compounds, (3) epidermal growth factor (EGF) inhibitors that are antibodies, (4) EGF inhibitors that are small molecules, (5) vascular endolithial growth factor (VEGF) inhibitors that are antibodies, (6) VEGF kinase inhibitors that are small molecules, (7) estrogen receptor antagonists or selective estrogen receptor modulators (SERMs), (8) anti-tumor nucleoside derivatives, (9) epothilones, (10) topoisomerase inhibitors, (11) vinca alkaloids, (12) antibodies that are inhibitors of $\alpha V\beta 3$ integrins, (13) folate antagonists, (14) ribonucleotide reductase inhibitors, (15) anthracyclines, (16) biologics; (17) inhibitors of angiogenesis and/or suppressors of tumor necrosis factor alpha (TNF-alpha) such as thalidomide (or related imid), (18) Bcr/abl kinase inhibitors, (19) MEK1 and/or MEK 2 inhibitors that are small molecules, (20) IGF-1 and IGF-2 inhibitors that are small molecules, (21) small molecule inhibitors of RAF and BRAF kinases, (22) small molecule inhibitors of cell cycle dependent kinases such as CDK1, CDK2, CDK4 and CDK6, (23) alkylating agents, and (24) farnesyl protein transferase inhibitors; or

(5) for the manufacture of a medicament for treating treating cancer, said medicament being administered with at least one signal transduction inhibitor; or

(6) for the manufacture of a medicament for treating treating cancer, said cancer being selected from the group consisting of: lung cancer, pancreatic cancer, colon cancer, myeloid leukemias, thyroid cancer, myelodysplastic syndrome, bladder carcinoma, epidermal carcinoma, melanoma, breast cancer, prostate cancer, head and neck cancers, ovarian cancer, brain cancers, cancers of mesenchymal origin, sarcomas, tetracarcinomas, nuroblastomas, kidney carcinomas, hepatomas, non-Hodgkin's lymphoma, multiple myeloma, and anaplastic thyroid carcinoma; or

(7) for the manufacture of a medicament for treating cancer wherein said cancer is selected from the group consisting of: melanoma, pancreatic cancer, thryroid cancer, colorectal cancer, lung cancer, breast cancer, and ovarian cancer; or

(8) for the manufacture of a medicament for treating cancer, said medicament being used in combination with an effective amount of at least one chemotherapeutic agent, wherein said cancer is selected from the group consisting of: melanoma, pancreatic cancer, thryroid cancer, colorectal canc er, lung cancer, breast cancer, and ovarian cancer; or

(9) for the manufacture of a medicament for treating treating melanoma; or

(10) for the manufacture of a medicament for treating melanoma, said medicament being used in combination with at least one chemotherapeutic agent; or

(11) for the manufacture of a medicament for treating pancreatic cancer; or

(12) for the manufacture of a medicament for treating pancreatic cancer, said medicament being used in combination with at least one chemotherapeutic agent; or

(13) for the manufacture of a medicament for treating thyroid cancer; or

(14) for the manufacture of a medicament for treating thyroid cancer, said medicament being used, in combination with at least one chemotherapeutic agent; or

(15) for the manufacture of a medicament for treating colorectal cancer; or

(16) for the manufacture of a medicament for treating colorectal cancer, said medicament being used in combination with at least one chemotherapeutic agent; or

(17) for the manufacture of a medicament for treating lung cancer; or

(18) for the manufacture of a medicament for treating lung cancer, said medicament being used in combination with at least one chemotherapeutic agent; or

(19) for the manufacture of a medicament for treating breast cancer; or

(20) for the manufacture of a medicament for treating breast cancer, said medicament being used in combination with at least one chemotherapeutic agent; or

(21) for the manufacture of a medicament for treating ovarian cancer; or

(22) for the manufacture of a medicament for treating ovarian cancer, said medicament being used in combination with at least one chemotherapeutic agent; or

(23) for the manufacture of a medicament for treating hormone-dependent breast cancer, said medicament being used in combination with antihormonal agents; or

(24) for the manufacture of a medicament for treating hormone-dependent breast cancer, said medicament being used in combination with antihormonal agents, and at least one chemotherapeutic agent; or

(25) for the manufacture of a medicament for preventing hormone-dependent breast cancer, said medicament being used in combination with antihormonal agents; or

(26) for the manufacture of a medicament for preventing hormone-dependent breast cancer, said medicament being used in combination with antihormonal agents, and at least one chemotherapeutic agent; or

(27) for the manufacture of a medicament for treating brain cancer; or

(28) for the manufacture of a medicament for treating brain cancer, said medicament being used in combination with at least one chemotherapeutic agent; or

(29) for the manufacture of a medicament for treating brain cancer, said medicament being used in combination with a chemotherapeutic agent wherein said chemotherapeutic agent is temozolomide; or

(30) for the manufacture of a medicament for treating prostate cancer; or

(31) for the manufacture of a medicament for treating prostate cancer, said medicament being used in combination with at least one chemotherapeutic agent; or

(32) for the manufacture of a medicament for treating myelodysplastic syndrome; or

(33) for the manufacture of a medicament for treating myelodysplastic syndrome, said medicament being used in combination with at least one chemotherapeutic agent; or

(34) for the manufacture of a medicament for treating myeloid leukemias; or

(35) for the manufacture of a medicament for treating myeloid leukemias, said medicament being used in combination with at least one chemotherapeutic agent; or

(36) for the manufacture of a medicament for treating acute myelogenous leukemia; or

(37) for the manufacture of a medicament for treating acute myelogenous leukemia, said medicament being used in combination with at least one chemotherapeutic agent; or

(38) for the manufacture of a medicament for treating chronic myelomonocytic leukemia; or

(39) for the manufacture of a medicament for treating chronic myelomonocytic leukemia, said medicament being used in combination with at least one chemotherapeutic agent; or

(40) for the manufacture of a medicament for treating chronic myelogenous leukemia; or

(41) for the manufacture of a medicament for treating chronic myelogenous leukemia, said medicament being used in combination with at least one chemotherapeutic agent; or

(42) for the manufacture of a medicament for treating bladder cancer; or

(43) for the manufacture of a medicament for treating bladder cancer, said medicament being used in combination with at least one chemotherapeutic agent; or

(44) for the manufacture of a medicament for treating non-Hodgkin's lymphoma; or

(45) for the manufacture of a medicament for treating non-Hodgkin's lymphoma, said medicament being used in combination with at least one chemotherapeutic agent; or

(46) for the manufacture of a medicament for treating multiple myeloma; or

(47) for the manufacture of a medicament for treating multiple myeloma, said medicament being used in combination with at least one chemotherapeutic agent.

DERIVADOS POLICÍCLICOS DE INDAZOL Y SU USO COMO INHIBIDORES DE ERK PARA EL TRATAMIENTO DEL CANCER.

Campo de la Invención

Los procesos involucrados en el crecimiento, progresión y metástasis de tumor están mediados por las vías de señalización que están activadas en células cancerosas. La vía de ERK cumple una función central en la regulación del crecimiento de células de mamíferos al enviar señales extracelulares de los receptores de tirosina quinasa de la superficie celular unidos al ligando tales como la familia erbB, PDGF, FGF, y la quinasa tirosina del receptor VEGF. La activación de ERK es a través de una cascada de eventos de fosforilación que comienza con la activación de Ras. La activación de Ras conduce al reclutamiento y activación de Raf, una quinasa de serina-treonina. El Raf activado luego fosforila y activa MEK1/2, que luego fosforila y activa ERK1/2. Cuando está activado, ERK1/2 fosforila muchos blancos descendentes involucrados en una cantidad de eventos celulares incluyendo cambios cito esqueléticos y activación de la transcripción. La vía de ERK/MAPK es una de las más importantes para la proliferación celular y se considera que la vía de ERK/MAPK frecuentemente está activada en muchos tumores. Los genes Ras, que son ascendentes de ERK1/2, están mutados en varios cánceres incluyendo los tumores colo-rectales, melanoma, mama y de páncreas. La alta actividad de Ras está acompañada por una elevada actividad de ERK en muchos tumores humanos. Además, las mutaciones de BRAF, una quinasa de serina-treonina de la familia Raf, están asociadas con un aumento en la actividad de quinasa. Las mutaciones en BRAF se han identificado en melanomas (60%), cánceres de tiroides (más del 40%) y cánceres colo-rectales. Estas observaciones indican que la vía de señalización de ERK1/2 es una vía atractiva para terapias contra el cáncer y en un amplio espectro de tumores humanos.

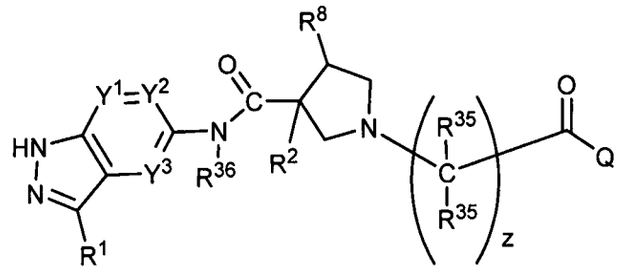
Por lo tanto, una contribución bienvenida al arte sería de moléculas pequeñas (es decir, compuestos) que inhiben la actividad de ERK (es decir, la actividad de ERK1 y ERK2), cuyas moléculas pequeñas serían útiles para el tratamiento de un amplio espectro de cánceres, tales como, por ejemplo, melanoma, cáncer de páncreas, cáncer de tiroides, cáncer colo-rectal, cáncer de pulmón, cáncer de mama, y cáncer de ovario. Dicha contribución se provee a través de esta invención.

SÍNTESIS DE LA INVENCIÓN

Esta invención provee compuestos que inhiben la actividad de ERK1 y/o la actividad de ERK2.

Los compuestos de esta invención inhiben, además, la fosforilación de ERK1 y ERK2.

De este modo, esta invención provee compuestos que son inhibidores de ERK (es decir, inhibidores de ERK1 y/o inhibidores de ERK2), dichos compuestos tienen la fórmula 1.0:



(1.0)

o sus sales, ésteres, y solvatos aceptables desde el punto de vista farmacéutico, en los cuales:

Y^1, Y^2, y Y^3 se seleccionan, cada uno en forma independiente, del grupo que consiste en: C, N y carbono sustituido;

Q se selecciona del grupo que consiste en: piperidinilo, piperazinilo, tetrahidropiridinilo (por ej., 1,2,3,6-tetrahidropiridinilo), piperazinilo en puente, piperidinilo en puente, tetrahidropiridinilo en puente, piperidinilo sustituido, piperazinilo sustituido, tetrahidropiridinilo sustituido (por ej., un 1,2,3,6-tetrahidro-

piridinilo sustituido), piperazinilo sustituido en puente, piperidinilo sustituido en puente, y tetrahidropiridinilo sustituido en puente;

z es de 1 hasta 3 (y con preferencia 1); y

R^1, R^2, R^8, R^{35} y R^{36} son como se los define más adelante.

Esta invención provee compuestos de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 165) en forma pura o aislada.

Esta invención provee compuestos de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 165) en forma pura.

Esta invención provee compuestos de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 165) en forma aislada.

Esta invención provee compuestos de fórmula 1.0.

Esta invención provee sales aceptables desde el punto de vista farmacéutico de los compuestos de fórmula 1.0.

Esta invención provee ésteres aceptables desde el punto de vista farmacéutico de los compuestos de fórmula 1.0.

Esta invención provee solvatos de los compuestos de fórmula 1.0.

Esta invención provee los compuestos finales de los Ejemplos 1 hasta 827.

Esta invención provee, además, una composición farmacéutica que comprende una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) y un vehículo aceptable desde el punto de vista farmacéutico.

Esta invención provee, además, una composición farmacéutica que comprende una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) y una cantidad efectiva de por

lo menos otro (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) principio farmacéuticamente activo (tales como, por ejemplo, un agente quimioterapéutico), y un vehículo aceptable desde el punto de vista farmacéutico.

Esta invención provee, además, un método para inhibir ERK (es decir, inhibir la actividad de ERK) en un paciente que necesita de dicho tratamiento que comprende administrar a dicho paciente una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143).

Esta invención provee, además, un método para inhibir ERK1 (es decir, inhibir la actividad de ERK1) en un paciente que necesita de dicho tratamiento que comprende administrar a dicho paciente una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143).

Esta invención provee, además, un método para inhibir ERK2 (es decir, inhibir la actividad de ERK2) en un paciente que necesita de dicho tratamiento que comprende administrar a dicho paciente una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143).

Esta invención provee, además, un método para inhibir ERK1 y ERK2 (es decir, inhibir la actividad de ERK1 y ERK2) en un paciente que necesita de dicho tratamiento que comprende administrar a dicho paciente una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143).

Esta invención provee, además, un método de tratamiento para el cáncer en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de por lo menos un (por ej., 1,

2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143).

Esta invención provee, además, un método de tratamiento para el cáncer en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143).

Esta invención provee, además, un método de tratamiento para el cáncer en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), en combinación con una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Esta invención provee, además, un método de tratamiento para el cáncer en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), en combinación con una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Esta invención provee, además, un método de tratamiento para el cáncer en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se

describe en cualquiera de las Realizaciones Nos. 1 hasta 143) en combinación con por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) inhibidor de transducción de señal.

Esta invención provee, además, un método de tratamiento para el cáncer en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) en combinación con por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) inhibidor de transducción de señal.

Esta invención provee, además, un método para tratamiento del cáncer de pulmón, cáncer de páncreas, cáncer de colon (por ej., cáncer colo-rectal), leucemias mieloides (por ej., AML, CML, y CMML), cáncer de tiroides, síndrome mielodisplásico (MDS), carcinoma de vejiga, carcinoma epidérmico, melanoma, cáncer de mama, cáncer de próstata, cánceres de cuello y cabeza (por ej., cáncer de células escamosas de cuello y cabeza), cáncer de ovario, cánceres de cerebro (por ej., gliomas, tales como glioma blastoma multiforme), cánceres de origen mesenquimal (por ej., fibrosarcomas y rabdomiosarcomas), sarcomas, tetracarcinomas, nuroblastomas, carcinomas de riñón, hepatomas, linfoma de no Hodgkin, mieloma múltiple, o carcinoma de tiroides anaplásico, en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143).

Esta invención provee, además, un método para tratamiento del cáncer de pulmón, cáncer de páncreas, cáncer de colon (por ej., cáncer colo-rectal),

leucemias mieloides (por ej., AML, CML, y CMML), cáncer de tiroides, síndrome mielodisplásico (MDS), carcinoma de vejiga, carcinoma epidérmico, melanoma, cáncer de mama, cáncer de próstata, cánceres de cuello y cabeza (por ej., cáncer de células escamosas de cuello y cabeza), cáncer de ovario, cánceres de cerebro (por ej., gliomas, tales como glioma blastoma multiforme), cánceres de origen mesenquimal (por ej., fibrosarcomas y rabdomiosarcomas), sarcomas, tetracarcinomas, nuroblastomas, carcinomas de riñón, hepatomas, linfoma de no Hodgkin, mieloma múltiple, o carcinoma de tiroides anaplásico en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), en combinación con una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Esta invención provee, además, un método para tratamiento del cáncer de pulmón, cáncer de páncreas, cáncer de colon (por ej., cáncer colo-rectal), leucemias mieloides (por ej., AML, CML, y CMML), cáncer de tiroides, síndrome mielodisplásico (MDS), carcinoma de vejiga, carcinoma epidérmico, melanoma, cáncer de mama, cáncer de próstata, cánceres de cuello y cabeza (por ej., cáncer de células escamosas de cuello y cabeza), cáncer de ovario, cánceres de cerebro (por ej., gliomas, tales como glioma blastoma multiforme), cánceres de origen mesenquimal (por ej., fibrosarcomas y rabdomiosarcomas), sarcomas, tetracarcinomas, nuroblastomas, carcinomas de riñón, hepatomas, linfoma de no Hodgkin, mieloma múltiple, o carcinoma de tiroides anaplásico en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1)

compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143).

Esta invención provee, además, un método para tratamiento del cáncer de pulmón, cáncer de páncreas, cáncer de colon (por ej., cáncer colo-rectal), leucemias mieloides (por ej., AML, CML, y CMML), cáncer de tiroides, síndrome mielodisplásico (MDS), carcinoma de vejiga, carcinoma epidérmico, melanoma, cáncer de mama, cáncer de próstata, cánceres de cuello y cabeza (por ej., cáncer de células escamosas de cuello y cabeza), cáncer de ovario, cánceres de cerebro (por ej., gliomas, tales como glioma blastoma multiforme), cánceres de origen mesenquimal (por ej., fibrosarcomas y rabdomiosarcomas), sarcomas, tetracarcinomas, nuroblastomas, carcinomas de riñón, hepatomas, linfoma de no Hodgkin, mieloma múltiple, o carcinoma de tiroides anaplásico en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), en combinación con una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Esta invención provee, además, un método de tratamiento para el cáncer en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), en las cuales dicho cáncer se selecciona del grupo que consiste en: melanoma, cáncer de páncreas, cáncer de tiroides, cáncer colo-rectal, cáncer de pulmón, cáncer de mama, y cáncer de ovario.

Esta invención provee, además, un método de tratamiento para el cáncer en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), en combinación con una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico en las cuales dicho cáncer se selecciona del grupo que consiste en: melanoma, cáncer de páncreas, cáncer de tiroides, cáncer colo-rectal, cáncer de pulmón, cáncer de mama, y cáncer de ovario.

Esta invención provee, además, un método de tratamiento para el cáncer en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), en las cuales dicho cáncer se selecciona del grupo que consiste en: melanoma, cáncer de páncreas, cáncer de tiroides, cáncer colo-rectal, cáncer de pulmón, cáncer de mama, y cáncer de ovario.

Esta invención provee, además, un método de tratamiento para el cáncer en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), en combinación con una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico en las cuales dicho cáncer se selecciona del grupo que

consiste en: melanoma, cáncer de páncreas, cáncer de tiroides, cáncer colo-rectal, cáncer de pulmón, cáncer de mama, y cáncer de ovario.

Esta invención provee, además, un método para tratamiento de un melanoma en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143).

Esta invención provee, además, un método para tratamiento de un melanoma en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), en combinación con una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Esta invención provee, además, un método para tratamiento de un melanoma en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143).

Esta invención provee, además, un método para tratamiento de un melanoma en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143),

en combinación con una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Esta invención provee, además, un método para tratamiento del cáncer de páncreas en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143).

Esta invención provee, además, un método para tratamiento del cáncer de páncreas en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), en combinación con una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Esta invención provee, además, un método para tratamiento del cáncer de páncreas en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143).

Esta invención provee, además, un método para tratamiento del cáncer de páncreas en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143),

en combinación con una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Esta invención provee, además, un método para tratamiento del cáncer de tiroides en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143).

Esta invención provee, además, un método para tratamiento del cáncer de tiroides en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 1431), en combinación con una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Esta invención provee, además, un método para tratamiento del cáncer de tiroides en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143).

Esta invención provee, además, un método para tratamiento del cáncer de tiroides en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143),

en combinación con una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Esta invención provee, además, un método para tratamiento del cáncer colo-rectal en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143).

Esta invención provee, además, un método para tratamiento del cáncer colo-rectal en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), en combinación con una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Esta invención provee, además, un método para tratamiento del cáncer colo-rectal en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143).

Esta invención provee, además, un método para tratamiento del cáncer colo-rectal en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143),

en combinación con una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Esta invención provee, además, un método para tratamiento del cáncer de pulmón en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143).

Esta invención provee, además, un método para tratamiento del cáncer de pulmón en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), en combinación con una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Esta invención provee, además, un método para tratamiento del cáncer de pulmón en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143).

Esta invención provee, además, un método para tratamiento del cáncer de pulmón en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143),

en combinación con una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Esta invención provee, además, un método para tratamiento del cáncer de mama en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143).

Esta invención provee, además, un método para tratamiento del cáncer de mama en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), en combinación con una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Esta invención provee, además, un método para tratamiento del cáncer de mama en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143).

Esta invención provee, además, un método para tratamiento del cáncer de mama en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143),

en combinación con una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Esta invención provee, además, un método para tratamiento del cáncer de ovario en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143).

Esta invención provee, además, un método para tratamiento del cáncer de ovario en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), en combinación con una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Esta invención provee, además, un método para tratamiento del cáncer de ovario en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143).

Esta invención provee, además, un método para tratamiento del cáncer de ovario en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143),

en combinación con una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Esta invención provee, además, métodos para el tratamiento del cáncer de mama (es decir, cáncer de mama post-menopáusico o pre-menopáusico, por ej., cáncer de mama dependiente de hormonas) en un paciente que necesita de dicho tratamiento, dicho tratamiento comprende la administración de una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) en combinación con terapias hormonales (es decir, agentes anti-hormonales).

Esta invención provee, además, métodos para el tratamiento del cáncer de mama (es decir, cáncer de mama post-menopáusico o pre-menopáusico, por ej., cáncer de mama dependiente de hormonas) en un paciente que necesita de dicho tratamiento, dicho tratamiento comprende la administración de una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) en combinación con terapias hormonales (es decir, agentes anti-hormonales).

Esta invención provee, además, métodos para el tratamiento del cáncer de mama (es decir, cáncer de mama post-menopáusico o pre-menopáusico, por ej., cáncer de mama dependiente de hormonas) en un paciente que necesita de dicho tratamiento, dicho tratamiento comprende la administración de una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) en combinación con terapias hormonales (es decir, agentes

anti-hormonales), y en combinación con una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Esta invención provee, además, métodos para el tratamiento del cáncer de mama (es decir, cáncer de mama post-menopáusico o pre-menopáusico, por ej., cáncer de mama dependiente de hormonas) en un paciente que necesita de dicho tratamiento, dicho tratamiento comprende la administración de una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) en combinación con terapias hormonales (es decir, agentes anti-hormonales), y en combinación con una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Los métodos para el tratamiento del cáncer de mama descritos aquí incluyen el tratamiento del cáncer de mama metastático y avanzado dependiente de las hormonas, terapia adyuvante para cáncer de mama en estadío inicial y primario dependiente de las hormonas, el tratamiento de carcinoma ductal in situ, y el tratamiento del cáncer de mama inflamatorio in situ.

Los métodos de tratamiento para el cáncer de mama dependiente de hormonas también pueden utilizarse para prevenir el cáncer de mama en pacientes que presentan riesgo de desarrollar cáncer de mama.

De este modo, esta invención provee, además, métodos para prevención del cáncer de mama (es decir, cáncer de mama post-menopáusico o pre-menopáusico, por ej., cáncer de mama dependiente de hormonas) en un paciente que necesita de dicho tratamiento, dicho tratamiento comprende la administración de una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las

Realizaciones Nos. 1 hasta 143) en combinación con terapias hormonales (es decir, agentes anti-hormonales).

Esta invención provee, además, métodos para prevención del cáncer de mama (es decir, cáncer de mama post-menopáusico o pre-menopáusico, por ej., cáncer de mama dependiente de hormonas) en un paciente que necesita de dicho tratamiento, dicho tratamiento comprende la administración de una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) en combinación con terapias hormonales (es decir, agentes anti-hormonales).

Esta invención provee, además, métodos para prevención del cáncer de mama (es decir, cáncer de mama post-menopáusico o pre-menopáusico, por ej., cáncer de mama dependiente de hormonas) en un paciente que necesita de dicho tratamiento, dicho tratamiento comprende la administración de una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) en combinación con terapias hormonales (es decir, agentes anti-hormonales), y en combinación con una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Esta invención provee, además, métodos para prevención del cáncer de mama (es decir, cáncer de mama post-menopáusico o pre-menopáusico, por ej., cáncer de mama dependiente de hormonas) en un paciente que necesita de dicho tratamiento, dicho tratamiento comprende la administración de una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1

hasta 143) en combinación con terapias hormonales (es decir, agentes anti-hormonales), y en combinación con una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Esta invención provee, además, un método para el tratamiento del cáncer de cerebro (por ej., glioma, tales como glioma blastoma multiforme) en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143).

Esta invención provee, además, un método para el tratamiento del cáncer de cerebro (por ej., glioma, tales como glioma blastoma multiforme) en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), en combinación con una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Esta invención provee, además, un método para el tratamiento del cáncer de cerebro (por ej., glioma, tales como glioma blastoma multiforme) a en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143).

Esta invención provee, además, un método para el tratamiento del cáncer de cerebro (por ej., glioma, tales como glioma blastoma multiforme) en un paciente que necesita de dicho tratamiento, dicho método comprende administrar

a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), en combinación con una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Esta invención provee, además, un método para el tratamiento del cáncer de cerebro (por ej., glioma, tales como glioma blastoma multiforme) en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), en combinación con una cantidad efectiva de un agente quimioterapéutico en el cual dicho agente quimioterapéutico es temozolomida.

Esta invención provee, además, un método para el tratamiento del cáncer de cerebro (por ej., glioma, tales como glioma blastoma multiforme) en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), en combinación con una cantidad efectiva de un agente quimioterapéutico, en el cual dicho agente quimioterapéutico es temozolomida.

Esta invención provee, además, un método para tratamiento del cáncer de próstata en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de por lo menos un

(por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143).

Esta invención provee, además, un método para tratamiento del cáncer de próstata en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), en combinación con una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Esta invención provee, además, un método para tratamiento del cáncer de próstata en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143).

Esta invención provee, además, un método para tratamiento del cáncer de próstata en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), en combinación con una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Esta invención provee, además, un método para tratamiento del síndrome mielodisplásico en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de por lo menos un

(por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143).

Esta invención provee, además, un método para tratamiento del síndrome mielodisplásico en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), en combinación con una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Esta invención provee, además, un método para tratamiento del síndrome mielodisplásico en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143).

Esta invención provee, además, un método para tratamiento del síndrome mielodisplásico en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), en combinación con una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Esta invención provee, además, un método para tratamiento de las leucemias mieloides en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de por lo

menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143).

Esta invención provee, además, un método para tratamiento de las leucemias mieloides en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), en combinación con una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Esta invención provee, además, un método para tratamiento de las leucemias mieloides en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143).

Esta invención provee, además, un método para tratamiento de las leucemias mieloides en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), en combinación con una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Esta invención provee, además, un método para tratamiento de la leucemia mielógena aguda (LMA) en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de por lo

menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143).

Esta invención provee, además, un método para tratamiento de la leucemia mielógena aguda (LMA) en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), en combinación con una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Esta invención provee, además, un método para tratamiento de la leucemia mielógena aguda (LMA) en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143).

Esta invención provee, además, un método para tratamiento de la leucemia mielógena aguda (LMA) en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), en combinación con una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Esta invención provee, además, un método para tratamiento de la leucemia mielomonocítica crónica (LMMC) en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de

fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143).

Esta invención provee, además, un método para tratamiento de la leucemia mielomonocítica crónica (LMMC) en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), en combinación con una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Esta invención provee, además, un método para tratamiento de la leucemia mielomonocítica crónica (LMMC) en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143).

Esta invención provee, además, un método para tratamiento de la leucemia mielomonocítica crónica (LMMC) en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), en combinación con una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Esta invención provee, además, un método para tratamiento de la leucemia mielógena crónica (leucemia mieloide crónica, LMC) en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una

cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143).

Esta invención provee, además, un método para tratamiento de la leucemia mielógena crónica (leucemia mieloide crónica, LMC) en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), en combinación con una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Esta invención provee, además, un método para tratamiento de la leucemia mielógena crónica (leucemia mieloide crónica, LMC) en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143).

Esta invención provee, además, un método para tratamiento de la leucemia mielógena crónica (leucemia mieloide crónica, LMC) en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), en combinación con una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Esta invención provee, además, un método para tratamiento de las leucemias mieloides en un paciente que necesita de dicho tratamiento, dicho

método comprende administrar a dicho paciente una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143).

Esta invención provee, además, un método para tratamiento de las leucemias mieloides en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), en combinación con una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Esta invención provee, además, un método para tratamiento de las leucemias mieloides en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143).

Esta invención provee, además, un método para tratamiento de las leucemias mieloides en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), en combinación con una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Esta invención provee, además, un método para tratamiento del cáncer de vejiga en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de por lo menos un (por ej., 1,

2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143).

Esta invención provee, además, un método para tratamiento del cáncer de vejiga en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), en combinación con una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Esta invención provee, además, un método para tratamiento del cáncer de vejiga en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143).

Esta invención provee, además, un método para tratamiento del cáncer de vejiga en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), en combinación con una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Esta invención provee, además, un método para tratamiento del linfoma de no Hodgkin en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de por lo menos un

(por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143).

Esta invención provee, además, un método para tratamiento del linfoma de no Hodgkin en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), en combinación con una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Esta invención provee, además, un método para tratamiento del linfoma de no Hodgkin en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143).

Esta invención provee, además, un método para tratamiento del linfoma de no Hodgkin en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), en combinación con una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Esta invención provee, además, un método para tratamiento del mieloma múltiple en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de por lo menos un

(por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143).

Esta invención provee, además, un método para tratamiento del mieloma múltiple en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), en combinación con una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Esta invención provee, además, un método para tratamiento del mieloma múltiple en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143).

Esta invención provee, además, un método para tratamiento del mieloma múltiple en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), en combinación con una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

En los métodos de esta invención los compuestos de esta invención pueden administrarse en forma concurrente o secuencial (es decir, en forma consecutiva) con los agentes quimioterapéuticos o el inhibidor de transducción de señal.

Los métodos de tratamiento para los cánceres descritos aquí pueden incluir en forma opcional la administración de una cantidad efectiva de radiación (es decir, los métodos de tratamiento para los cánceres descritos aquí incluyen en forma opcional la administración de terapia de rayos).

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

Como se describe aquí, salvo que se indique de otro modo, el uso de una droga o compuesto en el período específico es por ciclo de tratamiento. Por ejemplo, una vez por día significa una vez por día de cada uno de los días del ciclo de tratamiento. Dos veces por día significa dos veces por día cada día del ciclo de tratamiento. Una vez por semana significa una vez por semana durante el ciclo de tratamiento. Una vez cada tres semanas significa una vez cada tres semanas durante el ciclo de tratamiento.

Las siguientes abreviaturas tienen los siguientes significados, salvo que se las defina de otro modo:

ACN	Acetonitrilo
AcOH	Ácido acético
DAST	trifluoruro de (dietilamino)azufre
DCC	Diciclohexilcarbodiimida
DCU	Diciclohexilurea
DCM	Dichlorometano
DI	Agua desmineralizada
DIAD	Diisopropilazodicarboxilato
DIEA	Diisopropiletilamina
DMAP	4-Dimetilaminopiridina
DME	Dimetoxietano
DMF	Dimetilformamida
DMFDMA	N,N-Dimetilformamida dimetilacetal

DMSO	Dimetil sulfóxido
DTT	Ditiotreitol
EDCI	clorhidrato de 1—(3—dimetilamino—propil)—3—etilcarbodiimida
EtOAc	Acetato de etilo
EtOH	Etanol
HATU	N,N,N',N'—Tetrametil—O—(7—Azabenzotriazol—1—il)Uronio hexafluorofosfato
Hex	hexanos
HOBt	1-Hidroxolbenzotriazol
HPLC	Cromatografía Líquida de Alta Resolución
LCMS	Espectrometría de masa con Cromatografía Líquida
LDA	Diisopropilamida de litio
mCPBA	ácido *meta*-Cloroperoxibenzoico
MeOH	Metanol
MTT	(bromuro de 3—[4,5—dimetil—tiazol—2—yl]—2,5—diphenyltetrazolio, azul de Tiazolilo)
RMN	Resonancia magnética nuclear
PFP	Pentafluorofenol
PMB	p-metoxibencilo
Pir	Piridina
Rb	Balón
Rbt	Balón
RT	Temperatura ambiente
SEMCl	2-(Trimetilsilil)etoxi metil cloruro
TEA	Trietilamina
Tr	Trifenil metano

Trt	Trifenil metano
TrCl	Cloruro de Trifenil metano
TFA	Ácido Trifluoroacético
THF	Tetrahidrofurano
TLC	Cromatografía de fase delgada
TMS	Trimetilsililo

Como se usa aquí, salvo que se especifique de otro modo, los siguientes términos tienen los siguientes significados:

"agente contra el cáncer" significa un fármaco (medicamento o principio farmacéuticamente activo) para tratar el cáncer;

"agente anti-neoplásico" significa un fármaco (medicamento o principio farmacéuticamente activo) para tratar el cáncer (es decir, un agente quimioterapéutico);

"por lo menos uno", como se usa con referencia al número de compuestos de esta invención significa por ejemplo 1-6, en general 1-4, más generalmente 1, 2 o 3, y usualmente, uno o dos, y más usualmente uno;

"por lo menos uno", como se usa con referencia al número de agentes quimioterapéuticos usados, significa por ejemplo 1-6, en general 1-4, más generalmente 1, 2 o 3, y usualmente uno o dos, o uno;

"agente quimioterapéutico" significa un fármaco (medicamento o principio farmacéuticamente activo) para tratar el cáncer (es decir, y agente anti-neoplásico);

"compuesto" con referencia a los agentes anti-neoplásicos, incluye los agentes que son anticuerpos;

"en forma concurrente" significa (1) simultáneamente en el tiempo (por ej., al mismo tiempo); o (2) en momentos diferentes durante el transcurso de un cronograma de tratamiento común;

"en forma consecutiva" significa uno después del otro;

"diferente" como se usa en la frase "diferentes agentes anti-neoplásicos" significa que los agentes no son el mismo compuesto o estructura; con preferencia, "diferente" como se usa en la frase "diferentes agentes anti-neoplásicos" significa no de la misma clase de agentes anti-neoplásicos; por ejemplo, un agente anti-neoplásico es un taxano, y otro agente anti-neoplásico es un compuesto coordinador de platino;

"cantidad efectiva" o "cantidad terapéuticamente efectiva" pretende describir una cantidad de compuesto o una composición de la presente invención, o una cantidad de radiación, efectiva en el tratamiento o la inhibición de las enfermedades o afecciones descritas aquí, y de este modo producir el efecto terapéutico, de alivio, inhibidor o preventivo deseado; de este modo, por ejemplo, en los métodos de tratamiento para el cáncer descritos aquí "cantidad efectiva" (o "cantidad terapéuticamente efectiva") significa, por ejemplo, la cantidad del compuesto (o fármaco), o radiación, que produce: (a) la reducción, el alivio o la desaparición de uno o más síntomas causados por el cáncer, (b) la reducción del tamaño del tumor, (c) la eliminación del tumor, y/o (d) estabilización de la enfermedad a largo plazo (interrupción del crecimiento) del tumor; por ejemplo, en el tratamiento del cáncer de pulmón (por ej., cáncer de pulmón de células no pequeñas) una cantidad terapéuticamente efectiva es aquella cantidad que alivia o elimina la tos, la falta de aire y/o el dolor; además, por ejemplo, una cantidad efectiva, o a cantidad terapéuticamente efectiva del inhibidor de ERK (es decir, un compuesto de esta invención) es aquella cantidad que produce la reducción en la actividad de ERK (ERK1 y/o ERK2) y la fosforilación; la reducción en la actividad de ERK puede determinarse por el análisis de marcadores farmacodinámicos tales como RSK1,2 fosforilado y ERK1,2, fosforilado usando técnicas conocidas en el arte;

"Ej" en las tablas representa "Ejemplo";

"uno o más" tiene el mismo significado que "por lo menos uno";

"paciente" significa un animal, tal como un mamífero (por ej., un ser humano, y con preferencia un ser humano);

"prodroga" significa compuestos que se transforman rápidamente, por ejemplo, por hidrólisis en sangre, in vivo en el compuesto original, es decir, en los compuestos de fórmula 1.0 o en una sal y/o un solvato de éstos; una discusión exhaustiva se provee en T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series, y en Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987, ambas incorporadas aquí a modo de referencia; el alcance de esta invención incluye Prodrogas de los novedosos compuestos de esta invención;

en forma secuencial representa (1) administración de un componente del método ((a) compuesto de la invención, o (b) agente quimioterapéutico, inhibidor de transducción de señal y/o terapia de rayos) seguido de administración del otro componente o componentes; luego de la administración de un componente, el siguiente componente puede administrarse sustancialmente inmediatamente después del primer componente, o el siguiente componente puede administrarse después de un período de tiempo efectivo después del primer componente; el período de tiempo efectivo es la cantidad de tiempo dado para la realización del máximo beneficio desde la administración del primer componente; y

"solvato" significa una asociación física de un compuesto de esta invención con una o más moléculas de solvente; esta asociación física incluye grados variables de enlace covalente y iónico, incluyendo enlace con hidrógeno; en ciertos casos el solvato será capaz de aislamiento, por ejemplo cuando una o

más moléculas de solvente se incorporan en el retículo de cristal del sólido cristalino; "solvato" abarca tanto solvatos de fase en solución como susceptibles de aislarse; ejemplos no limitativos de solvatos apropiados incluyen etanolatos, metanolatos, y similares; "hidrato" es un solvato en el cual la molécula de solvente es H_2O.

Como se usa aquí, salvo que se especifique de otro modo, los siguientes términos tienen los siguientes significados, y salvo que se especifique de otro modo, las definiciones de cada término (es decir, resto o sustituyente) se aplican cuando ese término se usa individualmente o como componente de otro término (por ej., la definición de arilo es la misma para arilo y para la porción arilo del arilalquilo, alquilarilo, arilalquinilo, y similares):

"acilo" significa un grupo H-C(O)-, alquil-C(O)-, alquenil-C(O)-, Alquinil-C(O)-, cicloalquil-C(O)-, cicloalquenil-C(O)-, o cicloalquinil-C(O)- en el cual los varios grupos son como se los define más adelante (y como se los define a continuación, los restos alquilo, alquenilo, alquinilo, cicloalquilo, cicloalquenilo y cicloalquinilo pueden estar sustituidos); el enlace a través del resto de origen es a través del carbonilo; los acilos preferidos contienen un alquilo inferior; Ejemplos no limitativos de grupos acilo apropiados incluyen formilo, acetilo, propanoilo, 2-metilpropanoilo, butanoilo y ciclohexanoilo;

"alquenilo" significa un grupo hidrocarbonado alifático (cadena) que comprende por lo menos un enlace doble de carbono a carbono, en el cual la cadena puede ser recta o ramificada, y donde dicho grupo comprende aproximadamente 2 hasta aproximadamente 15 átomos de carbono; Los grupos alquenilo preferidos comprenden aproximadamente 2 hasta aproximadamente 12 átomos de carbono en la cadena; y con mayor preferencia aproximadamente 2 hasta aproximadamente 6 átomos de carbono en la cadena; ramificado significa que uno o más grupos alquilo inferior, tales como metilo, etilo o propilo, o grupos

alquenilo están unidos a una cadena alquenilo lineal; "alquenilo inferior" significa un grupo alquenilo que comprende aproximadamente 2 hasta aproximadamente 6 átomos de carbono en la cadena, y la cadena puede ser recta o ramificada; el término "alquenilo sustituido" significa que el grupo alquenilo está sustituido por uno o más sustituyentes seleccionados en forma independiente, y cada sustituyente se selecciona en forma independiente del grupo que consiste en: halo, alquilo, arilo, cicloalquilo, ciano, alcoxi y –S(alquilo); ejemplos no limitativos de grupos alquenilo apropiado incluyen etenilo, propenilo, n-butenilo, 3-metilbut-2-enilo, n-pentenilo, octenilo y decenilo;

"alcoxi" significa un grupo alquil-O- (es decir, el enlace a través del resto de origen es a través del oxígeno del éter) en el cual el grupo alquilo no está sustituido o está sustituido como se describe más adelante; ejemplos no limitativos de grupos alcoxi apropiados incluyen metoxi, etoxi, n-propoxi, isopropoxi, n-butoxi y heptoxi;

"alcoxicarbonilo" significa un grupo alquil-O-CO- (es decir, el enlace a través del resto de origen es a través del carbonilo) en el cual el grupo alquilo no está sustituido o está sustituido como se definió con anterioridad; ejemplos no limitativos de grupos alcoxicarbonilo apropiados incluyen metoxicarbonilo y etoxicarbonilo;

"alquilo" (incluyendo las porciones alquilo de otros restos, tales como trifluoroalquilo y alquiloxi) significa un grupo hidrocarbonado alifático (cadena) que puede ser recta o ramificada donde dicho grupo comprende aproximadamente 1 hasta aproximadamente 20 átomos de carbono en la cadena; los grupos alquilo preferidos comprenden aproximadamente 1 hasta aproximadamente 12 átomos de carbono en la cadena; los grupos alquilo más preferidos comprenden aproximadamente 1 hasta aproximadamente 6 átomos de carbono en la cadena; ramificado significa que uno o más grupos alquilo inferior, tales como metilo, etilo

o propilo, están unidos a una cadena alquilo lineal; " alquilo inferior" significa un grupo que comprende aproximadamente 1 hasta aproximadamente 6 átomos de carbono en la cadena, y dicha cadena puede ser recta o ramificada; el término " alquilo sustituido" significa que el grupo alquilo está sustituido por uno o más sustituyentes seleccionados en forma independiente, y donde cada sustituyente se selecciona en forma independiente del grupo que consiste en: halo, arilo, cicloalquilo, ciano, hidroxi, alcoxi, alquiltio, amino, -NH(alquilo), -NH(cicloalquilo), -$N(alquil)_2$, carboxi, –C(O)O-alquilo y –S(alquilo); ejemplos no limitativos de grupos alquilo apropiados incluyen metilo, etilo, n-propilo, isopropilo, n-butilo, t-butilo, n-pentilo, heptilo, nonilo, decilo, fluorometilo, trifluorometilo y ciclopropilmetilo;

"alquilarilo" (o alquilaril) significa un alquil-aril- (es decir, el enlace a través del resto de origen es a través del grupo arilo) en el cual el grupo alquilo no está sustituido o está sustituido como se definió con anterioridad, y el grupo arilo no está sustituido o está sustituido como se define más adelante; los alquilarilos preferidos comprenden un grupo alquilo inferior; ejemplos no limitativos de apropiados alquilarilo grupos incluyen o-tolilo, p-tolilo y xililo;

"alquilheteroarilo" significa un grupo alquil-heteroaril- (es decir, el enlace a través del resto de origen es a través del grupo heteroarilo) en el cual el alquilo no está sustituido o está sustituido como se definió con anterioridad y el grupo heteroarilo no está sustituido o está sustituido como se define más adelante;

"alquilsulfinilo" significa un alquil-S(O)- (es decir, el enlace a través del resto de origen es a través del sulfinil) en el cual el grupo alquilo no está sustituido o está sustituido como se definió con anterioridad; los grupos preferidos son aquellos en los cuales el grupo alquilo es alquilo inferior;

"alquilsulfonilo" significa un grupo alquil-$S(O_2)$- (es decir, el enlace a través del resto de origen es a través del sulfonilo) en el cual el grupo alquilo no

está sustituido o está sustituido como se definió con anterioridad; los grupos preferidos son aquellos en los cuales el grupo alquilo es alquilo inferior;

"alquiltio" significa un grupo alquil-S- (es decir, el enlace a través del resto de origen es a través del azufre) en el cual el grupo alquilo no está sustituido o está sustituido como se describió con anterioridad; ejemplos no limitativos de apropiados alquiltio grupos incluyen metiltio, etiltio, i-propiltio y heptiltio;

"alquinilo" significa un grupo hidrocarbonado alifático (cadena) que comprende por lo menos un enlace triple de carbono a carbono, en el cual la cadena puede ser recta o ramificada, y en el cual el grupo comprende aproximadamente 2 hasta aproximadamente 15 átomos de carbono en la cadena; los grupos alquinilo preferidos comprenden aproximadamente 2 hasta aproximadamente 12 átomos de carbono en la cadena; y con mayor preferencia aproximadamente 2 hasta aproximadamente 4 átomos de carbono en la cadena; Ramificado significa que uno o más inferior alquilo grupos, tales como metilo, etilo o propilo, están unidos a una cadena alquinilo lineal; "alquinilo inferior " significa un grupo alquinilo que comprende aproximadamente 2 hasta aproximadamente 6 átomos de carbono en la cadena, y la cadena puede ser recta o ramificada; ejemplos no limitativos de apropiados alquinilo grupos incluyen etinilo, propinilo, 2-butinilo, 3-metilbutinilo, n-pentinilo, y decinilo; el término "alquinilo sustituido " significa que el grupo alquinilo está sustituido por uno o más sustituyentes seleccionados en forma independiente, y cada sustituyente se selecciona en forma independiente del grupo que consiste en alquilo; arilo y cicloalquilo;

"amino" significa un $-NH_2$;

"aralquenilo" (o arilalquenilo) significa un grupo aril-alquenil- (es decir, el enlace a través del resto de origen es a través del grupo alquenilo) en el cual el grupo arilo no está sustituido o está sustituido como se define más adelante, y el grupo alquenilo no está sustituido o está sustituido como se definió con

anterioridad; los aralquenilos preferidos contienen un grupo alquenilo inferior; ejemplos no limitativos de grupos aralquenilo apropiados incluyen 2-fenetenilo y 2-naftiletenilo;

"aralquilo" (o arilalquilo) significa un grupo aril-alquil- (es decir, el enlace a través del resto de origen es a través del grupo alquilo) en el cual el arilo no está sustituido o está sustituido como se define más adelante y el alquilo no está sustituido o está sustituido como se definió con anterioridad; los aralquilos preferidos comprenden un grupo alquilo inferior; ejemplos no limitativos de apropiados aralquilo grupos incluyen bencilo, 2-fenetilo y naftalenilmetilo;

"aralquiloxi" (o arilalquiloxi) significa un grupo aralquil-O- (es decir, el enlace a través del resto de origen es a través del oxígeno del éter) en el cual el grupo aralquilo no está sustituido o está sustituido como se describió con anterioridad; ejemplos no limitativos de grupos aralquiloxi apropiados incluyen benciloxi y 1- o 2-naftalenmetoxi;

"aralcoxicarbonilo" significa un grupo aralquil-O-C(O)- (es decir, el enlace a través del resto de origen es a través del carbonilo) en el cual el grupo aralquilo no está sustituido o está sustituido como se definió con anterioridad; un ejemplo no limitativo de un grupo aralcoxicarbonilo apropiado es benciloxicarbonilo;

"aralquiltio" significa un grupo aralquil-S- (es decir, el enlace a través del resto de origen es a través del azufre) en el cual el grupo aralquilo no está sustituido o está sustituido como se describió con anterioridad; un ejemplo no limitativo de un grupo aralquiltio apropiado es benciltio;

"aroilo" significa un grupo aril-C(O)- (es decir, el enlace a través del resto de origen es a través del carbonilo) en el cual el grupo arilo no está sustituido o está sustituido como se define más adelante; ejemplos no limitativos de apropiados grupos incluyen benzoilo y 1- y 2-naftoilo;

"arilo" (a veces abreviado "ar") significa un sistema anular aromático monocíclico o multicíclico que comprende aproximadamente 6 hasta aproximadamente 14 átomos de carbono, con preferencia aproximadamente 6 hasta aproximadamente 10 átomos de carbono; el grupo arilo puede estar sustituido en forma opcional con uno o más "sustituyentes del sistema anular" seleccionados en forma independiente (definido más adelante). Ejemplos no limitativos de apropiados arilo grupos incluyen fenilo y naftilo;

"arilalquinilo" significa un grupo aril-alquinil- (es decir, el enlace a través del resto de origen es a través del grupo alquinilo) en el cual el grupo arilo no está sustituido o está sustituido como se definió con anterioridad, y el grupo alquinilo no está sustituido o está sustituido como se definió con anterioridad;

"arilaminoheteroarilo" significa un grupo aril-amino-heteroarilo (es decir, el enlace a través del resto de origen es a través del grupo heteroarilo) en el cual el grupo arilo no está sustituido o está sustituido como se definió con anterioridad, el grupo amino es como se definió con anterioridad (es decir, un –NH- aquí), y el grupo heteroarilo no está sustituido o está sustituido como se define más adelante;

"arilheteroarilo" significa un grupo aril-heteroaril- (es decir, el enlace a través del resto de origen es a través del grupo heteroarilo) en el cual el grupo arilo no está sustituido o está sustituido como se definió con anterioridad, y el grupo heteroarilo no está sustituido o está sustituido como se define más adelante;

"ariloxi" significa un grupo aril-O- (es decir, el enlace a través del resto de origen es a través del oxígeno del éter) en el cual el grupo arilo no está sustituido o está sustituido como se definió con anterioridad; ejemplos no limitativos de grupos ariloxi apropiados incluyen fenoxi y naftoxi;

"ariloxicarbonilo" significa un grupo aril-O-C(O)- (es decir, el enlace a través del resto de origen es a través del carbonilo) en el cual el grupo arilo no está sustituido o está sustituido como se definió con anterioridad; ejemplos no limitativos de grupos ariloxicarbonilo apropiados incluyen fenoxicarbonilo y naftoxicarbonilo;

"arilsulfinilo" significa un grupo aril-S(O)- (es decir, el enlace a través del resto de origen es a través del sulfinilo) en el cual arilo no está sustituido o está sustituido como se definió con anterioridad;

"arilsulfonilo" significa un grupo aril-$S(O_2)$- (es decir, el enlace a través del resto de origen es a través del sulfonilo) en el cual arilo no está sustituido o está sustituido como se definió con anterioridad;

"ariltio" significa un grupo aril-S- (es decir, el enlace a través del resto de origen es a través del azufre) en el cual el grupo arilo no está sustituido o está sustituido como se describió con anterioridad; ejemplos no limitativos de grupos ariltio apropiados incluyen feniltio y naftiltio;

"cicloalquenilo" significa un sistema anular no aromático mono o multicíclico que comprende aproximadamente 3 hasta aproximadamente 10 átomos de carbono, con preferencia aproximadamente 5 hasta aproximadamente 10 átomos de carbono que contiene por lo menos un enlace doble carbono-carbono; los anillos cicloalquenilo preferidos contienen aproximadamente 5 hasta aproximadamente 7 átomos en el anillo; el cicloalquenilo puede estar sustituido en forma opcional con uno o más "sustituyentes del sistema anular" seleccionados en forma independiente (definido más adelante); Ejemplos no limitativos de apropiados cicloalquenilos monocíclicos incluyen ciclopentenilo, ciclohexenilo, cicloheptenilo, y similares; un ejemplo no limitativo de un cicloalquenilo multicíclico apropiado es norbornilenilo;

"cicloalquilo" significa un sistema anular no aromático mono- o multicíclico que comprende aproximadamente 3 hasta aproximadamente 7 átomos de carbono, con preferencia aproximadamente 3 hasta aproximadamente 6 átomos de carbono; el cicloalquilo puede estar sustituido en forma opcional con uno o más "sustituyentes del sistema anular" seleccionados en forma independiente (definidos más adelante); ejemplos no limitativos de cicloalquilos monocíclicos apropiados incluyen ciclopropilo, ciclopentilo, ciclohexilo, cicloheptilo y similares; ejemplos no limitativos de cicloalquilos multicíclicos apropiados incluyen 1-decalin, norbornilo, adamantilo y similares;

"cicloalquilalquilo" significa un grupo cicloalquil-alquil- (es decir, el enlace a través del resto de origen es a través del grupo alquilo) en el cual el resto cicloalquilo no está sustituido o está sustituido como se definió con anterioridad, y el resto alquilo no está sustituido o está sustituido como se definió con anterioridad;

"halo" significa grupos fluoro, cloro, bromo, o yodo; los halos preferidos son flúor, cloro o bromo, y los más preferidos son fluoro y cloro;

"halógeno" significa flúor, cloro, bromo, o yodo; los halógenos preferidos son flúor, cloro y bromo;

"haloalquilo" significa un grupo alquilo, como se definió con anterioridad, en el cual uno o más átomos de hidrógeno en el alquilo está reemplazado por un grupo halo, como se definió con anterioridad;

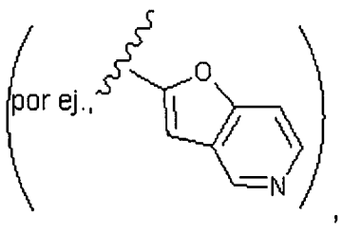
"heteroaralquenilo" significa un grupo heteroaril-alquenil- (es decir, el enlace a través del resto de origen es a través del grupo alquenilo) en el cual el grupo heteroarilo no está sustituido o está sustituido como se define más adelante, y el grupo alquenilo no está sustituido o está sustituido como se definió con anterioridad;

"heteroaralquilo" (o heteroarilalquilo) significa un grupo heteroaril-alquil- (es decir, el enlace a través del resto de origen es a través del grupo alquilo) en el cual el heteroarilo no está sustituido o está sustituido como se define más adelante, y el grupo alquilo no está sustituido o está sustituido como se definió con anterioridad; los heteroaralquilos preferidos comprenden un grupo alquilo que es un grupo alquilo inferior; ejemplos no limitativos de grupos aralquilo apropiados incluyen piridilmetilo, 2-(furan-3-il)etilo y quinolin-3-ilmetilo;

"heteroaralquiltio" significa un grupo heteroaralquil-S- en el cual el grupo heteroaralquilo no está sustituido o está sustituido como se definió con anterioridad;

"heteroarilo" significa un sistema anular aromático monocíclico o multicíclico que comprende aproximadamente 5 hasta aproximadamente 14 átomos en el anillo, con preferencia aproximadamente 5 hasta aproximadamente 10 átomos en el anillo, en el cual uno o más de los átomos en el anillo es un elemento distinto del carbono, por ejemplo nitrógeno, oxígeno o azufre, sólo o combinado; los heteroarilos preferidos comprenden aproximadamente 5 hasta aproximadamente 6 átomos en el anillo; el "heteroarilo" puede estar sustituido en forma opcional por uno o más "sustituyentes del sistema anular" seleccionados en forma independiente (definidos más adelante); el prefijo aza, oxa o tia antes del nombre de raíz del heteroarilo significa que por lo menos un átomo de nitrógeno, oxígeno o azufre, respectivamente, está presente como átomo del anillo; un átomo de nitrógeno de un heteroarilo puede oxidarse en forma opcional con el correspondiente N-óxido; ejemplos no limitativos de heteroarilos apropiados incluyen piridilo, pirazinilo, furanilo, tienilo, pirimidinilo, isoxazolilo, isotiazolilo, oxazolilo, tiazolilo, pirazolilo, furazanilo, pirrolilo, pirazolilo, triazolilo, 1,2,4-tiadiazolilo, pirazinilo, piridazinilo, quinoxalinilo, ftalazinilo, imidazo[1,2-a]piridinilo, imidazo[2,1-b]tiazolilo, benzofurazanilo, indolilo, azaindolilo, bencimidazolilo,

benzotienilo, quinolinilo, imidazolilo, tienopiridilo, quinazolinilo, tienopirimidilo, pirrolopiridilo, imidazopiridilo, isoquinolinilo, benzoazaindolilo, 1,2,4-triazinilo, benzotiazolilo, furopiridina



y similares;

"heteroarilalquinilo" (o heteroaralquinilo) significa un grupo heteroaril-alquinil- (es decir, el enlace a través del resto de origen es a través del grupo alquinilo) en el cual el grupo heteroarilo no está sustituido o está sustituido como se definió con anterioridad, y el grupo alquinilo no está sustituido o está sustituido como se definió con anterioridad;

"heteroarilarilo" (o heteroararilo) significa un grupo heteroaril-aril- (es decir, el enlace a través del resto de origen es a través del grupo arilo) en el cual el grupo heteroarilo no está sustituido o está sustituido como se definió con anterioridad, y el grupo arilo no está sustituido o está sustituido como se definió con anterioridad;

"heteroarilheteroarilarilo" significa un grupo heteroaril-heteroaril- (es decir, el enlace a través del resto de origen es a través del último grupo heteroarilo) en el cual cada grupo heteroarilo está no sustituido o sustituido en forma independiente como se definió con anterioridad;

"heteroarilsulfinilo" significa un grupo heteroaril-SO- en el cual el grupo heteroarilo no está sustituido o está sustituido como se definió con anterioridad;

"heteroarilsulfonilo" significa un grupo heteroaril-SO_2- en el cual el grupo heteroarilo no está sustituido o está sustituido como se definió con anterioridad;

"heteroariltio" significa un grupo heteroaril-S- en el cual el grupo heteroarilo no está sustituido o está sustituido como se definió con anterioridad;

"heterociclenilo" (o heterocicloalquenilo) significa un sistema anular no aromático, monocíclico o multicíclico que comprende aproximadamente 3 hasta aproximadamente 10 átomos en el anillo, con preferencia aproximadamente 5 hasta aproximadamente 10 átomos en el anillo, en el cual uno o más de los átomos en el sistema anular es un elemento distinto de carbono (por ejemplo uno o más heteroátomos seleccionados en forma independiente del grupo que consiste en un átomo de nitrógeno, oxígeno y azufre), y que contiene por lo menos un enlace doble carbono-carbono o enlace doble carbono-nitrógeno; no hay átomos de oxígeno y/o azufre adyacentes presentes en el sistema anular; Los anillos heterociclenilo preferidos contienen aproximadamente 5 hasta aproximadamente 6 átomos en el anillo; el prefijo aza, oxa o tia antes del nombre de raíz del heterociclenilo significa que por lo menos un átomo de nitrógeno, oxígeno o azufre, respectivamente, está presente como átomo del anillo; el heterociclenilo puede estar sustituido en forma opcional por uno o más "Sustituyentes del sistema anular" seleccionados en forma independiente (definidos más adelante); el átomo de nitrógeno o azufre del heterociclenilo puede estar oxidado en forma opcional al correspondiente N-óxido, S-óxido o S,S-dióxido; ejemplos no limitativos de grupos azaheterociclenilo monocíclicos apropiados incluyen 1,2,3,4- tetrahidropiridina, 1,2-dihidropiridilo, 1,4-dihidropiridilo, 1,2,3,6-tetrahidropiridina, 1,4,5,6-tetrahidropirimidina, 2-pirrolinilo, 3-pirrolinilo, 2-imidazolinilo, 2-pirazolinilo, y similares; Ejemplos no limitativos de apropiados grupos oxaheterociclenilo incluyen 3,4-dihidro-2H-pirano, dihidrofuranilo, fluorodihidrofuranilo, y similares; Un ejemplo no limitativo de un grupo oxaheterociclenilo multicíclico apropiado es 7-oxabiciclo[2,2,1]heptenilo;

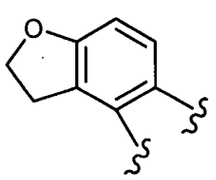
ejemplos no limitativos de anillos tiaheterociclenilo monocíclicos apropiados incluyen dihidrotiofenilo, dihidrotiopiranilo, y similares;

"heterocicloalquilalquilo" (o heterociclilalquilo) significa un grupo heterocicloalquil-alquil- (es decir, el enlace a través del resto de origen es a través del grupo alquilo) en el cual el grupo heterocicloalquilo (es decir, el grupo heterociclilo) no está sustituido o está sustituido como se define más adelante, y el grupo alquilo no está sustituido o está sustituido como se definió con anterioridad;

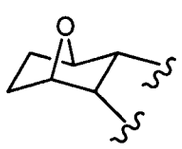
"heterociclilo" (o heterocicloalquilo) significa un sistema anular aromático saturado monocíclico o multicíclico que comprende aproximadamente 3 hasta aproximadamente 10 átomos en el anillo, con preferencia aproximadamente 5 hasta aproximadamente 10 átomos en el anillo, en el cual uno o más de los átomos en el sistema anular es un elemento distinto de carbono, por ejemplo nitrógeno, oxígeno o azufre, sólo o combinado; no hay átomos de oxígeno y/o azufre adyacentes presentes en el sistema anular; los heterociclilos preferidos contienen aproximadamente 5 hasta aproximadamente 6 átomos en el anillo; el prefijo aza, oxa o tia antes del nombre de raíz heterociclilo significa que por lo menos un átomo de nitrógeno, oxígeno o azufre respectivamente está presente como átomo del anillo; el heterociclilo puede estar sustituido en forma opcional por uno o más "sustituyentes del sistema anular" seleccionados en forma independiente (definidos más adelante); el átomo de nitrógeno o azufre del heterociclilo puede estar oxidado en forma opcional al correspondiente N-óxido, S-óxido o S,S-dióxido; ejemplos no limitativos de anillos heterociclilo monocíclicos apropiados incluyen piperidilo, pirrolidinilo, piperazinilo, morfolinilo, tiomorfolinilo, tiazolidinilo, 1,3-dioxolanilo, 1,4-dioxanilo, tetrahidrofuranoilo, tetrahidrotiofenilo, tetrahidrotiopiranilo, y similares;

"hidroxialquilo" significa un grupo HO-alquil- en el cual el grupo alquilo está sustituido o no sustituido como se definió con anterioridad; los hidroxialquilos preferidos comprenden un alquilo inferior; Ejemplos no limitativos de grupos hidroxialquilo apropiados incluyen hidroximetilo y 2-hidroxietilo; y

"sustituyente del sistema anular" significa a sustituyente unido a un sistema anular aromático o no aromático que, por ejemplo, reemplaza un hidrógeno disponible en el sistema anular; los sustituyentes del sistema anular se seleccionan, cada uno en forma independiente, del grupo que consiste en: alquilo, arilo, heteroarilo, aralquilo, alquilarilo, aralquenilo, heteroaralquilo, alquilheteroarilo, heteroaralquenilo, hidroxi, hidroxialquilo, alcoxi, ariloxi, aralcoxi, acilo, aroilo, halo, nitro, ciano, carboxi, alcoxicarbonilo, ariloxicarbonilo, aralcoxicarbonilo, alquilsulfonilo, arilsulfonilo, heteroarilsulfonilo, alquilsulfinilo, arilsulfinilo, heteroarilsulfinilo, alquiltio, ariltio, heteroariltio, aralquiltio, heteroaralquiltio, cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, $R^{60}R^{65}N$-, $R^{60}R^{65}N$-alquil-, $R^{60}R^{65}NC(O)$- y $R^{60}R^{65}NSO_2$-, en el cual R^{60} y R^{65} se seleccionan, cada uno en forma independiente, del grupo que consiste en: hidrógeno, alquilo, arilo, y aralquilo; "Sustituyente del sistema anular" también significa un anillo cíclico de 3 a 7 átomos en el anillo, donde 1-2 átomos en el anillo pueden ser heteroátomos, unidos a un anillo arilo, heteroarilo, heterociclilo o heterociclenilo sustituyendo en forma simultánea dos átomos de hidrógeno en dicho anillo arilo, heteroarilo, heterociclilo o heterociclenilo; Ejemplos no limitativos incluyen:



,



y similares.

Las líneas dibujadas dentro de un anillo significan que el enlace indicado puede estar unido a cualquiera de los átomos de carbono del anillo susceptibles de sustitución.

Cualquier carbono o heteroátomo con valencias no satisfechas en el texto, los esquemas, ejemplos, fórmula estructurales y cualquiera de las Tablas de esta invención se supone que tienen el átomo o los átomos de hidrógeno para satisfacer las valencias.

Uno o más compuestos de la invención también pueden existir como, o en forma opcional convertirse en, un solvato. La preparación de solvatos se conoce en general. De este modo, por ejemplo, M. Caira *et al*, *J. Pharmaceutical Sci.*, 93(3), 601-611 (2004) describen la preparación de the solvatos del fluconazol antifúngico en acetato de etilo como también a partir de agua. Preparaciones similares de solvatos, hemisolvato, hidratos y similares se describen en el texto escrito por E. C. van Tonder *et al*, *AAPS PharmSciTech.*, 5(1), article 12 (2004); y A. L. Bingham *et al*, *Chem. Commun.*, 603-604 (2001). Un proceso típico, no limitativo, implica la disolución del compuesto en cantidades deseadas de solvente deseado (orgánico o agua o sus mezclas) a una temperatura superior a la temperatura ambiente, y enfriar la solución a una velocidad suficiente para formar cristales que luego se aíslan por métodos estándar. Las técnicas analíticas tales como, por ejemplo espectroscopía por I. R., muestran la presencia del solvente (o agua) en los cristales como solvato (o hidrato).

El término "composición farmacéutica" también pretende abarcar tanto la composición a granel como las unidades de dosificación individuales formadas por más de un (por ej., dos) agentes farmacéuticamente activos tales como, por ejemplo, un compuesto de la presente invención y un agente adicional seleccionado de las listas de agentes adicionales descritos aquí, junto con cualquier excipiente inactivo para uso farmacéutico. La composición a granel y

cada una de las unidades de dosificación individuales pueden contener cantidades fijas de los "más de un agente farmacéuticamente activo" mencionados con anterioridad. La composición a granel es material que aún no se ha formado en unidades de dosificación individuales. Una dosificación alternativa es una unidad de dosificación oral tal como comprimidos, cápsulas, píldoras y similares. De manera similar, los métodos descritos aquí para el tratamiento de un paciente por medio de la administración de una composición farmacéutica de la presente invención también pretenden abarcar la administración de la mencionada composición a granel antes mencionada y las unidades de dosificación individuales.

Las prodrogas de los compuestos de la invención también se contemplan aquí. El término "prodroga", como se emplea aquí, denota un compuesto que es un precursor farmacológico que, luego de la administración a un sujeto, sufre conversión química por procesos metabólicos o químicos para producir un compuesto de fórmula 1.0 o una de sus sales y/o solvatos. Una discusión sobre prodrogas se provee en T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems* (1987) 14 of the A.C.S. Symposium Series, y en *Bioreversible Carriers in Drug Design,* (1987) Edward B. Roche, ed., American Pharmaceutical Association and Pergamon Press, ambas incorporadas aquí a modo de referencia.

Por ejemplo, si un compuesto de fórmula 1.0, o una de las sales, los hidratos o los solvatos aceptables desde el punto de vista farmacéutico del compuesto, contiene un grupo funcional ácido carboxílico, una prodroga puede comprender un éster formado por el reemplazo del átomo de hidrógeno del grupo ácido con un grupo tal como, por ejemplo, alquilo (C_1–C_8), alcanoiloxi (C_2-C_{12}) - metilo, 1-(alcanoiloxi)etilo que tiene desde 4 hasta 9 átomos de carbono, 1-metil-1-(alcanoiloxi)-etilo que tiene desde 5 hasta 10 átomos de carbono, alcoxicarboniloximetilo que tiene desde 3 hasta 6 átomos de carbono, 1-

(alcoxicarboniloxi)etilo que tiene desde 4 hasta 7 átomos de carbono, 1-metil-1-(alcoxicarboniloxi)etilo que tiene desde 5 hasta 8 átomos de carbono, N-(alcoxicarbonil)aminometilo que tiene desde 3 hasta 9 átomos de carbono, 1-(N-(alcoxi-carbonil)amino)etilo que tiene desde 4 hasta 10 átomos de carbono, 3-ftalidilo, 4-crotonolactonilo, gamma-butirolacton-4-ilo, di-N,N-alquilamino (C_1-C_2) alquilo (C_2-C_3) (tales como β-dimetilaminoetilo), carbamoilalquilo-(C_1-C_2), N,N-di alquilcarbamoil (C_1-C_2) alquilo (C1-C2) y piperidino-, pirrolidin- o morfolin-alquilo (C_2-C_3), y similares.

De manera similar, si un compuesto de fórmula 1.0 contiene un grupo funcional alcohol, una prodroga puede formarse por el reemplazo del átomo de hidrógeno del grupo alcohol con un grupo tal como, por ejemplo, alcanoiloximetilo (C_1-C_6), 1-((alcanoiloxi C_1-C_6))etilo, 1-metil-1-(alcanoiloxi (C_1-C_6))etilo, alcoxicarboniloximetilo (C_1-C_6), N-alcoxicarbonilaminometilo (C_1-C_6), succinoilo, alcanoilo (C_1-C_6), α-amino alcanilo (C_1-C_4), arilacilo y α-aminoacilo, o α-aminoacil-α-aminoacilo, donde cada grupo α-aminoacilo se selecciona en forma independiente de los L-aminoácidos naturales, $P(O)(OH)_2$, -P(O)(O alquil (C_1-C_6))$_2$ o glicosilo (el radical que se obtiene de la eliminación de un grupo hidroxilo de la forma semi acetal de un carbohidrato), y similares.

Si un compuesto de fórmula 1.0 incorpora un grupo funcional amina, una prodroga puede formarse por el reemplazo de un átomo de hidrógeno en el grupo amina con un grupo tal como, por ejemplo, R^{70}-carbonilo, $R^{70}O$-carbonilo, $NR^{70}R^{75}$-carbonilo donde R^{70} y R^{75} son cada uno en forma independiente alquilo (C_1-C_{10}), cicloalquilo (C_3-C_7), bencilo, o R^{70}-carbonilo es un α-aminoacilo natural o α-aminoacilo natural, —C(OH)C(O)OY^{80} donde Y^{80} es H, alquilo (C_1-C_6) o bencilo, —C(OY^{82})Y^{84} donde Y^{82} es alquilo (C_1-C_4) e Y^{84} es alquilo (C_1-C_6), carboxi alquilo (C_1-C_6), amino alquilo (C_1-C_4) o mono-N— o di-N,N-alquilaminoalquilo (C_1-C_6),

—C(Y^{86})Y^{88} donde Y^{86} es H o metilo e Y^{88} es mono-N— o di-N,N- alquilamino (C_1-C_6) morfolino, piperidin-1-ilo o pirrolidin-1-ilo, y similares.

Esta invención incluye, además, los compuestos de esta invención en forma aislada y purificada.

Las formas polimórficas de los compuestos de fórmula 1.0, y de las sales, solvatos y prodrogas de los compuestos de fórmula 1.0, pretenden incluirse en la presente invención.

Ciertos compuestos de la invención pueden existir en diferentes formas isométricas (por ej., enantiómeros, diastereoisómeros, atropisómeros). La invención contempla todos dichos isómeros tanto en forma pura como dentro de una mezcla, incluyendo mezclas racémicas. También se incluyen las formas enólicas.

Todos los estereoisómeros (por ejemplo, isómeros geométricos, isómeros ópticos y similares) de los presentes compuestos (incluyendo aquellos de las sales, solvatos y prodrogas de los compuestos como también las sales y solvatos de las prodrogas), tales como aquellos que pueden existir debido a carbonos asimétricos en varios sustituyentes, incluyendo las formas enantioméricas (que pueden existir en ausencia de carbonos asimétricos), formas rotaméricas, atropisómeros y formas diateroméricas, se contemplan dentro del alcance de esta invención. Los estereoisómeros individuales de los compuestos de la invención pueden, por ejemplo, ser sustancialmente libres de otros isómeros, o pueden mezclarse, por ejemplo, como racematos o con todos los otros estereoisómeros, u otros seleccionados. Los centros quirales de la presente invención pueden tener la configuración S o R como se define en las Recomendaciones de la *IUPAC* de 1974. El uso de los términos "sal", "solvato" "prodroga" y similares, pretende aplicarse en igual medida a la sal, el solvato y la prodroga de los enantiómeros,

estereoisómeros, rotámeros, tautómeros, racematos o prodrogas de los compuestos de la invención.

Las mezclas diasteroméricas pueden separarse en sus diasterómeros individuales sobre la base de sus diferencias físicas por métodos conocidos para aquellos expertos en el arte, tales como, por ejemplo, por cromatografía y/o cristalización funcional. Los enantiómeros pueden separarse por conversión de la mezcla enantiomérica en una mezcla diastereomérica por reacción con un compuesto ópticamente activo apropiado (por ej., auxiliares quirales tales como un alcohol quiral o cloruro ácido de Mosher), separación de los diastereómeros y conversión (por ej., hidrolizar) los diastereómeros individuales de los enantiómeros puros correspondientes. Además, algunos de los compuestos de Fórmula (I) pueden ser atropisómeros (por ej., biarilos sustituidos) y se consideran parte de esta invención. Los enantiómeros también pueden prepararse por el uso de de columna de HPLC quiral.

Los compuestos de fórmula 1.0 forman sales que también se encuentran dentro del alcance de esta invención. La referencia a un compuesto de fórmula 1.0 aquí incluye la referencia a sus sales, salvo que se indique de otro modo. El término "sal(es)", como se emplea aquí, denota sales ácidas formadas con ácidos orgánicos y/o inorgánicos, como también sales alcalinas formadas con bases orgánicas y/o inorgánicas. Además, cuando un compuesto de fórmula 1.0 contiene tanto un resto alcalino, tales como, sin carácter limitativo una piridina o imidazol, y un resto ácido, tales como, sin carácter limitativo un ácido carboxílico, los zwitteriones ("sales inertes") pueden formarse y se incluyen dentro del término "sal(es)" como se usa aquí. Se prefieren las sales aceptables desde el punto de vista farmacéutico (es decir, sales no tóxicas, fisiológicamente aceptables). Las sales de los compuestos de la fórmula 1.0 pueden formarse, por ejemplo, haciendo reaccionar un compuesto de fórmula 1.0 con una cantidad de ácido o

base, tales como una cantidad equivalente, en un medio tal como aquel en el cual la sal se precipita o en un medio acuoso seguido de liofilización. Los ácidos (y bases) que en general se consideran apropiados para la formación de sales útiles para uso farmacéutico a partir de compuestos farmacéuticos alcalinos (o ácidos) se describen, por ejemplo, en el texto escrito por S. Berge *et al*, *Journal of Pharmaceutical Sciences* (1977) 66(1) 1-19; P. Gould, *International J. of Pharmaceutics* (1986) 33 201-217; Anderson *et al*, *The Practice of Medicinal Chemistry* (1996), Academic Press, New York; en *The Orange Book* (Food & Drug Administration, Washington, D.C. on their website); y P. Heinrich Stahl, Camille G. Wermuth (Eds.), *Handbook of Pharmaceutical Salts: Properties, Selection, and Use*, (2002) Int'l. Union of Pure and Applied Chemistry, pp. 330-331. Estas descripciones se incorporan aquí a modo de referencia.

Las sales de adición con ácido ejemplificativas incluyen acetatos, adipatos, alginatos, ascorbatos, aspartatos, benzoatos, benensulfonatos, bisulfatos, boratos, butiratos, citratos, alcanforatos, alcanforsulfonatos, ciclopentanpropionatos, digluconatos, dodecilsulfatos, etansulfonatos, fumaratos, glucoheptanoatos, glicerofosfatos, semisulfatos, heptanoatos, hexanoatos, clorhidratos, bromhidratos, yodhidratos, 2-hidroxietansulfonatos, lactatos, maleatos, metansulfonatos, metil sulfatos, 2-naftalensulfonatos, nicotinatos, nitratos, oxalatos, pamoatos, pectinatos, persulfatos, 3-fenilpropionatos, fosfatos, picratos, pivalatos, propionatos, salicilatos, succinatos, sulfatos, sulfonatos (tales como los mencionados aquí), tartaratos, tiocianatos, toluensulfonatos (también conocidos como tosilatos,) undecanoatos, y similares.

Las sales alcalinas ejemplificativas incluyen sales de amonio, sales de metales alcalinos, tales como sales de sodio, litio y potasio, sales de metales alcalino térreo tales como sales de calcio y magnesio, sales de aluminio, sales de zinc, sales con bases orgánicas (por ejemplo, aminas orgánicas) tales como

benzatinas, dietilamina, diciclohexilaminas, hidrabaminas (formadas con N,N-bis(dehidroabietil)etilendiamina), N-metil-D-glucaminas, N-metil-D-glucamidas, t-butil aminas, piperazina, fenilciclohexil-amina, colina, trometamina, y sales con aminoácidos tales como arginina, lisina y similares. Los grupos alcalinos que contienen nitrógeno pueden cuaternizarse con agentes tales como haluros de alquilo inferior (por ej. cloruros, bromuros y yoduros de metilo, etilo, propilo, y butilo), dialquil sulfatos (por ej. dimetil, dietil, dibutil, y diamil sulfatos), haluros de cadena larga (por ej. cloruros, bromuros y yoduros de decilo, laurilo, miristilo y estearilo), haluros de aralquilo (por ej. bromuros de bencilo y fenetilo), y otros.

Todas dichas sales ácidas y alcalinas pretenden ser sales aceptables desde el punto de vista farmacéutico dentro del alcance de la invención y todas las sales ácidas y alcalinas se consideran equivalentes a las formas libres de los correspondientes compuestos para los fines de la invención.

Los compuestos de fórmula 1.0, y sus sales, solvatos y prodrogas, pueden existir en su forma tautomérica (por ejemplo, como éter de amida o imino). Todas dichas formas tautoméricas se contemplan aquí como parte de la presente invención.

En los sistemas anulares que contienen heteroátomos de esta invención, no hay grupos hidroxilo en los átomos de carbono adyacentes a N, O o S, y no hay grupos N o S en los carbonos adyacentes a otro heteroátomo. De este modo, por ejemplo, en el anillo:

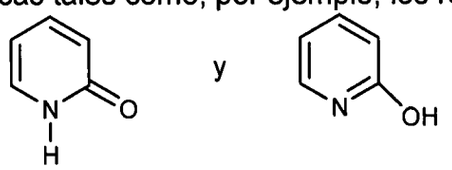


no hay un -OH unido directamente a los carbonos marcados 2 y 5.

Los compuestos de fórmula 1.0 pueden existir en diferentes formas tautoméricas, y todas dichas formas se abarcan dentro del alcance de la

invención. Además, por ejemplo, todas las formas ceto-enólicas y de imina-enamina de los compuestos se incluyen en la invención.

Formas tautoméricas tales como, por ejemplo, los restos:



se consideran equivalentes en ciertas realizaciones de esta invención.

El término "sustituido" significa que uno o más hidrógenos en el átomo designado está reemplazado con una selección del grupo indicado, siempre que la valencia normal del átomo designado en las circunstancias existentes no se exceda, y que la sustitución produzca un compuesto estable. Las combinaciones de sustituyentes y/o variables son permisibles sólo si dichas combinaciones producen compuestos estables. Por "compuesto estable" o "estructura estable" se entiende un compuesto que es lo suficientemente robusto para sobrevivir el aislamiento hasta un grado útil de pureza a partir de una mezcla de reacción, y formulación en un agente terapéutico eficaz.

El término "sustituido en forma opcional" significa la sustitución opcional con los grupos, radicales o restos específicos.

El término "purificado", "en forma purificada" o "en forma aislada y purificada" para un compuesto se refiere al estado físico de dicho compuesto luego de ser aislados a partir de un proceso de síntesis o fuente natural o combinación de los anteriores. De este modo, el término "purificado", "en forma purificada" o "en forma aislada y purificada" para un compuesto se refiere al estado físico de dicho compuesto luego de obtenerse a partir de un proceso de purificación o los procesos descritos aquí o conocidos por los expertos en el arte, en pureza suficiente para ser caracterizables por técnicas analíticas estándar descritas aquí o conocidas por los expertos en el arte.

Cuando un grupo funcional en un compuesto se denomina "protegido", esto significa que el grupo está en forma modificada para evitar las reacciones colaterales no deseadas en el sitio protegido cuando el compuesto se somete a reacción. Los grupos protectores apropiados son reconocidos por aquellos con experiencia en el arte como también por referencia a libros de texto estándares tales como, por ejemplo, T. W. Greene *et al*, *Protective Grupos in organic Synthesis* (1991), Wiley, New York.

Cuando cualquier variable (por ej., arilo, heterociclo, R^3, etc.) ocurre más de una vez en cualquier resto o en cualquier compuesto de fórmula 1.0, su definición en cada caso es independiente de su definición en cualquier otro caso.

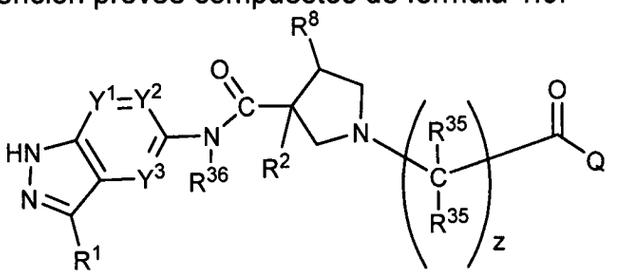
Como se usa aquí, el término "composición" pretende abarcar un producto que comprende los componentes específicos en las cantidades específicas, como también cualquier producto que se obtiene, directa o indirectamente, de la combinación de los componentes específicos en las cantidades específicas.

La presente invención también abarca compuestos isotópicamente rotulados de la presente invención que son idénticos a los mencionados aquí, aunque con la diferencia de que uno o más átomos están reemplazados por un átomo que tiene una masa atómica o un número de masa diferente de la masa atómica o número de masa usualmente encontrado en la naturaleza. Ejemplos de isótopos que pueden incorporarse en los compuestos de la invención incluyen los isótopos de hidrógeno, carbono, nitrógeno, oxígeno, fósforo, flúor y cloro, tales como ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, y ^{36}Cl, respectivamente.

Ciertos compuestos isotópicamente rotulados de fórmula 1.0 (por ej., aquellos marcados con ^{3}H y ^{14}C) son útiles en los ensayos de distribución en compuesto y/o tejido de sustrato. Los isótopos titulados (es decir, ^{3}H) y carbono-14 (es decir, ^{14}C) son particularmente preferidos por su facilidad de preparación y capacidad de detección. Además, la sustitución con isótopos más pesados tales

como deuterio (es decir, ^2H) pueden producir ventajas terapéuticas que surgen de una mayor estabilidad metabólica (por ej., aumento de la vida media in vivo o reducción de los requerimientos de dosificación) y por consiguiente pueden preferirse en algunas circunstancias. Los compuestos isotópicamente rotulados de fórmula 1.0 pueden prepararse generalmente siguiendo procedimientos análogos a aquellos descritos en los Esquemas y/o en los Ejemplos que siguen a continuación, sustituyendo un reactivo apropiado isotópicamente rotulado en lugar de un reactivo no isotópicamente rotulado.

Esta invención provee compuestos de fórmula 1.0:



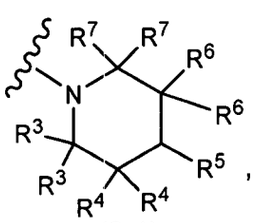
(1.0)

o sus sales, ésteres, o solvatos aceptables desde el punto de vista farmacéutico, en los cuales:

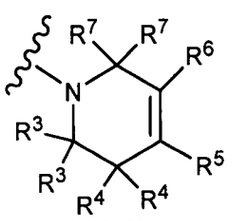
Y^1, Y^2, y Y^3 se seleccionan, cada uno en forma independiente, del grupo que consiste en: -CH=, -N= y $-CR^9$= (con preferencia Y^1, Y^2, e Y^3 son cada uno -CH=);

z es de 1 hasta 3 (es decir, 1, 2 o 3, y con preferencia 1);

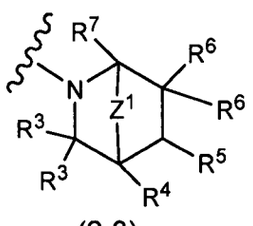
Q es un sustituyente seleccionado del grupo que consiste en:



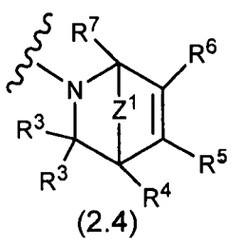
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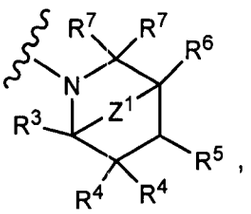
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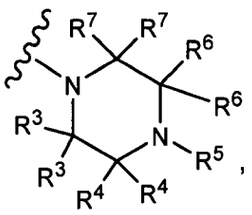


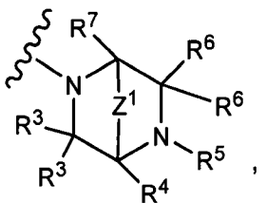
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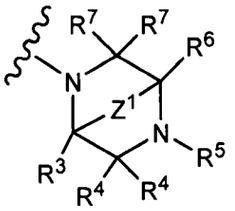


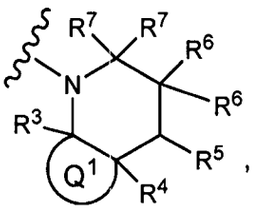
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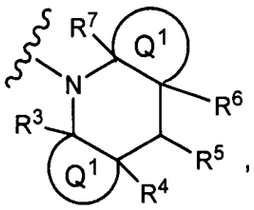

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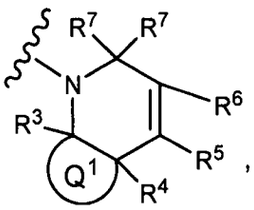

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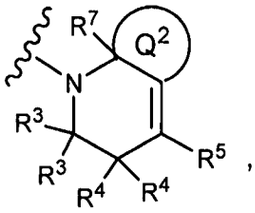

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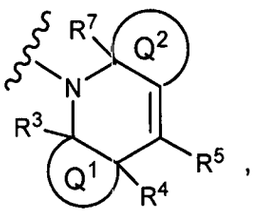

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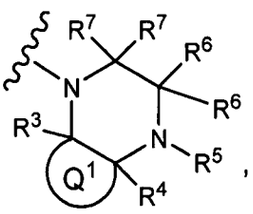

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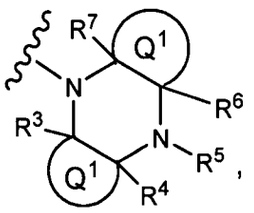

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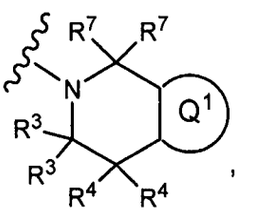

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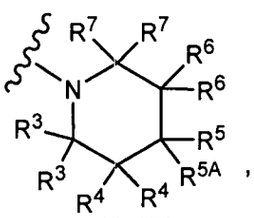

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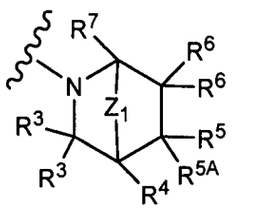

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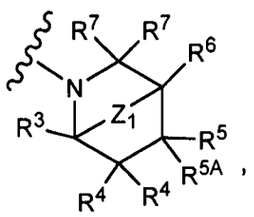

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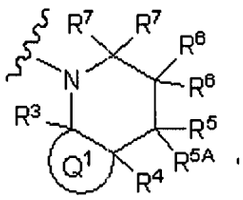

(2.15),

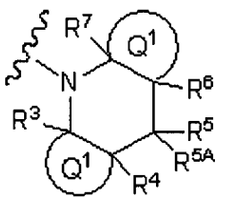

(2.16),


(2.17),

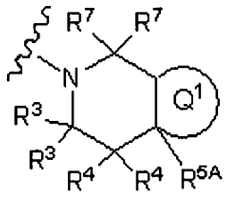

(2.18),


(2.19),


(2.20)


(2.21)

y


(2.22)

Cada Q^1 representa un anillo seleccionado en forma independiente del grupo que consiste en: cicloalquilo, cicloalquilo sustituido, heterocicloalquilo, heterocicloalquilo sustituido, arilo, arilo sustituido, heteroarilo, y heteroarilo sustituido, donde dichos anillos sustituidos están sustituidos con 1 hasta 3 sustituyentes seleccionados en forma independiente del grupo que consiste en: halo (por ej., Cl, F, Br) y los restos R^{10}; siempre que cuando Q^1 es arilo, heteroarilo, arilo sustituido o heteroarilo sustituido entonces los átomos de carbono en la unión del anillo (es decir, los dos átomos de carbono comunes a los anillos fusionados) no están sustituidos;

Q^2 representa un anillo seleccionado del grupo que consiste en: cicloalquilo, cicloalquilo sustituido, heterocicloalquilo, y heterocicloalquilo sustituido, donde dichos anillos sustituidos están sustituidos con 1 hasta 3 sustituyentes seleccionados en forma independiente del grupo que consiste en: los restos R^{10};

Z^1 representa $-(C(R^{24})_2)_w-$ donde cada R^{24} se selecciona en forma independiente del grupo que consiste en: H, alquilo (por ej., alquilo C_1 a C_6, por ejemplo metilo) y F, y donde w es 1, 2 o 3, y en general w es 1 o 2, y usualmente w es 1, y donde en un ejemplo cada R^{24} es H, y en otro ejemplo w es 1, y en otro ejemplo cada R^{24} es H y w es 1, con preferencia w es 1 y cada R^{24} es H (es decir, con preferencia Z^1 es $-CH_2-$);

Z^2 se selecciona del grupo que consiste en: $-N(R^{44})-$, -O- y $-C(R^{46})_2-$ (por ej., Z^2 es –NH-, -O- o $-CH_2-$);

m es 1 hasta 6;

n es 1 hasta 6;

p es 0 hasta 6;

t es 0, 1, o 2;

R^1 se selecciona del grupo que consiste en:

(1) -CN,

(2) $-NO_2$,

(3) $-OR^{10}$,

(4) $-SR^{10}$,

(5) $-N(R^{10})_2$,

(6) R^{10},

(7) $-C(O)R^{10}$ (en un ejemplo R^{10} es un anillo heterocicloalquilo de 4 a 6 miembros, en otro ejemplo R^{10} es un anillo heterocicloalquilo de 4 a 6 miembros que comprende un átomo de nitrógeno, y en otro ejemplo R^{10} es un anillo heterocicloalquilo de 4 a 6 miembros que comprende un átomo de nitrógeno donde dicho anillo está unido al resto carbonilo (-C(O)-) a través del nitrógeno del anillo),

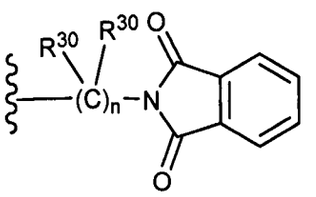
(8) $-(C(R^{30})_2)_n-NR^{32}-C(O)-R^{10}$ (por ej., $-(CH_2)_n-NH-C(O)-R^{10}$, por ejemplo donde n es 1), donde en un ejemplo n es 1, cada R^{30} es H, R^{32} es H, y R^{10} se selecciona del grupo que consiste en: cicloalquilo (por ej., ciclopropilo) y alquilo (por ej., metilo e i-propilo), y donde en otro ejemplo n es 1, cada R^{30} es H, R^{32} es H, y R^{10} se selecciona del grupo que consiste en: metilo, i-propilo y ciclopropilo,

(9) $-(C(R^{30})_2)_n-NR^{32}-S(O)_t-R^{10}$ (por ej., $-(CH_2)_n-NH-S(O)_t-R^{10}$, por ejemplo donde n es 1 y t es 2) en el cual en un ejemplo n es 1, cada R^{30} es H, R^{32} es H, t es 2, y R^{10} se selecciona del grupo que consiste en: cicloalquilo (por ej., ciclopropilo) y alquilo (por ej., metilo e i-propilo), y donde en otro ejemplo n es 1,

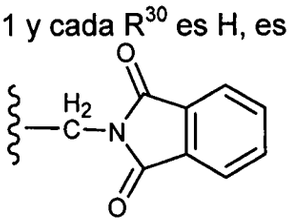
cada R^{30} es H, R^{32} es H, t es 2, R^{10} se selecciona del grupo que consiste en: metilo, i-propilo y ciclopropilo, y donde en otro ejemplo n es 1, cada R^{30} es H, R^{32} es H, t es 2, y R^{10} es metilo,

(10) $-(C(R^{30})_2)_n-NR^{32}-C(O)-N(R^{32})-R^{10}$ (por ej., $-(CH_2)_n-NH-C(O)-NH-R^{10}$, por ejemplo donde n es 1) en el cual en un ejemplo n es 1, cada R^{30} es H, cada R^{32} es H, y R^{10} es alquilo (por ej., metilo e i-propilo), y donde en otro ejemplo n es 1, cada R^{30} es H, cada R^{32} es H, y R^{10} se selecciona del grupo que consiste en: metilo e i-propilo,

(11)



donde en un ejemplo n es 1 y cada R^{30} es H, es decir, un resto de la fórmula:



,

(12) $-CF_3$,

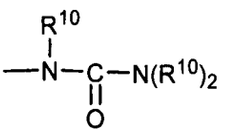
(13) $-C(O)OR^{10}$ donde en un ejemplo R^{10} se selecciona del grupo que consiste en: H, alquilo (por ej., metilo e isopropilo) y ciclopropilo (por ej., ciclopropilo), y donde en otro ejemplo R^{10} se selecciona del grupo que consiste en: H y alquilo, y donde en otro ejemplo R^{10} se selecciona del grupo que consiste en: H y metilo,

(14) $-(C(R^{30})_2)_nR^{13}$ (por ej., $-(CH_2)_nR^{13}$) en el cual en un ejemplo n es 1, cada R^{30} es H, y R^{13} se selecciona del grupo que consiste en: -OH y $-N(R^{10})_2$, donde cada R^{10} se selecciona en forma independiente, y donde en otro ejemplo n es 1, cada R^{30} es H, y R^{13} se selecciona del grupo que consiste en: -OH y $-N(R^{10})_2$, y cada R^{10} es H (es decir, R^{13} es -OH o $-NH_2$),

(15) alquenilo (por ej., $-CH=CHCH_3$),

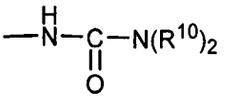
(16) $-NR^{32}-C(O)-R^{14}$ (por ej., $-NH-C(O)-R^{14}$) en el cual en un ejemplo R^{32} es H y R^{14} se selecciona del grupo que consiste en: cicloalquilo (por ej., ciclopropilo), alquilo (por ej., metilo y propilo), arilo (por ej., fenilo), amino (es decir, $-NH_2$), y heteroarilo (por ej., piridilo, tales como, por ejemplo 2- piridilo, 3-piridilo, 4-piridilo, pirazolilo y imidazolilo), y donde en otro ejemplo R^{32} es H y R^{14} se selecciona del grupo que consiste en: ciclopropilo, metilo, propilo, fenilo, y amino,

(17)



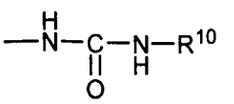
donde cada R^{10} se selecciona en forma independiente, por ejemplo:

(a) en un ejemplo el resto (17) es:



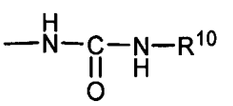
donde cada R^{10} se selecciona en forma independiente,

(b) en otro ejemplo el resto (17) es:



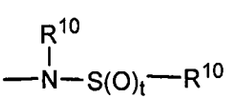
, y

(c) en otro ejemplo el resto (17) es:



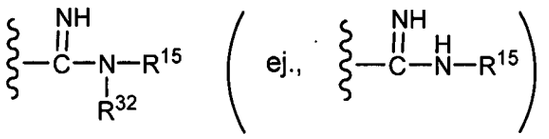
donde R^{10} se selecciona del grupo que consiste en: arilo (por ej., fenilo) y alquilo (por ej., etilo, y con preferencia R^{10} es fenilo o etilo,

(18)



donde cada R^{10} se selecciona en forma independiente, y donde en un ejemplo cada R^{10} se selecciona en forma independiente y t es 2, y donde en otro ejemplo el resto (18) es $-NH-S(O)_t-R^{10}$, y donde en otro ejemplo el resto (18) es $-NH-S(O)_t-$

R^{10} donde t es 2, y donde en otro ejemplo el resto (18) es -NH-$S(O)_t$-R^{10}. t es 2, y R^{10} es alquilo (por ej., metilo),

(19) 

(también se escribe como –C(NH)N(R^{15})R^{32} y –C(NH)NH(R^{15}), respectivamente), donde en un ejemplo R^{15} es –OH, y en otro ejemplo R^{32} es H y R^{15} es –OH,

(20) -C(O)-NR^{32}-($C(R^{30})_2$)$_p$-OR^{10} (por ej., -C(O)-NH-$(CH_2)_p$-OR^{10}, y, por ejemplo, -C(O)-NH-$(CH_2)_p$-OR^{10} donde p es 2) en el cual:

(a) en un ejemplo p es 2,

(b) en otro ejemplo R^{32} es H,

(c) en otro ejemplo R^{10} se selecciona del grupo que consiste en: H y alquilo (por ej., metilo),

(d) en otro ejemplo R^{10} se selecciona del grupo que consiste en: H y alquilo (por ej., metilo), y R^{32} es H,

(e) en otro ejemplo R^{10} se selecciona del grupo que consiste en: H y alquilo (por ej., metilo), R^{32} es H, un p es 2,

(f) en otro ejemplo R^{32} es H, cada R^{30} es H, y R^{10} es alquilo,

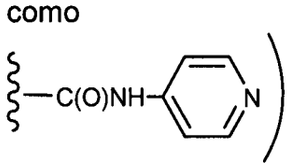
(g) en otro ejemplo R^{32} es H, cada R^{30} es H, y R^{10} es metilo,

(h) en otro ejemplo R^{32} es H, cada R^{30} es H, p es 2 y R^{10} es alquilo, y

(i) en otro ejemplo R^{32} es H, cada R^{30} es H, p es 2 y R^{10} es metilo,

(21) -C(O)N(R^{10})$_2$ donde cada R^{10} se selecciona en forma independiente, y con preferencia cada R^{10} se selecciona en forma independiente del grupo que consiste en: (a) H, (b) alquilo (por ej., metilo, butilo, e i-propilo), (c) heteroarilo (por ej., piridilo), (d) arilo (por ej., fenilo), y (e) cicloalquilo (por ej.,

ciclopropilo), donde por ejemplo, cada R^{10} se selecciona del grupo que consiste en: H, metilo, butilo, i-propilo, piridilo, fenilo y ciclopropilo, donde, por ejemplo, dicho resto $-C(O)N(R^{10})_2$ se selecciona del grupo que consiste en: $-C(O)NH_2$, $-C(O)NH(CH_3)$, $-C(O)NH(CH)(CH_3)_2$ (es decir, -C(O)NH(i-propilo)), $-C(O)NH(C_4H_9)$, $-C(O)NH(C_6H_5)$ (es decir, -C(O)NH(fenilo)), $-C(O)NH(C_3H_5)$ (es decir, -C(O)NH(ciclopropilo), y $-C(O)NH(C_5H_4N)$ (es decir, -C(O)NH(piridilo), tales como



(22) $-C(O)-NR^{32}-C(R^{18})_3$ (por ej., $-C(O)-NH-C(R^{18})_3$) en el cual cada R^{18} se selecciona en forma independiente del grupo que consiste en: R^{10} y $-C(O)OR^{19}$, y R^{19} se selecciona del grupo que consiste en: alquilo (por ej., metilo) y arilalquilo sustituido (por ej., $-CH_2C_6H_4OH$ (es decir, hidroxibencilo) tales como, por ejemplo, $-p-CH_2C_6H_4OH$ (es decir, p-OHbencilo), y donde:

(a) en un ejemplo R^{18} y R^{19} son como se definió con anterioridad con la salvedad de que por lo menos un sustituyente R^{18} es distinto de H (por ej., en un ejemplo un R^{18} es H y los restantes dos grupos R^{18} son distintos de H, y en otro ejemplo dos sustituyentes R^{18} son H y el restante sustituyente R^{18} es distinto de H),

(b) en otro ejemplo R^{18} se selecciona del grupo que consiste en: H, arilo (por ej., fenilo), arilo sustituido (por ej., fenilo sustituido, tales como, por ejemplo halofenil-, tales como, por ejemplo, flurofenilo (por ej., o-F-fenilo)), y $-C(O)OR^{19}$,

(c) en otro ejemplo R^{18} se selecciona del grupo que consiste en: H, fenilo, flurofenilo (por ej., o-F-fenilo), $-C(O)OCH_3$, $-C(O)OCH_2C_6H_4OH$ (es decir, -C(O)O(OHbencilo), tales como, -C(O)O(p-OHbencilo)),

(d) en otro ejemplo R^{18} se selecciona del grupo que consiste en: H, arilo (por ej., fenilo), arilo sustituido (por ej., fenilo sustituido, tales como, por ejemplo halofenil-, tales como, por ejemplo, flurofenilo (por ej., o-F-fenilo)), y $-C(O)OR^{19}$, siempre que por lo menos un sustituyente R^{18} es distinto de H (por ej., en un ejemplo un R^{18} es H y los restantes dos grupos R^{18} son distintos de H, y en otro ejemplo dos sustituyentes R^{18} son H y el restante sustituyente R^{18} es distinto de H),

(e) en otro ejemplo R^{18} se selecciona del grupo que consiste en: H, fenilo, flurofenilo (por ej., o-F-fenilo), $-C(O)OCH_3$, $-C(O)OCH_2C_6H_4OH$ (es decir, -C(O)O(OHbencilo), tales como, -C(O)O(p-OHbencilo)), siempre que por lo menos un sustituyente R^{18} sea distinto de H (por ej., en un ejemplo un R^{18} es H y los restantes dos grupos R^{18} son distintos de H, y en otro ejemplo dos sustituyentes R^{18} son H y el restante sustituyente R^{18} es distinto de H),

(f) en otro ejemplo R^{32} es H, y cada R^{18} se selecciona en forma independiente del grupo que consiste en: R^{10} y $-C(O)OR^{19}$, y R^{19} se selecciona del grupo que consiste en: alquilo (por ej., metilo) y arilalquilo sustituido (por ej., $-CH_2C_6H_4OH$ (es decir, hidroxibencilo) tales como, por ejemplo, $-p-CH_2C_6H_4OH$ (es decir, p-OHbencilo),

(g) en otro ejemplo R^{32} es H y R^{18} y R^{19} son como se definen en el párrafo (a),

(h) en otro ejemplo R^{32} es H y R^{18} y R^{19} son como se definen en el párrafo (b),

(i) en otro ejemplo R^{32} es H y R^{18} y R^{19} son como se definen en el párrafo (c),

(j) en otro ejemplo R^{32} es H y R^{18} y R^{19} son como se definen en el párrafo (d),

(k) en otro ejemplo R^{32} es H y R^{18} y R^{19} como se define en el párrafo (e), y

(l) en otro ejemplo R^{32} es H y R^{18} y R^{19} como se define en el párrafo (f),

(23) $-C(O)-NR^{32}-(C(R^{30})_2)_n-C(O)-N(R^{10})_2$ (por ej., $-C(O)-NH-(CH_2)_n-C(O)-NH_2$), y donde:

en un ejemplo R^{32} es H,

en otro ejemplo cada R^{30} es H,

en otro ejemplo n es 1,

en otro ejemplo n es 1 y R^{32} es H,

en otro ejemplo cada R^{10} es H,

en otro ejemplo R^{32} es H y cada R^{30} es H,

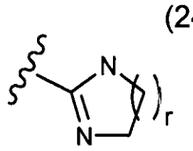
en otro ejemplo R^{32} es H, cada R^{30} es H y n es 1,

en otro ejemplo R^{32} es H, cada R^{30} es H, n es 1, y cada R^{10} es H,

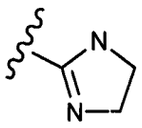
en otro ejemplo R^{32} es H, n es 1, cada R^{30} se selecciona en forma independiente del grupo que consiste en: H y alquilo, y cada R^{10} se selecciona en forma independiente del grupo que consiste en: H y alquilo, y

en otro ejemplo R^{32} es H, n es 1, y cada R^{30} se selecciona en forma independiente del grupo que consiste en: H, metilo, etilo e i-propilo (o cada R^{30} se selecciona en forma independiente del grupo que consiste en H e i-propilo, o un R^{30} es i-propilo y el otro R^{30} es H), y cada R^{10} se selecciona en forma independiente del grupo que consiste en: H metilo, etilo e i-propilo (o cada R^{10} es H),

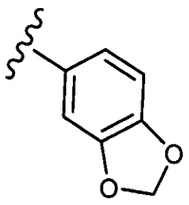
(24) heterocicloalquenilo, tales como, por ejemplo:



donde R es 1 hasta 3, y donde en un ejemplo R es 1, es decir, en un ejemplo el heterocicloalquenilo es dihidroimidazolilo, tales como, por ejemplo:



(25)



, y

(26) arilalquenil- (aralquenil-), por ejemplo, aril alquenil (C_2 a C_6) -, tales como por ejemplo, -CH=CH-fenilo;

R^2 se selecciona del grupo que consiste en:

(1) H,

(2) -CN,

(3) halo (por ej., F),

(4) alquilo (por ej., alquilo C_1 hasta C_6, tales como, por ejemplo, metilo, etilo y propilo),

(5) alquilo sustituido (por ej., alquilo C_1 a C_6 sustituido, tales como, por ejemplo, metilo sustituido y etilo sustituido) en el cual dicho alquilo sustituido está sustituido con 1 hasta 3 sustituyentes (por ej., 1 sustituyente) seleccionados del grupo que consiste en: (a) -OH, (b) -O-alquilo (por ej., -O-(alquilo C_1-C_3), tales como, por ejemplo, $-OCH_3$), (c) -O-alquilo (por ej., -O-(alquilo C_1-C_3)) sustituido con 1 hasta 3 átomos F (ejemplos de dicha porción alquilo sustituido -O- incluyen, sin carácter limitativo, $-OCHF_2$ y $-OCF_3$), y (d) $-N(R^{40})_2$ donde cada R^{40} se selecciona en forma independiente del grupo que consiste en: (i) H, (ii) alquilo C_1-C_3 (por ej., metilo), (iii) $-CF_3$, y (e) halo (por ejemplo F, Cl, y Br, y también por ejemplo F, ejemplos de un grupo halo alquilo sustituido incluyen, sin carácter limitativo, $-CHF_2$), (ejemplos de dichos grupos alquilo sustituidos descritos en (5) incluyen sin carácter limitativo $-CH(OH)CH_3$, $-CH_2OH$, y $-CH_2OCH_3$),

(6) alquinilo (por ej., etinilo),

(7) alquenilo (por ej., $-CH_2-CH=CH_2$),

(8) $-(CH_2)_mR^{11}$,

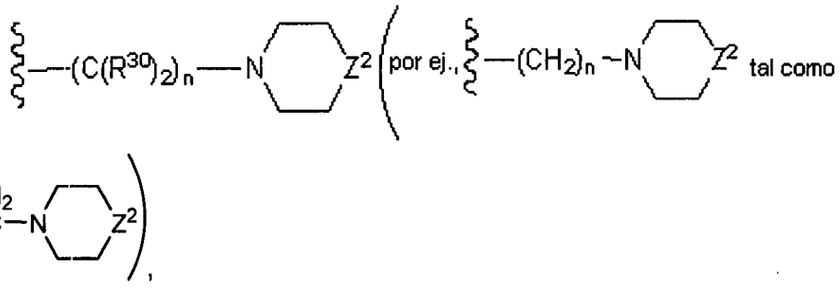
(9) $-N(R^{26})_2$,

(10) $-OR^{23}$ (por ej., -OH, $-OCH_3$ y –O-fenilo),

(11) $-N(R^{26})C(O)R^{42}$ donde en un ejemplo R^{26} es H o alquilo C_1 hasta C_6 (por ej., metilo) y R^{42} es alquilo (por ej., metilo), y en otro ejemplo $-N(R^{26})C(O)R^{42}$ es $-NHC(O)CH_3$,

(12) cicloalquilo (por ej., cicloalquilo C_3 a C_6, tales como, por ejemplo, ciclopropilo y ciclohexilo),

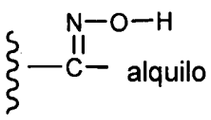
(13) cicloalquilalquilo (por ej., cicloalquil C_3 hasta C_6-alquilo (C_1 hasta C_3)-, tales como, por ejemplo, ciclopropil-CH_2- y ciclohexil-CH_2-),

(14) 

(15) –O-(sustituido alquilo) en el cual dicho alquilo sustituido está sustituido con 1 hasta 3 átomos F (ejemplos de dicho resto –O-(alquilo sustituido) incluyen, sin carácter limitativo, $-OCHF_2$ y $-OCF_3$),

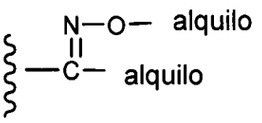
(16) $-S(O)_t$-alquilo, tales como, por ejemplo, (a) -S-alquilo (es decir, t es 0) tales como, por ejemplo, $-S-CH_3$, y (b) $-S(O)_2$-alquilo (es decir, t es 2) tales como, por ejemplo, $-S(O)_2CH_3$,

(17) –C(O)-alquilo (por ej., $-C(O)CH_3$),

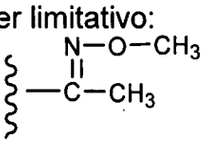
(18) 

donde el metilo es un ejemplo de dicho resto alquilo,

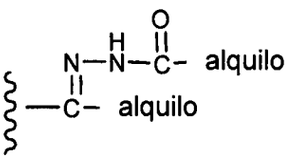
(19)



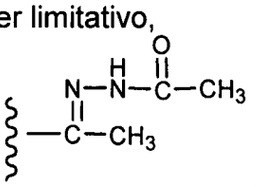
donde cada alquilo se selecciona en forma independiente, ejemplos de este resto incluyen, sin carácter limitativo:



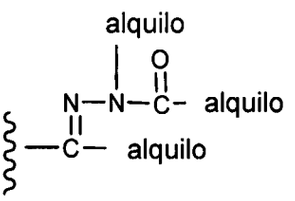
(20)



con cada alquilo seleccionado en forma independiente, ejemplos de este resto incluyen, sin carácter limitativo,



(21)



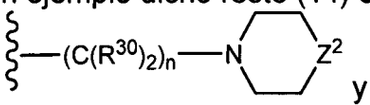
donde cada alquilo se selecciona en forma independiente,

(22) $-N(R^{48})-C(O)-R^{48}$ donde cada R^{48} se selecciona en forma independiente del grupo que consiste en: H y alquilo (por ej., alquilo C_1 hasta C_6, tales como, por ejemplo, metilo), y donde ejemplos de este resto incluyen, sin carácter limitativo, -NH-C(O)-H, y $-N(CH_3)-C(O)H$, y

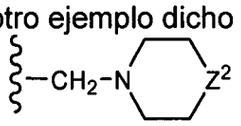
(23) –C(O)-alquilo, tales como, por ejemplo, -C(O)-alquilo (C_1-C_6), tales como, por ejemplo, $-C(O)CH_3$; y

donde:

(a) en un ejemplo dicho resto (14) es

 y n es 1,

(b) en otro ejemplo dicho resto (14) es

 (es decir, n es 1, y cada R^{30} es H),

(c) en otro ejemplo Z^2 es –NH- en (a),

(d) en otro ejemplo Z^2 es –NH- en (b),

(e) en otro ejemplo Z^2 es –O- en (a),

(f) en otro ejemplo Z^2 es –O- en (b),

(g) en otro ejemplo Z^2 es $-CH_2-$ en (a),

(h) en otro ejemplo Z^2 es $-CH_2-$ en (b),

(i) en otro ejemplo R^2 es $-(CH_2)_mR^{11}$ y m es 1,

(j) en otro ejemplo R^2 es $-N(R^{26})_2$,

(k) en otro ejemplo R^2 es $-N(R^{26})_2$, y cada R^{26} es H (es decir, R^2 es $-NH_2$),

(l) en otro ejemplo R^2 es $-OR^{23}$, y

(m) en otro ejemplo R^2 es –OH (es decir, R^{23} es H);

cada R^3, R^4, R^5, R^6 y R^7 se selecciona en forma independiente del grupo que consiste en:

(1) H,

(2) alquenilo (por ej., $-CH_2CH=CH_2$),

(3) alquenilo sustituido,

(4) alquilo,

(5) alquilo sustituido,

(6) cicloalquilo,

(7) cicloalquilo sustituido,

(8) cicloalquilalquilo-,

(9) sustituido cicloalquilalquilo-,

(10) heterocicloalquilo,

(11) heterocicloalquilo sustituido,

(12) heterocicloalquilalquilo-,

(13) sustituido heterocicloalquilalquilo-,

(14) $-C(O)R^{10}$ donde en un ejemplo R^{10} se selecciona del grupo que consiste en: alquilo (por ej., C_1 hasta C_6, por ej., metilo),

(15) arilheteroaril- (por ej., feniltiadiazolilo-),

(16) arilheteroaril- sustituido (por ej., feniltiadiazolilo- sustituido),

(17) heteroarilarilo-, tales como, por ejemplo, pirimidinilfenilo-, pirazinilfenilo-, piridinilfenil- (es decir, piridilfenilo-), furanilfenilo-, tienilfenilo-, tiazolilfenilo-, oxadiazolilfenilo-, y piridazinilfenilo-,

(18) heteroarilarilo- sustituido, tales como, por ejemplo, pirimidinilfenilo- sustituido, pirazinilfenilo sustituido, piridinilfenil- sustituido (es decir, piridilfenilo- sustituido), furanilfenilo- sustituido, tienilfenilo- sustituido, tiazolilfenilo- sustituido, pirimidinilfenilo sustituido, oxadiazolilfenilo- sustituido, y piridazinilfenilo- sustituido,

(19) arilo (por ej., fenilo),

(20) arilo sustituido (por ej., fenilo sustituido),

(21) heteroarilo (por ej., tiazolilo, tienilo, piridilo, y pirimidinilo),

(22) heteroarilo sustituido (por ej., tiazolilo sustituido, piridilo sustituido y pirimidinilo sustituido), ejemplos de grupos heteroarilo sustituido incluyen, por ejemplo bromotiazolilo-, bromopirimidinilo-, fluoropirimidinilo-, y etenilpirimidinilo-,

(23) heteroarilheteroaril- (por ej., pirimidinilpiridilo-, pirimidiniltiazolilo-, y pirimidinilpirazinilo-),

(24) sustituido heteroarilheteroaril- (por ej., sustituido pirimidinilpiridilo-, y sustituido pirimidinilpirazinilo-),

(25) arilaminoheteroaril- (por ej., fenil-NH-oxadiazolilo-),

(26) arilaminoheteroarilo sustituido (por ej., fenil-NH-oxadiazolilo-sustituido),

(27) arilalquinil- (por ej., aril alquinilo (C_2 a C_4) tales como, por ejemplo feniletinilo-),

(28) arilalquinil- sustituido (por ej., aril alquinilo (C_2 a C_4) -sustituido, tales como, por ejemplo, feniletinilo-sustituido),

(29) heteroarilalquinil- (por ej., heteroaril alquinilo (C_2 a C_4) -, tales como, por ejemplo, pirimidiniletinilo-),

(30) heteroarilalquinil-sustituido (por ej., heteroaril alquinilo (C_2 a C_4)sustituido, tales como, por ejemplo pirimidiniletinilo-sustituido),

(31) benzoheteroarilo (es decir, un fenilo fusionado y anillos heteroarilo), tales como, por ejemplo, benzotiazol y quinoxalina;

donde dichos grupos (7), (9), (11), (13), (16), (18), (20), (22), (24), (26), (28) y (30), R^3, R^4, R^5, R^6 y R^7 sustituidos están sustituidos con 1 hasta 3 sustituyentes seleccionados en forma independiente del grupo que consiste en: $-NH_2$, $-NHR^{20}$ (por ej., $-NHCH_2CH_3$ y $-NHCH_3$), $-N(R^{20})_2$ donde cada R^{20} se selecciona en forma independiente, alquilo (por ej., alquilo C_1 hasta C_6, por ej., metilo, etilo, e i-propilo), alquenilo (por ej., alquenilo C_2 hasta C_6, tales como, por ejemplo $-CH=CH_2$), halo (por ej., F, Cl y Br, y en otro ejemplo F), $-C(O)-NH-R^{28}$ (por ej., $-C(O)-NH-CH_3$), $-C(O)OR^{28}$ (por ej., $-C(O)OC_2H_5$), $-C(O)R^{28}$ (por ej., $-C(O)CH_3$), y $-OR^{20}$ (por ej., $-OCH_3$),

donde dichos grupos (3) y (5), R^3, R^4, R^5, R^6 y R^7 sustituidos están sustituidos con 1 hasta 3 sustituyentes seleccionados en forma independiente del grupo que consiste en: $-NH_2$, halo (por ej., F, Cl y Br, y en otro ejemplo F), -C(O)-

NH-R^{28} (por ej., -C(O)-NH-CH_3), -C(O)OR^{28} (por ej., -C(O)OC_2H_5), y -C(O)R^{28} (por ej., -C(O)CH_3), y

donde:

en un ejemplo dicho heteroarilo sustituido (resto (18) anterior) está sustituido con 1 hasta 3 sustituyentes seleccionados en forma independiente del grupo que consiste en: -NH_2, alquilo (por ej., alquilo C_1 hasta C_6, por ej., metilo), halo (por ej., F, Cl y Br, tales como, por ejemplo F),

en otro ejemplo dicho arilo sustituido (resto (20) anterior) está sustituido con 1 hasta 3 sustituyentes seleccionados en forma independiente del grupo que consiste en halo (por ej., F, Cl y Br), -C(O)-NH-R^{28} (por ej., -C(O)-NH-CH_3), -C(O)OR^{28} (por ej., -C(O)O-C_2H_5), y -C(O)R^{28} (por ej., -C(O)CH_3), y

en otro ejemplo dicho heteroarilo sustituido (resto (22) anterior) está sustituido con 1 hasta 3 sustituyentes seleccionados del grupo que consiste en: halo (por ej., Br, F, y Cl), alquenilo (por ej., alquenilo C_2 hasta C_6, tales como, por ejemplo, -CH=CH_2);

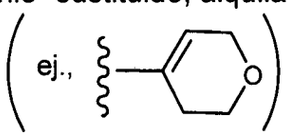
R^{5A} se selecciona del grupo que consiste en: halo (por ejemplo, F, Cl, y Br, y en otro ejemplo F), -OH, alquilo (por ej., alquilo C_1 hasta C_6, tales como, por ejemplo, -CH_3), –O-alquilo (tales como, por ejemplo, -O-(alquilo C_1 hasta C_6), además, por ejemplo, -O-(alquilo C_1 hasta C_3), también por ejemplo, -O-(alquilo C_1 hasta C_2), y en un ejemplo –O-CH_3);

R^8 se selecciona del grupo que consiste en: H, -OH, -N(R^{10})$_2$ (por ej., -NH_2), -NR^{10}C(O)R^{12} (por ej., -NHC(O)CH_3), y alquilo (por ej., metilo);

cada R^9 se selecciona en forma independiente del grupo que consiste en: halógeno, -CN, -NO_2, -OR^{10}, -SR^{10}, -N(R^{10})$_2$, y R^{10};

cada R^{10} se selecciona en forma independiente del grupo que consiste en: H, alquilo, arilo, arilalquilo, heteroarilo, heteroarilalquilo, cicloalquilo, cicloalquilalquilo, heterocicloalquilo, heterocicloalquilalquilo, alquilheteroarilo-,

alquilarilo-, alquilo sustituido, arilo sustituido, arilalquilo sustituido, heteroarilo sustituido, sustituido heteroarilalquilo, cicloalquilo sustituido, cicloalquilalquilo sustituido, heterocicloalquilo sustituido, heterocicloalquilalquilo sustituido, alquilheteroarilo- sustituido, alquilarilo- sustituido, heterocicloalquenilo

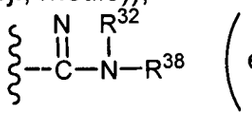
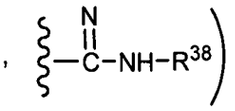


y heterocicloalquenilo sustituido, y donde:

dicho alquilo R^{10} sustituido está sustituido con 1 hasta 3 sustituyentes seleccionados en forma independiente del grupo que consiste en: $-NH_2$, $-NHR^{20}$, $-NO_2$, -CN, $-OR^{26}$, halo (por ej., F, Cl y Br, y en otro ejemplo F), $-C(O)-NH-R^{26}$ (por ej., $-C(O)-NH-CH_3$, es decir, R^{26} es alquilo, tales como metilo), $-C(O)OR^{26}$ (por ej., $-C(O)OC_2H_5$, es decir, R^{26} es alquilo, tales como etilo), y $-C(O)R^{26}$ (por ej., $-C(O)CH_3$, es decir, R^{26} es alquilo, tales como metilo), y

dicho arilo sustituido con R^{10}, arilalquilo sustituido, heteroarilo sustituido, heteroarilalquilo sustituido, cicloalquilo sustituido, cicloalquilalquilo sustituido, heterocicloalquilo sustituido, heterocicloalquilalquilo sustituido, alquilheteroaril-sustituido y alquilaril- sustituido están sustituidos con 1 hasta 3 sustituyentes seleccionados en forma independiente del grupo que consiste en: (1) $-NH_2$, (2) $-NO_2$, (3) -CN, (4) -OH, (5) $-OR^{20}$, (6) $-OCF_3$, (7) alquilo (por ej., alquilo C_1 hasta C_6) sustituido con 1 hasta 3 halo átomos seleccionados en forma independiente (por ej., F, Cl y Br), ejemplos del alquilo sustituido incluyen, sin carácter limitativo, $-CF_3$, $-CHF_2$ and$-CH_2F$, (8) $-C(O)R^{38}$ (por ej., R^{38} es H o alquilo (por ej., alquilo C_1 hasta C_6, tales como, por ejemplo, metilo o etilo), por ejemplo, R^{38} es alquilo (por ej., metilo), de este modo, un ejemplo de $-C(O)R^{38}$ es $-C(O)CH_3$), (9) alquilo (por ej., alquilo C_1 hasta C_6, por ej., metilo, etilo, e i-propilo), (10) alquenilo (por ej., alquenilo C_2 hasta C_6, tales como, por ejemplo $-CH=CH_2$), (11) halo (por ej., F, Cl y Br, y en otro ejemplo F), (12) $-C(O)-NH-R^{26}$

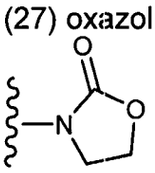
(por ej., -C(O)-NH-CH_3), (13) -C(O)OR^{38} (por ej., R^{38} es H o alquilo (por ej., alquilo C_1 hasta C_6, tales como, por ejemplo, metilo o etilo), por ejemplo, R^{38} es alquilo (por ej., metilo o etilo), de este modo, por ejemplo, -C(O)OR^{38} es -C(O)OC_2H_5), (14) -C(O)-NR^{32}-$(C(R^{30})_2)_n$-$N(R^{38})_2$ (por ej., -C(O)-NH-$(CH_2)_n$-$N(R^{38})_2$) (donde (a) en un ejemplo R^{32} es H, (b) en otro ejemplo cada R^{30} es H, (c) en otro ejemplo n es 2, (d) en otro ejemplo cada R^{38} se selecciona en forma independiente, (e) en otro ejemplo cada R^{38} se selecciona en forma independiente del grupo que consiste en: H y alquilo (por ej., metilo), (f) en otro ejemplo R^{32} es H, cada R^{30} es H, y cada R^{38} se selecciona en forma independiente, (g) en otro ejemplo R^{32} es H, cada R^{30} es H, y cada R^{38} se selecciona en forma independiente del grupo que consiste en: H y alquilo (por ej., metilo), (15) -$S(O)_tR^{38}$ (donde en un ejemplo t es 2, y en otro ejemplo R^{38} es alquilo (por ej., metilo o isopropilo), y en otro ejemplo t es 2 y R^{38} es alquilo (por ej., metilo o isopropilo)), (16) -C(O)-NR^{32}-R^{38} (por ej., -C(O)-NR^{32}-R^{38}) (donde un ejemplo R^{32} es H, en otro ejemplo R^{38} es alquilo (por ej., propilo), y en otro ejemplo R^{32} es H y R^{38} es alquilo (por ej., propilo)), (17) -NR^{32}-C(O)-R^{38} (por ej., -NH-C(O)-R^{38}) (donde en un ejemplo R^{32} es H, en otro ejemplo R^{38} es alquilo (por ej., metilo), y en otro ejemplo R^{32} es H y R^{38} es alquilo (por ej., metilo)),

(18)  (ej., )

(donde en un ejemplo R^{32} es H, en otro ejemplo R^{38} es H, y en otro ejemplo R^{32} es H y R^{38} es H), (19) –NHR^{20} (por ej., -$NHCH_3$, -NHC_2H_5), (20) cicloalquilo (por ej., cicloalquilo C_3 a C_6, tales como, por ejemplo, ciclopropilo), (21) –O-alquil-O-R^{20} (por ej., -O-alquil (C_1 hasta C_6)-OR^{20}, tales como, por ejemplo, -O-CH_2CH_2-OCH_3), (22) hidroxialquilo (por ej., hidroxialquilo (C_1 hasta C_6), tales como, por ejemplo, -CH_2OH y –$C(CH_3)_2OH$),

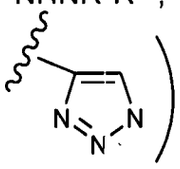
(23) –$N(R^{20})_2$ donde cada R^{20} se selecciona en forma independiente (por ej., -$N(CH_3)_2$), (24) –alquil-OR^{20} (por ej., -alquil (C_1 hasta C_6)-OR^{20}, tales como, por

ejemplo, $-CH_2OCH_3$), (25) –O-alquil-OH (por ej., -O-alquil (C_1 hasta C_6)-OH, tales como, por ejemplo, $-O-CH_2-CH_2-OH$), (26) –NH(hidroxialquilo) (por ej., -NH(hidroxialquilo (C_1 hasta C_6), tales como, por ejemplo, $-NH(CH_2CH_2OH)$), y (27) oxazolidinona, tales como, por ejemplo,



;

R^{11} se selecciona del grupo que consiste en: F, -OH, -CN, $-OR^{10}$, $-NHNR^1R^{10}$, $-SR^{10}$ y heteroarilo (por ej., triazolilo, tales como, por ejemplo,



;

R^{12} se selecciona del grupo que consiste en: alquilo, arilo, heteroarilo, cicloalquilo, cicloalquilalquilo, heterocicloalquilo y heterocicloalquilalquilo;

R^{14} se selecciona del grupo que consiste en: alquilo, arilo, heteroarilo, cicloalquilo, cicloalquilalquilo-, heterocicloalquilo, alquilheterocicloalquilo, heterocicloalquilalquilo-, alquilheteroaril- y alquilarilo-;

R^{15} se selecciona del grupo que consiste en: H, -OH, alquilo, arilo, heteroarilo, cicloalquilo, cicloalquilalquilo-, heterocicloalquilo y heterocicloalquilalquilo-, alquilheteroaril- y alquilarilo-;

R^{20} representa alquilo (por ej., alquilo C_1 hasta C_6, tales como, por ejemplo, metilo, etilo o isopropilo);

R^{23} se selecciona del grupo que consiste en: H, alquilo (por ej., alquilo C_1 a C_6, tales como, por ejemplo, metilo e i-propilo), arilo (por ej., fenilo), cicloalquilo (por ej., cicloalquilo C_3 a C_6, tales como, por ejemplo, ciclopropilo y ciclohexilo), y cicloalquilalquil- (por ej., cicloalquilalquilo- C_3 hasta C_6, tales como $-(CH_2)_n$-cicloalquilo, tales como $-(CH_2)_n$-cicloalquilo (C3 hasta C6), donde cada H de cada

resto $-(CH_2)_n-$ puede estar sustituido en forma independiente con un grupo alquilo (por ej., alquilo C_1 a C_6, tales como, por ejemplo, metilo), y donde en un ejemplo n es 1 y el resto $-CH_2-$ no está sustituido, es decir, $-CH_2$-cicloalquilo, tales como, $-CH_2$-ciclopropilo, es un ejemplo de dicho resto cicloalquilalquil-);

cada R^{26} se selecciona en forma independiente del grupo que consiste en: H y alquilo (por ej., alquilo C_1 a C_6, tales como, por ejemplo, metilo y etilo);

R^{28} es alquilo (por ej., alquilo C_1 a C_6, tales como, por ejemplo, metilo o etilo);

cada R^{30} se selecciona en forma independiente del grupo que consiste en: H, alquilo (por ej., alquilo C_1 a C_6, tales como, por ejemplo metilo, etilo e i-propilo), y F, y donde en un ejemplo cada R^{30} es H;

cada R^{32} se selecciona en forma independiente del grupo que consiste en: H y alquilo (por ej., alquilo C_1 a C_6, tales como, por ejemplo metilo, etilo y propilo), y donde cada R^{32} es en general H;

cada R^{35} se selecciona en forma independiente del grupo que consiste en: H y alquilo C_1 a C_6 (por ej., metilo, etilo, i-propilo, y propilo), y donde en un ejemplo ambos R^{35} sustituyentes son grupos alquilo iguales o diferentes (por ej., ambos grupos R^{35} son el mismo grupo alquilo, tal como metilo), y en otro ejemplo un grupo R^{35} es H y el otro grupo R^{35} es alquilo, tales como metilo), y en otro ejemplo cada R^{35} es con preferencia H;

R^{36} se selecciona del grupo que consiste en: H, alquilo (por ej., alquilo C_1 hasta C_6, tales como, por ejemplo, metilo, etilo y propilo), y –O-alquilo (por ej., -O-alquilo (C_1 hasta C_6), tales como, por ejemplo, -O-alquilo (C_1 hasta C_2), tales como, por ejemplo, $-OCH_3$), y con preferencia R^{36} se selecciona del grupo que consiste en H y metilo, y con mayor preferencia R^{36} es H;

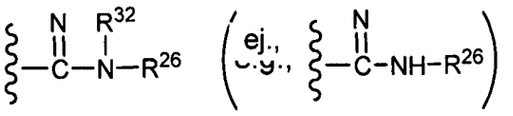
cada R^{38} se selecciona en forma independiente del grupo que consiste en: H, alquilo, arilo, arilalquilo, heteroarilo, heteroarilalquilo, cicloalquilo,

cicloalquilalquilo, heterocicloalquilo, heterocicloalquilalquilo, alquilheteroarilo-, alquilarilo-, alquilo sustituido, arilo sustituido, arilalquilo sustituido, heteroarilo sustituido, sustituido heteroarilalquilo, cicloalquilo sustituido, cicloalquilalquilo sustituido, heterocicloalquilo sustituido, heterocicloalquilalquilo sustituido, alquilheteroaril- sustituido y alquilarilo- sustituido, y donde:

dicho alquilo sustituido R^{38} está sustituido con 1 hasta 3 sustituyentes seleccionados en forma independiente del grupo que consiste en: $-NH_2$, $-NO_2$, -CN, $-OR^{26}$, halo (por ej., F, Cl y Br, y en otro ejemplo F), $-C(O)-NH-R^{28}$ (por ej., $-C(O)-NH-CH_3$), $-C(O)OR^{28}$ (por ej., $-C(O)OC_2H_5$), y $-C(O)R^{28}$ (por ej., $-C(O)CH_3$), y

dicho arilo sustituido R^{38}, arilalquilo sustituido, heteroarilo sustituido, sustituido heteroarilalquilo, cicloalquilo sustituido, cicloalquilalquilo sustituido, heterocicloalquilo sustituido, heterocicloalquilalquilo sustituido, alquilheteroaril-sustituido y alquilaril- sustituido están sustituidos con 1 hasta 3 sustituyentes seleccionados en forma independiente del grupo que consiste en: (1) $-NH_2$, (2) $-NO_2$, (3) -CN, (4) -OH, (5) $-OR^{20}$, (6) $-OCF_3$, (7) $-CF_3$, (8) $-C(O)R^{26}$ (por ej., R^{26} es H o alquilo C_1 hasta C_6, tales como, por ejemplo, metilo o etilo, por ejemplo, R^{26} es alquilo (por ej., metilo), de este modo, un ejemplo de $-C(O)R^{26}$ es $-C(O)CH_3$), (9) alquilo (por ej., alquilo C_1 hasta C_6, por ej., metilo, etilo, e i-propilo), (10) alquenilo (por ej., alquenilo C_2 hasta C_6, tales como, por ejemplo $-CH=CH_2$), (11) halo (por ej., F, Cl y Br, y en otro ejemplo F), (12) $-C(O)-NH-R^{26}$ (por ej., $-C(O)-NH-CH_3$), (13) $-C(O)OR^{26}$ (por ej., R^{26} es H o por ej., alquilo C_1 hasta C_6, tales como, por ejemplo, metilo o etilo, por ejemplo, R^{26} es alquilo (por ej., metilo o etilo), de este modo, por ejemplo, $-C(O)OR^{26}$ es $-C(O)OC_2H_5$), (14) $-C(O)-NR^{32}-(C(R^{30})_2)_n-N(R^{26})_2$ (por ej., $-C(O)-NH-(CH_2)_n-N(R^{26})_2$) (donde (a) en un ejemplo R^{32} es H, (b) en otro ejemplo cada R^{30} es H, (c) en otro ejemplo n es 2, (d) en otro ejemplo cada R^{26} se selecciona en forma independiente, (e) en otro ejemplo cada

R^{26} se selecciona en forma independiente del grupo que consiste en: H y metilo), (f) en otro ejemplo R^{32} es H, cada R^{30} es H, y cada R^{26} se selecciona en forma independiente, (g) en otro ejemplo R^{32} es H, cada R^{30} es H, y cada R^{26} se selecciona en forma independiente del grupo que consiste en: H y metilo), (15) $-S(O)_tR^{26}$ (donde en un ejemplo t es 2, y en otro ejemplo R^{26} es metilo, y en otro ejemplo t es 2 y R^{26} es metilo), (16) $-C(O)N(R^{32})(R^{26})$ (donde en un ejemplo R^{32} es H, en otro ejemplo R^{26} es alquilo (por ej., propilo), y en otro ejemplo R^{32} es H y R^{26} es alquilo (por ej., propilo)), (17) $-NR^{32}C(O)R^{26}$ (por ej., $-NHC(O)R^{26}$) (donde en un ejemplo R^{32} es H, en otro ejemplo R^{26} es alquilo (por ej., metilo), y en otro ejemplo R^{32} es H y R^{26} es alquilo (por ej., metilo)),

(18) 

(donde en un ejemplo R^{32} es H, en otro ejemplo R^{26} es H, y en otro ejemplo R^{32} es H y R^{26} es H); y (19) $-NHR^{20}$;

R^{42} se selecciona del grupo que consiste en: alquilo (por ej., alquilo C_1 hasta C_6, tales como, por ejemplo $-CH_3$), arilo (por ej., fenilo), heteroarilo (por ej., tiazolilo y piridilo), y cicloalquilo (por ej., cicloalquilo C_3 a C_6, tales como, por ejemplo, ciclopropilo);

R^{44} se selecciona del grupo que consiste en: H, alquilo (por ej., alquilo C_1 hasta C_6, tales como, por ejemplo, alquilo C_1 hasta C_3, tales como, por ejemplo, metilo, etilo e i-propilo), cicloalquilo (por ej., cicloalquilo C_3 hasta C_6, tales como, por ejemplo, ciclopropilo y ciclohexilo), y cicloalquilalquilo (por ej., cicloalquil (C_3 hasta C_6) alquilo (C_1 hasta C_6), tales como, por ejemplo, cicloalquil (C_3 hasta C_6)alquilo (C_1 hasta C_3), tales como, por ejemplo, cicloalquil-metilo- (C_3 hasta C_6), tales como, por ejemplo, ciclopropil-metil- y ciclohexil-metilo-), y en un ejemplo, R^{44} es H;

Cada R^{46} se selecciona en forma independiente del grupo que consiste en: H, alquilo (por ej., alquilo C_1 hasta C_6, tales como, por ejemplo, C_1 hasta C_3 alquilo, tales como, por ejemplo, metilo, etilo e i-propilo), cicloalquilo (por ej., cicloalquilo C_3 hasta C_6, tales como, por ejemplo, ciclopropilo y ciclohexilo), y cicloalquilalquilo (por ej., cicloalquil (C_3 hasta C_6) alquilo (C_1 hasta C_6), tales como, por ejemplo, cicloalquil (C_3 hasta C_6) alquilo (C_1 hasta C_3), tales como, por ejemplo, cicloalquil (C_3 hasta C_6) -metilo-, tales como, por ejemplo, ciclopropil-metil- y ciclohexil-metilo-), y en un ejemplo, cada R^{46} es H; y

con la salvedad de que:

(1) Q^1 es un anillo sustituido en el cual por lo menos un sustituyente es halo; y/o

(2) R^2 está alquilo sustituido en el cual dicho sustituyente es $-OCH_3$, o R^2 se selecciona del grupo que consiste en: $-CH_2OH$ y $-CH_2OCH_3$; y/o

(3) por lo menos uno de R^3, R^4, R^5, R^6, y R^7 es:

(i) seleccionado del grupo que consiste en: oxadiazolilfenilo-, piridazinilfenilo-, pirimidinilpirazinilo-, oxadiazolilfenilo- sustituido, piridazinilfenilo-sustituido, pirimidinilpirazinilo- sustituido, y benzoheteroarilo; o

(ii) seleccionado del grupo que consiste en:

(a) cicloalquilo sustituido,

(b) cicloalquilalquilo sustituido-,

(c) heterocicloalquilo sustituido,

(d) heterocicloalquilalquilo sustituido-,

(e) arilheteroarilo- sustituido,

(f) heteroarilarilo- sustituido,

(g) arilo sustituido,

(h) heteroarilo sustituido,

(i) heteroarilheteroarilo- sustituido,

(j) arilaminoheteroarilo- sustituido,

(k) arilalquinilo- sustituido, y

(l) heteroarilalquinilo- sustituido, y

donde por lo menos un sustituyente en por lo menos uno por lo menos uno de dicho grupo (ii)(a) hasta (ii)(l) R^3, R^4, R^5, R^6, o R^7 se selecciona del grupo que consiste en: $-NHR^{20}$ (por ej., $-NHCH_2CH_3$ y $-NHCH_3$), $-N(R^{20})_2$ (donde cada R^{20} se selecciona en forma independiente), y $-OR^{20}$ (por ej., $-OCH_3$); y/o

(4) R^{5A} es alquilo (por ej., alquilo C_1 hasta C_6, tales como, por ejemplo, $-CH_3$); y/o

(5) R^{10} es un arilo sustituido, y por lo menos un sustituyente se selecciona del grupo que consiste en:

(a) $-S(O)_tR^{38}$ donde R^{38} es isopropilo,

(b) –O-alquil-O-R^{20},

(c) hidroxialquilo,

(d) $-N(R^{20})_2$,

(e) –alquil-OR^{20},

(f) –O-alquil-OH,

(g) –NH(hidroxialquilo), y

(h) oxazolidinona; y/o

(6) R^{20} es isopropilo.

En otra realización de los compuestos de fórmula 1.0 la salvedad es que:

(1) Q^1 es un anillo sustituido en el cual por lo menos uno sustituyente es halo; y/o

(2) R^2 está alquilo sustituido en el cual dicho sustituyente es $-OCH_3$, o R^2 se selecciona del grupo que consiste en: $-CH_2OH$ y $-CH_2OCH_3$; y/o

(3) por lo menos uno de R^3, R^4, R^5, R^6, y R^7 es:

(i) seleccionado del grupo que consiste en: oxadiazolilfenilo-, piridazinilfenilo-, pirimidinilpirazinilo-, oxadiazolilfenilo- sustituido, piridazinilfenilo-sustituido, pirimidinilpirazinilo- sustituido, y benzoheteroarilo; o

(ii) seleccionado del grupo que consiste en:

(a) cicloalquilo sustituido,

(b) cicloalquilalquilo sustituido-,

(c) heterocicloalquilo sustituido,

(d) heterocicloalquilalquilo sustituido-,

(e) arilheteroarilo- sustituido,

(f) heteroarilarilo- sustituido,

(g) arilo sustituido,

(h) heteroarilo sustituido,

(i) heteroarilheteroarilo- sustituido,

(j) arilaminoheteroarilo- sustituido,

(k) arilalquinilo- sustituido, y

(l) heteroarilalquinilo- sustituido, y

donde por lo menos un sustituyente en por lo menos uno por lo menos uno de dicho grupo (ii)(a) hasta (ii)(l) R^3, R^4, R^5, R^6, o R^7 se selecciona del grupo que consiste en: $-NHR^{20}$ (por ej., $-NHCH_2CH_3$ y $-NHCH_3$), $-N(R^{20})_2$ (donde cada R^{20} se selecciona en forma independiente), y $-OR^{20}$ (por ej., $-OCH_3$); y/o

(4) R^{5A} es alquilo (por ej., alquilo C_1 hasta C_6, tales como, por ejemplo, $-CH_3$); y/o

(5) R^{10} es un arilo sustituido, y por lo menos uno sustituyente se selecciona del grupo que consiste en:

(a) $-O$-alquil-O-R^{20},

(b) hidroxialquilo,

(c) $-N(R^{20})_2$,

(d) –alquil-OR^{20},

(e) –O-alquil-OH,

(f) –NH(hidroxialquilo), y

(g) oxazolidinona; y/o

(6) R^{20} es isopropilo.

En otra realización de los compuestos de fórmula 1.0 la salvedad es que:

(1) Q^1 es un anillo sustituido en el cual por lo menos uno sustituyente es halo; y/o

(2) R^2 está alquilo sustituido en el cual dicho sustituyente es $–OCH_3$, o R^2 se selecciona del grupo que consiste en: $-CH_2OH$ y $–CH_2OCH_3$; y/o

(3) por lo menos uno de R^3, R^4, R^5, R^6, y R^7 es:

(i) seleccionado del grupo que consiste en: oxadiazolilfenilo-, piridazinilfenilo-, pirimidinilpirazinilo-, oxadiazolilfenilo- sustituido, piridazinilfenilo- sustituido, pirimidinilpirazinilo- sustituido, y benzoheteroarilo; o

(ii) seleccionado del grupo que consiste en:

(a) cicloalquilo sustituido,

(b) cicloalquilalquilo sustituido-,

(c) heterocicloalquilo sustituido,

(d) heterocicloalquilalquilo sustituido-,

(e) sustituido arilheteroarilo-,

(f) heteroarilarilo- sustituido,

(g) arilo sustituido,

(h) heteroarilo sustituido,

(i) heteroarilheteroarilo- sustituido,

(j) arilaminoheteroarilo- sustituido,

(k) arilalquinilo- sustituido, y

(l) heteroarilalquinilo- sustituido, y

donde por lo menos un sustituyente en por lo menos uno por lo menos uno de dicho grupo (ii)(a) hasta (ii)(l) R^3, R^4, R^5, R^6, o R^7 se selecciona del grupo que consiste en: -NHR^{20} (por ej., -$NHCH_2CH_3$ y –$NHCH_3$), -$N(R^{20})_2$ (donde cada R^{20} se selecciona en forma independiente), y –OR^{20} (por ej., -OCH_3); y/o

(4) R^{5A} es alquilo (por ej., alquilo C_1 hasta C_6, tales como, por ejemplo, -CH_3); y/o

(5) R^{10} es un arilo sustituido, y por lo menos uno sustituyente se selecciona del grupo que consiste en:

(a) –O-alquil-O-R^{20},

(b) hidroxialquilo,

(c) –$N(R^{20})_2$,

(d) –alquil-OR^{20},

(e) –O-alquil-OH,

(f) –NH(hidroxialquilo), y

(g) oxazolidinona.

En otra realización de los compuestos de fórmula 1.0 la salvedad es que:

(1) Q^1 es un anillo sustituido en el cual por lo menos uno sustituyente es halo; y/o

(2) por lo menos uno de R^3, R^4, R^5, R^6, y R^7 es:

(i) seleccionado del grupo que consiste en: oxadiazolilfenilo-, piridazinilfenilo-, pirimidinilpirazinilo-, oxadiazolilfenilo- sustituido, piridazinilfenilo-sustituido, pirimidinilpirazinilo- sustituido, y benzoheteroarilo; o

(ii) seleccionado del grupo que consiste en:

(a) cicloalquilo sustituido,

(b) cicloalquilalquilo sustituido-,

(c) heterocicloalquilo sustituido,

(d) heterocicloalquilalquilo sustituido-,

(e) sustituido arilheteroarilo-,

(f) heteroarilarilo- sustituido,

(g) arilo sustituido,

(h) heteroarilo sustituido,

(i) heteroarilheteroarilo- sustituido,

(j) arilaminoheteroarilo- sustituido,

(k) arilalquinilo- sustituido, y

(l) heteroarilalquinilo- sustituido, y

donde por lo menos un sustituyente en por lo menos uno por lo menos uno de dicho grupo (ii)(a) hasta (ii)(l) R^3, R^4, R^5, R^6, o R^7 se selecciona del grupo que consiste en: $-NHR^{20}$ (por ej., $-NHCH_2CH_3$ y $-NHCH_3$), $-N(R^{20})_2$ (donde cada R^{20} se selecciona en forma independiente), y $-OR^{20}$ (por ej., $-OCH_3$); y/o

(3) R^{5A} es alquilo (por ej., alquilo C_1 hasta C_6, tales como, por ejemplo, $-CH_3$); y/o

(4) R^{10} es un arilo sustituido, y por lo menos uno sustituyente se selecciona del grupo que consiste en:

(a) $-O$-alquil-O-R^{20},

(b) hidroxialquilo,

(c) $-N(R^{20})_2$,

(d) -alquil-OR^{20},

(e) $-O$-alquil-OH,

(f) –NH(hidroxialquilo), y

(g) oxazolidinona.

En otra realización de los compuestos de fórmula 1.0 la salvedad es que:

(1) Q^1 es un anillo sustituido en el cual por lo menos uno sustituyente es halo; y/o

(2) R^2 está alquilo sustituido en el cual dicho sustituyente es $-OCH_3$, o R^2 se selecciona del grupo que consiste en: $-CH_2OH$ y $-CH_2OCH_3$; y/o

(3) R^5 es:

(i) seleccionado del grupo que consiste en: oxadiazolilfenilo-, piridazinilfenilo-, pirimidinilpirazinilo-, oxadiazolilfenilo- sustituido, piridazinilfenilo- sustituido, pirimidinilpirazinilo- sustituido, y benzoheteroarilo; o

(ii) seleccionado del grupo que consiste en:

(a) cicloalquilo sustituido,

(b) cicloalquilalquilo sustituido-,

(c) heterocicloalquilo sustituido,

(d) heterocicloalquilalquilo sustituido-,

(e) sustituido arilheteroarilo-,

(f) heteroarilarilo- sustituido,

(g) arilo sustituido,

(h) heteroarilo sustituido,

(i) heteroarilheteroarilo- sustituido,

(j) arilaminoheteroarilo- sustituido,

(k) arilalquinilo- sustituido, y

(l) heteroarilalquinilo- sustituido, y

donde por lo menos un sustituyente en por lo menos uno por lo menos uno de dicho grupo (ii)(a) hasta (ii)(l) R^3, R^4, R^5, R^6, o R^7 se selecciona del grupo que consiste en: $-NHR^{20}$ (por ej., $-NHCH_2CH_3$ y $-NHCH_3$), $-N(R^{20})_2$ (donde cada R^{20} se selecciona en forma independiente), y $-OR^{20}$ (por ej., $-OCH_3$); y/o

(4) R^{5A} es alquilo (por ej., alquilo C_1 hasta C_6, tales como, por ejemplo, $-CH_3$); y/o

(5) R^{10} es un arilo sustituido, y por lo menos uno sustituyente se selecciona del grupo que consiste en:

(a) –O-alquil-O-R^{20},

(b) hidroxialquilo,

(c) –N(R^{20})$_2$,

(d) –alquil-OR^{20},

(e) –O-alquil-OH,

(f) –NH(hidroxialquilo), y

(g) oxazolidinona; y/o

(6) R^{20} es isopropilo.

En otra realización de los compuestos de fórmula 1.0 la salvedad es que:

(1) Q^1 es un anillo sustituido en el cual por lo menos uno sustituyente es halo; y/o

(2) R^2 está alquilo sustituido en el cual dicho sustituyente es –OCH_3, o R^2 se selecciona del grupo que consiste en: -CH_2OH y –CH_2OCH_3; y/o

(3) R^5 es:

(i) seleccionado del grupo que consiste en: oxadiazolilfenilo-, piridazinilfenilo-, pirimidinilpirazinilo-, oxadiazolilfenilo- sustituido, piridazinilfenilo-sustituido, pirimidinilpirazinilo- sustituido, y benzoheteroarilo; o

(ii) seleccionado del grupo que consiste en:

(a) cicloalquilo sustituido,

(b) cicloalquilalquilo sustituido-,

(c) heterocicloalquilo sustituido,

(d) heterocicloalquilalquilo sustituido-,

(e) sustituido arilheteroarilo-,

(f) heteroarilarilo- sustituido,

(g) arilo sustituido,

(h) heteroarilo sustituido,

(i) heteroarilheteroarilo- sustituido,

(j) arilaminoheteroarilo- sustituido,

(k) arilalquinilo- sustituido, y

(l) heteroarilalquinilo- sustituido, y

donde por lo menos un sustituyente en por lo menos uno por lo menos uno de dicho grupo (ii)(a) hasta (ii)(l) R^3, R^4, R^5, R^6, o R^7 se selecciona del grupo que consiste en: $-NHR^{20}$ (por ej., $-NHCH_2CH_3$ y $-NHCH_3$), $-N(R^{20})_2$ (donde cada R^{20} se selecciona en forma independiente), y $-OR^{20}$ (por ej., $-OCH_3$); y/o

(4) R^{5A} es alquilo (por ej., alquilo C_1 hasta C_6, tales como, por ejemplo, $-CH_3$); y/o

(5) R^{10} es un arilo sustituido, y por lo menos uno sustituyente se selecciona del grupo que consiste en:

(a) –O-alquil-O-R^{20},

(b) hidroxialquilo,

(c) $-N(R^{20})_2$,

(d) –alquil-OR^{20},

(e) –O-alquil-OH,

(f) –NH(hidroxialquilo), y

(g) oxazolidinona.

En otra realización de los compuestos de fórmula 1.0 la salvedad es que:

(1) Q^1 es un anillo sustituido en el cual por lo menos uno sustituyente es halo; y/o

(2) R^5 es:

(i) seleccionado del grupo que consiste en: oxadiazolilfenilo-, piridazinilfenilo-, pirimidinilpirazinilo-, oxadiazolilfenilo- sustituido, piridazinilfenilo-sustituido, pirimidinilpirazinilo- sustituido, y benzoheteroarilo; o

(ii) seleccionado del grupo que consiste en:

(a) cicloalquilo sustituido,

(b) cicloalquilalquilo sustituido-,

(c) heterocicloalquilo sustituido,

(d) heterocicloalquilalquilo sustituido-,

(e) sustituido arilheteroarilo-,

(f) heteroarilarilo- sustituido,

(g) arilo sustituido,

(h) heteroarilo sustituido,

(i) heteroarilheteroarilo- sustituido,

(j) arilaminoheteroarilo- sustituido,

(k) arilalquinilo- sustituido, y

(l) heteroarilalquinilo- sustituido, y

donde por lo menos un sustituyente en por lo menos uno por lo menos uno de dicho grupo (ii)(a) hasta (ii)(l) R^3, R^4, R^5, R^6, o R^7 se selecciona del grupo que consiste en: $-NHR^{20}$ (por ej., $-NHCH_2CH_3$ y $-NHCH_3$), $-N(R^{20})_2$ (donde cada R^{20} se selecciona en forma independiente), y $-OR^{20}$ (por ej., $-OCH_3$); y/o

(3) R^{5A} es alquilo (por ej., alquilo C_1 hasta C_6, tales como, por ejemplo, $-CH_3$); y/o

(4) R^{10} es un arilo sustituido, y por lo menos uno sustituyente se selecciona del grupo que consiste en:

(a) $-O$-alquil-$O-R^{20}$,

(b) hidroxialquilo,

(c) $-N(R^{20})_2$,

(d) –alquil-OR^{20},

(e) –O-alquil-OH,

(f) –NH(hidroxialquilo), y

(g) oxazolidinona.

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En otra realización de los compuestos de fórmula 1.0, Q^1 es un anillo sustituido en el cual por lo menos uno sustituyente es halo.

En otra realización de los compuestos de fórmula 1.0, R^2 está alquilo sustituido en el cual dicho sustituyente es $-OCH_3$.

En otra realización de los compuestos de fórmula 1.0, R^2 se selecciona del grupo que consiste en: $-CH_2OH$ y $-CH_2OCH_3$.

En otra realización de los compuestos de fórmula 1.0, por lo menos uno de R^3, R^4, R^5, R^6, y R^7 es:

(i) seleccionado del grupo que consiste en: oxadiazolilfenilo-, piridazinilfenilo-, pirimidinilpirazinilo-, oxadiazolilfenilo- sustituido, piridazinilfenilo- sustituido, pirimidinilpirazinilo- sustituido, y benzoheteroarilo; o

(ii) seleccionado del grupo que consiste en:

(a) cicloalquilo sustituido,

(b) cicloalquilalquilo sustituido-,

(c) heterocicloalquilo sustituido,

(d) heterocicloalquilalquilo sustituido-,

(e) sustituido arilheteroarilo-,

(f) heteroarilarilo- sustituido,

(g) arilo sustituido,

(h) heteroarilo sustituido,

(i) heteroarilheteroarilo- sustituido,

(j) arilaminoheteroarilo- sustituido,

(k) arilalquinilo- sustituido, y

(l) heteroarilalquinilo- sustituido, y

donde por lo menos un sustituyente en por lo menos uno por lo menos uno de dicho grupo (ii)(a) hasta (ii)(l) R^3, R^4, R^5, R^6, o R^7 se selecciona del grupo que

consiste en: -NHR^{20} (por ej., -$NHCH_2CH_3$ y –$NHCH_3$), -$N(R^{20})_2$ (donde cada R^{20} se selecciona en forma independiente), y –OR^{20} (por ej., -OCH_3).

En otra realización de los compuestos de fórmula 1.0 por lo menos uno de R^3, R^4, R^5, R^6, y R^7 se selecciona del grupo que consiste en: oxadiazolilfenilo-, piridazinilfenilo-, pirimidinilpirazinilo-, oxadiazolilfenilo- sustituido, piridazinilfenilo-sustituido, pirimidinilpirazinilo- sustituido, y benzoheteroarilo.

En otra realización de los compuestos de fórmula 1.0 por lo menos uno de R^3, R^4, R^5, R^6, y R^7 se selecciona del grupo que consiste en:

(a) cicloalquilo sustituido,

(b) cicloalquilalquilo sustituido-,

(c) heterocicloalquilo sustituido,

(d) heterocicloalquilalquilo sustituido-,

(e) sustituido arilheteroarilo-,

(f) heteroarilarilo- sustituido,

(g) arilo sustituido,

(h) heteroarilo sustituido,

(i) heteroarilheteroarilo- sustituido,

(j) arilaminoheteroarilo- sustituido,

(k) arilalquinilo- sustituido, y

(l) heteroarilalquinilo- sustituido, y

donde por lo menos un sustituyente en por lo menos uno por lo menos uno de dicho grupo (ii)(a) hasta (ii)(l) R^3, R^4, R^5, R^6, o R^7 se selecciona del grupo que consiste en: -NHR^{20} (por ej., -$NHCH_2CH_3$ y –$NHCH_3$), -$N(R^{20})_2$ (donde cada R^{20} se selecciona en forma independiente), y –OR^{20} (por ej., -OCH_3).

En otra realización de los compuestos de fórmula 1.0, R^5 es:

(i) seleccionado del grupo que consiste en: oxadiazolilfenilo-, piridazinilfenilo-, pirimidinilpirazinilo-, oxadiazolilfenilo- sustituido, piridazinilfenilo-sustituido, pirimidinilpirazinilo- sustituido, y benzoheteroarilo; o

(ii) seleccionado del grupo que consiste en:

(a) cicloalquilo sustituido,

(b) cicloalquilalquilo sustituido-,

(c) heterocicloalquilo sustituido,

(d) heterocicloalquilalquilo sustituido-,

(e) sustituido arilheteroarilo-,

(f) heteroarilarilo- sustituido,

(g) arilo sustituido,

(h) heteroarilo sustituido,

(i) heteroarilheteroarilo- sustituido,

(j) arilaminoheteroarilo- sustituido,

(k) arilalquinilo- sustituido, y

(l) heteroarilalquinilo- sustituido, y

donde por lo menos un sustituyente en por lo menos uno por lo menos uno de dicho grupo (ii)(a) hasta (ii)(l) R^3, R^4, R^5, R^6, o R^7 se selecciona del grupo que consiste en: -NHR^{20} (por ej., -$NHCH_2CH_3$ y –$NHCH_3$), -$N(R^{20})_2$ (donde cada R^{20} se selecciona en forma independiente), y –OR^{20} (por ej., -OCH_3).

En otra realización de los compuestos de fórmula 1.0 R^5 se selecciona del grupo que consiste en: oxadiazolilfenilo-, piridazinilfenilo-, pirimidinilpirazinilo-, oxadiazolilfenilo- sustituido, piridazinilfenilo- sustituido, pirimidinilpirazinilo-sustituido, y benzoheteroarilo.

En otra realización de los compuestos de fórmula 1.0 R^5 se selecciona del grupo que consiste en:

(a) cicloalquilo sustituido,

(b) cicloalquilalquilo sustituido-,

(c) heterocicloalquilo sustituido,

(d) heterocicloalquilalquilo sustituido-,

(e) sustituido arilheteroarilo-,

(f) heteroarilarilo- sustituido,

(g) arilo sustituido,

(h) heteroarilo sustituido,

(i) heteroarilheteroarilo- sustituido,

(j) arilaminoheteroarilo- sustituido,

(k) arilalquinilo- sustituido, y

(l) heteroarilalquinilo- sustituido, y

donde por lo menos un sustituyente en por lo menos uno por lo menos uno de dicho grupo (ii)(a) hasta (ii)(l) R^3, R^4, R^5, R^6, o R^7 se selecciona del grupo que consiste en: -NHR^{20} (por ej., -$NHCH_2CH_3$ y –$NHCH_3$), -$N(R^{20})_2$ (donde cada R^{20} se selecciona en forma independiente), y –OR^{20} (por ej., -OCH_3).

En otra realización de los compuestos de fórmula 1.0, R^{5A} es alquilo (por ej., alquilo C_1 hasta C_6, tales como, por ejemplo, -CH_3).

En otra realización de los compuestos de fórmula 1.0, R^{10} es un arilo sustituido, y por lo menos uno sustituyente se selecciona del grupo que consiste en:

(a) -$S(O)_tR^{38}$ donde R^{38} es isopropilo,

(b) –O-alquil-O-R^{20},

(c) hidroxialquilo,

(d) –$N(R^{20})_2$,

(e) –alquil-OR^{20},

(f) –O-alquil-OH,

(g) –NH(hidroxialquilo), y

(h) oxazolidinona.

En otra realización de los compuestos de fórmula 1.0, R^{10} es un arilo sustituido, y por lo menos uno sustituyente se selecciona del grupo que consiste en:

(a) –O-alquil-O-R^{20},

(b) hidroxialquilo,

(c) –N(R^{20})$_2$,

(d) –alquil-OR^{20},

(e) –O-alquil-OH,

(f) –NH(hidroxialquilo), y

(g) oxazolidinona.

En otra realización de los compuestos de fórmula 1.0, R^{20} es isopropilo.

Cuando R^1 es un grupo cicloalquilo (es decir, R^1 es R^{10} donde R^{10} es cicloalquilo), ejemplos dicho grupo cicloalquilo incluyen, sin carácter limitativo, ciclopropilo y ciclobutilo.

Cuando R^1 es un grupo heterocicloalquilo (es decir, R^1 es R^{10} donde R^{10} es heterocicloalquilo), ejemplos de dicho grupo heterocicloalquilo incluyen, sin carácter limitativo, morfolinilo, pirrolidinilo, piperidinilo y piperazinilo.

Cuando R^1 es un grupo heteroarilo (es decir, R^1 es R^{10} y R^{10} es heteroarilo), ejemplos de dicho grupo heteroarilo incluyen, sin carácter limitativo,

(a) unheteroarilo sustituido,

(b) heteroarilo sustituido con 1 hasta 3 sustituyentes seleccionados en forma independiente del grupo que consiste en: –C(O)R^{38} (por ej., R^{38} es alquilo tales como metilo) ,–NHR^{20} (por ej., -$NHCH_3$), -OR^{20} (por ej., -OCH_3), cicloalquilo (por ej., ciclopropilo) y halo (por ej., Cl),

(c) heteroarilo seleccionados del grupo que consiste en: pirrolilo, pirazolilo, imidazolilo, furanilo, tienilo, tiazolilo, piridilo, piridilo N-O, y pirimidinilo,

(d) heteroarilo seleccionados del grupo que consiste en: pirrolilo, pirazolilo, imidazolilo, furanilo, tienilo, tiazolilo, piridilo, piridilo N-O, y pirimidinilo, donde dicho heteroarilo está sustituido con 1 hasta 3 sustituyentes seleccionados en forma independiente del grupo que consiste en: $-C(O)R^{38}$ (por ej., R^{38} es alquilo tales como metilo) ,$-NHR^{20}$ (por ej., $-NHCH_3$), $-OR^{20}$ (por ej., $-OCH_3$), cicloalquilo (por ej., ciclopropilo) y halo (por ej., Cl), y

(e) heteroarilo seleccionado del grupo que consiste en: tienilo sustituido con $-C(O)R^{38}$ (tales como, por ejemplo, tienilo sustituido con $-C(O)CH_3$), tiazolilo sustituido con $-NHR^{20}$ tales como, por ejemplo (tiazolilo sustituido con $-NHCH_3$), piridilo sustituido con halo (tales como, por ejemplo, piridilo sustituido con –Cl), piridilo sustituido con $-OR^{20}$ (tales como, por ejemplo, piridilo sustituido con metilo), y pirimidinilo sustituido con $-OR^{20}$ (tales como, por ejemplo, pirimidinilo sustituido con $-OCH_3$).

Cuando R^1 es un grupo heteroarilo (es decir, R^1 es R^{10} y R^{10} es heteroarilalquilo), ejemplos de dicho grupo heteroarilo incluyen, sin carácter limitativo,

(a) heteroarilalquil- no sustituido

(b) heteroarilalquil- sustituido con 1 hasta 3 sustituyentes seleccionados en forma independiente del grupo que consiste en: $-C(O)R^{38}$ (por ej., R^{38} es alquilo tales como metilo), $-NHR^{20}$ (por ej., $-NHCH_3$), $-OR^{20}$ (por ej., $-OCH_3$), y halo (por ej., Cl),

(c) heteroarilalquil- seleccionado del grupo que consiste en: pirrolilalquil- (por ej., pirrolilCH_2-), pirazolilalquil- (por ej., pirazolilCH_2-), imidazolilalquil- (por ej., imdazolil-CH_2-), furanilalquil- (por ej., furanilCH_2-), tienilalquil- (por ej., tienilCH_2-), tiazolilalquil- (por ej., tiazolilCH_2-), piridilalquil- (por ej., piridilCH_2-), piridilo N-O alquil- (por ej., piridil(N-O)CH_2-), y pirimidinilalquil- (por ej., pirimidinilCH_2-),

(d) heteroarilalquil- seleccionados del grupo que consiste en: pirrolilalquil- (por ej., pirrolilCH_2-), pirazolilalquil- (por ej., pirazolilCH_2-), imidazolilalquil- (por ej., imdazolilCH_2-), furanilalquil- (por ej., furanilCH_2-), tienilalquil- (por ej., tienilCH_2-), tiazolilalquil- (por ej., tiazolilCH_2-), piridilalquil- (por ej., piridilCH_2-), piridilo N-O alquil- (por ej., piridil(N-O)CH_2-), y pirimidinilalquil- (por ej., pirimidinilCH_2-), donde dicho heteroarilo está sustituido con 1 hasta 3 sustituyentes seleccionados en forma independiente del grupo que consiste en: $-C(O)R^{38}$ (por ej., R^{38} es alquilo tales como metilo) ,$-NHR^{20}$ (por ej., $-NHCH_3$), $-OR^{20}$ (por ej., $-OCH_3$), y halo (por ej., Cl), y

(e) heteroarilalquil- seleccionados del grupo que consiste en: tienilalquil- sustituido con un grupo $-C(O)R^{20}$ (tales como, por ejemplo, tienilCH_2- sustituido con $-C(O)CH_3$), tiazolilalquil- sustituido con $-NHR^{20}$ tales como, por ejemplo (tiazolilCH_2- sustituido con $-NHCH_3$), piridilalquil- sustituido con halo (tales como, por ejemplo, piridilCH_2- sustituido con –Cl), piridilalquil- sustituido con $-OR^{20}$ (tales como, por ejemplo, piridilCH_2- sustituido con metilo), y pirimidinilalquil- sustituido con $-OR^{20}$ (tales como, por ejemplo, pirimidinilCH_2- sustituido con $-OCH_3$).

Cuando R^1 es un grupo arilo (es decir, R^1 es R^{10} y R^{10} es arilo), ejemplos de dicho grupo arilo incluyen, sin carácter limitativo, fenilo y naftilo, y con preferencia fenilo.

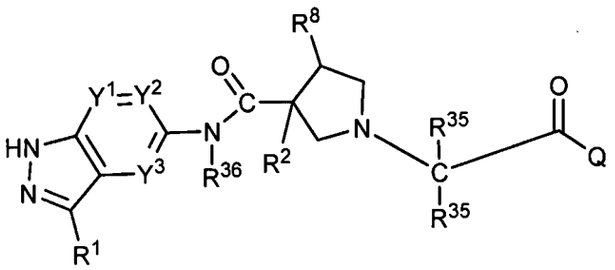
Cuando R^1 es un grupo arilalquilo (es decir, R^1 es R^{10} y R^{10} es arilalquilo), ejemplos de dicho grupo aril alquilo incluyen, sin carácter limitativo, $-(C(R^{30})_2)_n$fenilo (por ej., $-(CH_2)_n$fenilo), donde en un ejemplo dicho arilalquilo- es $-(C(R^{30})_2)_n$fenilo donde n es 1, y en otro ejemplo dicho arilalquil- es $-(CH_2)_n$fenilo donde n es 1 (es decir, dicho arilalquil- es bencilo).

Cuando R^1 es un grupo arilalquilo sustituido (es decir, R^1 es R^{10} y R^{10} es un arilalquilo sustituido), ejemplos de dicho grupo aril alquilo sustituido incluyen, sin carácter limitativo, $-(C(R^{30})_2)_n$fenilo sustituido (por ej., $-(CH_2)_n$fenilo sustituido),

donde en un ejemplo dicho arilalquil- sustituido es -$(C(R^{30})_2)_n$ fenilo sustituido donde n es 1, y en otro ejemplo dicho arilalquil-sustituido es -$(CH_2)_n$fenilo sustituido donde n es 1 (es decir, dicho arilalquil- sustituido está sustituido bencilo), donde el resto arilo de dicho arilalquilo sustituido está sustituido con 1 hasta 3 sustituyentes seleccionados en forma independiente del grupo que consiste en: halo (por ej., F, Cl y Br), -CF_3, y –OR^{20} (por ej., -OCH_3).

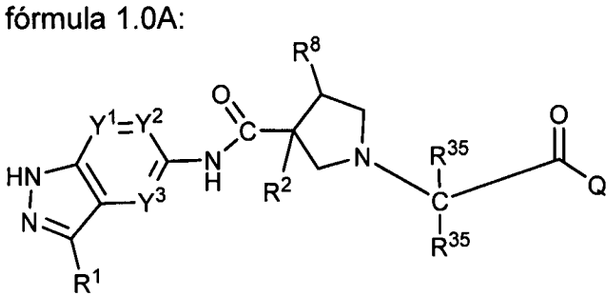
Aquellas personas con experiencia en el arte apreciarán que cuando Q^1 es arilo, arilo sustituido, heteroarilo o heteroarilo sustituido los dos átomos de carbono comunes a los dos anillos fusionados no están sustituidos. De este modo, no hay grupos R^3 y grupos R^4 en 2.9 cuando Q^1 es arilo, arilo sustituido, heteroarilo o heteroarilo sustituido. No hay grupos R^3 y ni R^4 en 2.10 cuando Q^1 fusionado en las posiciones R^3 y R^4 es arilo, arilo sustituido, heteroarilo o heteroarilo sustituido. No hay grupos R^6 y ni R^7 en 2.10 cuando Q^1 fusionado en las posiciones R^6 y R^7 es arilo, arilo sustituido, heteroarilo o heteroarilo sustituido. No hay grupos R^3 y ni grupos R^4 en 2.11 cuando Q^1 fusionado en las posiciones R^3 y R^4 positions es arilo, arilo sustituido, heteroarilo o heteroarilo sustituido. No hay grupos R^3 y ni grupos R^4 en 2.13 cuando Q^1 fusionado en las posiciones R^3 y R^4 positions es arilo, arilo sustituido, heteroarilo o heteroarilo sustituido. No hay grupos R^3 y ni grupos R^4 en 2.14 cuando Q^1 fusionado en las posiciones R^3 y R^4 positions es arilo, arilo sustituido, heteroarilo o heteroarilo sustituido. No hay grupos R^3 y ni grupos R^4 en 2.15 cuando Q^1 fusionado en las posiciones R^3 y R^4 positions es arilo, arilo sustituido, heteroarilo o heteroarilo sustituido. No hay grupos R^6 y ni grupos R^7 en 2.15 cuando Q^1 fusionado en las posiciones R^3 y R^4 positions es arilo, arilo sustituido, heteroarilo o heteroarilo sustituido.

En una realización de los compuestos de fórmula 1.0, z es 1. De este modo, en esta realización los compuestos de fórmula 1.0 tienen la fórmula 1.0A1:



(1.0A1)

En otra realización de los compuestos de fórmula 1.0, z es 1 y R^{36} es H. De este modo, en esta realización los compuestos de fórmula 1.0 tienen la fórmula 1.0A:



(1.0A)

En otra realización de los compuestos de fórmula 1.0, Z es 1 y and R^{36} es $-OCH_3$.

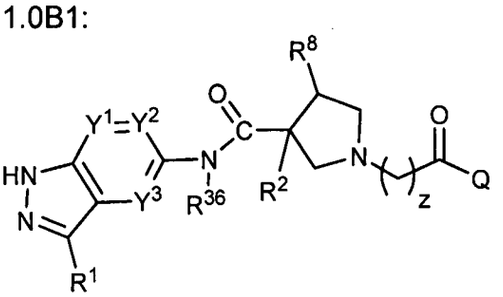
En otra realización de los compuestos de fórmula 1.0, z es 1, y cada R^{35} se selecciona en forma independiente del grupo que consiste en: H, metilo, etilo, i-propilo y propilo (por ej., un R^{35} es H y el otro es metilo, o ambos sustituyentes R^{35} son metilo, o con preferencia ambos sustituyentes R^{35} are H).

En otra realización de los compuestos de fórmula 1.0, z es 1, cada R^{35} se selecciona en forma independiente del grupo que consiste en: H, metilo, etilo, i-propilo y propilo (por ej., un R^{35} es H y el otro es metilo, o ambos sustituyentes R^{35} son metilo, o con preferencia ambos sustituyentes R^{35} are H), y R^{36} se selecciona del grupo que consiste en: H, metilo, etilo y propilo.

En otra realización de los compuestos de fórmula 1.0, z es 1, cada R^{35} se selecciona en forma independiente del grupo que consiste en: H, metilo, etilo, i-propilo y propilo (por ej., un R^{35} es H y el otro es metilo, o ambos sustituyentes R^{35} son metilo, o con preferencia ambos sustituyentes R^{35} are H), y R^{36} se selecciona del grupo que consiste en: H y metilo.

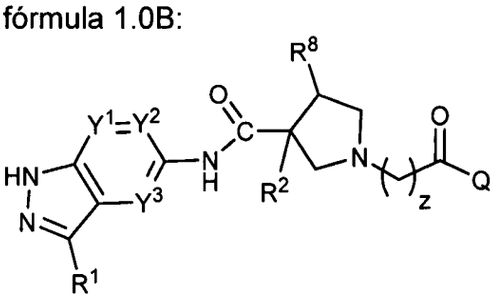
En otra realización de los compuestos de fórmula 1.0, z es 1, cada R^{35} se selecciona en forma independiente del grupo que consiste en: H, metilo, etilo, i-propilo y propilo (por ej., un R^{35} es H y el otro es metilo, o ambos sustituyentes R^{35} son metilo, o con preferencia ambos sustituyentes R^{35} are H), y R^{36} es: H.

En otra realización de los compuestos de fórmula 1.0, cada R^{35} es H. De este modo, en esta realización los compuestos de fórmula 1.0 tienen la fórmula 1.0B1:



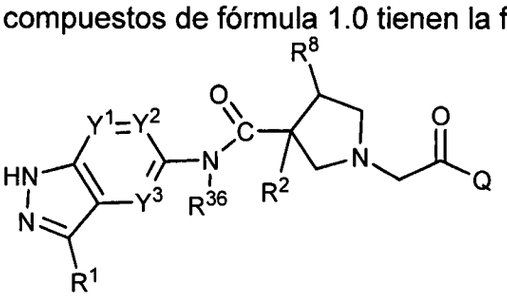
(1.0B1)

En otra realización de los compuestos de fórmula 1.0, cada R^{35} es H y R^{36} es H. De este modo, en esta realización los compuestos de fórmula 1.0 tienen la fórmula 1.0B:



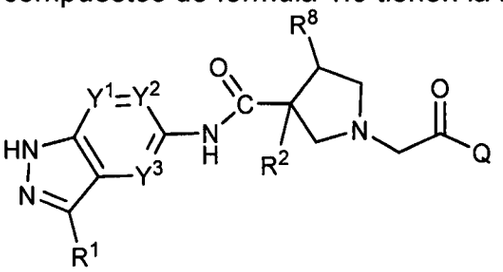
(1.0B)

En otra realización de los compuestos de fórmula 1.0, z es con preferencia 1 y cada R^{35} es con preferencia H. De este modo, en esta realización los compuestos de fórmula 1.0 tienen la fórmula 1.0C1:



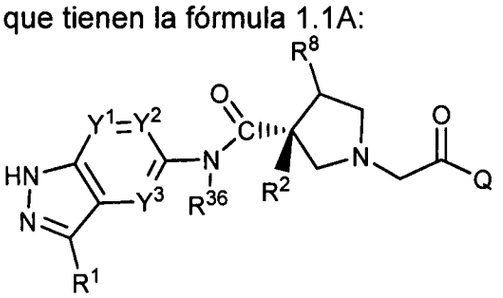
(1.0C1)

En otra realización de los compuestos de fórmula 1.0, z es con preferencia 1, cada R^{35} es con preferencia H, y R^{36} es H. De este modo, con preferencia los compuestos de fórmula 1.0 tienen la fórmula 1.0C:



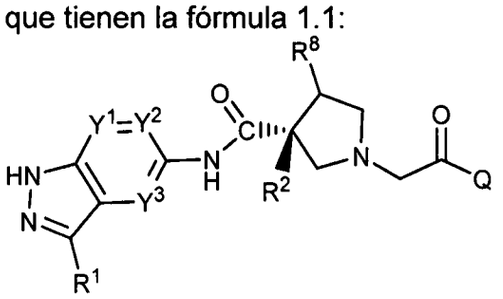
(1.0C)

Otra realización de esta invención se refiere a compuestos de fórmula 1.0 que tienen la fórmula 1.1A:



(1.1A)

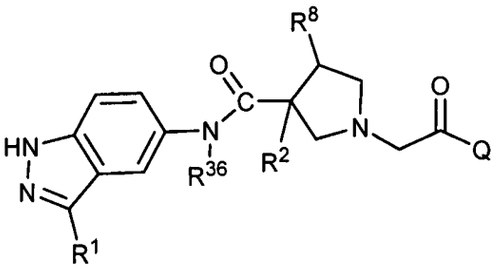
Otra realización de esta invención se refiere a compuestos de fórmula 1.0 que tienen la fórmula 1.1:



(1.1)

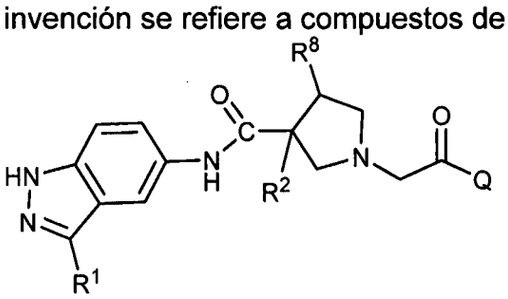
donde todos los sustituyentes son como se los definió para la fórmula 1.0.

Otra realización de esta invención se refiere a compuestos de fórmulas 1.0 y 1.1A en los cuales Y^1, Y^2, y Y^3 son -CH=. De este modo, una realización de esta invención se refiere a compuestos de fórmula 1.2A:



(1.2A)

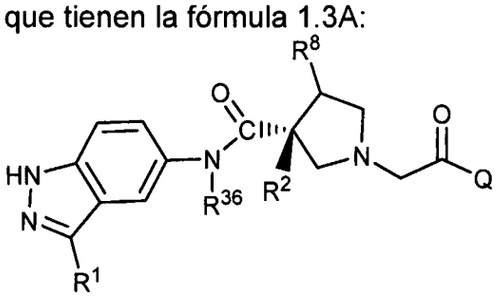
Otra realización de esta invención se refiere a compuestos de fórmulas 1.0 y 1.1 en los cuales Y^1, Y^2, y Y^3 son -CH=. De este modo, una realización de esta invención se refiere a compuestos de fórmula 1.2:



(1.2)

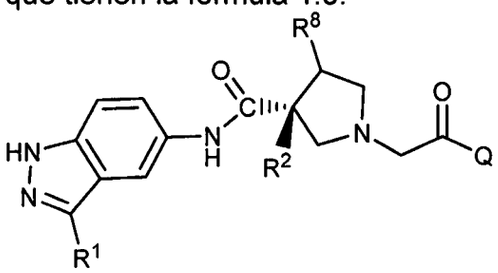
donde todos los sustituyentes son como se los definió para la fórmula 1.0.

Otra realización de esta invención se refiere a compuestos de fórmula 1.0 que tienen la fórmula 1.3A:



(1.3A)

Otra realización de esta invención se refiere a compuestos de fórmula 1.0 que tienen la fórmula 1.3:



(1.3)

donde todos los sustituyentes son como se los definió para la fórmula 1.0.

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Ejemplos de Q incluyen, sin carácter limitativo: restos 2.1, 2.2, 2.3., 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 2.10, 2.11, 2.14, o 2.15 donde cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y alquilo (por ej., alquilo C_1 hasta C_6, tales como, por ejemplo metilo).

Ejemplos de Q también incluyen, sin carácter limitativo: restos 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 2.10, 2.11, 2.14, o 2,15 donde cada R^3, R^4, R^6, y R^7 es H.

Ejemplos de Q también incluyen, sin carácter limitativo: restos 2.17, 2.18, 2.19, 2.20 y 2.21 donde cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y alquilo (por ej., alquilo C_1 hasta C_6, tales como, por ejemplo metilo).

Ejemplos de Q también incluyen, sin carácter limitativo: restos 2.17, 2.18, 2.19, 2.20 y 2.21 donde cada R^3, R^4, R^6, y R^7 es H.

Ejemplos de Q incluyen, sin carácter limitativo: restos 2.12, 2.13, o 2.16 donde cada R^3, R^4, y R^7 se selecciona en forma independiente del grupo que consiste en: H y alquilo (por ej., alquilo C_1 hasta C_6, tales como, por ejemplo metilo).

Ejemplos de Q también incluyen, sin carácter limitativo: restos 2.12, 2.13, o 2.16 donde cada R^3, R^4, y R^7 es H.

Ejemplos de Q incluyen, sin carácter limitativo: resto 2.22 donde cada R^3, R^4, y R^7 se selecciona en forma independiente del grupo que consiste en: H y alquilo (por ej., alquilo C_1 hasta C_6, tales como, por ejemplo metilo).

Ejemplos de Q también incluyen, sin carácter limitativo: resto 2.22 donde cada R^3, R^4, y R^7 es H.

De este modo, en un ejemplo de Q, Q es un resto 2.1 donde cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y alquilo (por ej., alquilo C_1 hasta C_6, tales como, por ejemplo metilo).

En otro ejemplo de Q, Q es un resto 2.1 donde cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y metilo.

En otro ejemplo de Q, Q es un resto 2.1 donde cada R^3, R^4, R^6, y R^7 es H.

En otro ejemplo de Q, Q es un resto 2.2 donde cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y alquilo (por ej., alquilo C_1 hasta C_6, tales como, por ejemplo metilo).

En otro ejemplo de Q, Q es un resto 2.2 donde cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y metilo.

En otro ejemplo de Q, Q es un resto 2.2 donde cada R^3, R^4, R^6, y R^7 es H.

En otro ejemplo de Q, Q es un resto 2.3 donde cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y alquilo (por ej., alquilo C_1 hasta C_6, tales como, por ejemplo metilo).

En otro ejemplo de Q, Q es un resto 2.3 donde cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y metilo.

En otro ejemplo de Q, Q es un resto 2.3 donde cada R^3, R^4, R^6, y R^7 es H.

En otro ejemplo de Q, Q es un resto 2.4 donde cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y alquilo (por ej., alquilo C_1 hasta C_6, tales como, por ejemplo metilo).

En otro ejemplo de Q, Q es un resto 2.4 donde cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y metilo.

En otro ejemplo de Q, Q es un resto 2.4 donde cada R^3, R^4, R^6, y R^7 es H.

En otro ejemplo de Q, Q es un resto 2.5 donde cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y alquilo (por ej., alquilo C_1 hasta C_6, tales como, por ejemplo metilo).

En otro ejemplo de Q, Q es un resto 2.5 donde cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y metilo.

En otro ejemplo de Q, Q es un resto 2.5 donde cada R^3, R^4, R^6, y R^7 es H.

En otro ejemplo de Q, Q es un resto 2.6 donde cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y alquilo (por ej., alquilo C_1 hasta C_6, tales como, por ejemplo metilo).

En otro ejemplo de Q, Q es un resto 2.6 donde cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y metilo.

En otro ejemplo de Q, Q es un resto 2.7 donde cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y alquilo (por ej., alquilo C_1 hasta C_6, tales como, por ejemplo metilo).

En otro ejemplo de Q, Q es un resto 2.7 donde cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y metilo.

En otro ejemplo de Q, Q es un resto 2.7 donde cada R^3, R^4, R^6, y R^7 es H.

En otro ejemplo de Q, Q es un resto 2.8 donde cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y alquilo (por ej., alquilo C_1 hasta C_6, tales como, por ejemplo metilo).

En otro ejemplo de Q, Q es un resto 2.8 donde cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y metilo.

En otro ejemplo de Q, Q es un resto 2.8 donde cada R^3, R^4, R^6, y R^7 es H.

En otro ejemplo de Q, Q es un resto 2.9 o 2,10 donde cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y alquilo (por ej., alquilo C_1 hasta C_6, tales como, por ejemplo metilo).

En otro ejemplo de Q, Q es un resto 2.9 o 2,10 donde cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y metilo.

En otro ejemplo de Q, Q es un resto 2.9 o 2,10 donde cada R^3, R^4, R^6, y R^7 es H.

En otro ejemplo de Q, Q es un resto 2.11 donde cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y alquilo (por ej., alquilo C_1 hasta C_6, tales como, por ejemplo metilo).

En otro ejemplo de Q, Q es un resto 2.11 donde cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y metilo.

En otro ejemplo de Q, Q es un resto 2.11 donde cada R^3, R^4, R^6, y R^7 es H.

En otro ejemplo de Q, Q es un resto 2.12 o 2.13 donde cada R^3, R^4, y R^7 se selecciona en forma independiente del grupo que consiste en: H y alquilo (por ej., alquilo C_1 hasta C_6, tales como, por ejemplo metilo).

En otro ejemplo de Q, Q es un resto 2.12 o 2.13 donde cada R^3, R^4, y R^7 se selecciona en forma independiente del grupo que consiste en: H y metilo.

En otro ejemplo de Q, Q es un resto 2.12 o 2.13 donde cada R^3, R^4, y R^7 es H.

En otro ejemplo de Q, Q es un resto 2.14 o 2.15 donde cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y alquilo (por ej., alquilo C_1 hasta C_6, tales como, por ejemplo metilo).

En otro ejemplo de Q, Q es un resto 2.14 o 2.15 donde cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y metilo.

En otro ejemplo de Q, Q es un resto 2.14 o 2.15 donde cada R^3, R^4, R^6, y R^7 es H.

En otro ejemplo de Q, Q es un resto 2.16 donde cada R^3, R^4, y R^7 es H.

En otro ejemplo de Q, Q es un resto 2.17 donde cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y alquilo (por ej., alquilo C_1 hasta C_6, tales como, por ejemplo metilo).

En otro ejemplo de Q, Q es un resto 2.17 donde cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y metilo.

En otro ejemplo de Q, Q es un resto 2.17 donde cada R^3, R^4, R^6, y R^7 es H.

En otro ejemplo de Q, Q es un resto 2.18 donde cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y alquilo (por ej., alquilo C_1 hasta C_6, tales como, por ejemplo metilo).

En otro ejemplo de Q, Q es un resto 2.18 donde cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y metilo.

En otro ejemplo de Q, Q es un resto 2.18 donde cada R^3, R^4, R^6, y R^7 es H.

En otro ejemplo de Q, Q es un resto 2.19 donde cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y alquilo (por ej., alquilo C_1 hasta C_6, tales como, por ejemplo metilo).

En otro ejemplo de Q, Q es un resto 2.19 donde cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y metilo.

En otro ejemplo de Q, Q es un resto 2.19 donde cada R^3, R^4, R^6, y R^7 es H.

En otro ejemplo de Q, Q es un resto 2.20 donde cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y alquilo (por ej., alquilo C_1 hasta C_6, tales como, por ejemplo metilo).

En otro ejemplo de Q, Q es un resto 2.20 donde cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y metilo.

En otro ejemplo de Q, Q es un resto 2.20 donde cada R^3, R^4, R^6, y R^7 es H.

En otro ejemplo de Q, Q es un resto 2.21 donde cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y alquilo (por ej., alquilo C_1 hasta C_6, tales como, por ejemplo metilo).

En otro ejemplo de Q, Q es un resto 2.21 donde cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y metilo.

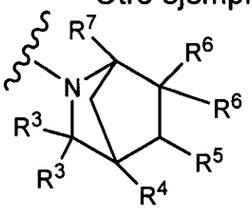
En otro ejemplo de Q, Q es un resto 2.21 donde cada R^3, R^4, R^6, y R^7 es H.

En otro ejemplo de Q, Q es un resto 2.22 donde cada R^3, R^4, y R^7 se selecciona en forma independiente del grupo que consiste en: H y alquilo (por ej., alquilo C_1 hasta C_6, tales como, por ejemplo metilo).

En otro ejemplo de Q, Q es un resto 2.22 donde cada R^3, R^4, y R^7 se selecciona en forma independiente del grupo que consiste en: H y metilo.

En otro ejemplo de Q, Q es un resto 2.22 donde cada R^3, R^4, y R^7 es H.

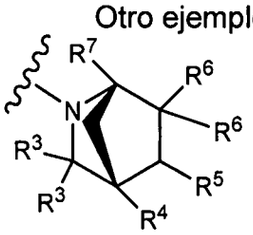
Otro ejemplo del sustituyente Q 2.3 es:



(2.3A)

(es decir, cada R^{24} es H y w es 1).

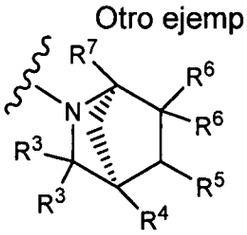
Otro ejemplo del sustituyente Q 2.3 es:



(2.3B)

(es decir, cada R^{24} es H y w es 1).

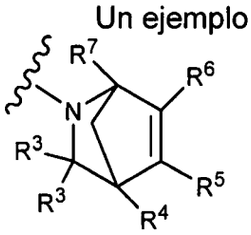
Otro ejemplo del sustituyente Q 2.3 es:



(2.3C)

(es decir, cada R^{24} es H y w es 1).

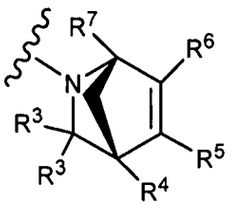
Un ejemplo del sustituyente Q 2.4 es:



(2.4A)

(es decir, cada R^{24} es H y w es 1).

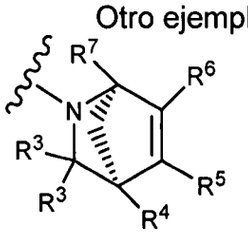
Otro ejemplo del sustituyente Q 2.4 es:



(2.4B)

(es decir, cada R^{24} es H y w es 1).

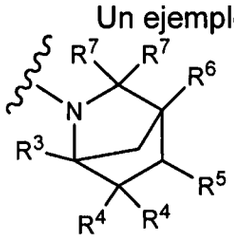
Otro ejemplo del sustituyente Q 2.4 es:



(2.4C)

(es decir, cada R^{24} es H y w es 1).

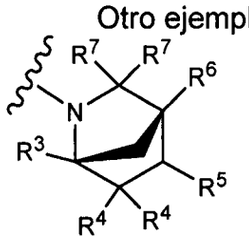
Un ejemplo del sustituyente Q 2.5 es:



(2.5A)

(es decir, cada R^{24} es H y w es 1).

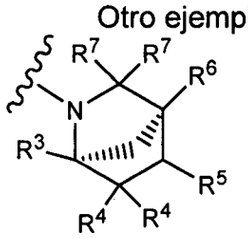
Otro ejemplo del sustituyente Q 2.5 es:



(2.5B)

(es decir, cada R^{24} es H y w es 1).

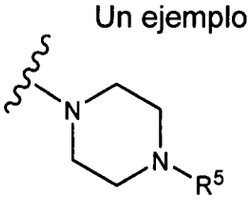
Otro ejemplo del sustituyente Q 2.5 es:



(2.5C)

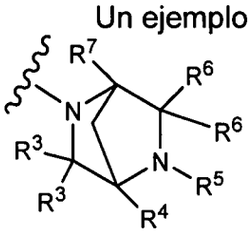
(es decir, cada R^{24} es H y w es 1).

Un ejemplo del sustituyente Q 2.6 es:



(2.6A)

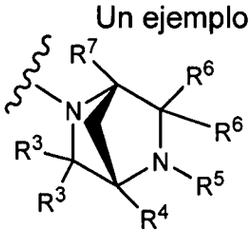
Un ejemplo del sustituyente Q 2.7 es:



(2.7A)

(es decir, cada R^{24} es H y w es 1).

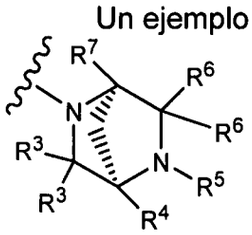
Un ejemplo del sustituyente Q 2.7 es:



(2.7B)

(es decir, cada R^{24} es H y w es 1).

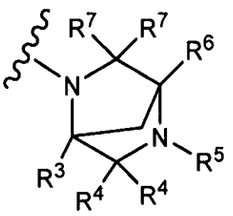
Un ejemplo del sustituyente Q 2.7 es:



(2.7C)

(es decir, cada R^{24} es H y w es 1).

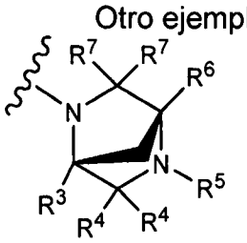
Un ejemplo del sustituyente Q 2.8 es:



(2.8A)

(es decir, cada R^{24} es H y w es 1).

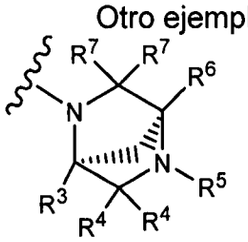
Otro ejemplo del sustituyente Q 2.8 es:



(2.8B)

(es decir, cada R^{24} es H y w es 1).

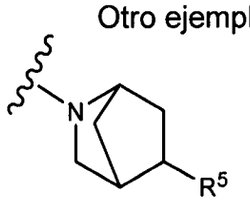
Otro ejemplo del sustituyente Q 2.8 es:



(2.8C)

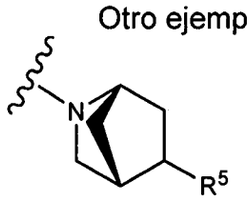
(es decir, cada R^{24} es H y w es 1).

Otro ejemplo del sustituyente Q 2.3 es:



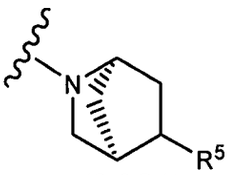
(2.3A1)

Otro ejemplo del sustituyente Q 2.3 es:



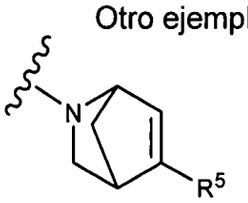
(2.3B1)

Otro ejemplo del sustituyente Q 2.3 es:



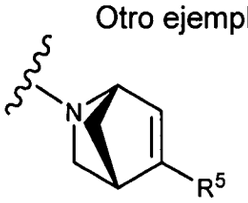
(2.3C1)

Otro ejemplo del sustituyente Q 2.4 es:



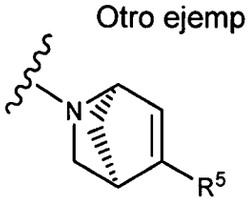
(2.4A1)

Otro ejemplo del sustituyente Q 2.4 es:



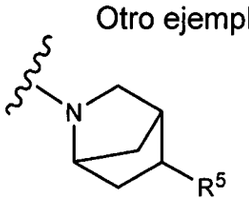
(2.4B1)

Otro ejemplo del sustituyente Q 2.4 es:



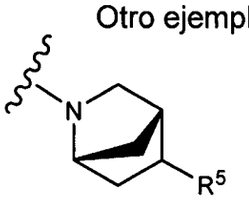
(2.4C1)

Otro ejemplo del sustituyente Q 2.5 es:



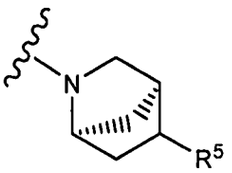
(2.5A1)

Otro ejemplo del sustituyente Q 2.5 es:



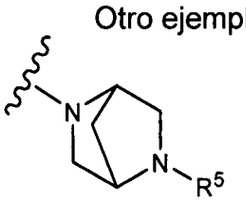
(2.5B1)

Otro ejemplo del sustituyente Q 2.5 es:



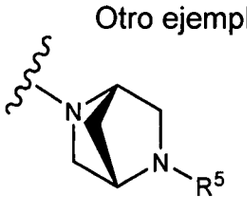
(2.5C1)

Otro ejemplo del sustituyente Q 2.7 es:



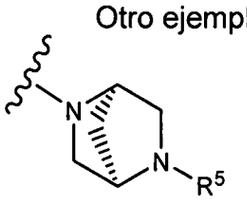
(2.7A1)

Otro ejemplo del sustituyente Q 2.7 es:



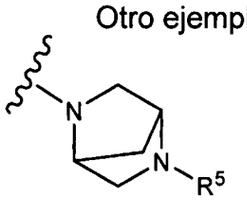
(2.7B1)

Otro ejemplo del sustituyente Q 2.7 es:



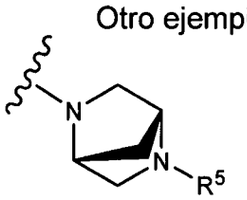
(2.7C1)

Otro ejemplo del sustituyente Q 2.8 es:



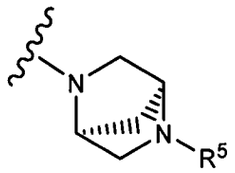
(2.8A1)

Otro ejemplo del sustituyente Q 2.8 es:



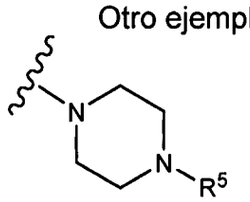
(2.8B1)

Otro ejemplo del sustituyente Q 2.8 es:



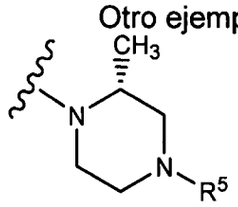
(2.8C1)

Otro ejemplo del sustituyente Q es el anillo de piperazina:

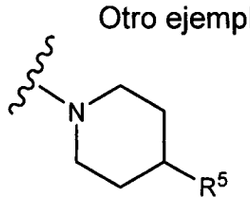


sustituido con uno o dos sustituyentes seleccionados en forma independiente del grupo que consiste en grupos R^3, siempre que dicho uno o dos sustituyentes no son H. En una realización dichos sustituyentes se seleccionan del grupo que consiste en grupos alquilo (por ej., alquilo C_1 hasta C_6, por ej., metilo). En otra realización hay un sustituyente en dicho anillo piperazina. En otra realización hay un sustituyente en dicho anillo piperazina y dicho sustituyente es metilo.

Otro ejemplo del sustituyente Q es el anillo de piperazina:

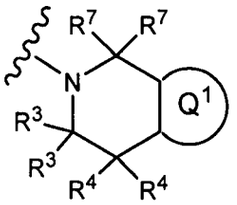


Otro ejemplo del sustituyente Q es el anillo de piperidina:



sustituido con uno o dos sustituyentes seleccionados en forma independiente del grupo que consiste en grupos R^3, siempre que dicho uno o dos sustituyentes no son H. En una realización dichos sustituyentes se seleccionan del grupo que consiste en alquilo grupos (por ej., alquilo C_1 hasta C_6, por ej., metilo). En otra realización hay un sustituyente en dicho anillo de piperidina. En otra realización hay un sustituyente en dicho anillo de piperidina y dicho sustituyente es metilo.

En un ejemplo del sustituyente Q 2.16

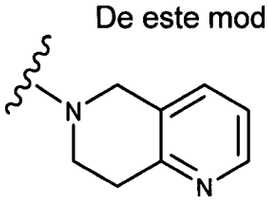


(2.16)

Q^1 es heteroarilo.

En otro ejemplo del sustituyente Q 2.16 Q^1 es arilo.

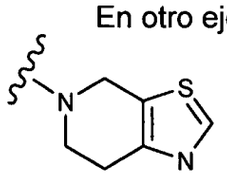
De este modo, un ejemplo del sustituyente Q 2.16 es 2.16A:



(2.16A)

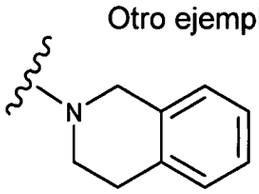
(es decir, Q^1 es piridilo, y cada R^3, R^4 y R^7 es H).

En otro ejemplo, el sustituyente Q 2.16 es 2.16A1:



(2.16A1)

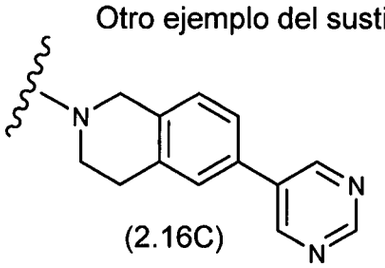
Otro ejemplo del sustituyente Q 2.16 es 2.16B:



(2.16B)

(es decir, Q^1 es fenilo, y cada R^3, R^4 y R^7 es H).

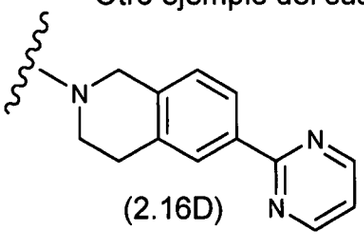
Otro ejemplo del sustituyente Q 2.16 es 2.16C



(2.16C)

(es decir, Q^1 es fenilo sustituido, y cada R^3, R^4 y R^7 es H).

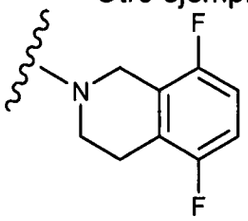
Otro ejemplo del sustituyente Q 2.16 es 2.16D



(2.16D)

(es decir, Q^1 es fenilo sustituido, y cada R^3, R^4 y R^7 es H).

Otro ejemplo del sustituyente Q 2.16 es 2.16E



(2.16E)

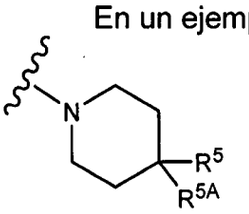
Cuando el sustituyente Q comprende dos anillos Q^1, cada anillo Q^1 se selecciona en forma independiente. En general, los anillos cicloalquilo Q^1 y los anillos cicloalquilo sustituido Q^1 comprenden 5 hasta 7 carbonos en el anillo. En general, los anillos heterocicloalquilo Q^1 y los anillos heterocicloalquilo sustituidos Q^1 comprenden 5 hasta 7 carbonos en el anillo y comprenden 1 hasta 3 (en general 1 o 2, o en general 1) heteroátomos anulares seleccionados del grupo que consiste en: O, N y S. En general, el heteroarilo anillos Q^1 y los anillos heteroarilo sustituido Q^1 comprenden 5 hasta 7 carbonos en el anillo y comprenden 1 hasta 3 (en general 1 o 2, o en general 1) heteroátomos anulares seleccionados del grupo que consiste en: O, N y S. Ejemplos de los anillos Q^1 incluyen, sin carácter limitativo: piperidinilo, piperazinilo, piranilo, pirrolidinilo, morfolinilo, tiomorfolinilo, piridilo, pirimidinilo, pirrolilo, pirazolilo, furanilo, tienilo, tiazolilo, imidazolilo, ciclopentilo, ciclohexilo y cicloheptilo. Ejemplos de the anillos Q^1 también incluyen, sin carácter limitativo: piperidinilo sustituido, piperazinilo sustituido, piranilo sustituido, pirrolidinilo sustituido, morfolinilo sustituido, tiomorfolinilo sustituido, piridilo sustituido, pirimidinilo sustituido, pirrolilo sustituido,

pirazolilo sustituido, furanilo sustituido, tienilo sustituido, tiazolilo sustituido, imidazolilo sustituido, ciclopentilo sustituido, ciclohexilo sustituido y cicloheptilo sustituido donde dicho sustituido anillos Q^1 están sustituidos con 1 hasta 3 sustituyentes seleccionados de los restos R^{10}.

En general, los anillos cicloalquilo Q^2 y los anillos cicloalquilo sustituido Q^2 comprenden 5 hasta 7 carbonos en el anillo. En general, los anillos heterocicloalquilo Q^2 y los anillos heterocicloalquilo Q^1 comprenden 5 hasta 7 carbonos en el anillo y comprenden 1 hasta 3 (en general 1 o 2, o en general 1) heteroátomos anulares seleccionados del grupo que consiste en: O, N y S.

Ejemplos de los anillos Q^2 incluyen, sin carácter limitativo: piperidinilo, piperazinilo, piranilo, pirrolidinilo, ciclopentilo, ciclohexilo y cicloheptilo. Ejemplos de los anillos Q^2 también incluyen, sin carácter limitativo: piperidinilo sustituido, piperazinilo sustituido, piranilo sustituido, pirrolidinilo sustituido, morfolinilo sustituido, tiomorfolinilo sustituido, ciclopentilo sustituido, ciclohexilo sustituido y cicloheptilo sustituido donde dicho sustituido anillos Q^1 están sustituidos con 1 hasta 3 sustituyentes seleccionados de los restos R^{10}.

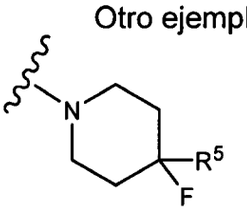
En un ejemplo el sustituyente Q 2.17 es:



(2.17A)

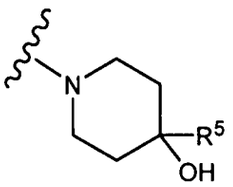
donde R^{5A} es halo.

Otro ejemplo del sustituyente Q 2.17 es:



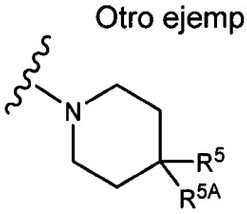
(2.17B)

Otro ejemplo del sustituyente Q 2.17 es:



(2.17C)

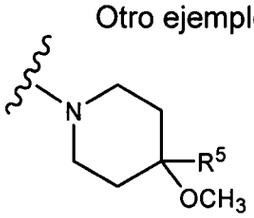
Otro ejemplo del sustituyente Q 2.17 es:



(2.17D)

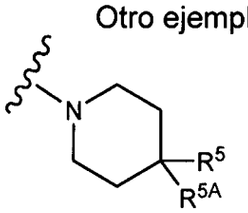
donde R^{5A} es alcoxi, es decir, -O-alquilo (C_1 hasta C_6), tales como, por ejemplo, -O-alquilo (C_1 hasta C_3), o -O-alquilo (C_1 hasta C_2).

Otro ejemplo del sustituyente Q 2.17 es:



(2.17E)

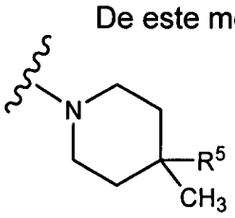
Otro ejemplo del sustituyente Q 2.17 es:



(2.17F)

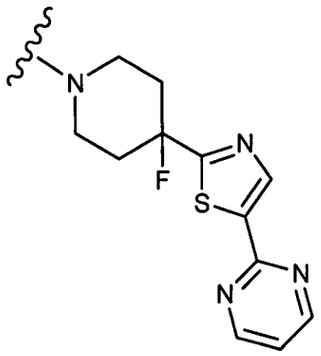
donde R^{5A} es alquilo (por ej., -alquilo (C_1 hasta C_6), tales como, por ejemplo, -alquilo (C_1 hasta C_3), o -alquilo (C_1 hasta C_2)).

De este modo, otro ejemplo del sustituyente Q 2.17 es:

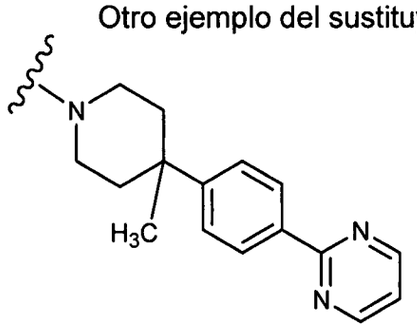


(2.17G)

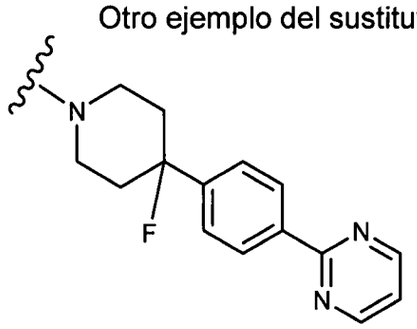
Otro ejemplo del sustituyente Q 2.17 es:



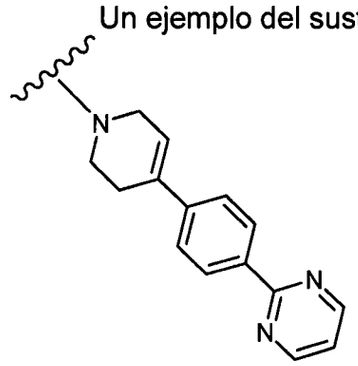
Otro ejemplo del sustituyente Q 2.17 es:



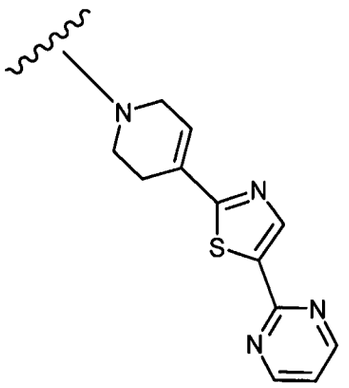
Otro ejemplo del sustituyente Q 2.17 es:



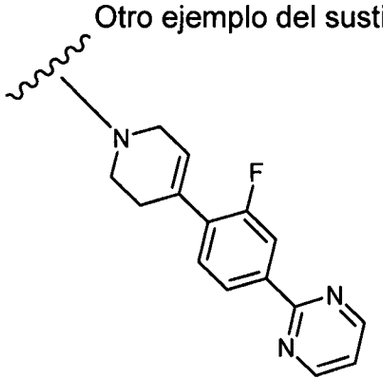
Un ejemplo del sustituyente Q 2.2 es:



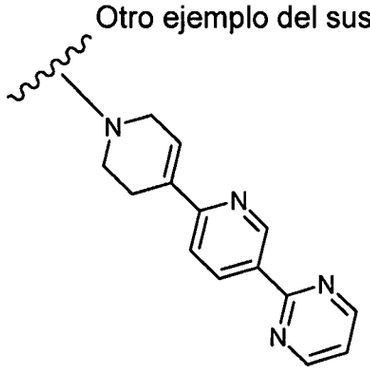
Otro ejemplo del sustituyente Q 2.2 es:



Otro ejemplo del sustituyente Q 2.2 es:

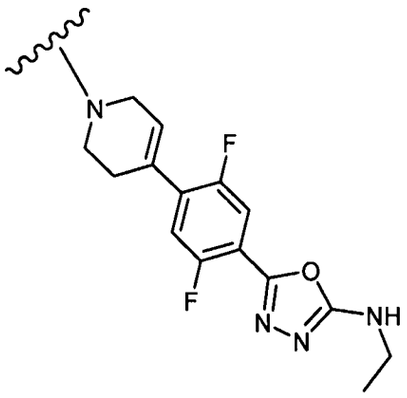


Otro ejemplo del sustituyente Q 2.2 es:

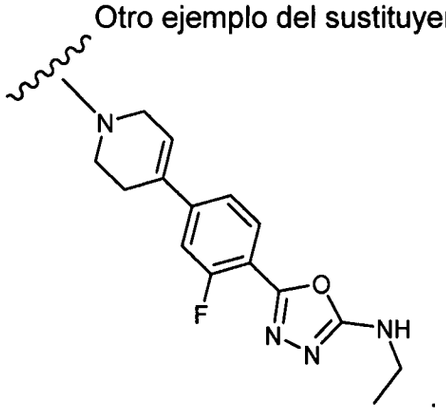


Otro ejemplo del sustituyente Q 2.2 es:

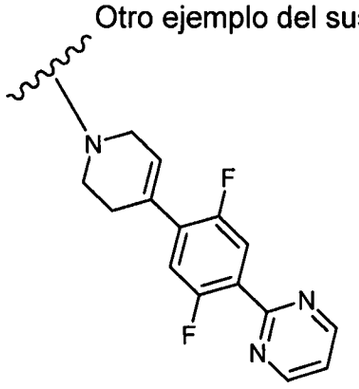
536



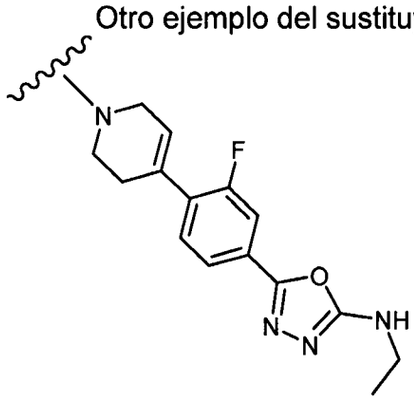
Otro ejemplo del sustituyente Q 2.2 es:



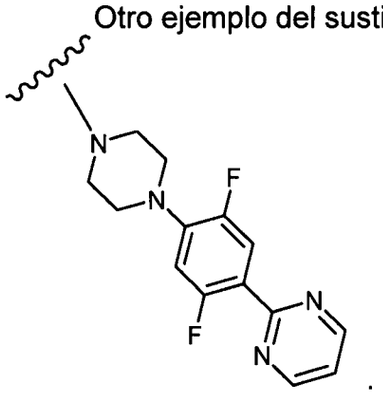
Otro ejemplo del sustituyente Q 2.2 es:



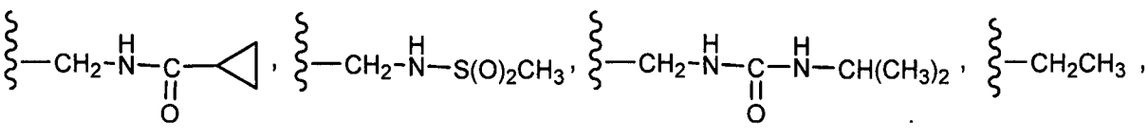
Otro ejemplo del sustituyente Q 2.2 es:

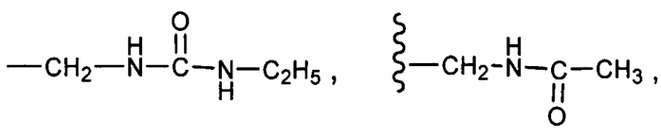


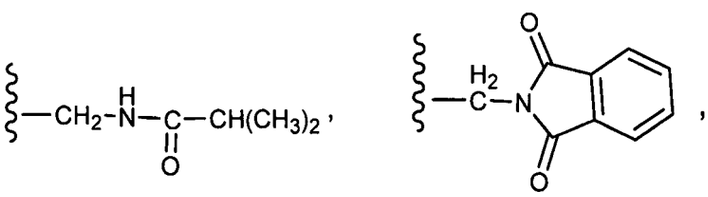
Otro ejemplo del sustituyente Q 2.6 es:

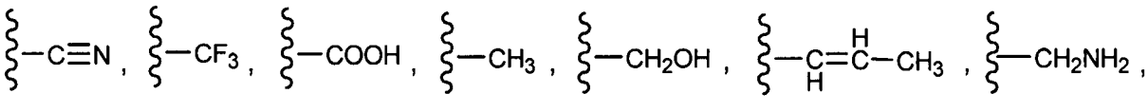


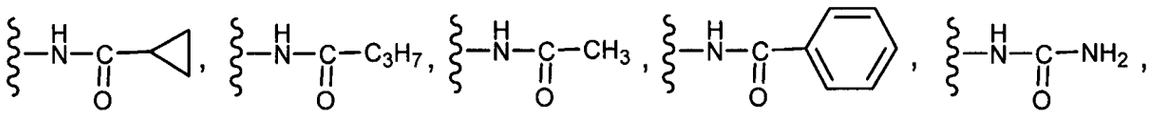
Ejemplos de R^1 para los compuestos de esta invención (por ej., compuestos de fórmulas 1.0, 1.0A1, 1.0B1, 1.0C1, 1,1, 1,1A, 1,2, 1,2A, 1,3 y 1,3A) incluyen, sin carácter limitativo:

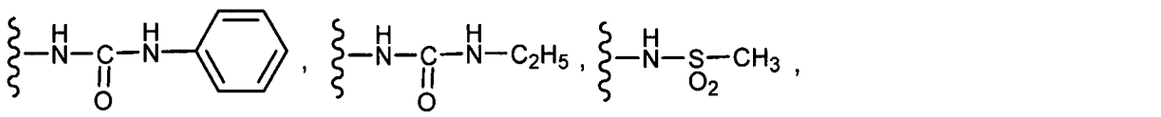


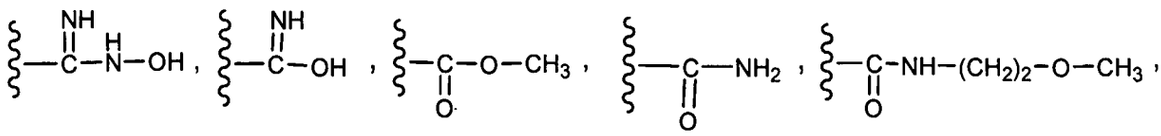


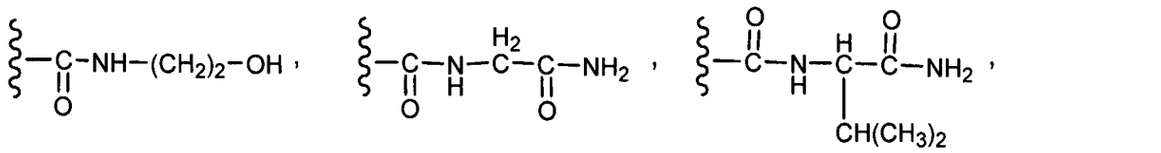


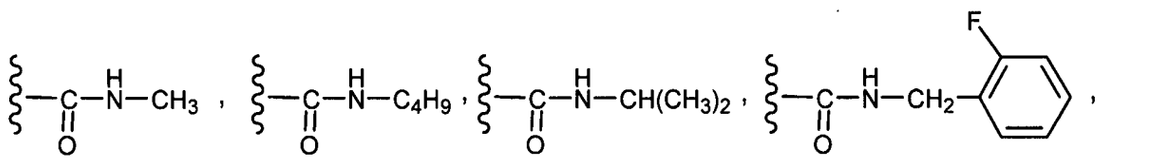


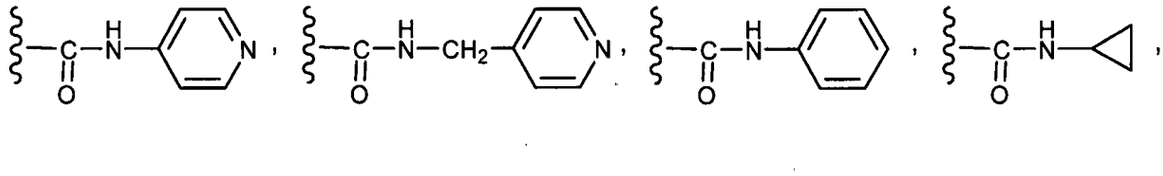


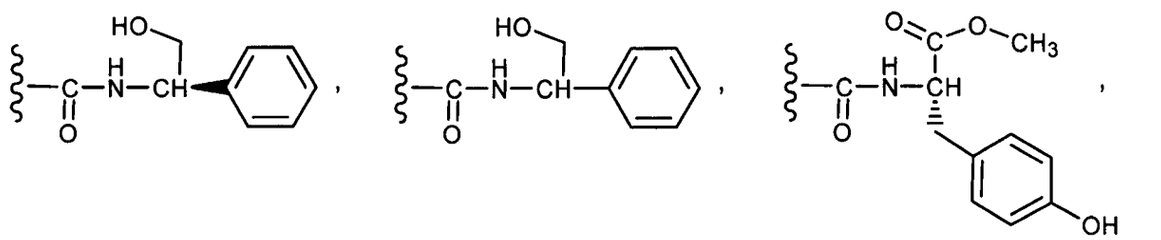


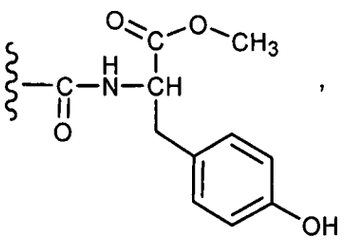
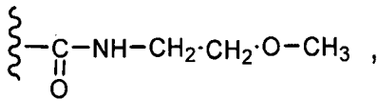
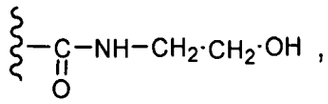
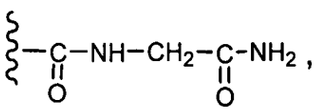
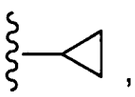
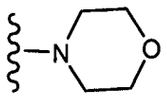
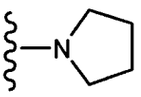
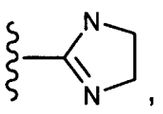
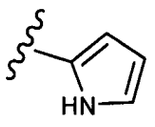
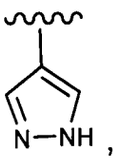
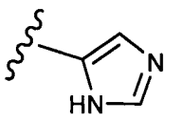
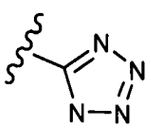
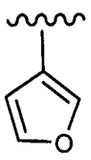
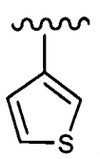
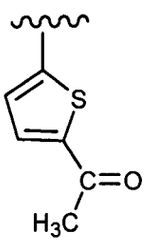
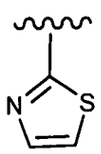
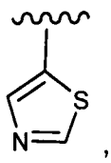
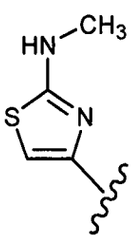
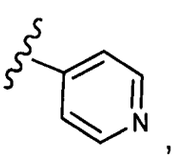
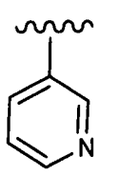
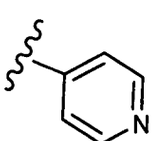
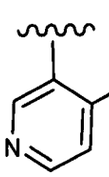
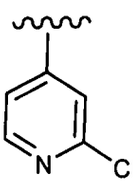
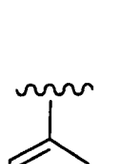
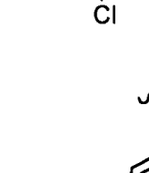


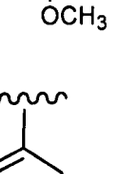









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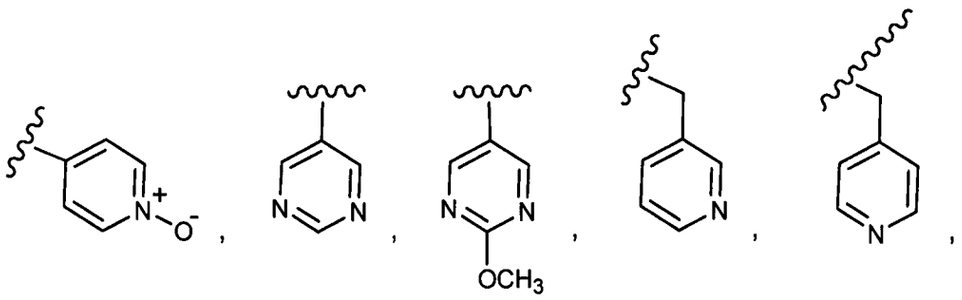
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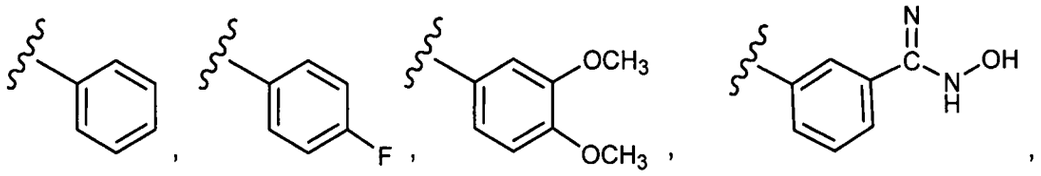
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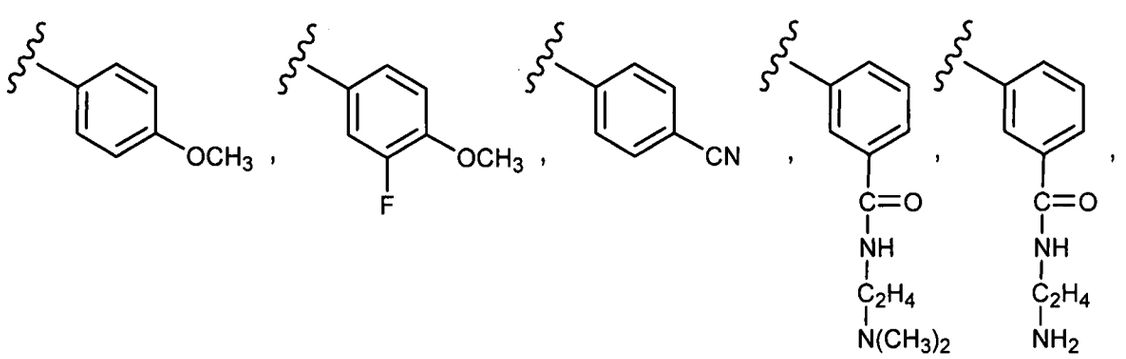
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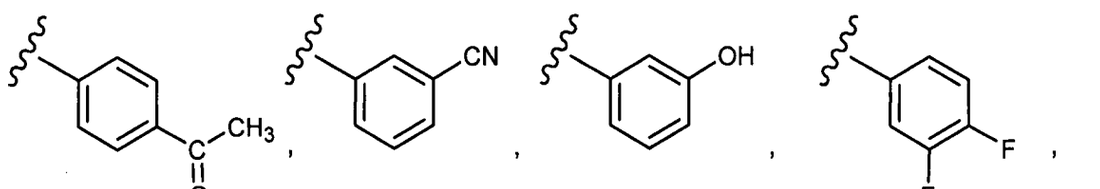
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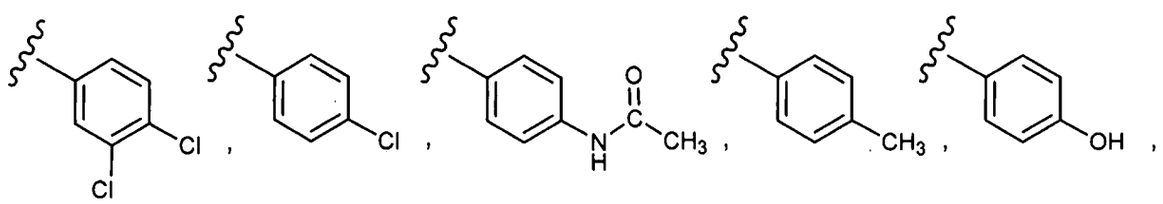
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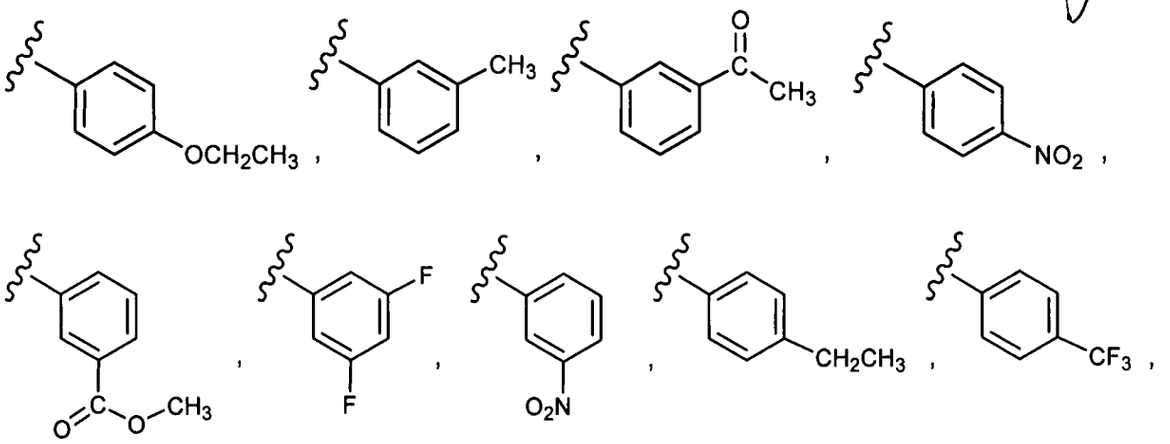


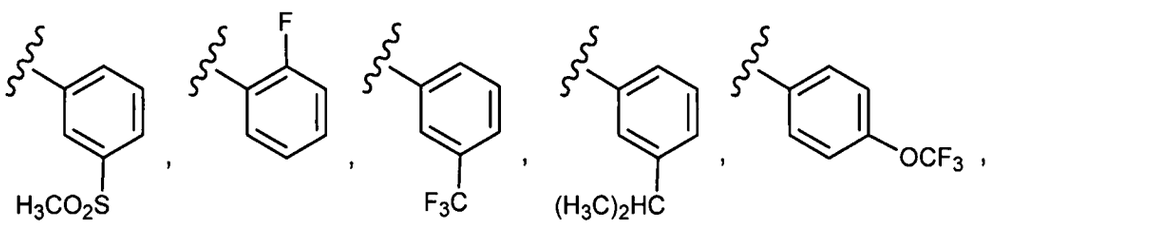


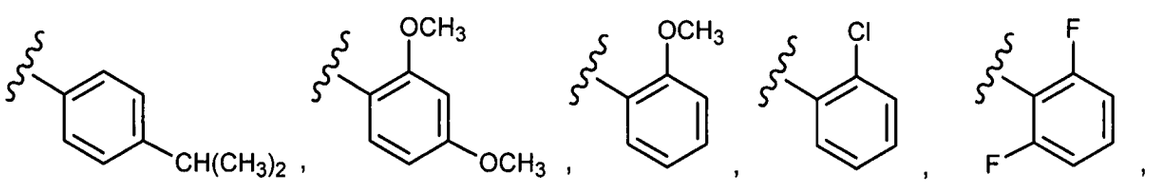


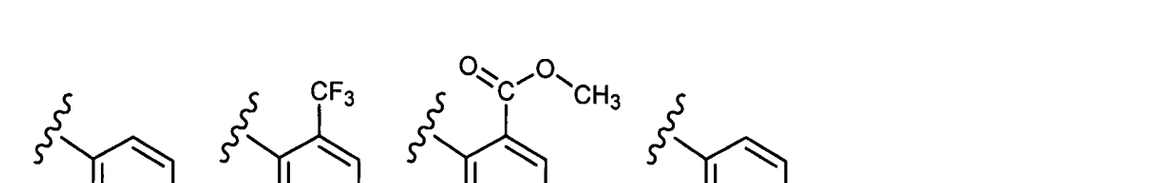


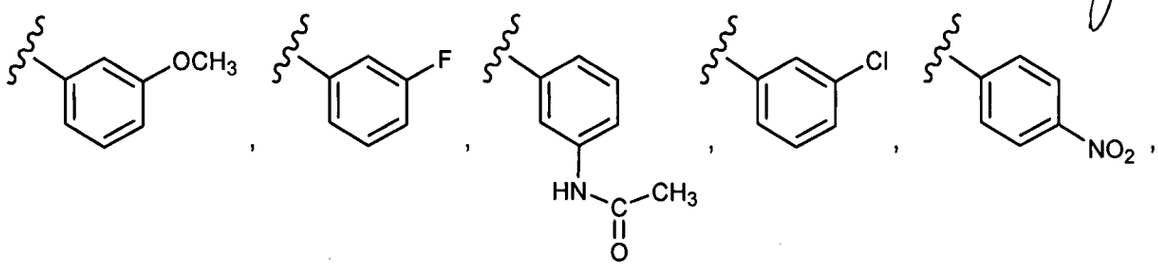


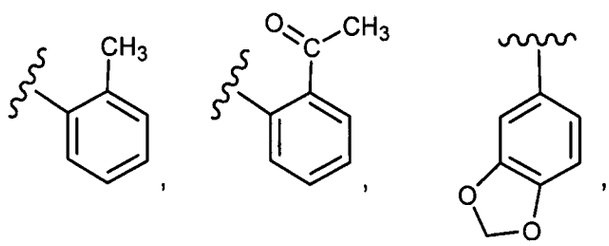


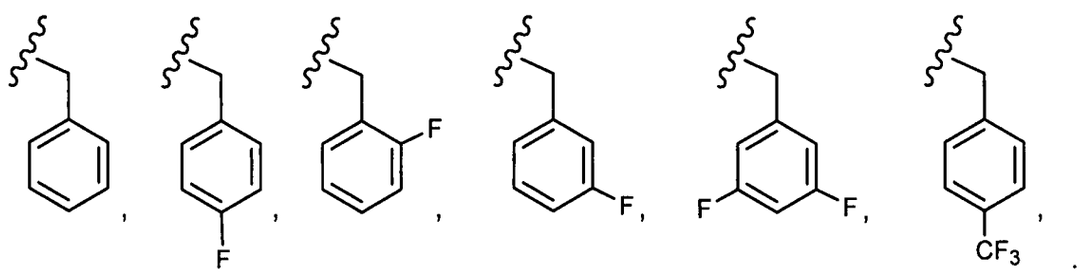


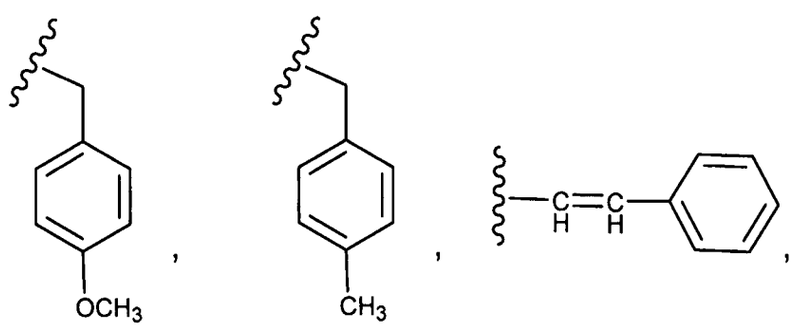


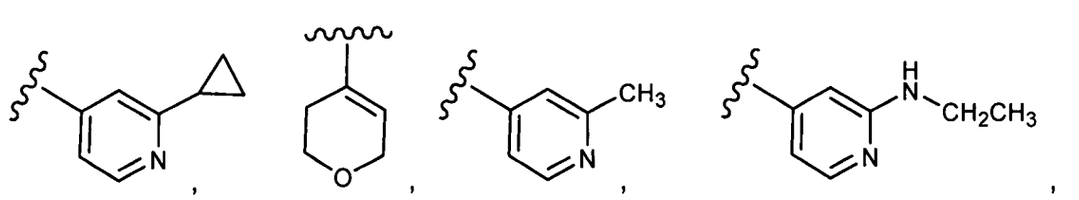


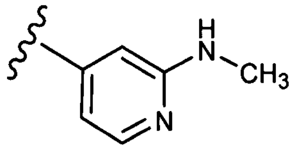
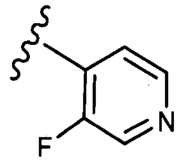
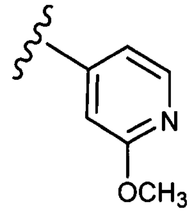


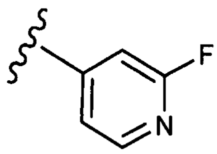
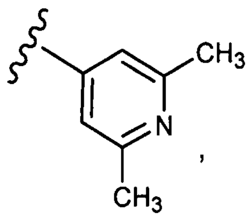
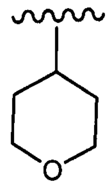
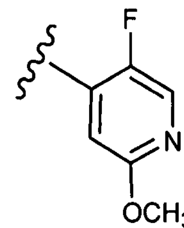


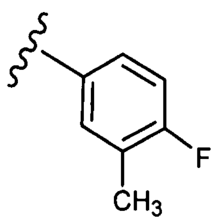
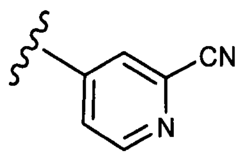
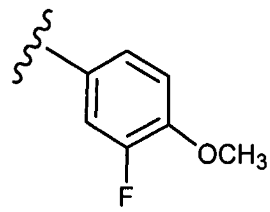
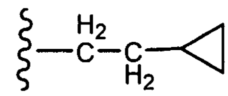


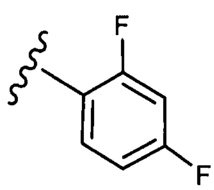
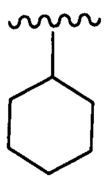
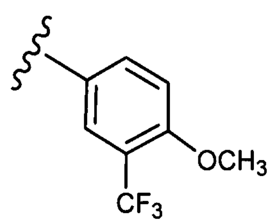
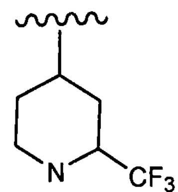


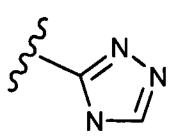
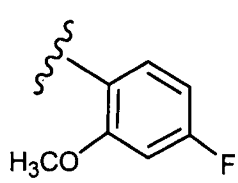
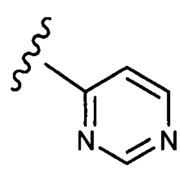
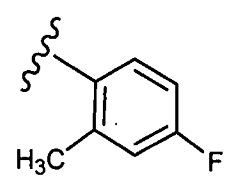


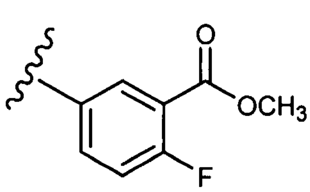
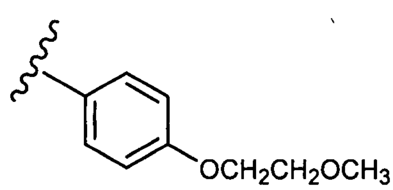
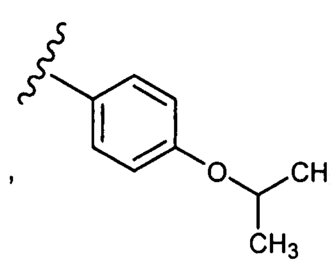

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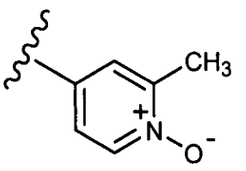
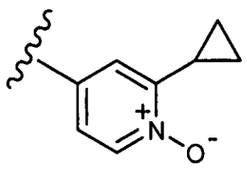
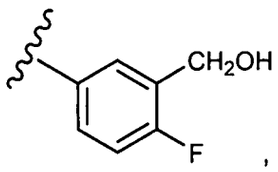
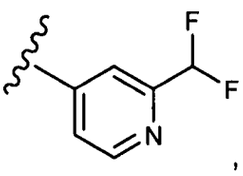
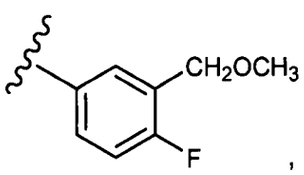
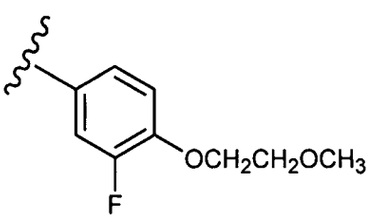
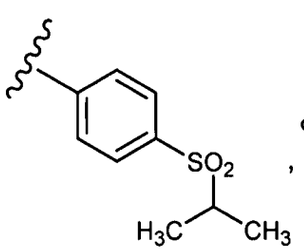
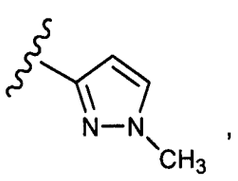
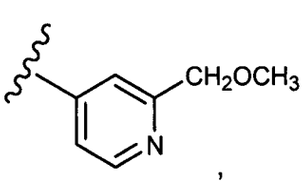
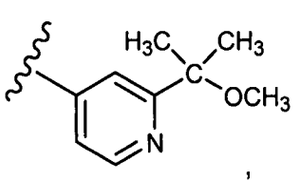
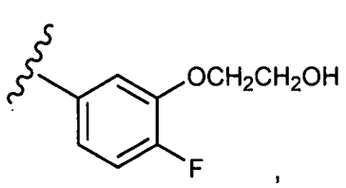
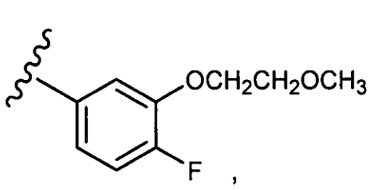
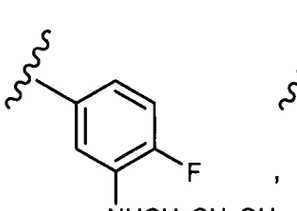
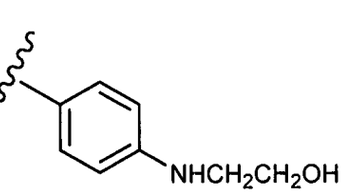
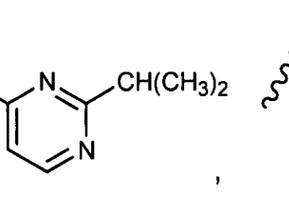
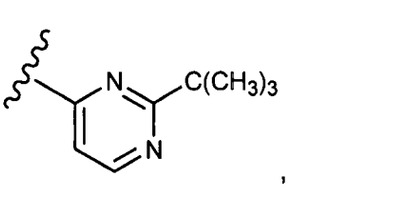

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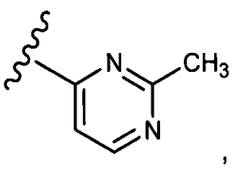
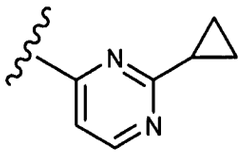
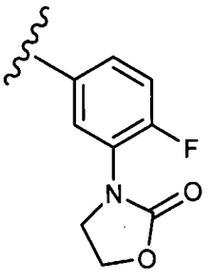
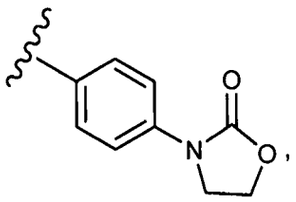

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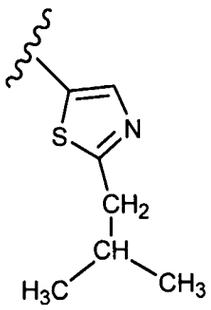
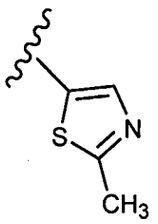
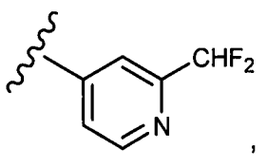
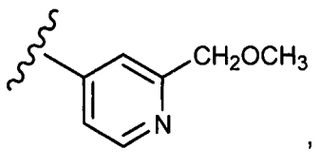

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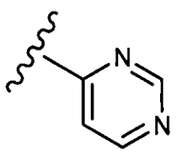
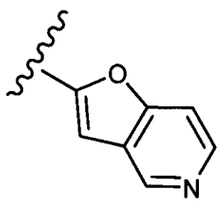

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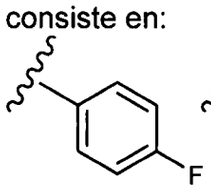
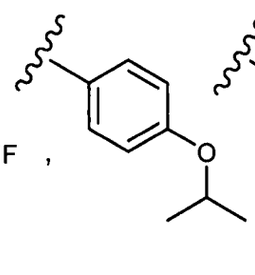
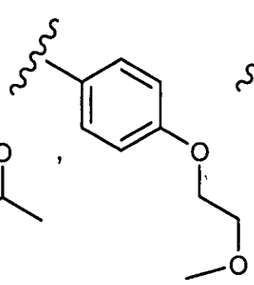
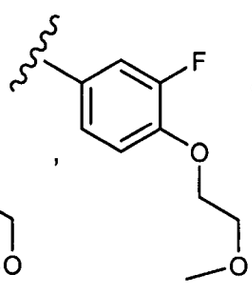
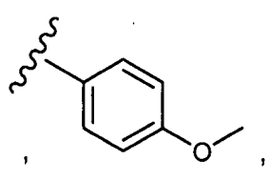

















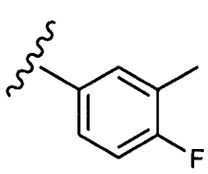
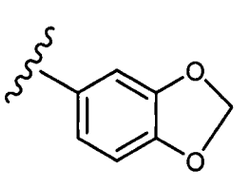
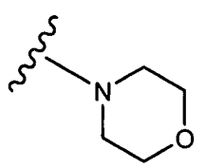
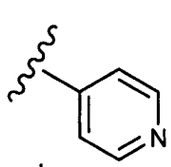
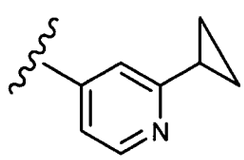

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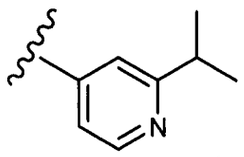
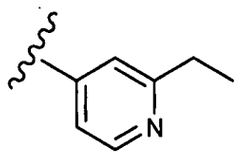
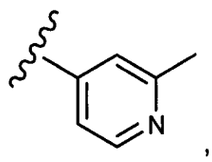
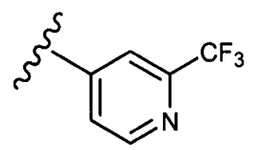
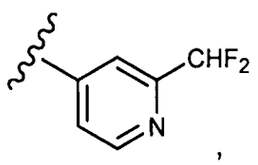
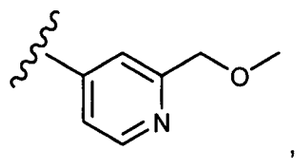
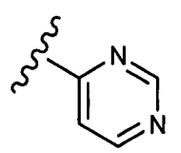
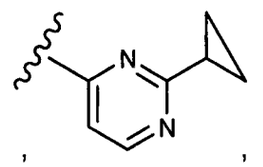
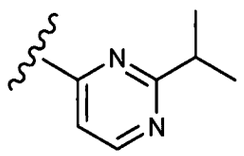
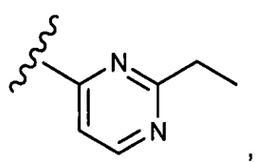
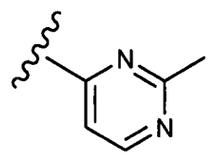
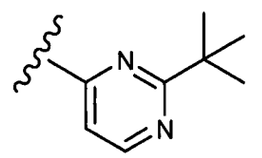


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En una realización de esta invención, R^1 se selecciona del grupo que consiste en:

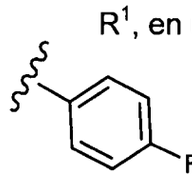

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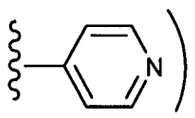

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R^1, en una realización de esta invención, es arilo (por ej., fenilo).

R^1, en una realización de esta invención es arilo sustituido, tales como,

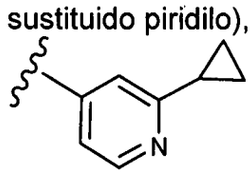

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R^1, en otra realización de esta invención, es heteroarilo (por ej., en una realización R^1 es piridilo N-óxido, y en otra realización R^1 es piridilo, tales como

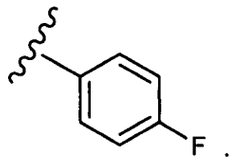

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R^1, en una realización de esta invención, es heteroarilo sustituido (por ej., sustituido piridilo).

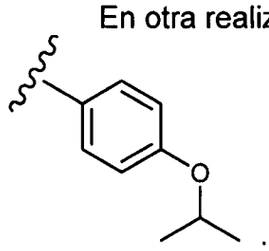
R^1, en una realización de esta invención, es heteroarilo sustituido (por ej., sustituido piridilo), tales como, por ejemplo:


.

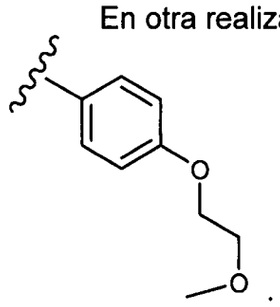
En otra realización de esta invención R^1 es:



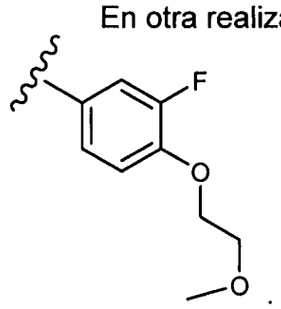
En otra realización de esta invención R^1 es:



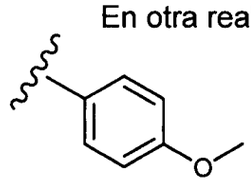
En otra realización de esta invención R^1 es:



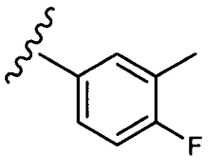
En otra realización de esta invención R^1 es:



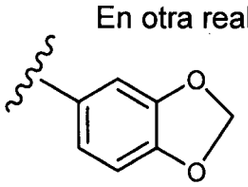
En otra realización de esta invención R^1 es:



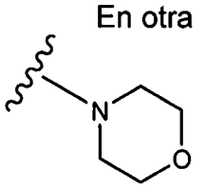
En otra realización de esta invención R^1 es:



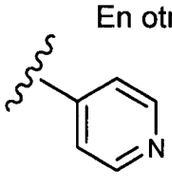
En otra realización de esta invención R^1 es:



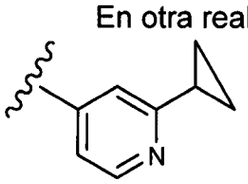
En otra realización de esta invención R^1 es:



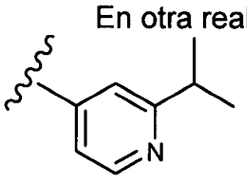
En otra realización de esta invención R^1 es:



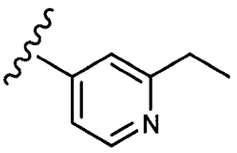
En otra realización de esta invención R^1 es:



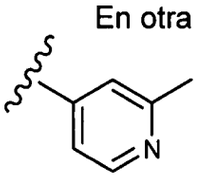
En otra realización de esta invención R^1 es:



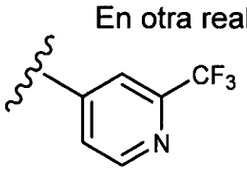
En otra realización de esta invención R^1 es:



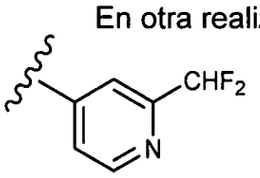
En otra realización de esta invención R^1 es:



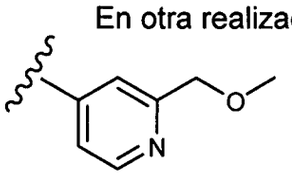
En otra realización de esta invención R^1 es:



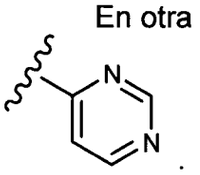
En otra realización de esta invención R^1 es:



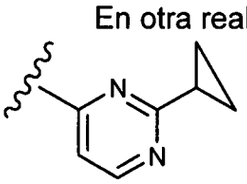
En otra realización de esta invención R^1 es:



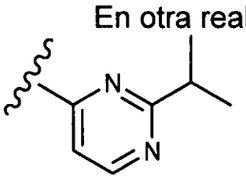
En otra realización de esta invención R^1 es:



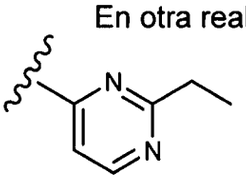
En otra realización de esta invención R^1 es:



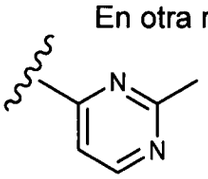
En otra realización de esta invención R^1 es:



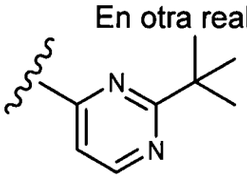
En otra realización de esta invención R^1 es:



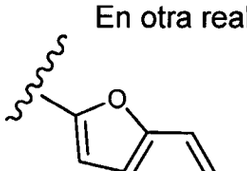
En otra realización de esta invención R^1 es:



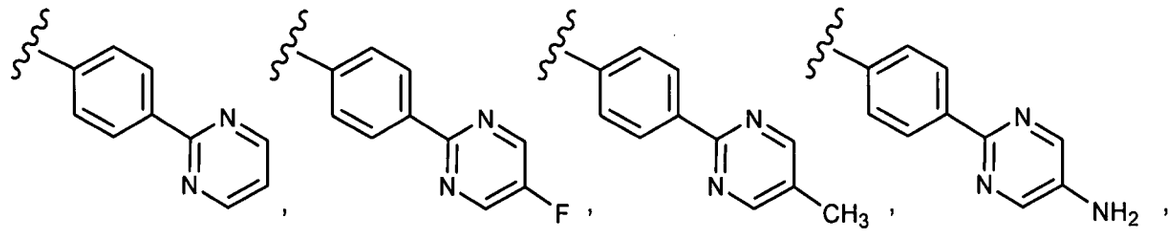
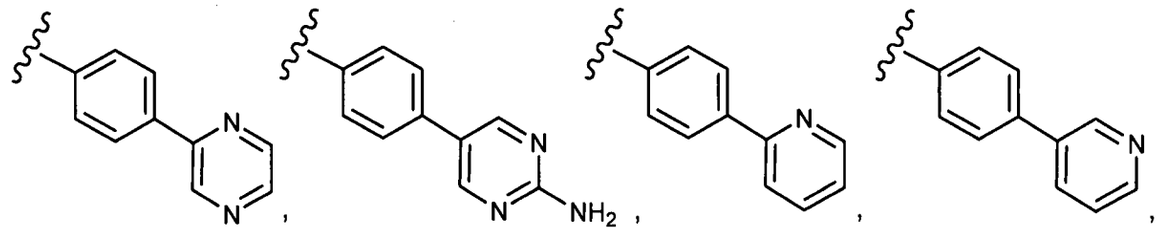
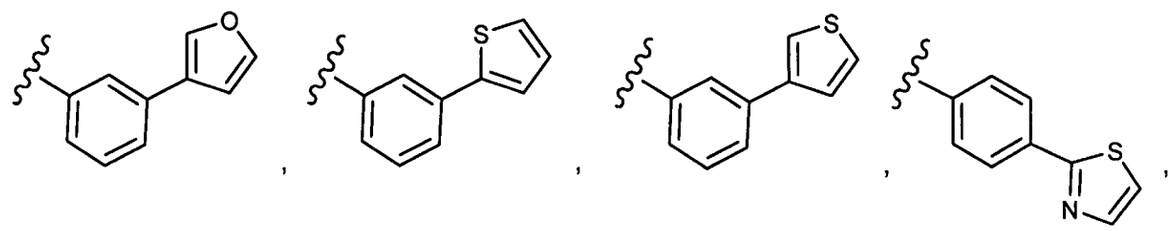
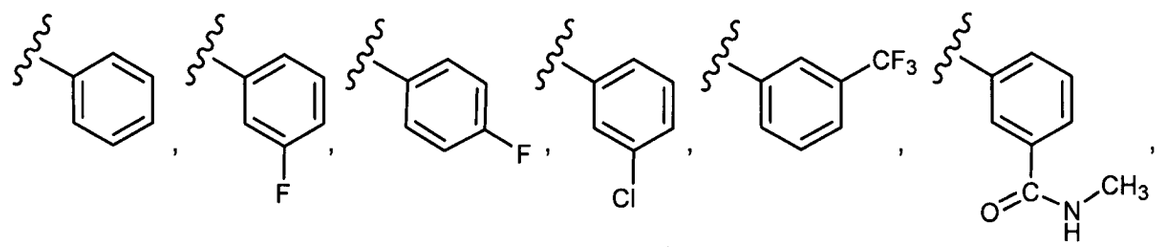
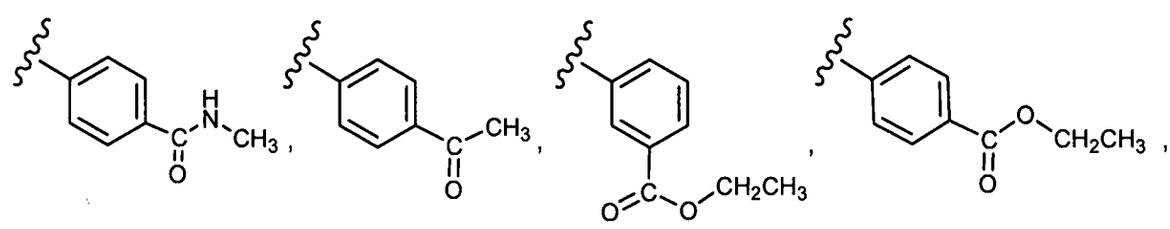
En otra realización de esta invención R^1 es:

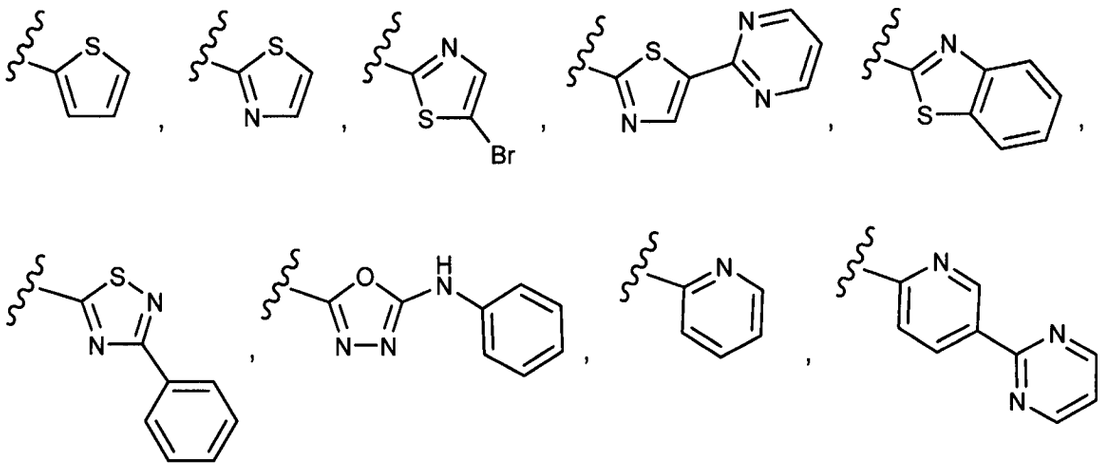


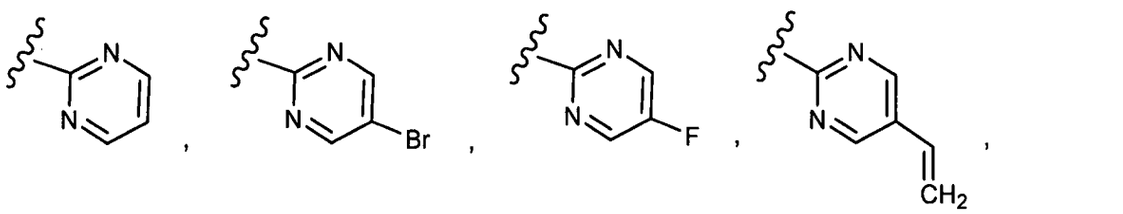
En otra realización de esta invención R^1 es:

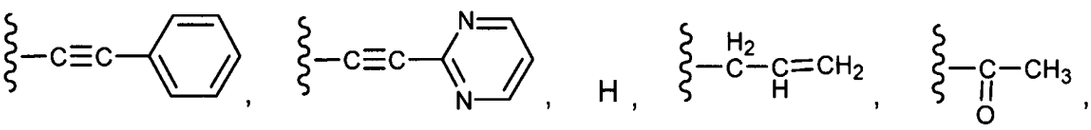


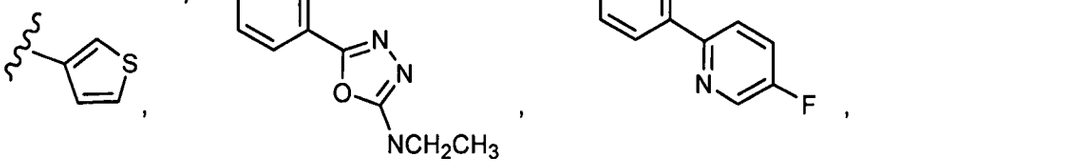
Ejemplos de R^5 para los compuestos de esta invención (por ej., compuestos de fórmulas 1.0, 1.0A1, 1.0B1, 1.0C1, 1.1, 1.1A, 1.2, 1.2A, 1,3 y 1,3A) incluyen sin carácter limitativo:

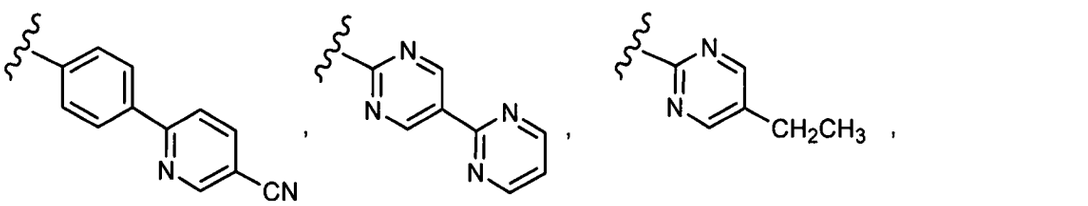








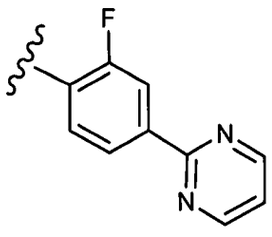
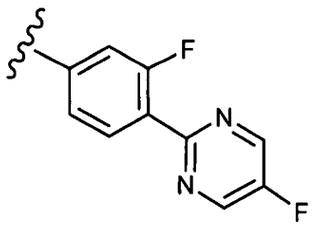
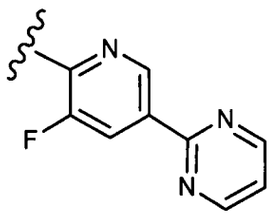
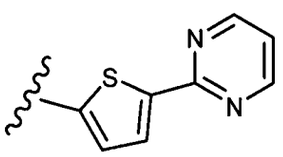
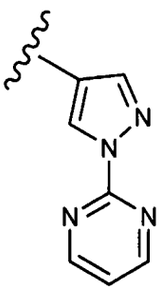
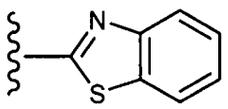
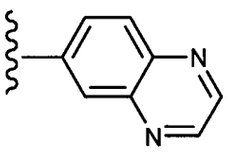
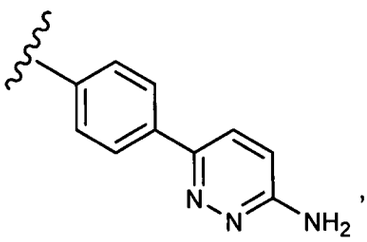
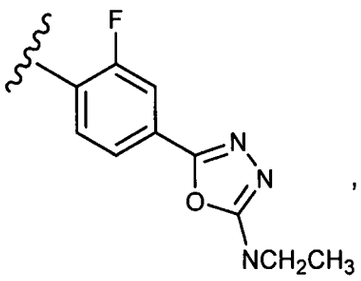
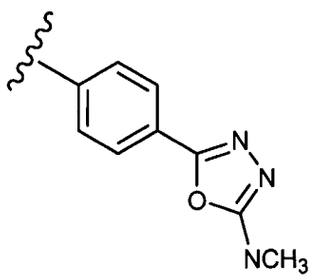
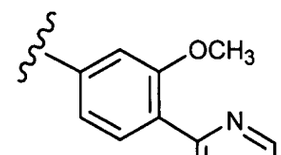
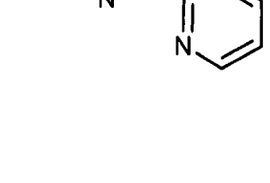
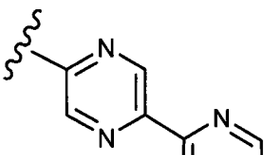




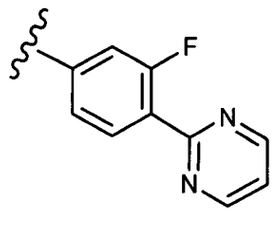
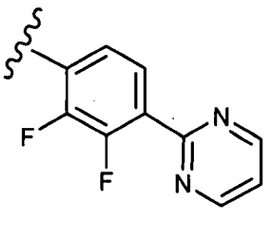
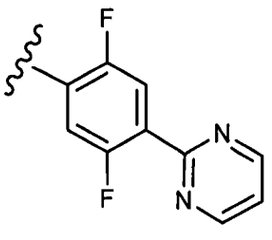




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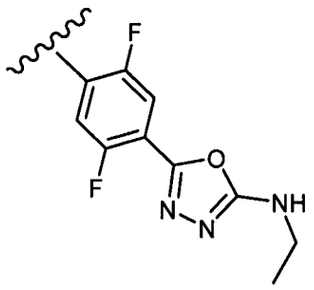
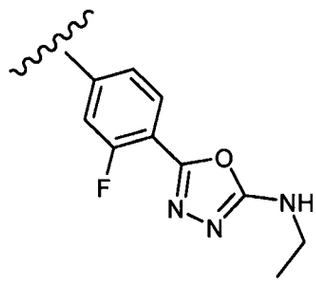
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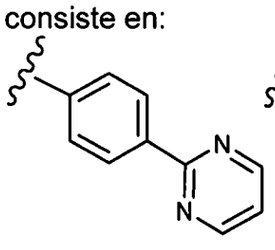
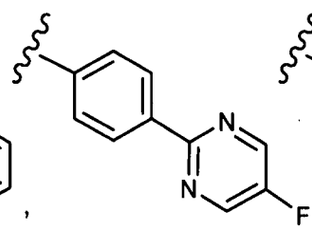
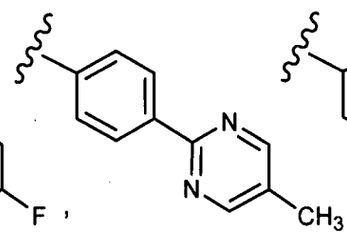
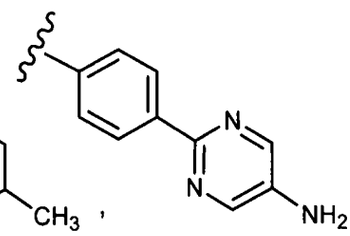
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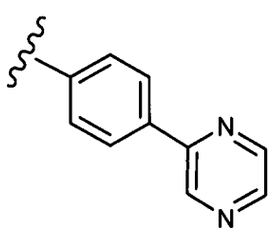
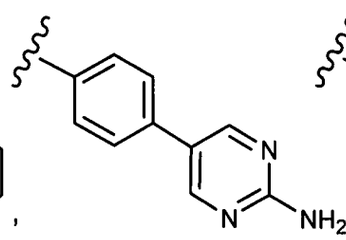
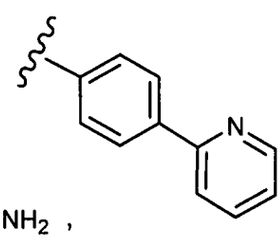
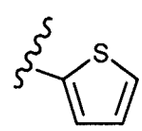
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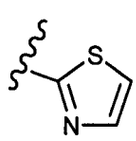
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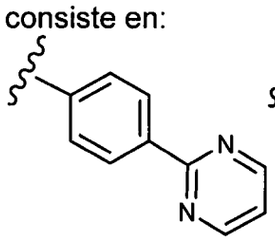
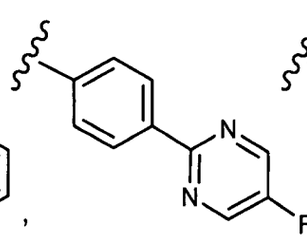
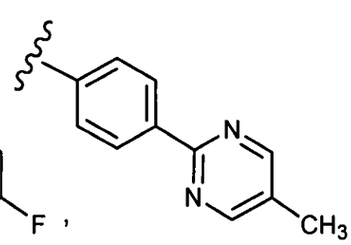
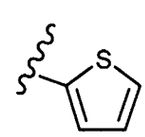
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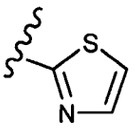

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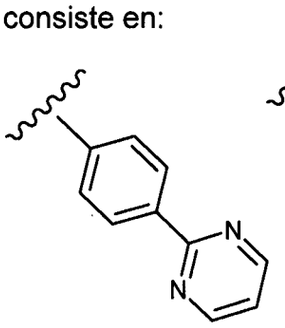
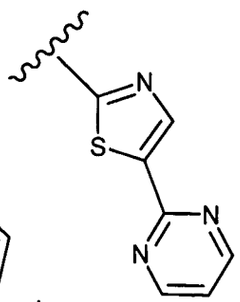
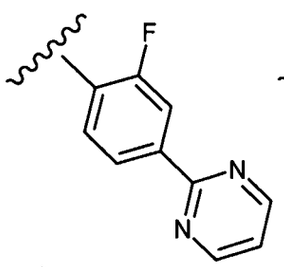
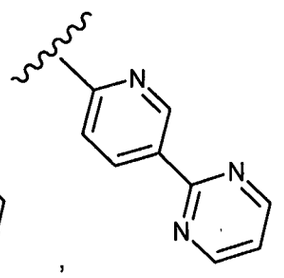
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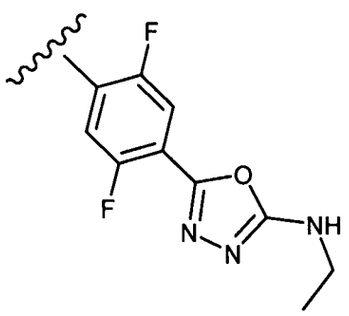
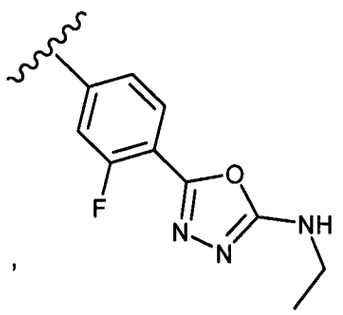
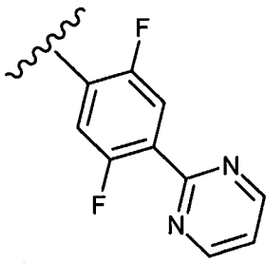
En otra realización de esta invención, R^5 se selecciona del grupo que consiste en:

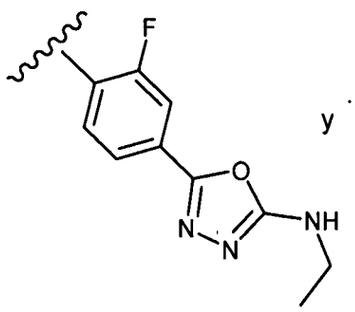
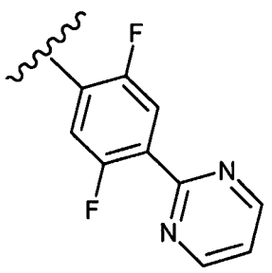

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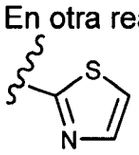
En otra realización de esta invención, R^5 se selecciona del grupo que consiste en:

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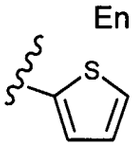
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 y  .

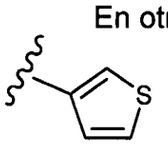
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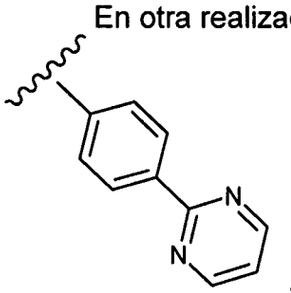
En otra realización de esta invención, R^5 es:



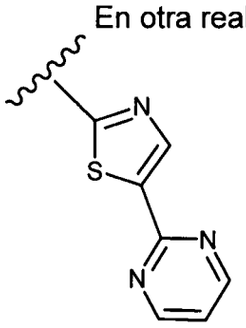
En otra realización de esta invención, R^5 es:



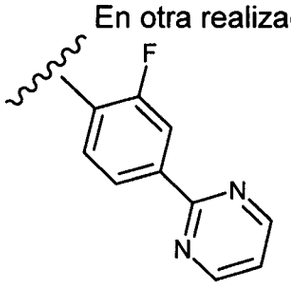
En otra realización de esta invención, R^5 es:



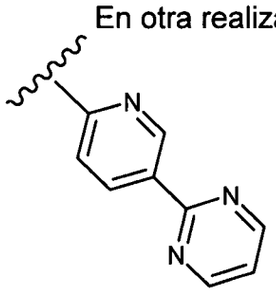
En otra realización de esta invención, R^5 es:



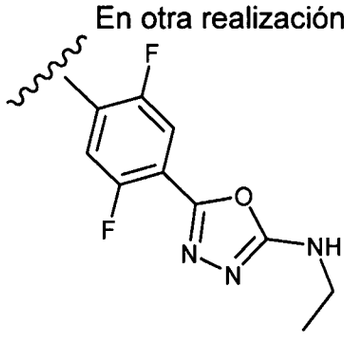
En otra realización de esta invención, R^5 es:



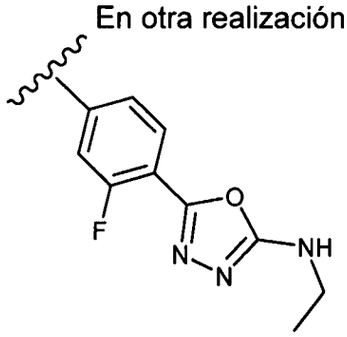
En otra realización de esta invención, R^5 es:



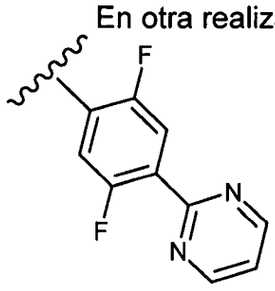
En otra realización de esta invención, R^5 es:



En otra realización de esta invención, R^5 es:

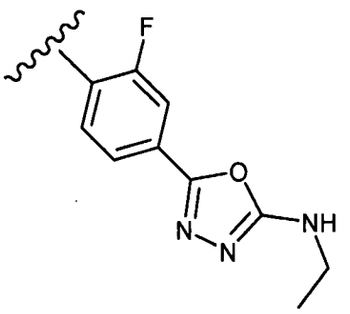


En otra realización de esta invención, R^5 es:

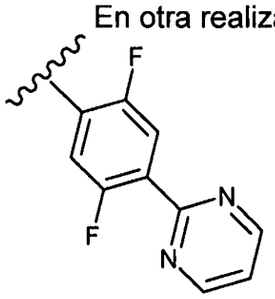


En otra realización de esta invención, R^5 es:

560



En otra realización de esta invención, R^5 es:



R^2, en una realización de esta invención, es $-(CH_2)_mR^{11}$, en el cual R^{11} es $-OR^{10}$.

R^2, en otra realización de esta invención, es $-(CH_2)_mR^{11}$, en el cual R^{11} es $-OR^{10}$, y R^{10} es H o alquilo.

R^2, en otra realización de esta invención, es $-(CH_2)_mR^{11}$, en el cual R^{11} es $-OR^{10}$, y R^{10} alquilo (por ej., metilo).

R^2, en otra realización de esta invención, es $-(CH_2)_mR^{11}$, donde m es 1 y R^{11} es $-OR^{10}$.

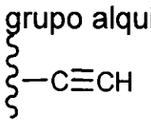
R^2, en otra realización de esta invención, es $-(CH_2)_mR^{11}$, donde m es 1, R^{11} es $-OR^{10}$, y R^{10} es H o alquilo.

R^2, en otra realización de esta invención, es $-(CH_2)_mR^{11}$, donde m es 1, R^{11} es $-OR^{10}$, y R^{10} alquilo.

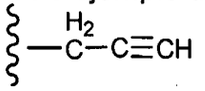
R^2, en otra realización de esta invención, es $-(CH_2)_mR^{11}$, donde m es 1, R^{11} es $-OR^{10}$, y R^{10} metilo (es decir, R^2 es $-CH_2OCH_3$).

R^2, en otra realización de esta invención, es $-OR^{23}$ donde R^{23} es alquilo, y dicho alquilo es metilo (es decir, R^2 es $-OCH_3$).

R^2, en otra realización de esta invención, es alquinilo. Un ejemplo de un grupo alquinilo es etinilo:



Otro ejemplo de un grupo alquinilo es propinilo:



R^2, en otra realización de esta invención, es alquenilo. Un ejemplo de un grupo alquenilo es $-CH_2-CH=CH_2$.

R^2, en otra realización de esta invención, es $-OCH_3$.

R^2, en otra realización de esta invención, es $-S(O)_t$-alquilo.

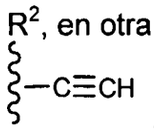
R^2, en otra realización de esta invención, es -S-alquilo (es decir, t es 0) tales como, por ejemplo, $-S-CH_3$.

R^2, en otra realización de esta invención, es $-S(O)_2$-alquilo (es decir, t es 2) tales como, por ejemplo, $-S(O)_2CH_3$.

R^2, en otra realización de esta invención, es $-SCH_3$.

R^2, en otra realización de esta invención, es $-S(O)_2CH_3$.

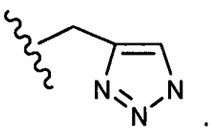
R^2, en otra realización de esta invención, es etinilo



R^2, en otra realización de esta invención, es $-CH_2OCH_3$.

Con preferencia R^2 se selecciona del grupo que consiste en: etinilo, $-OCH_3$, y $-CH_2OCH_3$.

Ejemplos adicionales del grupo R^2 $-(CH_2)_mR^{11}$ incluyen, sin carácter limitativo $-CH_2OH$, $-CH_2CN$, $-CH_2OC_2H_5$, $-(CH_2)_3OCH_3$, $-CH_2F$ y $-CH_2$-triazolilo, tales como,



Ejemplos adicionales de R^2 incluyen, sin carácter limitativo, H, $-CH_2$-morfolinilo, $-SCH_3$, $-OC_2H_5$, $-OCH(CH_3)_2$, $-CH_2N(CH_3)_2$, -CN, $-CH(OH)CH_3$, $-C(O)CH_3$, $-CH_2C{\equiv}CCH_3$, $-CH(CH_3)_2$, $-C(CH_3){=}CH_2$, $-C(CH_3){=}NOCH_3$, $-C(CH_3){=}NOH$, $-C(CH_3){=}NNHC(O)CH_3$, $-NH_2$, -NHC(O)H, $-NHCH_3$, $-CH_2$-O-CH_2-ciclopropilo, $-CH_2$-O-CHF_2, $-OCHF_2$, $-CHF_2$, $-CH_2C(CH_3){=}CH_3$, $-CH_2CH_2CH_3$, $-N(CH_3)_2$, $-CH_2CH_3$, $-CF_3$, $-CH{=}CH_2$, y $-C(OH)(CH_3)_2$.

R^3, en una realización de esta invención, se selecciona en forma independiente del grupo que consiste en: H y alquilo.

R^3, en otra realización de esta invención, se selecciona en forma independiente del grupo que consiste en: H y metilo.

R^3, en otra realización de esta invención, es H.

R^4, en una realización de esta invención, es H.

R^4, en otra realización de esta invención, se selecciona del grupo que consiste en: H y alquilo.

R^4, en otra realización de esta invención, se selecciona del grupo que consiste en: H y metilo.

R^6, en una realización de esta invención, es R^6 H.

R^7, en una realización de esta invención, se selecciona en forma independiente del grupo que consiste en: H y alquilo.

R^7, en otra realización de esta invención, se selecciona en forma independiente del grupo que consiste en: H y metilo.

R^7, en una realización de esta invención, es H.

R^8, en una realización de esta invención, es H.

Y^1, en una realización de esta invención, es carbono.

Y^2, en una realización de esta invención, es carbono.

Y^3 en una realización de esta invención, es carbono.

Y^1, Y^2 y Y^3, en una realización de esta invención, sobre carbono.

Una realización de esta invención se refiere a un compuesto de fórmula 1.0, con preferencia un compuesto de fórmula 1.0C1 y con mayor preferencia un compuesto de fórmula 1.0C, (por ej., 1.1, 1.1A, 1.2, 1.2A, 1.3 o 1.3A) en el cual el sustituyente Q es 2,16, y cada R^3, R^4, y R^7 se selecciona en forma independiente del grupo que consiste en: H y metilo.

Una realización de esta invención se refiere a un compuesto de fórmula 1.0, con preferencia un compuesto de fórmula 1.0C1 y con mayor preferencia un compuesto de fórmula 1.0C, (por ej., 1.1, 1.1A, 1.2, 1.2A, 1.3 o 1.3A) en el cual el sustituyente Q es 2,16A, y cada R^3, R^4, y R^7 se selecciona en forma independiente del grupo que consiste en: H y metilo.

Una realización de esta invención se refiere a un compuesto de fórmula 1.0, con preferencia un compuesto de fórmula 1.0C1 y con mayor preferencia un compuesto de fórmula 1.0C, (por ej., 1.1, 1.1A, 1.2, 1.2A, 1.3 o 1.3A) en el cual el sustituyente Q es 2,16B, y cada R^3, R^4, y R^7 se selecciona en forma independiente del grupo que consiste en: H y metilo.

Una realización de esta invención se refiere a un compuesto de fórmula 1.0, con preferencia un compuesto de fórmula 1.0C1 y con mayor preferencia un compuesto de fórmula 1.0C, (por ej., 1.1, 1.1A, 1.2, 1.2A, 1.3 o 1.3A) en el cual el sustituyente Q es 2,16, y cada R^3, R^4, y R^7 es H.

Una realización de esta invención se refiere a un compuesto de fórmula 1.0, con preferencia un compuesto de fórmula 1.0C1 y con mayor preferencia un compuesto de fórmula 1.0C, (por ej., 1.1, 1.1A, 1.2, 1.2A, 1.3 o 1.3A) en el cual el sustituyente Q es 2,16A, y cada R^3, R^4, y R^7 es H.

Una realización de esta invención se refiere a un compuesto de fórmula 1.0, con preferencia un compuesto de fórmula 1.0C1 y con mayor preferencia un compuesto de fórmula 1.0C, (por ej., 1.1, 1.1A, 1.2, 1.2A, 1.3 o 1.3A) en el cual el sustituyente Q es 2,16B, y cada R^3, R^4, y R^7 es H.

Los compuestos de esta invención inhiben la actividad de ERK1 y ERK2 De este modo, esta invención provee, además, un método para inhibir ERK en mamíferos, especialmente en humanos por medio de la administración de una cantidad efectiva (por ej., una cantidad terapéuticamente efectiva) de uno o más (por ej., uno) compuestos de esta invención. La administración de los compuestos de esta invención a pacientes, para inhibir ERK1 y/o ERK2, es útil en el tratamiento de cáncer.

En cualquiera de los métodos de tratamiento para el cáncer descritos aquí, salvo que se indique de otro modo, los métodos can incluyen en forma opcional la administración de una cantidad efectiva de uno o más (por ej., 1, 2 o 3, o 1 o 2, o 1) agentes quimioterapéuticos. Los agentes quimioterapéuticos pueden administrarse en forma concurrente o secuencial con los compuestos de esta invención.

Los métodos de tratamiento para el cáncer descritos aquí incluyen métodos en los cuales se usa una combinación de fármacos (es decir, compuestos, o principio farmacéuticamente activos, o composición farmacéuticas) (es decir, los métodos de tratamiento para el cáncer de esta invención incluyen terapias de combinación). Aquellas personas con experiencia en el arte apreciarán que las drogas se administran en general en forma individual como una composición farmacéutica. El uso de una composición farmacéutica que comprende más de una droga se encuentra dentro del alcance de esta invención.

En cualquiera de los métodos de tratamiento para el cáncer descritos aquí, salvo que se indique de otro modo, los métodos pueden incluir en forma opcional

la administración de una cantidad efectiva de terapia de rayos. Para la terapia de rayos, se prefiere la radiación γ.

Ejemplos de cánceres que pueden tratarse con la aplicación de los métodos de esta invención incluyen, sin carácter limitativo: (A) cáncer de pulmón (por ej., adenocarcinoma de pulmón y cáncer de pulmón de células no pequeñas), (B) cáncer de páncreas (por ej., carcinoma de páncreas tales como, por ejemplo, carcinoma de páncreas exócrino), (C) cáncer de colon (por ej., carcinomas colorrectales, tales como, por ejemplo, adenocarcinoma de colon y adenoma de colon), (D) leucemias mieloides (por ejemplo, leucemia mielógena aguda (LMA), CML, y CMML), (E) cáncer de tiroides, (F) síndrome mielodisplásico (MDS), (G) carcinoma de vejiga, (H) carcinoma epidérmico, (I) melanoma, (J) cáncer de mama, (K) cáncer de próstata, (L) cánceres de cuello y cabeza (por ej., cáncer de células escamosas de cuello y cabeza), (M) cáncer de ovario, (N) cánceres de cerebro (por ej., gliomas, tales como glioma blastoma multiforme), (O) cánceres de origen mesenquimal (por ej., fibrosarcomas y rabdomiosarcomas), (P) sarcomas, (Q) tetracarcinomas, (R) nuroblastomas, (S) carcinomas de riñón, (T) hepatomas, (U) linfoma de no Hodgkin, (V) mieloma múltiple, y (W) carcinoma de tiroides anaplásico.

Agentes quimioterapéuticos (agente anti-neoplásico) incluyen sin carácter limitativo: agentes que afectan los microtúbulos, agentes alquilantes, antimetabolitos, productos naturales y sus derivados, hormonas y esteroides (incluyendo análogos sintéticos), y sintéticos.

Ejemplos de agentes alquilantes (incluyendo mostazas de nitrógeno, derivados de etilenimina, alquil sulfonatos, nitrosoureas y triazenos) incluyen: Mostaza de Uracilo, Clormetina, Ciclofosfamida (Cytoxan®), Ifosfamida, Melphalan, Clorambucil, Pipobroman, Trietilen-melamina, Trietilentiofosforamina, Busulfan, Carmustina, Lomustina, Streptozocin, Dacarbazina, y Temozolomida.

Ejemplos de antimetabolitos (incluyendo antagonistas del ácido fólico, análogos de pirimidina, análogos de purina e inhibidores de adenosina desamidasa) incluyen: Metotrexato, 5-Fluorouracilo, Floxuridina, Citarabina, 6-Mercaptopurina, 6-Tioguanina, Fosfato de fludarabina, Pentostatina, y Gemcitabina.

Ejemplos de productos naturales y sus derivados (incluyendo alcaloides vinca, antibióticos anti-tumorales, enzimas, linfocinas y epipodofilotoxinas) incluyen: Vinblastina, Vincristina, Vindesina, Bleomycin, Dactinomicina, Daunorubicina, Doxorubicina, Epirubicina, Idarubicina, Paclitaxel (paclitaxel es un agente que afecta los microtúbulos y se encuentra en el mercado como Taxol®), derivados de Paclitaxel (por ej. taxotere), Mitramicina, Deoxico-formicina, Mitomicina-C, L-Asparaginasa, Interferones (especialmente IFN-a), Etoposida, y Teniposida.

Ejemplos de hormonas y esteroides (incluyendo análogos sintéticos) incluyen: 17α-Etinilestradiol, Dietilstilbestrol, Testosterona, Prednisona, Fluoximesterona, Propionato de dromostanolona, Testolactona, Megestrolacetato, Tamoxifeno, Metilprednisolona, Metil-testosterona, Prednisolona, Triamcinolona, Clorotrianiseno, Hidroxiprogesterona, Aminoglutetimida, Estramustina, Medroxiprogesteronacetato, Leuprolida, Flutamida, Toremifeno, y Zoladex.

Ejemplos de sintéticos (incluyendo complejos inorgánicos tales como complejos de coordinación de platino): Cisplatino, Carboplatino, Hidroxiurea, Amsacrina, Procarbazina, Mitotano, Mitoxantrona, Levamisol, y Hexametilmelamina.

Ejemplos de otros agentes quimioterapéuticos incluyen: Navelbeno, CPT-11, Anastrazol, Letrazol, Capecitabinbe, Reloxafina, y Droloxafina.

Un agente que afecta los microtúbulos (por ej., paclitaxel, un derivado de paclitaxel o un compuesto símil paclitaxel), como se usa aquí, es un compuesto

que interfiere con la mitosis celular, es decir, tiene un efecto anti-mitótico, al afectar la formación y/o acción de los microtúbulos. Dichos agentes pueden ser, por ejemplo, agentes estabilizadores de microtúbulos o agentes que interrumpen la formación de microtúbulos.

Agentes que afectan los microtúbulos, útiles en los métodos de esta invención, son conocidos para aquellas personas con experiencia en el arte e incluyen, sin carácter limitativo: Allocolchicina (NSC 406042), Halichondrina B (NSC 609395), Colchicina (NSC 757), derivados de Colchicina (por ej., NSC 33410), Dolastatin 10 (NSC 376128), Maitansina (NSC 153858), Rizoxina (NSC 332598), Paclitaxel (Taxol®, NSC 125973), derivados del Paclitaxel (por ej., Taxotere, NSC 608832), Tiocolquicina (NSC 361792), Tritil Cisteína (NSC 83265), Sulfato de Vinblastina (NSC 49842), Sulfato de Vincristina (NSC 67574), Epotilona A, Epotilona, Discodermolida (ver Service, (1996) Science, 274:2009), Estramustina, Nocodazol, MAP4, y similares. Ejemplos de dichos agentes se describen en, por ejemplo, Bulinski (1997) J. Cell Sci. 110:3055-3064, Panda (1997) Proc. Natl. Acad. Sci. USA 94:10560-10564, Muhlradt (1997) Cancer Res. 57:3344-3346, Nicolaou (1997) Nature 387:268-272, Vasquez (1997) Mol. Biol. Cell. 8:973-985, y Panda (1996) J. Biol. Chem. 271:29807-29812.

Agentes quimioterapéuticos con actividad símil paclitaxel incluyen, sin carácter limitativo, paclitaxel y derivados de paclitaxel (compuestos símil paclitaxel) y análogos. Paclitaxel y sus derivados (por ej. Taxol y Taxotere) se encuentran disponibles en el mercado. Además, los métodos para producir paclitaxel y los derivados y análogos de paclitaxel son conocidos para aquellos con experiencia en el arte (ver, por ej., Patentes de EE UU Nos.: 5.569.729; 5.565.478; 5.530.020; 5.527.924; 5.508.447; 5.489.589; 5.488.116; 5.484.809; 5.478.854; 5.478.736; 5.475.120; 5.468.769; 5.461.169; 5.440.057; 5.422.364; 5.411.984; 5.405.972; y 5.296.506).

En forma más específica, el término "paclitaxel" como se usa aquí se refiere a la droga disponible en el mercado como Taxol® (número de NSC: 125973). Taxol® inhibe la replicación de células eucarióticas al potenciar la polimierización de los restos de tubulina en los manojos de microtúbulos estabilizados que son incapaces de reorganizarse en estructuras apropiadas para mitosis. De los muchos medicamentos quimioterapéuticos disponibles, paclitaxel ha generado interés debido a su eficacia en ensayos clínicos contra tumores refractarios a los fármacos, incluyendo tumores de ovarios y de las glándulas mamarias (Hawkins (1992) Oncology, 6: 17-23, Horwitz (1992) Trends Pharmacol. Sci. 13: 134-146, Rowinsky (1990) J. Natl. Canc. Inst. 82: 1247-1259).

Agentes adicionales que afectan los microtúbulos pueden evaluarse usando uno de muchos de dichos ensayos conocidos en el arte, por ej., un ensayo semi-automático que mide la actividad de polimerización de tubulina de los análogos de paclitaxel en combinación con un ensayo celular para medir el potencial de estos compuestos para bloquear las células en la mitosis (ver Lopes (1997) Cancer Chemother. Pharmacol. 41:37-47).

En general, la actividad de un compuesto experimental se determina mediante el contacto de una célula con ese compuesto y determinando si el ciclo celular se interrumpe o no, en particular, a través de la inhibición de un evento mitótico. Dicha inhibición puede mediarse por la interrupción del aparato mitótico, por ej., la interrupción de la formación de bucles normales. Las células en las cuales se interrumpe la mitosis pueden caracterizarse por una morfología alterada (por ej., compactación de los microtúbulos, aumento del número de cromosomas, etc.).

Los compuestos con posible actividad de polimerización de tubulina pueden seleccionarse in vitro. Por ejemplo, los compuestos se seleccionan contra células WR21 cultivadas (derivadas de la línea 69-2 wap-ras de ratones) para

evaluar la inhibición de la proliferación y/o morfología celular alterada, en particular para determinar la compactación de microtúbulos. La evaluación sistemática in vivo de compuestos de evaluación positivos puede realizarse entonces usando ratones lampiños que llevan células tumorales WR21. Los protocolos detallados para este método de evaluación sistemática se describen en el texto escrito por Porter (1995) Lab. Anim. Sci., 45(2):145-150.

Otros métodos de evaluación sistemática de compuestos para determinar la actividad deseada son conocidos para aquellos con experiencia en el arte. Normalmente dichos ensayos incluyen ensayos para determinar la inhibición de la formación y/o interrupción de microtúbulos. Los ensayos para la formación de microtúbulos se describen, por ejemplo, en el texto de Gaskin et al. (1974) J. Molec. Biol., 89: 737-758. Patente de EE UU No. 5.569.720 provee, además, ensayos in vitro e in vivo para compuestos con actividad del tipo paclitaxel.

De este modo, en los métodos de esta invención donde por lo menos se usa un agente quimioterapéutico, ejemplos de dicho agentes quimioterapéuticos incluyen aquellos seleccionados del grupo que consiste en: agentes que afectan los microtúbulos, agentes alquilantes, antimetabolitos, productos naturales y sus derivados, hormonas y esteroides (incluyendo análogos sintéticos), y sintéticos.

En los métodos de esta invención donde se usa por lo menos un agente quimioterapéutico, ejemplos de dicho agentes quimioterapéuticos también incluyen: (1) taxanos, (2) compuestos coordinadores de platino, (3) inhibidores del factor de crecimiento epidérmico (FCE) que son anticuerpos, (4) inhibidores del FCE que son moléculas pequeñas, (5) inhibidores del factor de crecimiento endolitial vascular (VEGF) que son anticuerpos, (6) inhibidores de quinasa de VEGF que son moléculas pequeñas, (7) antagonistas del receptor de estrógenos o moduladores selectivos del receptor de estrógenos (SERMs), (8) derivados de nucleósidos anti-tumorales, (9) epotilonas, (10) inhibidores de topoisomerasa, (11)

alcaloides vinca, (12) anticuerpos que son inhibidores de αVβ3 integrinas, (13) antagonistas de folato, (14) inhibidores de la ribonucleótido reductasa, (15) antraciclinas, (16) agentes biológicos; (17) inhibidores de la angiogénesis y/o supresores del factor de necrosis tumoral alfa (TNF-alfa) tales como talidomida (o imida relacionada), (18) inhibidores de la quinasa Bcr/abl, (19) inhibidores de MEK1 y/o MEK 2 que son moléculas pequeñas, (20) inhibidores de IGF-1 y IGF-2 que son moléculas pequeñas, (21) inhibidores de moléculas pequeñas de quinasas RAF y BRAF, (22) inhibidores de moléculas pequeñas de quinasas dependientes del ciclo celular tales como CDK1, CDK2, CDK4 y CDK6, (23) agentes alquilantes, y (24) inhibidores de la farnesil transferasa de la proteína (también conocidos como inhibidores de FPT o FTI (es decir, inhibidores de transferencia de farnesilo)).

En los métodos de esta invención donde se usa por lo menos un agente quimioterapéutico, ejemplos de tales agentes quimioterapéuticos incluyen:

(1) taxanos tales como paclitaxel (TAXOL®) y/o docetaxel (Taxotere®);

(2) compuestos coordinadores de platino, tales como, por ejemplo, carboplatino, cisplatino y oxaliplatino (por ej. Eloxatin);

(3) inhibidores del FCE que son anticuerpos, tales como: anticuerpos de HER2 (tales como, por ejemplo trastuzumab (Herceptin®., Genentech, Inc.), Cetuximab (Erbitux, IMC-C225, ImClone Systems), EMD 72000 (Merck KGaA), anticuerpo monoclonal anti-EFGR ABX (Abgenix), TheraCIM-h-R3 (Center of Molecular Immunology), anticuerpo monoclonal 425 (Merck KGaA), anticuerpo monoclonal ICR-62 (ICR, Sutton, England); Herzyme (Elan Pharmaceutical Technologies y Ribozyme Pharmaceuticals), PKI 143 (Novartis), EKB 569 (Wyeth-Ayerst), GW 572016 (GlaxoSmithKline), CI 1033 (Pfizer Global Research y Development), conjugado trastuzmab-maitansinoide (Genentech, Inc.),

mitumomab (Imclone Systems and Merck KGaA) y Melvax II (Imclone Systems and Merck KgaA);

(4) inhibidores del FCE que son moléculas pequeñas, tales como, Tarceva (TM) (OSI-774, OSI Pharmaceuticals, Inc.), y Iressa (ZD 1839, Astra Zeneca);

(5) inhibidores de VEGF que son anticuerpos tales como: bevacizumab (Genentech, Inc.), y IMC-1C11 (ImClone Systems), DC 101 (un receptor 2 de KDR VEGF de ImClone Systems);

(6) inhibidores de quinasa de VEGF que son moléculas pequeñas tales como SU 5416 (de Sugen, Inc), SU 6688 (de Sugen, Inc.), Bay 43-9006 (un inhibidor mixto de VEGF y bRAF de Bayer Pharmaceuticals y Onyx Pharmaceuticals);

(7) antagonistas del receptor de estrógenos o moduladores selectivos del receptor de estrógenos (SERMs), tales como tamoxifeno, idoxifeno, raloxifeno, trans-2,3-dihidroraloxifeno, levormeloxifeno, droloxifeno, MDL 103,323, y acolbifeno (Schering Corp.);

(8) derivados de nucleósidos anti-tumorales tales como 5-fluorouracilo, gemcitabina, capecitabina, citarabina (Ara-C), fludarabina (F-Ara-A), decitabina, y clorodesoxiadenosina (Cda, 2-Cda);

(9) epotilonas tales como BMS-247550 (Bristol-Myers Squibb), y EPO906 (Novartis Pharmaceuticals);

(10) inhibidores de topoisomerasa tales como topotecan (Glaxo SmithKline), y Camptosar (Pharmacia);

(11) alcaloides vinca, tales como, navelbina (Anvar and Fabre, Francia), vincristina y vinblastina;

(12) anticuerpos que son inhibidores de αVβ3 integrinas, tales como, LM-609 (ver, Clinical Cancer Research, Vol. 6, page 3056-3061, August 2000, cuya descripción se incorpora aquí a modo de referencia a ésta);

(13) antagonistas de folato, tales como Methotrexate (MTX), y Premetrexed (Alimta);

(14) inhibidores de la ribonucleótido reductasa, tales como Hidroxiurea (HU);

(15) antraciclinas, tales como Daunorubicina, Doxorubicina (Adriamicina), y Idarubicina;

(16) agentes biológicos, tales como interferón (por ej., Intron-A y Roferon), interferón pegilado (por ej., Peg-Intron y Pegasys), y Rituximab (Rituxan, anticuerpo usado para el tratamiento de linfoma de no Hodgkin);

(17) talidomida (o imida relacionada);

(18) inhibidores de la quinasa Bcr/abl, tales como, por ejemplo Gleevec (STI-571), AMN-17, ONO12380, SU11248 (Sunitinib) y BMS-354825

(19) inhibidores de MEK1 y/o MEK2, tales como PD0325901 y Arry-142886 (AZD6244);

(20) inhibidores de IGF-1 y IGF-2 que son moléculas pequeñas, tales como, por ejemplo, NVP-AEW541;

(21) inhibidores de moléculas pequeñas de quinasas RAF y BRAF, tales como, por ejemplo, BAY 43-9006 (Sorafenib);

(22) inhibidores de moléculas pequeñas de quinasas dependientes del ciclo celular tales como CDK1, CDK2, CDK4 y CDK6, tales como, por ejemplo, CYC202, BMS387032, y Flavopiridol;

(23) agentes alquilantes, tales como, por ejemplo, Temodar® marca de temozolomida;

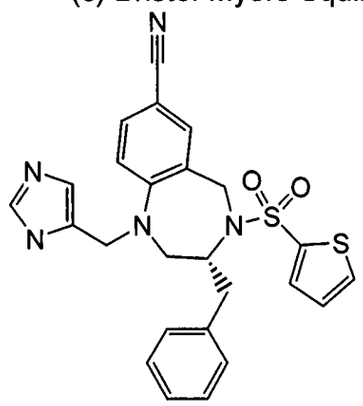
(24) inhibidores de la farnesil transferasa de la proteína, tales como, por ejemplo:

(a) Sarasar® marca de lonifarnib (es decir, 4—[2—[4—(3,10—dibromo—8—cloro—6,11—dihidro—5H—benzo[5,6]ciclohepta[1.2—*b*]biridin—

11—il)—1—piperidinil)—2—oxoetil]—1—piperidinecarboxamida, ver por ejemplo, EE UU 5.874.442 concedida el 23 de febrero de 1999, y EE UU 6.632.455 concedida el 14 de octubre de 2003 cuyas revelaciones se incorporan aquí a modo de referencia),

(b) Zarnestra® marca de tipifarnib (es decir, (R)—6—amino[(4—clorofenil)(1—metil—1H—imidazol—5—il)metil]—4—(3—clorofenil)—1—metil—2(1H)—quinolinona, ver por ejemplo, WO 97/16443 publicada el 9 de mayo de 1997 y EE UU 5.968.952 concedida el 19 de octubre de 1999, cuyas revelaciones se incorporan aquí a modo de referencia), y

(c) Bristol-Myers Squibb 214662:



(ver WO97/30992 publicada el 28 de agosto de 1997, EE UU 6.011.029 concedida el 4 de enero de 2000, y EE UU 6.455.523, cuyas revelaciones se incorporan aquí a modo de referencia).

Los inhibidores de la quinasa Bcr/abl, inhibidores del receptor de EGF, y anticuerpos HER-2 (inhibidores del receptor de EGF son anticuerpos) descritos anteriormente como también conocidos como inhibidor de transducción de señales. Por lo tanto, los agentes quimioterapéuticos, como se usa aquí, incluyen inhibidores de transducción de señal.

Los inhibidores de transducción de señal típicos, que son agentes quimioterapéuticos, incluyen sin carácter limitativo: (i) inhibidores de la quinasa Bcr/abl tales como, por ejemplo, STI 571 (Gleevec), (ii) Inhibidor del receptor del

factor de crecimiento epidérmico (EGF) tales como, por ejemplo, *inhibidores de quinasa* (Iressa, OSI-774) y anticuerpos (Imclone: C225 [Goldstein et al. (1995), Clin Cancer Res. 1:1311-1318], y Abgenix: ABX-EGF) y (iii) inhibidores del receptor de HER-2/neu tales como, por ejemplo, Herceptin® (trastuzumab).

Métodos de administración segura y efectiva de la mayoría de estos agentes quimioterapéuticos son conocidos para aquellas personas con experiencia en el arte. Además, su administración se describe en la bibliografía estándar. Por ejemplo, la administración de muchos de los agentes quimioterapéuticos se describen en la "Physicians' Desk Reference" (PDR), por ej., 1996 edition (Medical Economics Company, Montvale, NJ 07645-1742, USA), the Physician's Desk Reference, 56th Edition, 2002 (publicada por Medical Economics company, Inc. Montvale, NJ 07645-1742), y la Physician's Desk Reference, 57th Edition, 2003 (publicada por Thompson PDR, Montvale, NJ 07645-1742); cuyas descripciones se incorporan a modo de referencia.

Por ejemplo, el compuesto de fórmula 1.0 (por ej., una composición farmacéutica que comprende el compuesto de fórmula 1.0); puede administrarse por vía oral (por ej., como una cápsula), y los agentes quimioterapéuticos pueden administrarse por vía endovenosa, usualmente como solución IV. El uso de una composición farmacéutica que comprende más de una droga se encuentra dentro del alcance de esta invención.

El compuesto de fórmula 1.0 y los agentes quimioterapéuticos se administran en dosificaciones terapéuticamente efectivas para obtener resultados clínicamente aceptables, por ej., reducción o eliminación de los síntomas o del tumor. De este modo, el compuesto de fórmula 1.0 y agentes quimioterapéuticos pueden administrarse en forma concurrente o en forma consecutiva in un protocolo de tratamiento. La administración de los agentes quimioterapéuticos

puede realizarse de acuerdo con protocolos de tratamiento ya conocidos en el arte.

En general cuando más de un agente quimioterapéutico se usa en los métodos de esta invención, los agentes quimioterapéuticos se administran el mismo día ya sea en forma concurrente o en forma consecutiva en su forma de dosificación estándar. Por ejemplo, los agentes quimioterapéuticos usualmente se administran por vía endovenosa, con preferencia por un goteo IV usando soluciones IV conocidas en el arte (por ej., solución salina isotónica (NaCl al 0,9%) o solución de dextrosa (por ej., dextrosa al 5%)).

Cuando se usan dos o más agentes quimioterapéuticos, los agentes quimioterapéuticos se administran en general el mismo día; sin embargo, aquellas personas con experiencia en el arte apreciarán que los agentes quimioterapéuticos pueden administrarse en días diferentes y en semanas diferentes. El médico con experiencia puede administrar los agentes quimioterapéuticos de acuerdo con su cronograma de dosificación recomendada del fabricante del agente y puede ajustar el cronograma de acuerdo con las necesidades del paciente, por ej., en base a la respuesta del paciente al tratamiento. Por ejemplo, cuando se usa gemcitabina en combinación con un compuesto coordinador de platino, tales como, por ejemplo, cisplatino, para tratar el cáncer de pulmón, tanto la gemcitabina y el cisplatino se administran el mismo día el día uno del ciclo de tratamiento, y luego se administra gemcitabina sola el día 8 y nuevamente se administra sola el día 15

Los compuestos de esta invención y agentes quimioterapéuticos pueden administrarse en un protocolo de tratamiento que usualmente dura de una a siete semanas, y normalmente se repite desde 6 hasta 12 veces. En general el protocolo de tratamiento puede durar de una a cuatro semanas. Los protocolos de tratamiento de una a tres semanas también pueden utilizarse. Un protocolo de

tratamiento de una a dos semanas también puede utilizarse. Durante este protocolo o ciclo de tratamiento los compuestos de esta invención pueden administrarse diariamente mientras que los agentes quimioterapéuticos pueden administrarse una o más veces por semana. En general, un compuesto de esta invención puede administrarse diariamente (es decir, una vez por día), y en una realización dos veces por día, y el agente quimioterapéutico se administra una vez por semana o una vez cada tres semanas. Por ejemplo, los taxanos (por ej., Paclitaxel (por ej., Taxol®) o Docetaxel (por ej.,Taxotere®)) pueden administrarse una vez por semana o una vez cada tres semanas.

Sin embargo, aquellas personas con experiencia en el arte apreciarán que protocolos de tratamiento pueden variarse de acuerdo con las necesidades del paciente. De este modo, la combinación de compuestos (drogas) usados en los métodos de esta invención pueden administrarse en variaciones de los protocolos descritos con anterioridad. Por ejemplo, los compuestos de esta invención pueden administrarse en forma discontinua en lugar de continuamente durante el ciclo de tratamiento. De este modo, por ejemplo, durante el ciclo de tratamiento los compuestos de esta invención pueden administrarse diariamente durante una semana y luego discontinuarse durante una semana, con esta administración repitiéndose durante el ciclo de tratamiento. O los compuestos de esta invención pueden administrarse diariamente durante dos semanas y discontinuarse durante una semana, con esta administración repitiéndose durante el ciclo de tratamiento. De este modo, los compuestos de esta invención pueden administrarse diariamente durante una o más semanas durante el ciclo y discontinuarse durante una o más semanas durante el ciclo, con este patrón de administración repitiéndose durante el ciclo de tratamiento. Este tratamiento discontinuo también puede basarse en los números de días en lugar de una semana completa. Por ejemplo, administrando diariamente durante 1 hasta 6 días, sin dosificación

durante 1 hasta 6 días con este patrón repitiéndose durante el protocolo de tratamiento. El número de días (o semanas) en el cual los compuestos de esta invención no se administran no tienen que ser iguales al número de días (o semanas) en el cual los compuestos de esta invención se administran Usualmente, si se usa un protocolo de administración discontinua se usa, el número de días o semanas que se administran los compuestos de esta invención es por lo menos igual o mayor que el número de días o semanas que los compuestos de esta invención no se administran.

El agente quimioterapéutico podría administrarse por infusión en bolo o continua. El agente quimioterapéutico podría administrarse diariamente hasta una vez por semana, o una vez cada dos semanas, o una vez cada tres semanas, o una vez cada cuatro semanas durante el ciclo de tratamiento. Si se administra diariamente durante el ciclo de tratamiento, esta administración diaria puede ser discontinua durante el número de semanas del ciclo de tratamiento. Por ejemplo, administrarse durante una semana (o un número de días), sin dosis durante una semana (o un número de días, con el patrón de repetición durante el ciclo de tratamiento.

Los compuestos de esta invención pueden administrarse oralmente , con preferencia como forma de dosificación sólida, y en una realización como una cápsula, y mientras que la dosis diaria terapéuticamente efectiva total pueden administrarse en una a cuatro, o una hasta dos dosis dividida por día, en general, la dosis terapéuticamente efectiva se administra una vez o dos veces por día, y en una realización dos veces por día. Los compuestos de esta invención pueden administrarse en una cantidad de aproximadamente 50 hasta aproximadamente 400 mg una vez por día, y pueden administrarse en una cantidad de aproximadamente 50 hasta aproximadamente 300 mg una vez por día. Los compuestos de esta invención se administran en general en una cantidad de

aproximadamente 50 hasta aproximadamente 350 mg dos veces por día, usualmente 50 mg hasta aproximadamente 200 mg dos veces por día, y en una realización aproximadamente 75 mg hasta aproximadamente 125 mg administrados dos veces por día, y en otra realización aproximadamente 100 mg administrados dos veces por día.

Si el paciente responde al tratamiento, o es estable, luego de la finalización del ciclo de tratamiento, el ciclo de tratamiento puede repetirse de acuerdo con el criterio del médico con experiencia. Luego de la finalización del ciclo de tratamientos, el paciente puede continuar con los compuestos de esta invención con la misma dosis que se administró en el protocolo de tratamiento, o, si la dosis era de menos de 200 mg dos veces por día, la dosis puede elevarse hasta 200 mg dos veces por día. Esta dosis de mantenimiento puede continuarse hasta que el paciente progresa o ya no puede tolerar la dosis (en cuyo caso la dosis puede reducirse y el paciente puede continuar con la dosis reducida).

Los agentes quimioterapéuticos, usados con los compuestos de esta invención, se administran en sus dosificaciones normalmente prescriptas durante el ciclo de tratamiento (es decir, los agentes quimioterapéuticos se administran de acuerdo con el estándar de la práctica para la administración de estos medicamentos). Por ejemplo: (a) aproximadamente 30 hasta aproximadamente 300 mg/m^2 para los taxanos; (b) aproximadamente 30 hasta aproximadamente 100 mg/m^2 para Cisplatino; (c) ABC de aproximadamente 2 hasta aproximadamente 8 para Carboplatino; (d) aproximadamente 2 hasta aproximadamente 4 mg/m^2 para inhibidores del FCE que son anticuerpos; (e) aproximadamente 50 hasta aproximadamente 500 mg/m^2 para inhibidores del FCE que son moléculas pequeñas; (f) aproximadamente 1 hasta aproximadamente 10 mg/m^2 para inhibidores de quinasa de VEGF que son anticuerpos; (g) aproximadamente 50 hasta aproximadamente 2400 mg/m^2 para

inhibidores de VEGF que son moléculas pequeñas; (h) aproximadamente 1 hasta aproximadamente 20 mg para SERMs; (i) aproximadamente 500 hasta aproximadamente 1250 mg/m^2 para los nucleósidos anti-tumorales 5-Fluorouracilo, Gemcitabina y Capecitabina; (j) para el nucleósido anti-tumoral Citarabina (Ara-C) 100-200 mg/m^2/día para 7 hasta 10 días cada 3 hasta 4 semanas, y altas dosis para leucemia refractario y linfoma, es decir, 1 hasta 3 gm/m^2 durante una hora cada 12 horas para 4-8 dosis cada 3 hasta cuatro semanas; (k) para el nuclelósido anti-tumoral Fludarabina (F-ara-A) 10-25mg/m^2/día cada 3 hasta 4 semanas; (l) para el nuclelósido anti-tumoral Decitabina 30 hasta 75 mg/m^2 durante tres días cada 6 semanas durante un máximo de 8 ciclos; (m) para el nuclelósido anti-tumoral Clorodeoxiadenosine (CdA, 2-CdA) 0,05-0,1 mg/kg/día como infusión continua durante hasta 7 días cada 3 hasta 4 semanas; (n) aproximadamente 1 hasta aproximadamente 100 mg/m^2 para epotilonas; (o) aproximadamente 1 hasta aproximadamente 350 mg/m^2 para inhibidores de topoisomerasa; (p) aproximadamente 1 hasta aproximadamente 50 mg/m^2 para alcaloides vinca; (q) para el antagonista de folato Metotrexato (MTX) 20-60 mg/m^2 por administración oral, IV o IM cada 3 hasta 4 semanas, el régimen de dosificación intermedia es de 80-250 mg/m^2 IV durante 60 minutos cada 3 hasta 4 semanas, y el régimen de dosis alta es de 250-1000 mg/m^2 IV administrada con leucovorin cada 3 hasta 4 semanas; (r) para el antagonista de folato Premetrexed (Alimta) 300-600 mg/m^2 (10 minutos de infusión IV el día 1) cada 3 semanas; (s) para el inhibidor de ribonucleotida reductasa Hidroxiurea (HU) 20-50 mg/kg/día (según la necesidad para reducir el recuento de glóbulos); (t) el compuesto coordinador de platino Oxaliplatin (Eloxatin) 50-100 mg/m^2 cada 3 hasta 4 semanas (con preferencia usado para tumores sólidos tales como cáncer de pulmón de células no pequeñas, cáncer colo-rectal y cáncer de ovario); (u) para la antraciclina daunorubicina 10-50

mg/m^2/día IV para 3-5 días cada 3 hasta 4 semanas; (v) para la antraciclina Doxorubicina (Adriamicina) 50-100 mg/m^2 de infusión continua IV durante 1-4 días cada 3 hasta 4 semanas, o 10-40 mg/m^2 IV por semana; (w) para la antraciclina Idarubicina 10-30 mg/m^2 diariamente para 1-3 días como infusión IV lenta durante 10-20 minutos cada 3 hasta 4 semanas; (x) para el agente biológico interferón (Intron-A, Roferon) 5 hasta 20 millones de UI tres veces por semana; (y) para el agente biológico interferón pegilado (Peg-intron, Pegasys) 3 hasta 4 microgramos/kg/día subcutánea crónica (hasta la recaída o pérdida de actividad); (z) para el agente biológico Rituximab (Rituxan) (anticuerpo usado para linfoma de no Hodgkin) 200-400 mg/m^2 IV por semana durante 4-8 semanas para 6 meses; (aa) para el agente de alquilación temozolomida 75 mg/m^2 hasta 250 mg/m^2, por ejemplo, 150 mg/m^2, o por ejemplo, 200 mg/m^2, tales como 200 mg/m^2 para 5 días; y (bb) para el inhibidor de MEK1 y/o MEK2 PD0325901, 15 mg hasta 30 mg, por ejemplo, 15 mg diariamente para 21 días cada 4 semanas.

Gleevec puede usarse por vía oral en una cantidad de aproximadamente 200 hasta aproximadamente 800 mg/día.

Talidomida (y las imidas relacionadas) puede usarse por vía oral en cantidades de aproximadamente 200 hasta aproximadamente 800 mg/día, y puede administrarse en forma continua o hasta producir recaída o toxicidad. Ver por ejemplo Mitsiades et al., "Apoptotic signaling induced by immunomodulatory thalidomide analoqs in human mieloma multiple cells; therapeutic implications", Blood, 99(12):4525-30, June 15, 2002, cuya descripción se incorpora aquí a modo de referencia a ésta.

El inhibidor de FPT Sarasar® (marca de lonifarnib) puede administrarse por vía oral (por ej., cápsula) en cantidades de aproximadamente 50 hasta aproximadamente 200 mg administrados dos veces por día, o en cantidades de aproximadamente 75 hasta aproximadamente 125 mg administrados dos veces

por día, o en cantidades de aproximadamente 100 hasta aproximadamente 200 mg administrados dos veces por día, o en una cantidad de aproximadamente 100 mg administrados dos veces por día.

Paclitaxel (por ej., Taxol®, por ejemplo, puede administrarse una vez por semana en una cantidad de aproximadamente 50 hasta aproximadamente 100 mg/m^2 y en otro ejemplo aproximadamente 60 hasta aproximadamente 80 mg/m^2. En otro ejemplo Paclitaxel (por ej., Taxol® puede administrarse una vez cada tres semanas en una cantidad de aproximadamente 150 hasta aproximadamente 250 mg/m^2 y en otro ejemplo aproximadamente 175 hasta aproximadamente 225 mg/m^2.

En otro ejemplo, Docetaxel (por ej., Taxotere®) puede administrarse una vez por semana en una cantidad de aproximadamente 10 hasta aproximadamente 45 mg/m^2. En otro ejemplo Docetaxel (por ej., Taxotere®) puede administrarse una vez cada tres semanas en una cantidad de aproximadamente 50 hasta aproximadamente 100 mg/m^2.

En otro ejemplo Cisplatino puede administrarse una vez por semana en una cantidad de aproximadamente 20 hasta aproximadamente 40 mg/m^2. En otro ejemplo Cisplatino puede administrarse una vez cada tres semanas en una cantidad de aproximadamente 60 hasta aproximadamente 100 mg/m^2.

En otro ejemplo Carboplatino puede administrarse una vez por semana en una cantidad para proporcionar un ABC de aproximadamente 2 hasta aproximadamente 3. En otro ejemplo Carboplatino puede administrarse una vez cada tres semanas en una cantidad para proporcionar un ABC de aproximadamente 5 hasta aproximadamente 8.

Otras realizaciones de esta invención se describen a continuación. Las realizaciones se han numerado con la finalidad de hacer más fácil la referencia a las realizaciones. El término "en cualquiera de las Realizaciones No." o el término

"de cualquiera de las Realizaciones Nos.", como se usa a continuación, significa que la realización particular que usa ese término pretende cubrir cualquiera de las realizaciones a las que se hace referencia como si una de las realizaciones referidas se hubiera descrito en forma individual. "Nos." es la abreviatura para Números.

La Realización No. 1 se refiere a un compuesto de fórmula 1.0, con preferencia un compuesto de fórmula 1.0C, en el cual Q se selecciona del grupo que consiste en sustituyentes 2.1, 2.2. 2.3, 2.3A, 2.3B, 2.3C, 2.4A, 2.4B, 2.4C, 2.5A, 2.5B, 2.5C, 2.6A, 2.7A, 2.7B, 2.7C, 2.8A, 2.8B, 2.8C, 2.9 hasta 2.14, 2.15, 2.16 (por ej., 2.16A o 2.16B), 2.17, 2.17A, 2.17B, 2.17C, 2.17D, 2.17E, 2.18, 2.19, 2.20, 2.21 y 2.22.

La Realización No. 2 se refiere a un compuesto de Fórmula 1.1 en los cuales Q se selecciona del grupo que consiste en sustituyentes 2.1, 2.2. 2.3, 2.3A, 2.3B, 2.3C, 2.4A, 2.4B, 2.4C, 2.5A, 2.5B, 2.5C, 2.6A, 2.7A, 2.7B, 2.7C, 2.8A, 2.8B, 2.8C, 2.9 hasta 2.14, 2.15, 2.16 (por ej., 2.16A o 2.16B), 2.17, 2.17A, 2.17B, 2.17C, 2.17D, 2.17E, 2.18, 2.19, 2.20, 2.21 y 2.22.

La Realización No. 3 se refiere a un compuesto de Fórmula 1.2 en el cual Q se selecciona del grupo que consiste en sustituyentes 2.1, 2.2. 2.3, 2.3A, 2.3B, 2.3C, 2.4A, 2.4B, 2.4C, 2.5A, 2.5B, 2.5C, 2.6A, 2.7A, 2.7B, 2.7C, 2.8A, 2.8B, 2.8C, 2.9 hasta 2.14, 2.15, 2.16 (por ej., 2.16A o 2.16B), 2.17, 2.17A, 2.17B, 2.17C, 2.17D, 2.17E, 2.18, 2.19, 2.20, 2.21 y 2.22.

La Realización No. 4 se refiere a un compuesto de Fórmula 1.3 en el cual Q se selecciona del grupo que consiste en sustituyentes 2.1, 2.2. 2.3, 2.3A, 2.3B, 2.3C, 2.4A, 2.4B, 2.4C, 2.5A, 2.5B, 2.5C, 2.6A, 2.7A, 2.7B, 2.7C, 2.8A, 2.8B, 2.8C, 2.9 hasta 2.14, 2.15, 2.16 (por ej., 2.16A o 2.16B), 2.17, 2.17A, 2.17B, 2.17C, 2.17D, 2.17E, 2.18, 2.19, 2.20, 2.21 y 2.22.

La Realización No. 5 se refiere a un compuesto de fórmula 1.0, con preferencia un compuesto de fórmula 1.0C1 y con mayor preferencia un compuesto de fórmula 1.0C, (por ej., 1.1, 1.1A, 1.2. 1.2A, 1.3 o 1.3A) en el cual el sustituyente Q es 2.1.

La Realización No. 6 se refiere a un compuesto de fórmula 1.0, con preferencia un compuesto de fórmula 1.0C1 y con mayor preferencia un compuesto de fórmula 1.0C, (por ej., 1.1, 1.1A, 1.2. 1.2A, 1.3 o 1.3A) en el cual el sustituyente Q es 2.2.

La Realización No. 7 se refiere a un compuesto de fórmula 1.0 (por ej., 1.1, 1.1A, 1.2. 1.2A, 1.3 o 1.3A) en el cual el sustituyente Q es 2.3 (por ej., 2.3A, 2.3B o 2.3C).

La Realización No. 8 se refiere a un compuesto de fórmula 1.0, con preferencia un compuesto de fórmula 1.0C, (por ej., 1.1, 1.1A, 1.2. 1.2A, 1.3 o 1.3A) en el cual el sustituyente Q es 2.4 (por ej., 2.4A, 2.4B o 2.4C).

La Realización No. 9 se refiere a un compuesto de fórmula 1.0, con preferencia un compuesto de fórmula 1.0C1 y con mayor preferencia un compuesto de fórmula 1.0C, (por ej., 1.1, 1.1A, 1.2. 1.2A, 1.3 o 1.3A) en el cual el sustituyente Q es 2.5 (por ej., 2.5A, 2.5B o 2.5C).

La Realización No. 10 se refiere a cualquiera de los compuestos de fórmulas a un compuesto de fórmula 1.0, con preferencia un compuesto de fórmula 1.0C1 y con mayor preferencia un compuesto de fórmula 1.0C, (por ej., 1.1, 1.1A, 1.2. 1.2A, 1.3 o 1.3A) en el cual el sustituyente Q es 2.6 (por ej., 2.6A).

La Realización No. 11 se refiere a un compuesto de fórmula 1.0, con preferencia un compuesto de fórmula 1.0C1 y con mayor preferencia un compuesto de fórmula 1.0C, (por ej., 1.1, 1.1A, 1.2. 1.2A, 1.3 o 1.3A) en el cual el sustituyente Q es 2.7.

La Realización No. 12 se refiere a un compuesto de fórmula 1.0, con preferencia un compuesto de fórmula 1.0C1 y con mayor preferencia un compuesto de fórmula 1.0C, (por ej., 1.1, 1.1A, 1.2. 1.2A, 1.3 o 1.3A) en el cual el sustituyente Q es 2.8.

La Realización No. 13 se refiere a un compuesto de fórmula 1.0, con preferencia un compuesto de fórmula 1.0C1 y con mayor preferencia un compuesto de fórmula 1.0C, (por ej., 1.1, 1.1A, 1.2. 1.2A, 1.3 o 1.3A) en el cual el sustituyente Q es 2.9.

La Realización No. 14 se refiere a un compuesto de fórmula 1.0, con preferencia un compuesto de fórmula 1.0C1 y con mayor preferencia un compuesto de fórmula 1.0C, (por ej., 1.1, 1.1A, 1.2. 1.2A, 1.3 o 1.3A) en el cual el sustituyente Q es 2.10.

La Realización No. 15 se refiere a un compuesto de fórmula 1.0, con preferencia un compuesto de fórmula 1.0C1 y con mayor preferencia un compuesto de fórmula 1.0C, (por ej., 1.1, 1.1A, 1.2. 1.2A, 1.3 o 1.3A) en el cual el sustituyente Q es 2.11.

La Realización No. 16 se refiere a un compuesto de fórmula 1.0, con preferencia un compuesto de fórmula 1.0C1 y con mayor preferencia un compuesto de fórmula 1.0C, (por ej., 1.1, 1.1A, 1.2. 1.2A, 1.3 o 1.3A) en el cual el sustituyente Q es 2.12.

La Realización No. 17 se refiere a un compuesto de fórmula 1.0, con preferencia un compuesto de fórmula 1.0C1 y con mayor preferencia un compuesto de fórmula 1.0C, (por ej., 1.1, 1.1A, 1.2. 1.2A, 1.3 o 1.3A) en el cual el sustituyente Q es 2.13.

La Realización No. 18 se refiere a un compuesto de fórmula 1.0, con preferencia un compuesto de fórmula 1.0C1 y con mayor preferencia un

compuesto de fórmula 1.0C, (por ej., 1.1, 1.1A, 1.2. 1.2A, 1.3 o 1.3A) en el cual el sustituyente Q es 2.14.

La Realización No. 19 se refiere a un compuesto de fórmula 1.0, con preferencia un compuesto de fórmula 1.0C1 y con mayor preferencia un compuesto de fórmula 1.0C, (por ej., 1.1, 1.1A, 1.2. 1.2A, 1.3 o 1.3A) en el cual el sustituyente Q es 2.15.

La Realización No. 20 se refiere a un compuesto de fórmula 1.0, con preferencia un compuesto de fórmula 1.0C1 y con mayor preferencia un compuesto de fórmula 1.0C, (por ej., 1.1, 1.1A, 1.2. 1.2A, 1.3 o 1.3A) en el cual el sustituyente Q es 2.16.

La Realización No. 21 se refiere a un compuesto de fórmula 1.0, con preferencia un compuesto de fórmula 1.0C1 y con mayor preferencia un compuesto de fórmula 1.0C, (por ej., 1.1, 1.1A, 1.2. 1.2A, 1.3 o 1.3A) en el cual el sustituyente Q es 2.17 (por ej., 2.17A, 2.17B, 2.17C, 2.17D, o 2.17E).

La Realización No. 22 se refiere a un compuesto de fórmula 1.0, con preferencia un compuesto de fórmula 1.0C1 y con mayor preferencia un compuesto de fórmula 1.0C, (por ej., 1.1, 1.1A, 1.2. 1.2A, 1.3 o 1.3A) en el cual el sustituyente Q es 2.18.

La Realización No. 23 se refiere a un compuesto de fórmula 1.0, con preferencia un compuesto de fórmula 1.0C1 y con mayor preferencia un compuesto de fórmula 1.0C, (por ej., 1.1, 1.1A, 1.2. 1.2A, 1.3 o 1.3A) en el cual el sustituyente Q es 2.19.

La Realización No. 24 se refiere a un compuesto de fórmula 1.0, con preferencia un compuesto de fórmula 1.0C1 y con mayor preferencia un compuesto de fórmula 1.0C, (por ej., 1.1, 1.1A, 1.2. 1.2A, 1.3 o 1.3A) en el cual el sustituyente Q es 2.20.

La Realización No. 25 se refiere a un compuesto de fórmula 1.0, con preferencia un compuesto de fórmula 1.0C1 y con mayor preferencia un compuesto de fórmula 1.0C, (por ej., 1.1, 1.1A, 1.2. 1.2A, 1.3 o 1.3A) en el cual el sustituyente Q es 2.21.

La Realización No. 26 se refiere a un compuesto de fórmula 1.0, con preferencia un compuesto de fórmula 1.0C1 y con mayor preferencia un compuesto de fórmula 1.0C, (por ej., 1.1, 1.1A, 1.2. 1.2A, 1.3 o 1.3A) en el cual el sustituyente Q es 2.22.

La Realización No. 27 se refiere a un compuesto de Fórmula 1.3 en el cual sustituyente Q es 2.1.

La Realización No. 28 se refiere a un compuesto de Fórmula 1.3 en el cual sustituyente Q es 2.2.

La Realización No. 29 se refiere a un compuesto de Fórmula 1.3 en el cual sustituyente Q es 2.3.

La Realización No. 30 se refiere a un compuesto de Fórmula 1.3 en el cual sustituyente Q es 2.6.

La Realización No. 31 se refiere a un compuesto de Fórmula 1.3 en el cual sustituyente Q es 2.6A.

La Realización No. 32 se refiere a un compuesto de Fórmula 1.3 en el cual sustituyente Q es 2.7A.

La Realización No. 33 se refiere a un compuesto de Fórmula 1.3 en el cual sustituyente Q es 2.7B.

La Realización No. 34 se refiere a un compuesto de Fórmula 1.3 en el cual sustituyente Q es 2.7C.

La Realización No. 35 se refiere a un compuesto de Fórmula 1.3 en el cual sustituyente Q es 2.17.

La Realización No. 36 se refiere a un compuesto de Fórmula 1.3 en el cual sustituyente Q es 2.17A.

La Realización No. 37 se refiere a un compuesto de Fórmula 1.3 en el cual sustituyente Q es 2.17B.

La Realización No. 38 se refiere a un compuesto de Fórmula 1.3 en el cual sustituyente Q es 2.17C.

La Realización No. 39 se refiere a un compuesto de Fórmula 1.3 en el cual sustituyente Q es 2.17D.

La Realización No. 40 se refiere a un compuesto de Fórmula 1.3 en el cual sustituyente Q es 2.17E.

La Realización No. 41 se refiere a un compuesto de fórmula 1.0, con preferencia un compuesto de fórmula 1.0C1 y con mayor preferencia un compuesto de fórmula 1.0C, (por ej., 1.1, 1.1A, 1.2. 1.2A, 1.3 o 1.3A) en el cual cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y alquilo.

La Realización No. 42 se refiere a un compuesto de fórmula 1.0, con preferencia un compuesto de fórmula 1.0C1 y con mayor preferencia un compuesto de fórmula 1.0C, (por ej., 1.1, 1.1A, 1.2. 1.2A, 1.3 o 1.3A) en el cual cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y metilo.

La Realización No. 43 se refiere a un compuesto de fórmula 1.0, con preferencia un compuesto de fórmula 1.0C1 y con mayor preferencia un compuesto de fórmula 1.0C, (por ej., 1.1, 1.1A, 1.2. 1.2A, 1.3 o 1.3A) en el cual cada R^3, R^4, R^6, y R^7 es H.

La Realización No. 44 se refiere a un compuesto de fórmula 1.0, con preferencia un compuesto de fórmula 1.0C1 y con mayor preferencia un compuesto de fórmula 1.0C, (por ej., 1.1, 1.1A, 1.2. 1.2A, 1.3 o 1.3A) en el cual el

sustituyente Q se selecciona del grupo que consiste en: restos 2.1, 2.2. 2.3A, 2.3B, y 2.3C.

La Realización No. 45 se refiere a un compuesto de fórmula 1.0, con preferencia un compuesto de fórmula 1.0C1 y con mayor preferencia un compuesto de fórmula 1.0C, (por ej., 1.1, 1.1A, 1.2. 1.2A, 1.3 o 1.3A) en el cual el sustituyente Q se selecciona del grupo que consiste en: restos 2.1, 2.2. 2.3A, 2.3B, y 2.3C, y cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y alquilo.

La Realización No. 46 se refiere a un compuesto de fórmula 1.0, con preferencia un compuesto de fórmula 1.0C1 y con mayor preferencia un compuesto de fórmula 1.0C, (por ej., 1.1, 1.1A, 1.2. 1.2A, 1.3 o 1.3A) en el cual el sustituyente Q se selecciona del grupo que consiste en: restos 2.1, 2.2. 2.3A, 2.3B, y 2.3C, y cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y metilo.

La Realización No. 47 se refiere a un compuesto de fórmula 1.0, con preferencia un compuesto de fórmula 1.0C1 y con mayor preferencia un compuesto de fórmula 1.0C, (por ej., 1.1, 1.1A, 1.2. 1.2A, 1.3 o 1.3A) en el cual el sustituyente Q se selecciona del grupo que consiste en: restos 2.1, 2.2. 2.3A, 2.3B, y 2.3C, y cada R^3, R^4, R^6, y R^7 es H.

La Realización No. 48 se refiere a un compuesto de fórmula 1.0, con preferencia un compuesto de fórmula 1.0C1 y con mayor preferencia un compuesto de fórmula 1.0C, (por ej., 1.1, 1.1A, 1.2. 1.2A, 1.3 o 1.3A) en el cual el sustituyente Q se selecciona del grupo que consiste en: resto 2.17.

La Realización No. 49 se refiere a un compuesto de fórmula 1.0, con preferencia un compuesto de fórmula 1.0C1 y con mayor preferencia un compuesto de fórmula 1.0C, (por ej., 1.1, 1.1A, 1.2. 1.2A, 1.3 o 1.3A) en el cual el sustituyente Q se selecciona del grupo que consiste en: resto 2.17, y cada R^3, R^4,

R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y alquilo.

La Realización No. 50 se refiere a un compuesto de fórmula 1.0, con preferencia un compuesto de fórmula 1.0C1 y con mayor preferencia un compuesto de fórmula 1.0C, (por ej., 1.1, 1.1A, 1.2. 1.2A, 1.3 o 1.3A) en el cual el sustituyente Q se selecciona del grupo que consiste en: resto 2.17, y cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y metilo.

La Realización No. 51 se refiere a un compuesto de fórmula 1.0, con preferencia un compuesto de fórmula 1.0C1 y con mayor preferencia un compuesto de fórmula 1.0C, (por ej., 1.1, 1.1A, 1.2. 1.2A, 1.3 o 1.3A) en el cual el sustituyente Q se selecciona del grupo que consiste en: resto 2.17, y cada R^3, R^4, R^6, y R^7 es H.

La Realización No. 52 se refiere a un compuesto de fórmula 1.0, con preferencia un compuesto de fórmula 1.0C1 y con mayor preferencia un compuesto de fórmula 1.0C, (por ej., 1.1, 1.1A, 1.2. 1.2A, 1.3 o 1.3A) en el cual el sustituyente Q se selecciona del grupo que consiste en: restos 2.1, y: (1) cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y alquilo, o (2) cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y metilo, o (3) cada R^3, R^4, R^6, y R^7 es H.

La Realización No. 53 se refiere a un compuesto de fórmula 1.0, con preferencia un compuesto de fórmula 1.0C1 y con mayor preferencia un compuesto de fórmula 1.0C, (por ej., 1.1, 1.1A, 1.2. 1.2A, 1.3 o 1.3A) en el cual el sustituyente Q se selecciona del grupo que consiste en: restos 2.2. y: (1) cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y alquilo, o (2) cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y metilo, o (3) cada R^3, R^4, R^6, y R^7 es H.

La Realización No. 54 se refiere a un compuesto de fórmula 1.0, con preferencia un compuesto de fórmula 1.0C1 y con mayor preferencia un compuesto de fórmula 1.0C, (por ej., 1.1, 1.1A, 1.2. 1.2A, 1.3 o 1.3A) en el cual el sustituyente Q se selecciona del grupo que consiste en: restos 2.3A, 2.3B, 2.3C, y: (1) cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y alquilo, o (2) cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y metilo, o (3) cada R^3, R^4, R^6, y R^7 es H.

La Realización No. 55 se refiere a un compuesto de Fórmula 1.2 o 1.3 donde cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y alquilo.

La Realización No. 56 se refiere a un compuesto de Fórmula 1.2 o 1.3 donde cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y metilo.

La Realización No. 57 se refiere a un compuesto de Fórmula 1.2 o 1.3 donde cada R^3, R^4, R^6, y R^7 es H.

La Realización No. 58 se refiere a un compuesto de Fórmula 1.2 o 1.3 en el cual el sustituyente Q se selecciona del grupo que consiste en: restos 2.1, 2.2. 2.3A, 2.3B y 2.3C.

La Realización No. 59 se refiere a un compuesto de Fórmula 1.2 o 1.3 en el cual el sustituyente Q se selecciona del grupo que consiste en: restos 2.1, 2.2. 2.3A, 2.3B y 2.3C, y cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y alquilo.

La Realización No. 60 se refiere a un compuesto de Fórmula 1.2 o 1.3 en el cual el sustituyente Q se selecciona del grupo que consiste en: restos 2.1, 2.2. 2.3A, 2.3B y 2.3C, y cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y metilo.

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La Realización No. 61 se refiere a un compuesto de Fórmula 1.2 o 1.3 en el cual el sustituyente Q se selecciona del grupo que consiste en: restos 2.1, 2.2. 2.3A, 2.3B y 2.3C, y cada R^3, R^4, R^6, y R^7 es H.

La Realización No. 62 se refiere a un compuesto de Fórmula 1.2 o 1.3 en el cual el sustituyente Q es un resto 2.17.

La Realización No. 63 se refiere a un compuesto de Fórmula 1.2 o 1.3 en el cual el sustituyente Q es un resto 2.17, y cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y alquilo.

La Realización No. 64 se refiere a un compuesto de Fórmula 1.2 o 1.3 en el cual el sustituyente Q es un resto 2.17, y cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y metilo.

La Realización No. 65 se refiere a un compuesto de Fórmula 1.2 o 1.3 en el cual el sustituyente Q es un resto 2.17, y cada R^3, R^4, R^6, y R^7 es H.

La Realización No. 66 se refiere a un compuesto de Fórmula 1.2 o 1.3 en el cual el sustituyente Q se selecciona del grupo que consiste en: resto 2.1, y: (1) cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y alquilo, o (2) cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y metilo, o (3) cada R^3, R^4, R^6, y R^7 es H.

La Realización No. 67 se refiere a un compuesto de Fórmula 1.2 o 1.3 en el cual el sustituyente Q se selecciona del grupo que consiste en: resto 2.2. y: (1) cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y alquilo, o (2) cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y metilo, o (3) cada R^3, R^4, R^6, y R^7 es H.

La Realización No. 68 se refiere a un compuesto de Fórmula 1.2 o 1.3 en el cual el sustituyente Q se selecciona del grupo que consiste en: restos 2.3A, 2.3B

y 2.3C, y: (1) cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y alquilo, o (2) cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y metilo, o (3) cada R^3, R^4, R^6, y R^7 es H.

La Realización No. 69 se refiere a un compuesto de Fórmula 1.3 donde cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y alquilo.

La Realización No. 70 se refiere a un compuesto de Fórmula 1.3 donde cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y metilo.

La Realización No. 71 se refiere a un compuesto de Fórmula 1.3 donde cada R^3, R^4, R^6, y R^7 es H.

La Realización No. 72 se refiere a un compuesto de Fórmula 1.3 en el cual sustituyente Q se selecciona del grupo que consiste en: restos 2.1, 2.2. 2.3A, 2.3B y 2.3C.

La Realización No. 73 se refiere a un compuesto de Fórmula 1.3 en el cual sustituyente Q se selecciona del grupo que consiste en: restos 2.1, 2.2. 2.3A, 2.3B y 2.3C, y cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y alquilo.

La Realización No. 74 se refiere a un compuesto de Fórmula 1.3 en el cual sustituyente Q se selecciona del grupo que consiste en: restos 2.1, 2.2. 2.3A, 2.3B y 2.3C, y cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y metilo.

La Realización No. 75 se refiere a un compuesto de Fórmula 1.3 en el cual sustituyente Q se selecciona del grupo que consiste en: restos 2.1, 2.2. 2.3A, 2.3B y 2.3C, y cada R^3, R^4, R^6, y R^7 es H.

La Realización No. 76 se refiere a un compuesto de Fórmula 1.3 en el cual sustituyente Q es un resto 2.17.

La Realización No. 77 se refiere a un compuesto de Fórmula 1.3 en el cual sustituyente Q es un resto 2.17, y cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y alquilo.

La Realización No. 78 se refiere a un compuesto de Fórmula 1.3 en el cual sustituyente Q es un resto 2.17, y cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y metilo.

La Realización No. 79 se refiere a un compuesto de Fórmula 1.3 en el cual sustituyente Q es un resto 2.17, y cada R^3, R^4, R^6, y R^7 es H.

La Realización No. 80 se refiere a un compuesto de Fórmula 1.3 en el cual sustituyente Q se selecciona del grupo que consiste en: resto 2.1, y: (1) cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y alquilo, o (2) cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y metilo, o (3) cada R^3, R^4, R^6, y R^7 es H.

La Realización No. 81 se refiere a un compuesto de Fórmula 1.3 en el cual sustituyente Q se selecciona del grupo que consiste en: resto 2.2. y: (1) cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y alquilo, o (2) cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y metilo, o (3) cada R^3, R^4, R^6, y R^7 es H.

La Realización No. 82 se refiere a un compuesto de Fórmula 1.3 en el cual sustituyente Q se selecciona del grupo que consiste en: restos 2.3A1, 2.3B y 2.3C, y: (1) cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y alquilo, o (2) cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y metilo, o (3) cada R^3, R^4, R^6, y R^7 es H.

La Realización No. 83 se refiere a un compuesto de fórmula 1.0, con preferencia un compuesto de fórmula 1.0C1 y con mayor preferencia un compuesto de fórmula 1.0C, (por ej., 1.1, 1.1A, 1.2. 1.2A, 1.3 o 1.3A) en el cual el sustituyente Q se selecciona del grupo que consiste en: restos 2.6, 2.7A, 2.7B y 2.7C.

La Realización No. 84 se refiere a un compuesto de fórmula 1.0, con preferencia un compuesto de fórmula 1.0C1 y con mayor preferencia un compuesto de fórmula 1.0C, (por ej., 1.1, 1.1A, 1.2. 1.2A, 1.3 o 1.3A) en el cual el sustituyente Q se selecciona del grupo que consiste en: restos 2.6, 2.7A, 2.7B y 2.7C, y cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y alquilo.

La Realización No. 85 se refiere a un compuesto de fórmula 1.0, con preferencia un compuesto de fórmula 1.0C1 y con mayor preferencia un compuesto de fórmula 1.0C, (por ej., 1.1, 1.1A, 1.2. 1.2A, 1.3 o 1.3A) en el cual el sustituyente Q se selecciona del grupo que consiste en: restos 2.6, 2.7A, 2.7B y 2.7C, y cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y metilo.

La Realización No. 86 se refiere a un compuesto de fórmula 1.0, con preferencia un compuesto de fórmula 1.0C1 y con mayor preferencia un compuesto de fórmula 1.0C, (por ej., 1.1, 1.1A, 1.2. 1.2A, 1.3 o 1.3A) en el cual el sustituyente Q se selecciona del grupo que consiste en: restos 2.6, 2.7A, 2.7B y 2.7C, y cada R^3, R^4, R^6, y R^7 es H.

La Realización No. 87 se refiere a un compuesto de fórmula 1.0, con preferencia un compuesto de fórmula 1.0C1 y con mayor preferencia un compuesto de fórmula 1.0C, (por ej., 1.1, 1.1A, 1.2. 1.2A, 1.3 o 1.3A) en el cual el sustituyente Q se selecciona del grupo que consiste en: resto 2.6, y: (1) cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y

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alquilo, o (2) cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y metilo, o (3) cada R^3, R^4, R^6, y R^7 es H.

La Realización No. 88 se refiere a un compuesto de fórmula 1.0, con preferencia un compuesto de fórmula 1.0C1 y con mayor preferencia un compuesto de fórmula 1.0C, (por ej., 1.1, 1.1A, 1.2. 1.2A, 1.3 o 1.3A) en el cual el sustituyente Q se selecciona del grupo que consiste en: resto 2.7A, y: (1) cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y alquilo, o (2) cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y metilo, o (3) cada R^3, R^4, R^6, y R^7 es H.

La Realización No. 89 se refiere a un compuesto de fórmula 1.0, con preferencia un compuesto de fórmula 1.0C1 y con mayor preferencia un compuesto de fórmula 1.0C, (por ej., 1.1, 1.1A, 1.2. 1.2A, 1.3 o 1.3A) en el cual el sustituyente Q se selecciona del grupo que consiste en: restos 2.7B y 2.7C, y: (1) cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y alquilo, o (2) cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y metilo, o (3) cada R^3, R^4, R^6, y R^7 es H.

La Realización No. 90 se refiere a un compuesto de Fórmula 1.2 o 1.3 en el cual el sustituyente Q se selecciona del grupo que consiste en: restos 2.6, 2.7A, 2.7B y 2.7C.

La Realización No. 91 se refiere a un compuesto de Fórmula 1.2 o 1.3 en el cual el sustituyente Q se selecciona del grupo que consiste en: restos 2.6, 2.7A, 2.7B y 2.7C, y cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y alquilo.

La Realización No. 92 se refiere a un compuesto de Fórmula 1.2 o 1.3 en el cual el sustituyente Q se selecciona del grupo que consiste en: restos 2.6, 2.7A,

2.7B y 2.7C, y cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y metilo.

La Realización No. 93 se refiere a un compuesto de Fórmula 1.2 o 1.3 en el cual el sustituyente Q se selecciona del grupo que consiste en: restos 2.6, 2.7A, 2.7B y 2.7C, y cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H.

La Realización No. 94 se refiere a un compuesto de Fórmula 1.2 o 1.3 en el cual el sustituyente Q se selecciona del grupo que consiste en: resto 2.6, y: (1) cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y alquilo, o (2) cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y metilo, o (3) cada R^3, R^4, R^6, y R^7 es H.

La Realización No. 95 se refiere a un compuesto de Fórmula 1.2 o 1.3 en el cual el sustituyente Q se selecciona del grupo que consiste en: resto 2.7A, y: (1) cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y alquilo, o (2) cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y metilo, o (3) cada R^3, R^4, R^6, y R^7 es H.

La Realización No. 96 se refiere a un compuesto de Fórmula 1.2 o 1.3 en el cual el sustituyente Q se selecciona del grupo que consiste en: restos 2.7A y 2.7B, y: (1) cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y alquilo, o (2) cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y metilo, o (3) cada R^3, R^4, R^6, y R^7 es H.

La Realización No. 97 se refiere a un compuesto de Fórmula 1.3 en el cual sustituyente Q se selecciona del grupo que consiste en: restos 2.6, 2.7A, 2.7B y 2.7C.

La Realización No. 98 se refiere a un compuesto de Fórmula 1.3 en el cual sustituyente Q se selecciona del grupo que consiste en: restos 2.6, 2.7A, 2.7B y 2.7C, y cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y alquilo.

La Realización No. 99 se refiere a un compuesto de Fórmula 1.3 en el cual sustituyente Q se selecciona del grupo que consiste en: restos 2.6, 2.7A, 2.7B y 2.7C, y cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y metilo.

La Realización No. 100 se refiere a un compuesto de Fórmula 1.3 en el cual sustituyente Q se selecciona del grupo que consiste en: restos 2.6, 2.7A, 2.7B y 2.7C, y cada R^3, R^4, R^6, y R^7 es H.

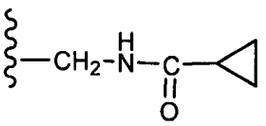
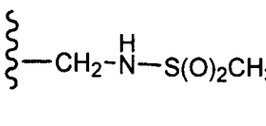
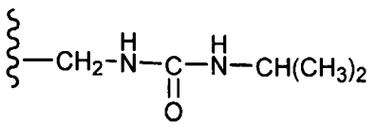
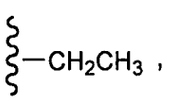
La Realización No. 101 se refiere a un compuesto de Fórmula 1.3 en el cual sustituyente Q se selecciona del grupo que consiste en: resto 2.6, y: (1) cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y alquilo, o (2) cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y metilo, o (3) cada R^3, R^4, R^6, y R^7 es H.

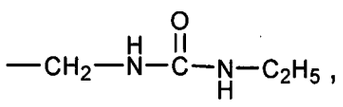
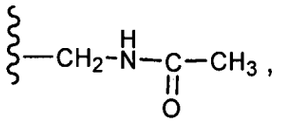
La Realización No. 102 se refiere a un compuesto de Fórmula 1.3 en el cual sustituyente Q se selecciona del grupo que consiste en: resto 2.7A, y: (1) cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y alquilo, o (2) cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y metilo, o (3) cada R^3, R^4, R^6, y R^7 es H.

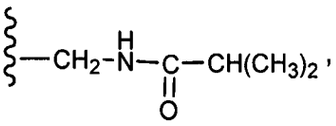
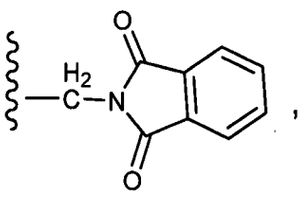
La Realización No. 103 se refiere a un compuesto de Fórmula 1.3 en el cual sustituyente Q se selecciona del grupo que consiste en: restos 2.7B y 2.7C, y: (1) cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y alquilo, o (2) cada R^3, R^4, R^6, y R^7 se selecciona en forma

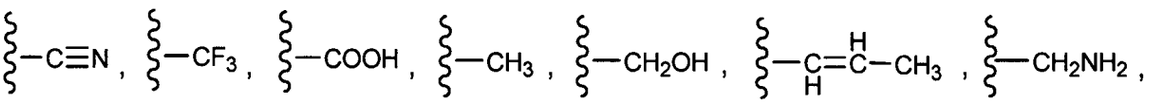
independiente del grupo que consiste en: H y metilo, o (3) cada R^3, R^4, R^6, y R^7 es H.

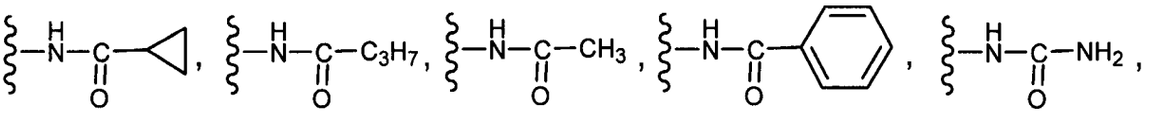
La Realización No. 104 se refiere a un compuesto de cualquiera de las Realizaciones Nos. 1 hasta 103, en el cual R^1 se selecciona del grupo que consiste en:

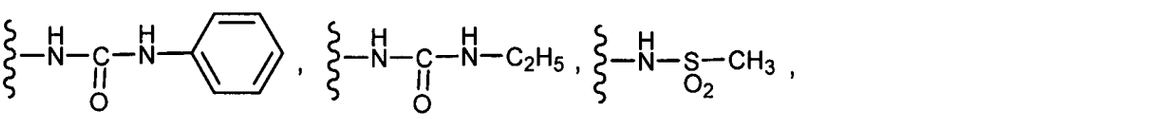





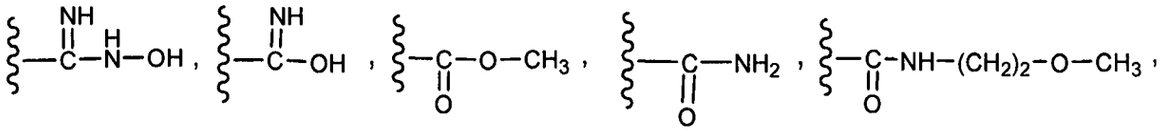



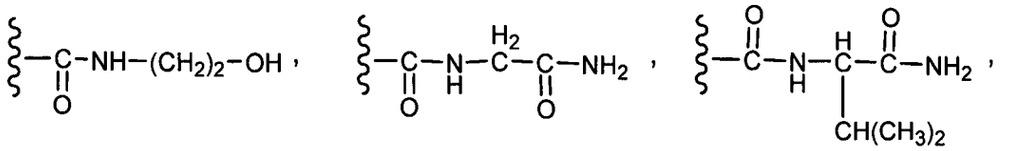


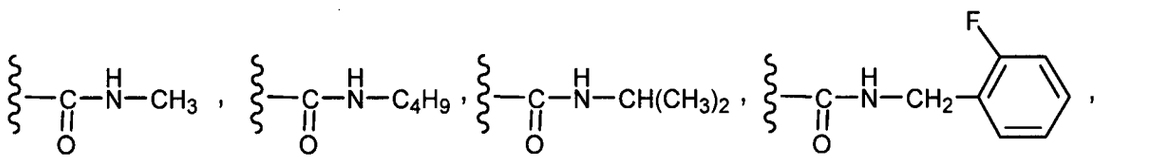


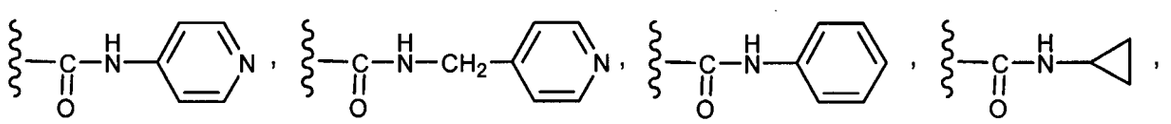


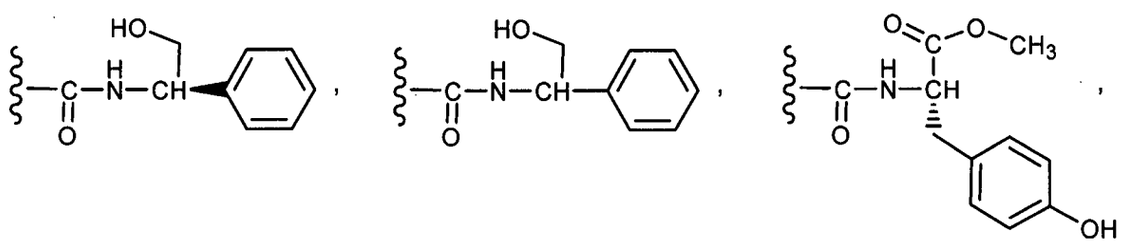
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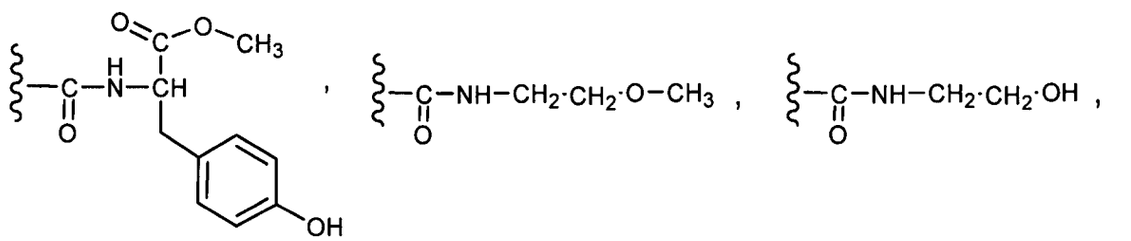


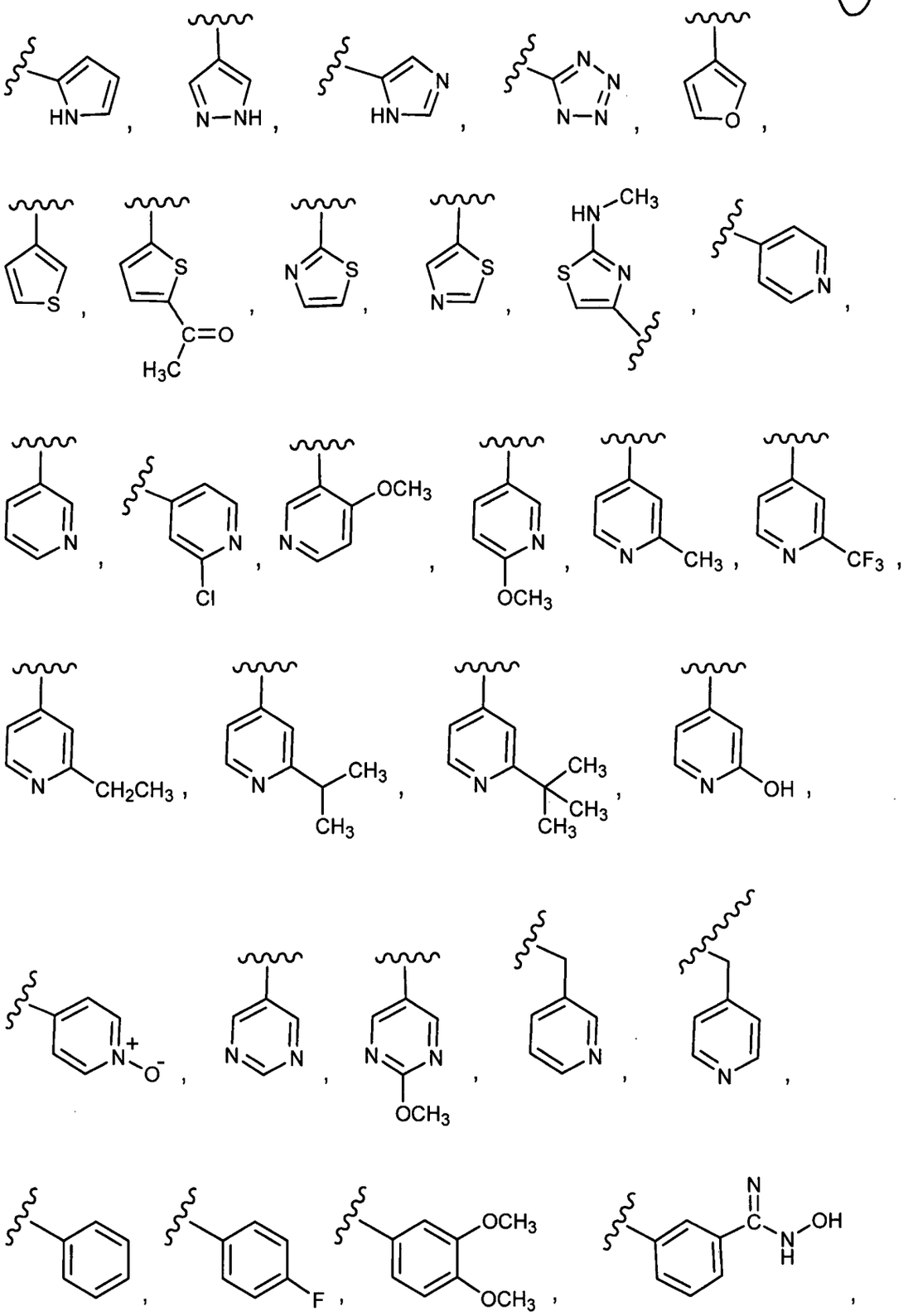


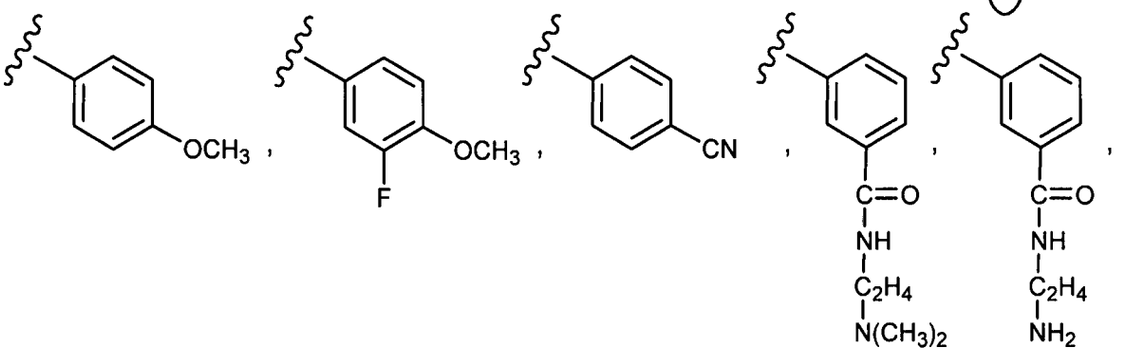


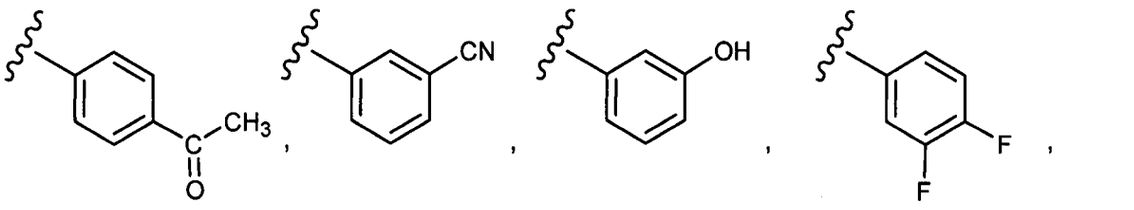


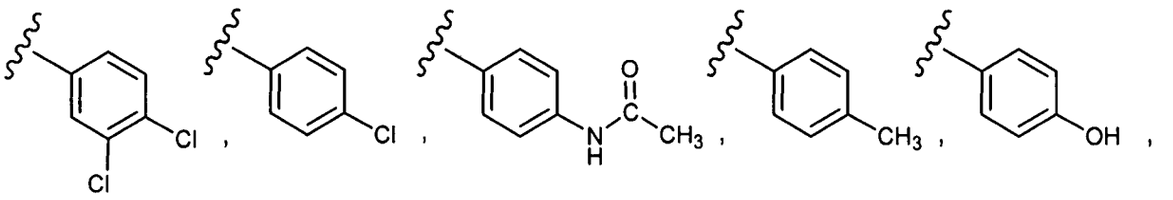


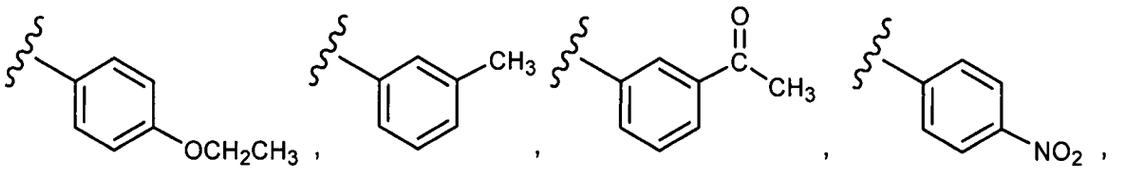


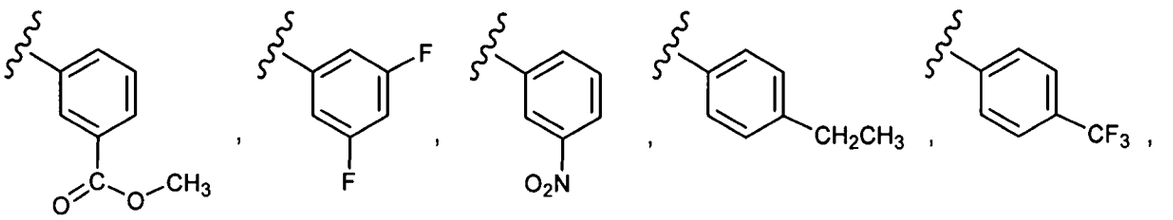


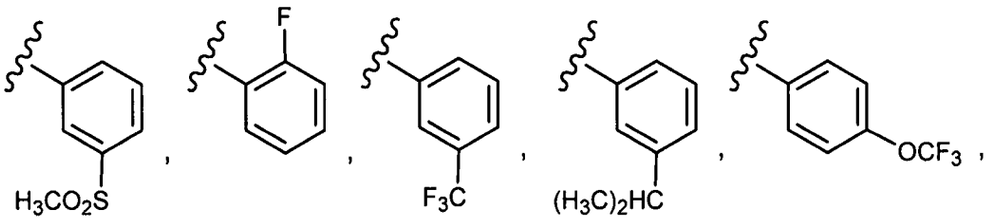

OCH3
OCH3
F
CN
C=O
NH
C2H4
N(CH3)2
C=O
NH
C2H4
NH2

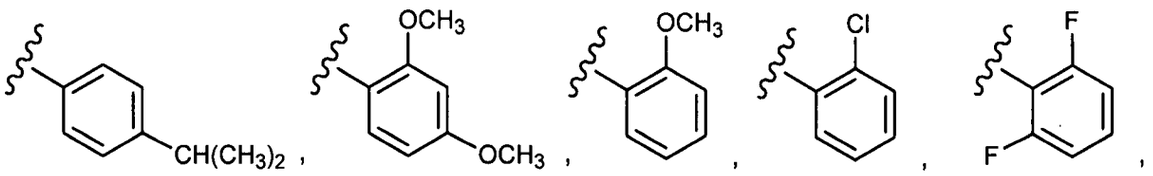

CH3
C
O
CN
OH
F
F

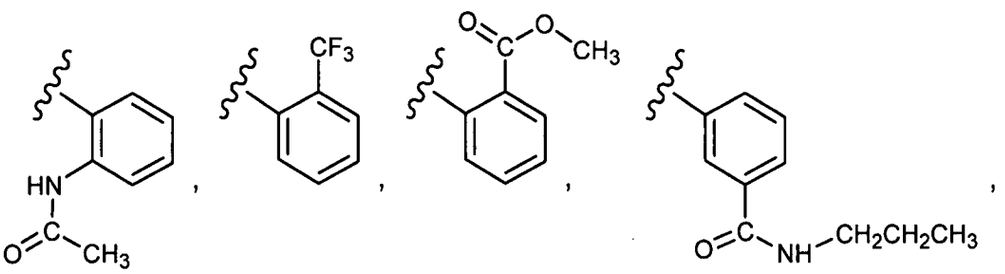

Cl
Cl
Cl
N
H
C
O
CH3
CH3
OH

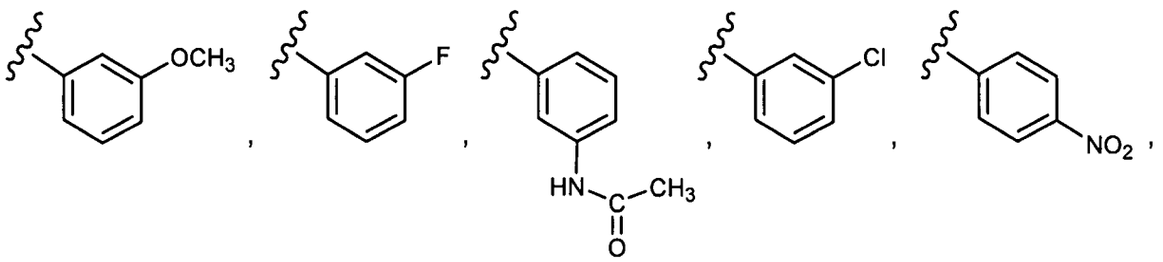

OCH2CH3
CH3
C
O
CH3
NO2

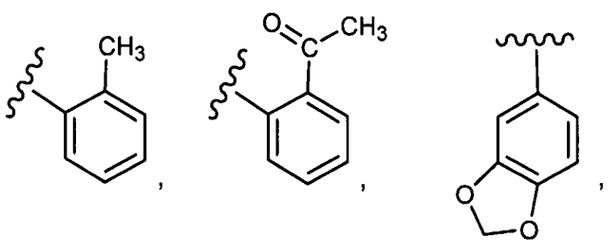

O
C
O
CH3
F
F
O2N
CH2CH3
CF3

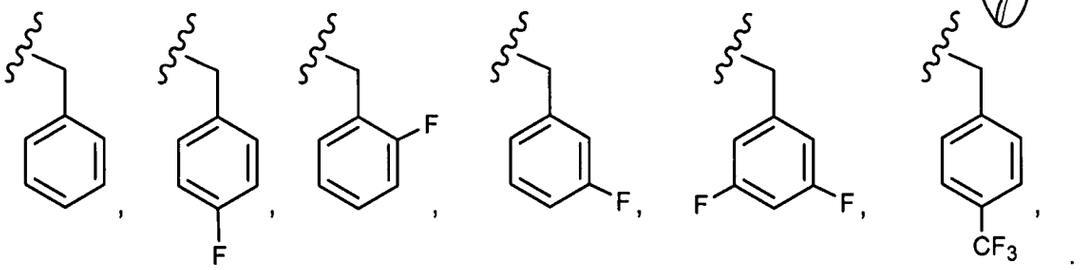

F
H_3CO_2S
F_3C
$(H_3C)_2HC$
OCF_3

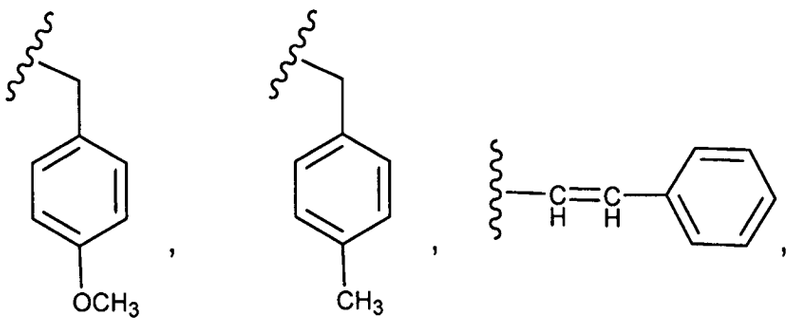

$CH(CH_3)_2$
OCH_3
OCH_3
Cl
F
F

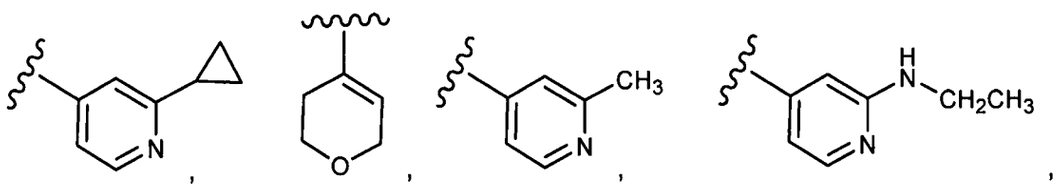

HN
O
CH_3
CF_3
O
O
CH_3
O
NH
$CH_2CH_2CH_3$

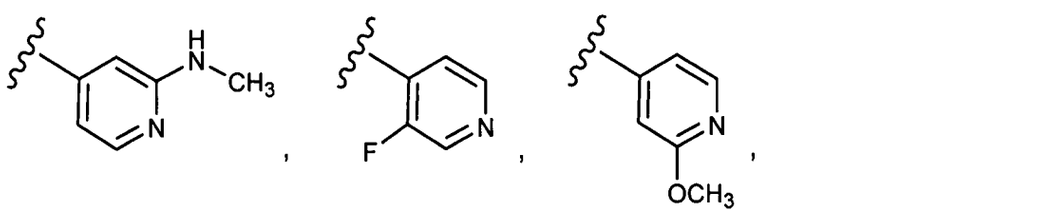

OCH_3
F
HN
C
CH_3
O
Cl
NO_2

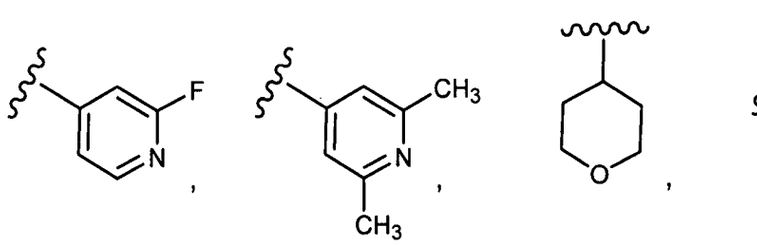

CH_3
O
C
CH_3
O
O

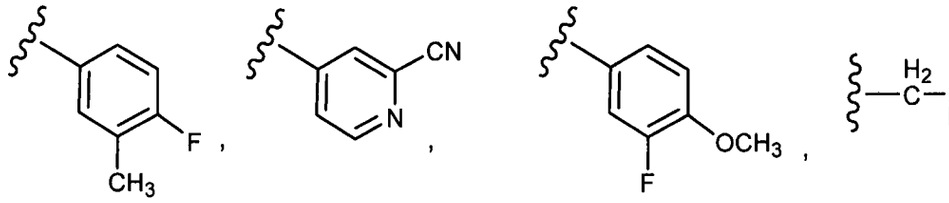


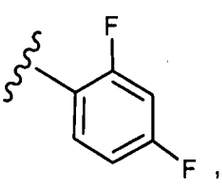
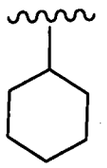
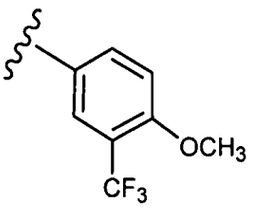
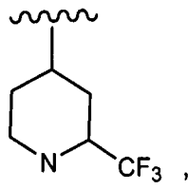
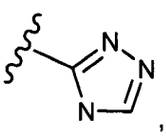
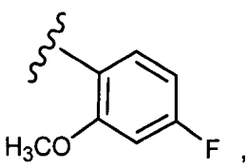
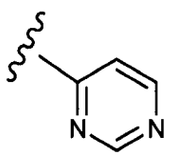
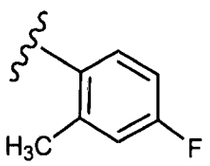
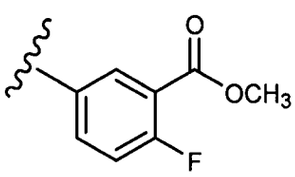
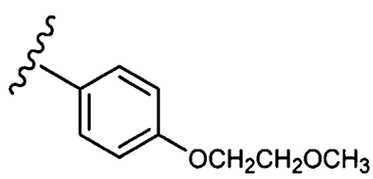
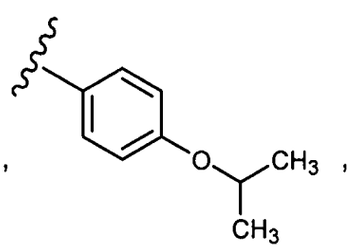
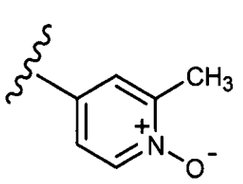
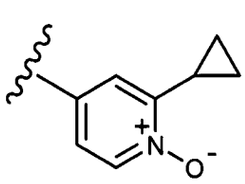
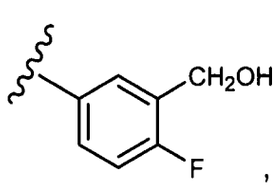
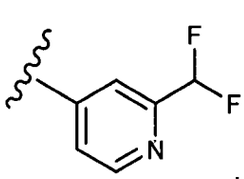
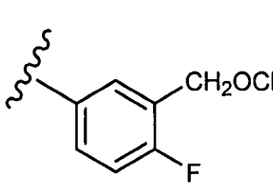


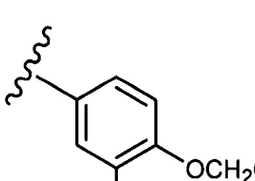
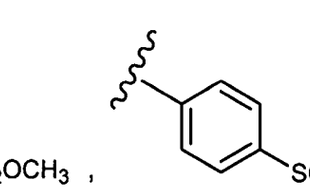
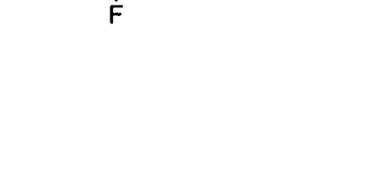
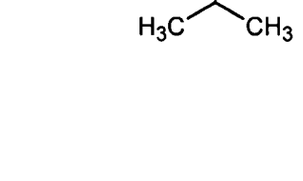


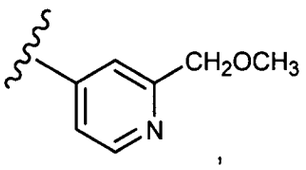
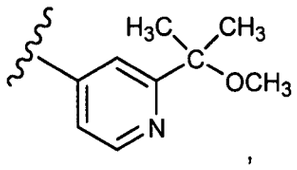
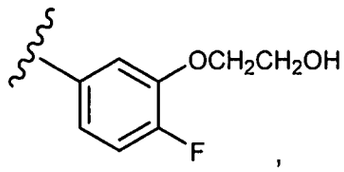
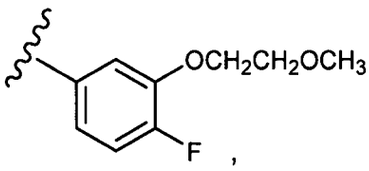
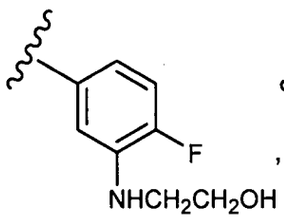
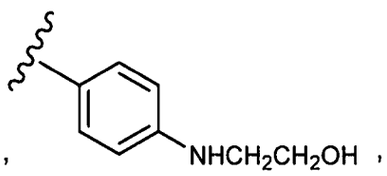
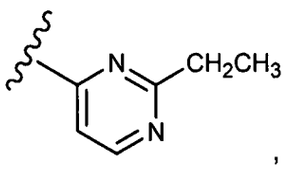
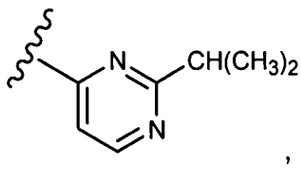
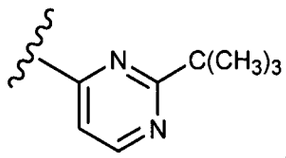
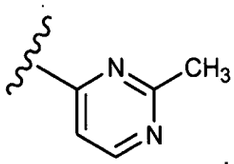
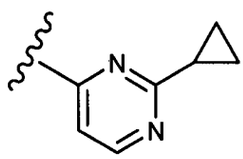
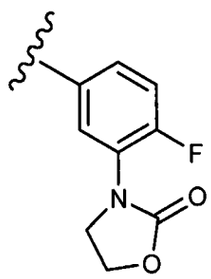
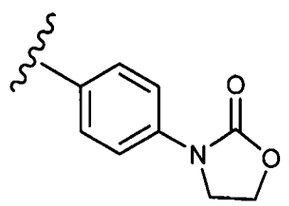
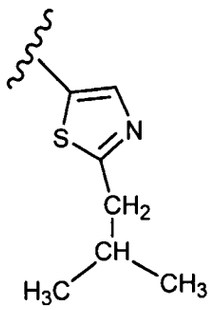
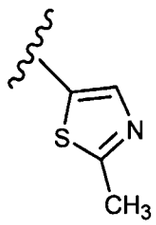
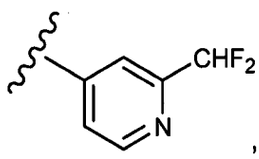
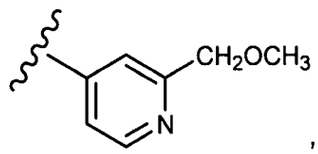


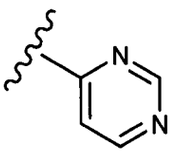
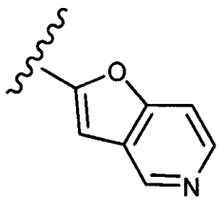




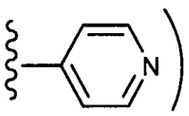






CH2OCH3
N
,

H3C
CH3
C
OCH3
N
,

OCH2CH2OH
F
,

OCH2CH2OCH3
F
,

F
NHCH2CH2OH
,

NHCH2CH2OH
,

N
CH2CH3
N
,

N
CH(CH3)2
N
,

N
C(CH3)3
N
,

N
CH3
N
,

N
N
,

F
N
O
O

O
N
O
,

S
N
CH2
CH
H3C
CH3

S
N
CH3
,

CHF2
N
,

CH2OCH3
N
,

 y  .

La Realización No. 105 se refiere a un compuesto de cualquiera de las Realizaciones Nos. 1 hasta 103, en el cual R^1 es arilo (por ej., fenilo).

La Realización No. 106 se refiere a un compuesto de cualquiera de las Realizaciones Nos. 1 hasta 103, en el cual R^1 es arilo sustituido (por ej., sustituido fenilo).

La Realización No. 107 se refiere a un compuesto de cualquiera de las Realizaciones Nos. 1 hasta 103, en el cual R^1 es heteroarilo (por ej., piridilo, tales como ).

La Realización No. 108 se refiere a un compuesto de cualquiera de las Realizaciones Nos. 1 hasta 103, en el cual R^1 es heteroarilo sustituido (por ej., sustituido piridilo).

La Realización No. 109 se refiere a un compuesto de cualquiera de las Realizaciones Nos. 1 hasta 103, en el cual R^1 es piridilo sustituido con cicloalquilo (por ej., ciclopropilo).

La Realización No. 110 se refiere a un compuesto de cualquiera de las Realizaciones Nos. 1 hasta 103, en el cual R^1 es piridilo sustituido con ciclopropilo.

La Realización No. 111 se refiere a un compuesto de cualquiera de las Realizaciones Nos. 1 hasta 103, en el cual R^1 es:

 .

La Realización No. 112 se refiere a un compuesto de cualquiera de las Realizaciones Nos. 1 hasta 103, en el cual R^1 es fenilo sustituido con halo.

La Realización No. 113 se refiere a un compuesto de cualquiera de las Realizaciones Nos. 1 hasta 103, en el cual R^1 es fenilo sustituido con F.

La Realización No. 114 se refiere a un compuesto de cualquiera de las Realizaciones Nos. 1 hasta 103, en el cual R^1 es p-F-fenilo.

La Realización No. 115 se refiere a un compuesto de cualquiera de las Realizaciones Nos. 1 hasta 103, en el cual R^1 es piridilo sustituido con $-CF_3$.

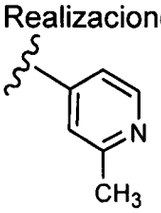
La Realización No. 116 se refiere a un compuesto de cualquiera de las Realizaciones Nos. 1 hasta 103, en el cual R^1 es:



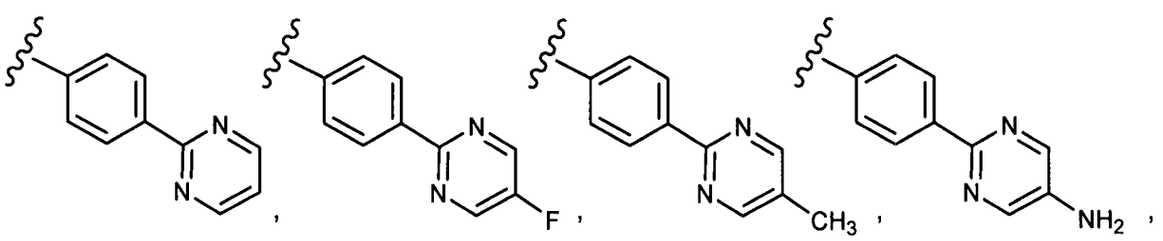
La Realización No. 117 se refiere a un compuesto de cualquiera de las Realizaciones Nos. 1 hasta 103, en el cual R^1 es piridilo sustituido con alquilo.

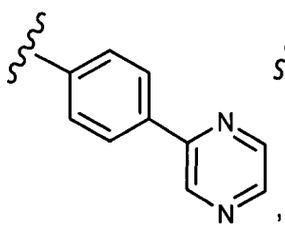
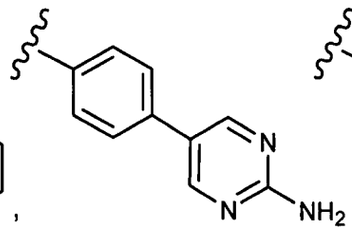
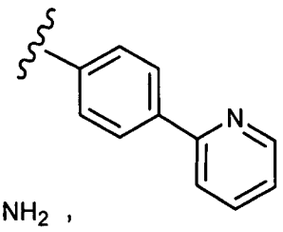
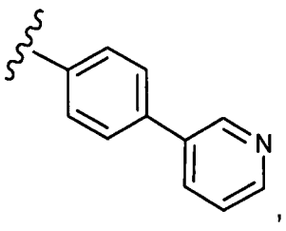
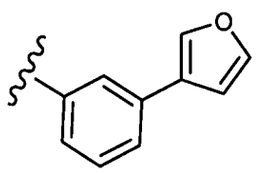
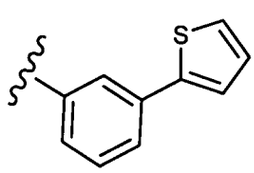
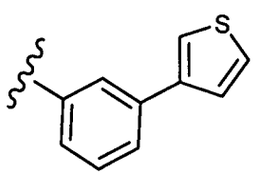
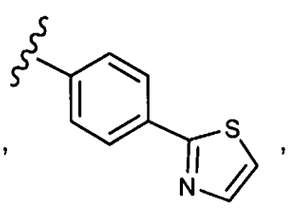
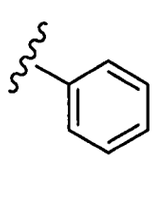
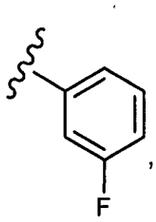
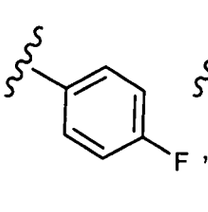
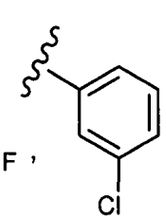
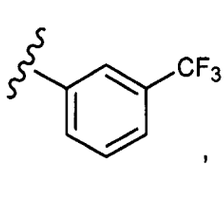
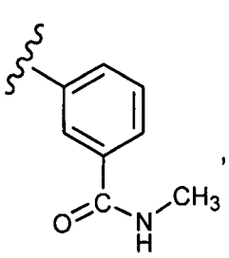
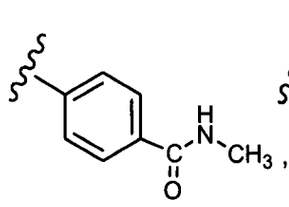
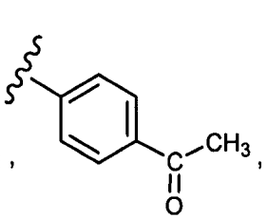
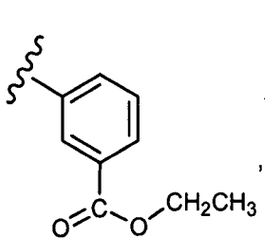
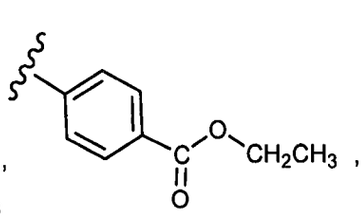
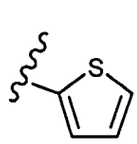
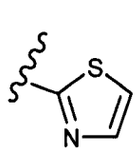
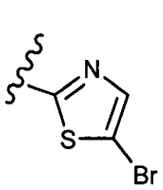
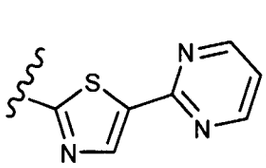
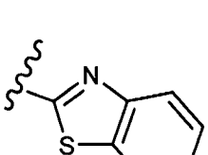
La Realización No. 118 se refiere a un compuesto de cualquiera de las Realizaciones Nos. 1 hasta 103, en el cual R^1 es piridilo sustituido con metilo.

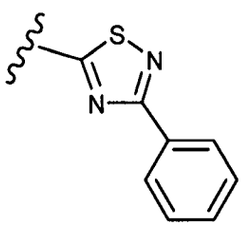
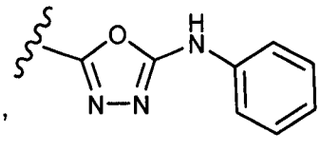
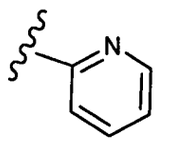
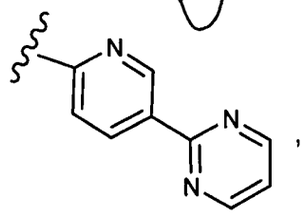
La Realización No. 119 se refiere a un compuesto de cualquiera de las Realizaciones Nos. 1 hasta 103, en el cual R^1 es:

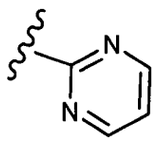
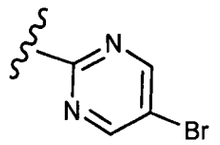
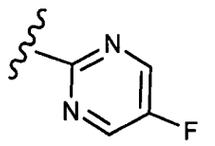
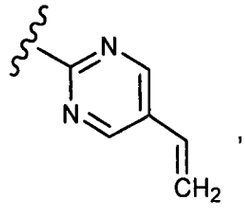


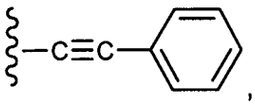
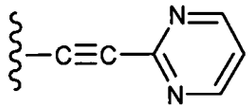
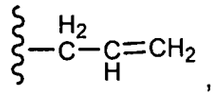
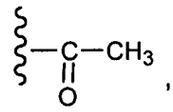
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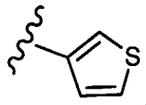
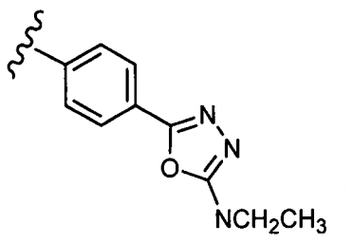
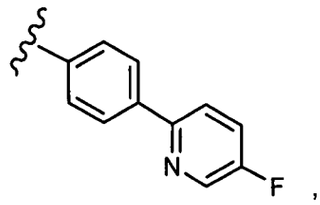


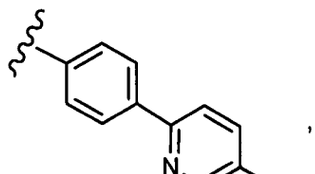
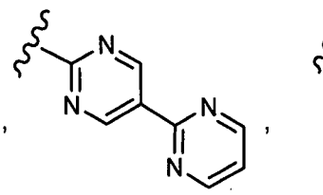
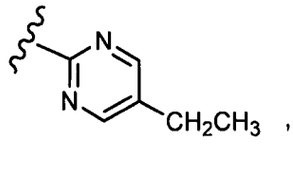
























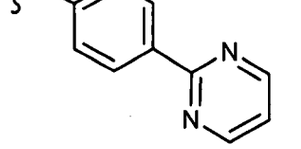

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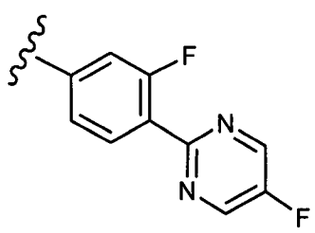
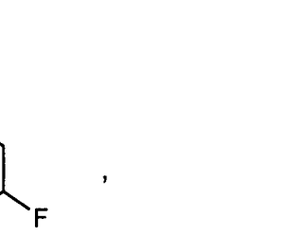

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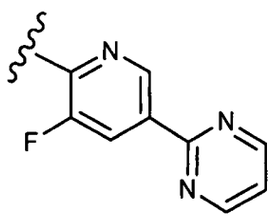
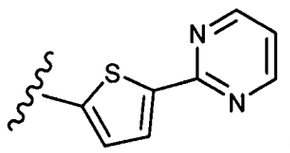
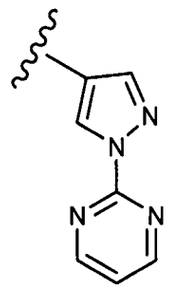
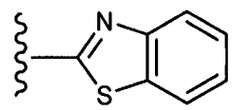
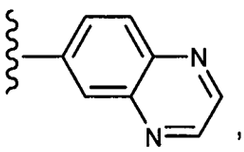
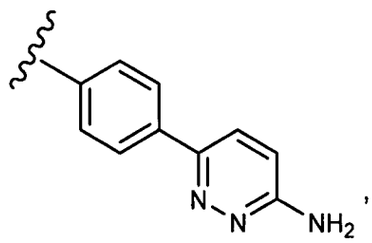
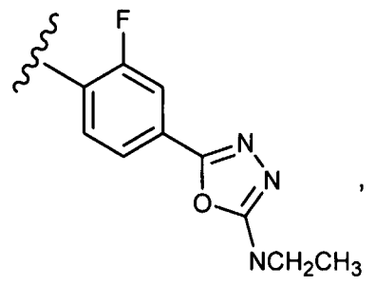
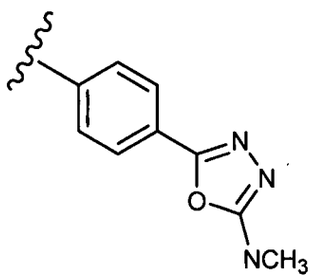
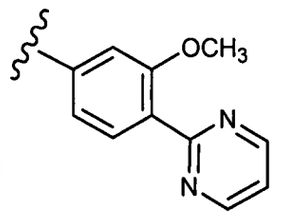
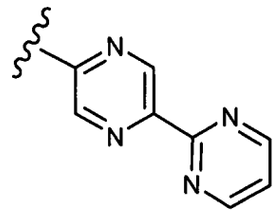
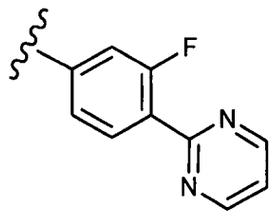
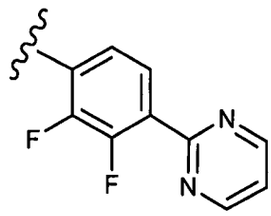
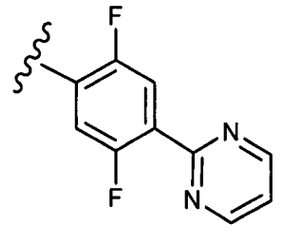
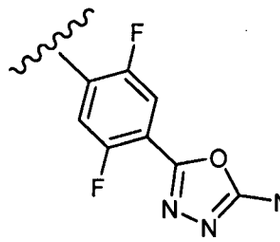
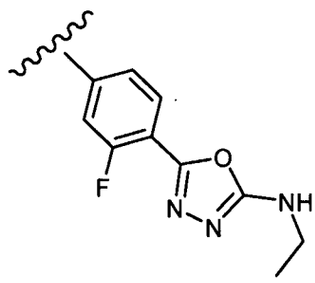

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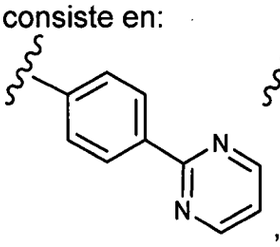
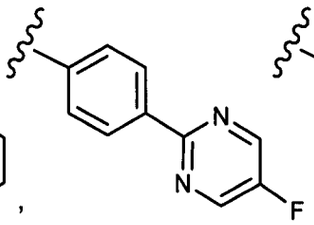
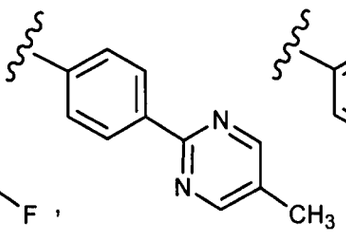
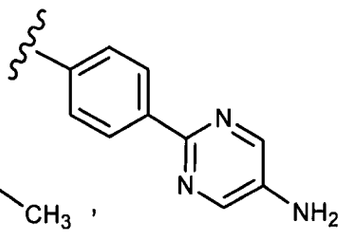

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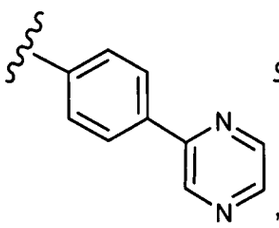
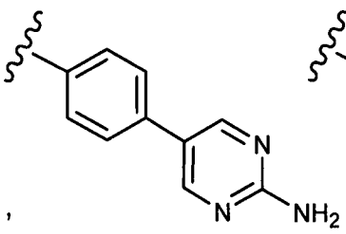
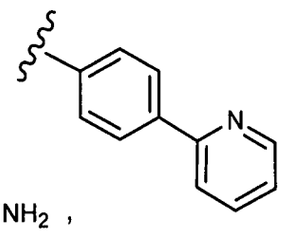
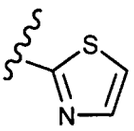

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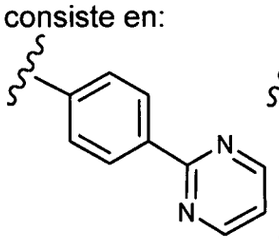
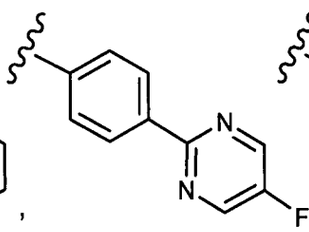
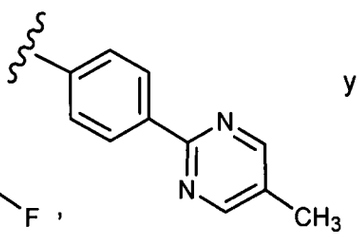
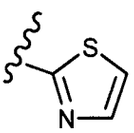

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La Realización No. 121 se refiere a un compuesto de cualquiera de las Realizaciones Nos. 1 hasta 103 en el cual R^5 se selecciona del grupo que consiste en:

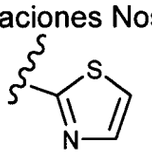

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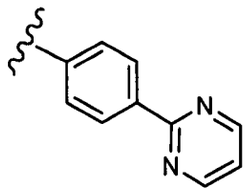
La Realización No. 122 se refiere a un compuesto de cualquiera de las Realizaciones Nos. 1 hasta 103 en el cual R^5 se selecciona del grupo que consiste en:


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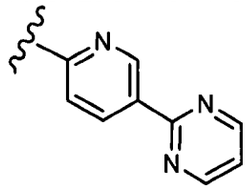
La Realización No. 123 se refiere a un compuesto de cualquiera de las Realizaciones Nos. 1 hasta 103 en el cual R^5 es


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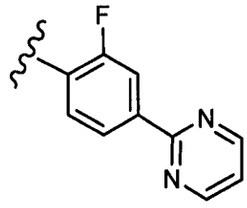
La Realización No. 124 se refiere a un compuesto de cualquiera de las Realizaciones Nos. 1 hasta 103 en el cual R^5 es



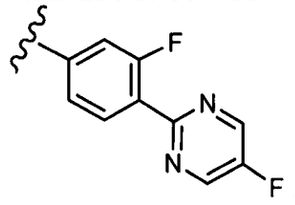
La Realización No. 125 se refiere a un compuesto de cualquiera de las Realizaciones Nos. 1 hasta 103 en el cual R^5 es



La Realización No. 126 se refiere a un compuesto de cualquiera de las Realizaciones Nos. 1 hasta 103 en el cual R^5 es



La Realización No. 127 se refiere a un compuesto de cualquiera de las Realizaciones Nos. 1 hasta 103 en el cual R^5 es



La Realización No. 128 se refiere a un compuesto de cualquiera de las Realizaciones Nos. 1 hasta 103 en el cual R^1 se selecciona del grupo que consiste en the R^1 grupos of cualquiera de las Realizaciones Nos. 104, 105, 106, 107, 108, 109, 110, 111, 112. 113, 114, 115, 116, 117, 118, o 119 y donde R^5 se selecciona del grupo que consiste en the R^5 grupos en cualquiera de las Realizaciones No. 120, 121, 122. 123, 124, 125, 126, o 127.

La Realización No. 129 se refiere a un compuesto de cualquiera de las Realizaciones Nos. 1 hasta 128 donde R^2 se selecciona del grupo que consiste en H, $-CH_2OH$ y $-CH_2F$.

La Realización No. 130 se refiere a un compuesto de cualquiera de las Realizaciones Nos. 1 hasta 128 donde R^2 es H.

La Realización No. 131 se refiere a un compuesto de cualquiera de las Realizaciones Nos. 1 hasta 128 donde R^2 es $-OR^{23}$ donde R^{23} es alquilo.

La Realización No. 132 se refiere a un compuesto de cualquiera de las Realizaciones Nos. 1 hasta 128 donde R^2 es $-OCH_3$.

La Realización No. 133 se refiere a un compuesto de cualquiera de las Realizaciones Nos. 1 hasta 128 donde R^2 es –CN.

La Realización No. 134 se refiere a un compuesto de cualquiera de las Realizaciones Nos. 1 hasta 128 donde R^2 es $-OCHF_2$.

La Realización No. 135 se refiere a un compuesto de cualquiera de las Realizaciones Nos. 1 hasta 30, 32 hasta 35, 41, 42, 44 hasta 46, 48 hasta 50, 52 hasta 56, 58 hasta 60, 62 hasta 64, 66 hasta 70, 72 hasta 74, 76 hasta 78, 80 hasta 85, 87 hasta 92, 94 hasta 99 y 101 hasta 134 donde R^3 es $-CH_3$, siempre que, como lo apreciarán aquellas personas con experiencia en el arte, la Realización No. 135 no se aplica a ninguna realización anterior en la cual R^3 ya se ha limitado a H.

La Realización No. 136 se refiere a un compuesto de cualquiera de las Realizaciones Nos. 1 hasta 30, 32 hasta 35, 41, 42, 44 hasta 46, 48 hasta 50, 52 hasta 56, 58 hasta 60, 62 hasta 64, 66 hasta 70, 72 hasta 74, 76 hasta 78, 80 hasta 85, 87 hasta 92, 94 hasta 99 y 101 hasta 134 donde R^4 es $-CH_3$, siempre que, como lo apreciarán aquellas personas con experiencia en el arte, la Realización No. 135 no se aplica a ninguna realización anterior en la cual R^4 ya se ha limitado a H.

La Realización No. 137 se refiere a un compuesto de cualquiera de las Realizaciones Nos. 1 hasta 15, 18 hasta 19, 21 hasta 30, 32 hasta 35, 41 hasta 42, 44 hasta 46, 48 hasta 50, 52 hasta 56, 58 hasta 60, 62, 64, 66 hasta 70, 72

hasta 74, 76 hasta 78, 80 hasta 85, 87 hasta 92, 94 hasta 99 y 101 hasta 134 donde R^6 es $-CH_3$, siempre que, como lo apreciarán aquellas personas con experiencia en el arte, la Realización No. 135 no se aplica a ninguna realización anterior en la cual R^6 ya se ha limitado a H, o donde R^6 está ausente de la fórmula (por ej., cuando Q es 2.12. 2.13 o 2.16).

La Realización No. 138 se refiere a un compuesto de cualquiera de las Realizaciones Nos. 1 hasta 30, 32 hasta 35, 41, 42, 44 hasta 46, 48 hasta 50, 52 hasta 56, 58 hasta 60, 62 hasta 64, 66 hasta 70, 72 hasta 74, 76 hasta 78, 80 hasta 85, 87 hasta 92, 94 hasta 99 y 101 hasta 134 donde R^7 es $-CH_3$, siempre que, como lo apreciarán aquellas personas con experiencia en el arte, la Realización No. 135 no se aplica a ninguna realización anterior en la cual R^7 ya se ha limitado a H.

La Realización No. 139 se refiere a compuestos seleccionados del grupo que consiste en los compuestos finales de los Ejemplos 612 hasta 827.

De este modo una realización se refiere al compuesto final del Ejemplo 612. Otra realización se refiere al compuesto final del Ejemplo 613. Otra realización se refiere al compuesto final del Ejemplo 614. Otra realización se refiere al compuesto final del Ejemplo 615. Otra realización se refiere al compuesto final del Ejemplo 616. Otra realización se refiere al compuesto final del Ejemplo 617. Otra realización se refiere al compuesto final del Ejemplo 618. Otra realización se refiere al compuesto final del Ejemplo 619. Otra realización se refiere al compuesto final del Ejemplo 620. Otra realización se refiere al compuesto final del Ejemplo 621. Otra realización se refiere al compuesto final del Ejemplo 622. Otra realización se refiere al compuesto final del Ejemplo 623. Otra realización se refiere al compuesto final del Ejemplo 624. Otra realización se refiere al compuesto final del Ejemplo 625. Otra realización se refiere al compuesto final del Ejemplo 626. Otra realización se refiere al compuesto final

del Ejemplo 627. Otra realización se refiere al compuesto final del Ejemplo 628. Otra realización se refiere al compuesto final del Ejemplo 629. Otra realización se refiere al compuesto final del Ejemplo 630. Otra realización se refiere al compuesto final del Ejemplo 631. Otra realización se refiere al compuesto final del Ejemplo 632. Otra realización se refiere al compuesto final del Ejemplo 633. Otra realización se refiere al compuesto final del Ejemplo 634. Otra realización se refiere al compuesto final del Ejemplo 635. Otra realización se refiere al compuesto final del Ejemplo 636. Otra realización se refiere al compuesto final del Ejemplo 637. Otra realización se refiere al compuesto final del Ejemplo 638. Otra realización se refiere al compuesto final del Ejemplo 639. Otra realización se refiere al compuesto final del Ejemplo 640. Otra realización se refiere al compuesto final del Ejemplo 641. Otra realización se refiere al compuesto final del Ejemplo 642. Otra realización se refiere al compuesto final del Ejemplo 643. Otra realización se refiere al compuesto final del Ejemplo 644. Otra realización se refiere al compuesto final del Ejemplo 645. Otra realización se refiere al compuesto final del Ejemplo 646. Otra realización se refiere al compuesto final del Ejemplo 647. Otra realización se refiere al compuesto final del Ejemplo 648. Otra realización se refiere al compuesto final del Ejemplo 649. Otra realización se refiere al compuesto final del Ejemplo 650. Otra realización se refiere al compuesto final del Ejemplo 651. Otra realización se refiere al compuesto final del Ejemplo 652. Otra realización se refiere al compuesto final del Ejemplo 653. Otra realización se refiere al compuesto final del Ejemplo 654. Otra realización se refiere al compuesto final del Ejemplo 655. Otra realización se refiere al compuesto final del Ejemplo 656. Otra realización se refiere al compuesto final del Ejemplo 657. Otra realización se refiere al compuesto final del Ejemplo 658. Otra realización se refiere al compuesto final del Ejemplo 659. Otra realización se refiere al compuesto final del Ejemplo 660. Otra realización se refiere al

compuesto final del Ejemplo 661. Otra realización se refiere al compuesto final del Ejemplo 662. Otra realización se refiere al compuesto final del Ejemplo 663. Otra realización se refiere al compuesto final del Ejemplo 664. Otra realización se refiere al compuesto final del Ejemplo 665. Otra realización se refiere al compuesto final del Ejemplo 666. Otra realización se refiere al compuesto final del Ejemplo 667. Otra realización se refiere al compuesto final del Ejemplo 668. Otra realización se refiere al compuesto final del Ejemplo 669. Otra realización se refiere al compuesto final del Ejemplo 670. Otra realización se refiere al compuesto final del Ejemplo 671. Otra realización se refiere al compuesto final del Ejemplo 672. Otra realización se refiere al compuesto final del Ejemplo 673. Otra realización se refiere al compuesto final del Ejemplo 674. Otra realización se refiere al compuesto final del Ejemplo 675. Otra realización se refiere al compuesto final del Ejemplo 676. Otra realización se refiere al compuesto final del Ejemplo 677. Otra realización se refiere al compuesto final del Ejemplo 678. Otra realización se refiere al compuesto final del Ejemplo 679. Otra realización se refiere al compuesto final del Ejemplo 680. Otra realización se refiere al compuesto final del Ejemplo 681. Otra realización se refiere al compuesto final del Ejemplo 682. Otra realización se refiere al compuesto final del Ejemplo 683. Otra realización se refiere al compuesto final del Ejemplo 684. Otra realización se refiere al compuesto final del Ejemplo 685. Otra realización se refiere al compuesto final del Ejemplo 686. Otra realización se refiere al compuesto final del Ejemplo 687. Otra realización se refiere al compuesto final del Ejemplo 688. Otra realización se refiere al compuesto final del Ejemplo 689. Otra realización se refiere al compuesto final del Ejemplo 690. Otra realización se refiere al compuesto final del Ejemplo 691. Otra realización se refiere al compuesto final del Ejemplo 692. Otra realización se refiere al compuesto final del Ejemplo 693. Otra realización se refiere al compuesto final del Ejemplo 694. Otra realización se

refiere al compuesto final del Ejemplo 695. Otra realización se refiere al compuesto final del Ejemplo 696. Otra realización se refiere al compuesto final del Ejemplo 697. Otra realización se refiere al compuesto final del Ejemplo 698. Otra realización se refiere al compuesto final del Ejemplo 699. Otra realización se refiere al compuesto final del Ejemplo 700. Otra realización se refiere al compuesto final del Ejemplo 701. Otra realización se refiere al compuesto final del Ejemplo 702. Otra realización se refiere al compuesto final del Ejemplo 703. Otra realización se refiere al compuesto final del Ejemplo 704. Otra realización se refiere al compuesto final del Ejemplo 705. Otra realización se refiere al compuesto final del Ejemplo 706. Otra realización se refiere al compuesto final del Ejemplo 707. Otra realización se refiere al compuesto final del Ejemplo 708. Otra realización se refiere al compuesto final del Ejemplo 709. Otra realización se refiere al compuesto final del Ejemplo 710. Otra realización se refiere al compuesto final del Ejemplo 711. Otra realización se refiere al compuesto final del Ejemplo 712. Otra realización se refiere al compuesto final del Ejemplo 713. Otra realización se refiere al compuesto final del Ejemplo 714. Otra realización se refiere al compuesto final del Ejemplo 715. Otra realización se refiere al compuesto final del Ejemplo 716. Otra realización se refiere al compuesto final del Ejemplo 717. Otra realización se refiere al compuesto final del Ejemplo 718. Otra realización se refiere al compuesto final del Ejemplo 719. Otra realización se refiere al compuesto final del Ejemplo 720. Otra realización se refiere al compuesto final del Ejemplo 721. Otra realización se refiere al compuesto final del Ejemplo 722. Otra realización se refiere al compuesto final del Ejemplo 723. Otra realización se refiere al compuesto final del Ejemplo 724. Otra realización se refiere al compuesto final del Ejemplo 725. Otra realización se refiere al compuesto final del Ejemplo 726. Otra realización se refiere al compuesto final del Ejemplo 727. Otra realización se refiere al compuesto final del Ejemplo 728.

Otra realización se refiere al compuesto final del Ejemplo 729. Otra realización se refiere al compuesto final del Ejemplo 730. Otra realización se refiere al compuesto final del Ejemplo 731. Otra realización se refiere al compuesto final del Ejemplo 732. Otra realización se refiere al compuesto final del Ejemplo 733. Otra realización se refiere al compuesto final del Ejemplo 734. Otra realización se refiere al compuesto final del Ejemplo 735. Otra realización se refiere al compuesto final del Ejemplo 736. Otra realización se refiere al compuesto final del Ejemplo 737. Otra realización se refiere al compuesto final del Ejemplo 738. Otra realización se refiere al compuesto final del Ejemplo 739. Otra realización se refiere al compuesto final del Ejemplo 740. Otra realización se refiere al compuesto final del Ejemplo 741. Otra realización se refiere al compuesto final del Ejemplo 742. Otra realización se refiere al compuesto final del Ejemplo 743. Otra realización se refiere al compuesto final del Ejemplo 744. Otra realización se refiere al compuesto final del Ejemplo 745. Otra realización se refiere al compuesto final del Ejemplo 746. Otra realización se refiere al compuesto final del Ejemplo 747. Otra realización se refiere al compuesto final del Ejemplo 748. Otra realización se refiere al compuesto final del Ejemplo 749. Otra realización se refiere al compuesto final del Ejemplo 750. Otra realización se refiere al compuesto final del Ejemplo 751. Otra realización se refiere al compuesto final del Ejemplo 752. Otra realización se refiere al compuesto final del Ejemplo 753. Otra realización se refiere al compuesto final del Ejemplo 754. Otra realización se refiere al compuesto final del Ejemplo 755. Otra realización se refiere al compuesto final del Ejemplo 756. Otra realización se refiere al compuesto final del Ejemplo 757. Otra realización se refiere al compuesto final del Ejemplo 758. Otra realización se refiere al compuesto final del Ejemplo 759. Otra realización se refiere al compuesto final del Ejemplo 760. Otra realización se refiere al compuesto final del Ejemplo 761. Otra realización se refiere al compuesto final

del Ejemplo 762. Otra realización se refiere al compuesto final del Ejemplo 763. Otra realización se refiere al compuesto final del Ejemplo 764. Otra realización se refiere al compuesto final del Ejemplo 765. Otra realización se refiere al compuesto final del Ejemplo 766. Otra realización se refiere al compuesto final del Ejemplo 767. Otra realización se refiere al compuesto final del Ejemplo 768. Otra realización se refiere al compuesto final del Ejemplo 769. Otra realización se refiere al compuesto final del Ejemplo 770. Otra realización se refiere al compuesto final del Ejemplo 671. Otra realización se refiere al compuesto final del Ejemplo 772. Otra realización se refiere al compuesto final del Ejemplo 773. Otra realización se refiere al compuesto final del Ejemplo 774. Otra realización se refiere al compuesto final del Ejemplo 775. Otra realización se refiere al compuesto final del Ejemplo 776. Otra realización se refiere al compuesto final del Ejemplo 777. Otra realización se refiere al compuesto final del Ejemplo 778. Otra realización se refiere al compuesto final del Ejemplo 779. Otra realización se refiere al compuesto final del Ejemplo 780. Otra realización se refiere al compuesto final del Ejemplo 781. Otra realización se refiere al compuesto final del Ejemplo 782. Otra realización se refiere al compuesto final del Ejemplo 783. Otra realización se refiere al compuesto final del Ejemplo 784. Otra realización se refiere al compuesto final del Ejemplo 785. Otra realización se refiere al compuesto final del Ejemplo 786. Otra realización se refiere al compuesto final del Ejemplo 787. Otra realización se refiere al compuesto final del Ejemplo 788. Otra realización se refiere al compuesto final del Ejemplo 789. Otra realización se refiere al compuesto final del Ejemplo 790. Otra realización se refiere al compuesto final del Ejemplo 791. Otra realización se refiere al compuesto final del Ejemplo 792. Otra realización se refiere al compuesto final del Ejemplo 793. Otra realización se refiere al compuesto final del Ejemplo 794. Otra realización se refiere al compuesto final del Ejemplo 795. Otra realización se refiere al

compuesto final del Ejemplo 796. Otra realización se refiere al compuesto final del Ejemplo 797. Otra realización se refiere al compuesto final del Ejemplo 798. Otra realización se refiere al compuesto final del Ejemplo 799. Otra realización se refiere al compuesto final del Ejemplo 800. Otra realización se refiere al compuesto final del Ejemplo 801. Otra realización se refiere al compuesto final del Ejemplo 802. Otra realización se refiere al compuesto final del Ejemplo 803. Otra realización se refiere al compuesto final del Ejemplo 804. Otra realización se refiere al compuesto final del Ejemplo 805. Otra realización se refiere al compuesto final del Ejemplo 806. Otra realización se refiere al compuesto final del Ejemplo 807. Otra realización se refiere al compuesto final del Ejemplo 808. Otra realización se refiere al compuesto final del Ejemplo 809. Otra realización se refiere al compuesto final del Ejemplo 810. Otra realización se refiere al compuesto final del Ejemplo 811. Otra realización se refiere al compuesto final del Ejemplo 812. Otra realización se refiere al compuesto final del Ejemplo 813. Otra realización se refiere al compuesto final del Ejemplo 814. Otra realización se refiere al compuesto final del Ejemplo 815. Otra realización se refiere al compuesto final del Ejemplo 816. Otra realización se refiere al compuesto final del Ejemplo 817. Otra realización se refiere al compuesto final del Ejemplo 818. Otra realización se refiere al compuesto final del Ejemplo 819. Otra realización se refiere al compuesto final del Ejemplo 820. Otra realización se refiere al compuesto final del Ejemplo 821. Otra realización se refiere al compuesto final del Ejemplo 822. Otra realización se refiere al compuesto final del Ejemplo 823. Otra realización se refiere al compuesto final del Ejemplo 824. Otra realización se refiere al compuesto final del Ejemplo 825. Otra realización se refiere al compuesto final del Ejemplo 826. Otra realización se refiere al compuesto final del Ejemplo 827.

La Realización No. 140 se refiere al compuesto final del Ejemplo 622.

La Realización No. 141 se refiere al compuesto final del Ejemplo 613.

La Realización No. 142 se refiere al compuesto final del Ejemplo 825.

La Realización No. 143 se refiere a un compuesto de cualquiera de las Realizaciones Nos. 1 hasta 142 en forma pura y aislada.

La Realización No. 144 se refiere a una composición farmacéutica que comprende una cantidad efectiva de por lo menos uno compuesto (por ej., 1, 2 o 3, o 1 o 2, o 1, y usualmente 1) de fórmula 1.0, con preferencia un compuesto de fórmula 1.0C, y un vehículo aceptable desde el punto de vista farmacéutico.

La Realización No. 145 se refiere a una composición farmacéutica que comprende una cantidad efectiva de un compuesto de fórmula 1.0, con preferencia un compuesto de fórmula 1.0C, y un vehículo aceptable desde el punto de vista farmacéutico.

La Realización No. 146 se refiere a una composición farmacéutica que comprende una cantidad efectiva de por lo menos uno compuesto (por ej., 1, 2 o 3, o 1 o 2, o 1, y usualmente 1) de fórmula 1.1, y un vehículo aceptable desde el punto de vista farmacéutico.

La Realización No. 147 se refiere a una composición farmacéutica que comprende una cantidad efectiva de un compuesto de Fórmula 1.1 y un vehículo aceptable desde el punto de vista farmacéutico.

La Realización No. 148 se refiere a una composición farmacéutica que comprende una cantidad efectiva de por lo menos uno compuesto (por ej., 1, 2 o 3, o 1 o 2, o 1, y usualmente 1) de fórmula 1.2, y un vehículo aceptable desde el punto de vista farmacéutico.

La Realización No. 149 se refiere a una composición farmacéutica que comprende una cantidad efectiva de un compuesto de Fórmula 1.2 y un vehículo aceptable desde el punto de vista farmacéutico.

La Realización No. 150 se refiere a una composición farmacéutica que comprende una cantidad efectiva de por lo menos uno compuesto (por ej., 1, 2 o 3, o 1 o 2, o 1, y usualmente 1) de fórmula 1.3, y un vehículo aceptable desde el punto de vista farmacéutico.

La Realización No. 151 se refiere a una composición farmacéutica que comprende una cantidad efectiva de un compuesto de Fórmula 1.3 y un vehículo aceptable desde el punto de vista farmacéutico.

La Realización No. 152 se refiere a una composición farmacéutica que comprende una cantidad efectiva de por lo menos uno compuesto (por ej., 1, 2 o 3, o 1 o 2, o 1, y usualmente 1) of cualquiera de las Realizaciones Nos. 1 hasta 142 y un vehículo aceptable desde el punto de vista farmacéutico.

La Realización No. 153 se refiere a una composición farmacéutica que comprende una cantidad efectiva de un compuesto de cualquiera de las Realizaciones Nos. 1 hasta 142 y un vehículo aceptable desde el punto de vista farmacéutico.

La Realización No. 154 se refiere a una composición farmacéutica que comprende una cantidad efectiva de por lo menos uno compuesto (por ej., 1, 2 o 3, o 1 o 2, o 1, y usualmente 1) of La Realización No. 143 y un vehículo aceptable desde el punto de vista farmacéutico.

La Realización No. 155 se refiere a una composición farmacéutica que comprende una cantidad efectiva de un compuesto de La Realización No. 143 y un vehículo aceptable desde el punto de vista farmacéutico.

La Realización No. 156 se refiere a una composición farmacéutica de cualquiera de las Realizaciones Nos. 144 hasta 155 que comprende, además, una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, o 1 o 2, o 1, y usualmente 1) otro principio farmacéuticamente activo.

La Realización No. 157 se refiere a una composición farmacéutica de cualquiera de las Realizaciones Nos. 144 hasta 155 que comprende, además, una cantidad efectiva de otro (es decir, uno distinto) principio farmacéuticamente activo.

La Realización No. 158 se refiere a una composición farmacéutica de cualquiera de las Realizaciones Nos. 144 hasta 155 que comprende, además, una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, o 1 o 2, o 1, y usualmente 1) agente quimioterapéutico.

La Realización No. 159 se refiere a una composición farmacéutica de cualquiera de las Realizaciones Nos. 144 hasta 155 que comprende, además, una cantidad efectiva de un agente quimioterapéutico.

La Realización No. 160 se refiere a un método de tratamiento para el cáncer en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de por lo menos uno (1, 2 o 3, o 1 o 2, o 1, y usualmente 1) compuesto de fórmula 1.0 (con preferencia fórmula 1.0C).

La Realización No. 161 se refiere a un método de tratamiento para el cáncer en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de un compuesto de fórmula 1.0 (con preferencia fórmula 1.0C).

La Realización No. 162 se refiere a un método de tratamiento para el cáncer en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de por lo menos uno (1, 2 o 3, o 1 o 2, o 1, y usualmente 1) compuesto de fórmula 1.1.

La Realización No. 163 se refiere a un método de tratamiento para el cáncer en un paciente que necesita de dicho tratamiento, dicho método

comprende administrar a dicho paciente una cantidad efectiva de un compuesto de fórmula 1.1.

La Realización No. 164 se refiere a un método de tratamiento para el cáncer en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de por lo menos uno (1, 2 o 3, o 1 o 2, o 1, y usualmente 1) compuesto de fórmula 1.2.

La Realización No. 165 se refiere a un método de tratamiento para el cáncer en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de un compuesto de fórmula 1.2.

La Realización No. 166 se refiere a un método de tratamiento para el cáncer en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de por lo menos uno (1, 2 o 3, o 1 o 2, o 1, y usualmente 1) compuesto de fórmula 1.3.

La Realización No. 167 se refiere a un método de tratamiento para el cáncer en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de un compuesto de fórmula 1.3.

La Realización No. 168 se refiere a un método de tratamiento para el cáncer en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de por lo menos uno (1, 2 o 3, o 1 o 2, o 1, y usualmente 1) compuesto de cualquiera de las Realizaciones Nos. 1 hasta 143.

La Realización No. 169 se refiere a un método de tratamiento para el cáncer en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de un compuesto de cualquiera de las Realizaciones Nos. 1 hasta 143.

La Realización No. 170 se refiere a un método de tratamiento para el cáncer en cualquiera de las Realizaciones No. 160 hasta 169 que comprende, además, la administración de una cantidad efectiva de por lo menos uno (1, 2 o 3, o 1 o 2, o 1, y usualmente 1) agente quimioterapéutico.

La Realización No. 171 se refiere a un método de tratamiento para el cáncer en cualquiera de las Realizaciones No. 160 hasta 169 que comprende, además, la administración de una cantidad efectiva de un agente quimioterapéutico.

La Realización No. 172 se refiere a un método de tratamiento para el cáncer en un paciente que necesita de dicho tratamiento que comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica de cualquiera de las Realizaciones Nos. 144 hasta 159.

La Realización No. 173 se refiere a un método de tratamiento para el cáncer en un paciente que necesita de dicho tratamiento que comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica de cualquiera de las Realizaciones Nos. 144 hasta 155.

La Realización No. 174 se refiere a un método de tratamiento para el cáncer en un paciente que necesita de dicho tratamiento que comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica de cualquiera de las Realizaciones Nos. 144 hasta 155, en combinación con una cantidad efectiva de por lo menos uno (1, 2 o 3, o 1 o 2, o 1, y usualmente 1) agente quimioterapéutico

La Realización No. 175 se refiere a un método de tratamiento para el cáncer en un paciente que necesita de dicho tratamiento que comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica de cualquiera de las Realizaciones Nos. 144 hasta 155, en combinación con una cantidad efectiva de un agente quimioterapéutico.

La Realización No. 176 se refiere a un método de tratamiento para el cáncer of cualquiera de las Realizaciones Nos. 170, 171, 174 y 175 en el cual el agente quimioterapéutico se selecciona del grupo que consiste en: paclitaxel, docetaxel, carboplatino, cisplatino, gemcitabina, tamoxifeno, Herceptina, Cetuximab, Tarceva, Iressa, bevacizumab, navelbina, IMC-1C11, SU5416 y SU6688.

La Realización No. 177 se refiere a un método de tratamiento para el cáncer of cualquiera de las Realizaciones Nos. 170, 171, 174 y 175 en el cual el agente quimioterapéutico se selecciona del grupo que consiste en: paclitaxel, docetaxel, carboplatino, cisplatino, navelbina, gemcitabina, y Herceptina.

La Realización No. 178 se refiere a un método de tratamiento para el cáncer of cualquiera de las Realizaciones Nos. 170, 171, 174 y 175 en el cual el agente quimioterapéutico se selecciona del grupo que consiste en: Ciclofosfamida, 5-Fluorouracilo, Temozolomida, Vincristina, Cisplatino, Carboplatino, y Gemcitabina.

La Realización No. 179 se refiere a un método de tratamiento para el cáncer of cualquiera de las Realizaciones Nos. 170, 171, 174 y 175 en el cual el agente quimioterapéutico se selecciona del grupo que consiste en: Gemcitabina, Cisplatino y Carboplatino.

Esta invención provee, además, un método de tratamiento para el cáncer en un paciente que necesita de dicho tratamiento, dicho tratamiento comprende administrar a dicho paciente una cantidad terapéuticamente efectiva por lo menos un (por ej., 1, 2 o 3, o 1 o 2, o 1, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), y cantidades terapéuticamente efectivas de por lo menos un (por ej., 1, 2 o 3, o 1 o 2, o 2, o 1) agente quimioterapéutico seleccionados del grupo que consiste en: (1) taxanos, (2) compuestos coordinadores de platino, (3) inhibidores del factor de

crecimiento epidérmico (FCE) que son anticuerpos, (4) inhibidores del FCE que son moléculas pequeñas, (5) inhibidores del factor de crecimiento endolitial vascular (VEGF) que son anticuerpos, (6) inhibidores de quinasa de VEGF que son moléculas pequeñas, (7) antagonistas del receptor de estrógenos o moduladores selectivos del receptor de estrógenos (SERMs), (8) derivados de nucleósidos anti-tumorales, (9) epotilonas, (10) inhibidores de topoisomerasa, (11) alcaloides vinca, (12) anticuerpos que son inhibidores de αVβ3 integrinas, (13) antagonistas de folato, (14) inhibidores de la ribonucleótido reductasa, (15) antraciclinas, (16) agentes biológicos; (17) inhibidores de la angiogénesis y/o supresores del factor de necrosis tumoral alfa (TNF-alfa) tales como talidomida (o imida relacionada), (18) inhibidores de la quinasa Bcr/abl, (19) inhibidores de MEK1 y/o MEK 2 que son moléculas pequeñas, (20) inhibidores de IGF-1 y IGF-2 que son moléculas pequeñas, (21) inhibidores de moléculas pequeñas de quinasas RAF y BRAF, (22) inhibidores de moléculas pequeñas de quinasas dependientes del ciclo celular tales como CDK1, CDK2. CDK4 y CDK6, (23) agentes alquilantes, y (24) inhibidores de la farnesil transferasa de la proteína (también conocidos como inhibidores de FPT o FTI (es decir, inhibidores de transferencia de farnesilo)).

Esta invención provee, además, un método de tratamiento para el cáncer en un paciente que necesita de dicho tratamiento, dicho tratamiento comprende administrar a dicho paciente una cantidad terapéuticamente efectiva por lo menos un (por ej., 1, 2 o 3, o 1 o 2, o 1, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), y cantidades terapéuticamente efectivas de por lo menos dos (por ej., 2 o 3, o 2. y usualmente 2) diferentes agentes anti-neoplásicos seleccionados del grupo que consiste en: (1) taxanos, (2) compuestos coordinadores de platino, (3) inhibidores del factor de crecimiento epidérmico (FCE) que son anticuerpos, (4) inhibidores

del FCE que son moléculas pequeñas, (5) inhibidores del factor de crecimiento endolitial vascular (VEGF) que son anticuerpos, (6) inhibidores de quinasa de VEGF que son moléculas pequeñas, (7) antagonistas del receptor de estrógenos o moduladores selectivos del receptor de estrógenos (SERMs), (8) derivados de nucleósidos anti-tumorales, (9) epotilonas, (10) inhibidores de topoisomerasa, (11) alcaloides vinca, (12) anticuerpos que son inhibidores de αVβ3 integrinas, (13) antagonistas de folato, (14) inhibidores de la ribonucleótido reductasa, (15) antraciclinas, (16) agentes biológicos; (17) inhibidores de la angiogénesis y/o supresores del factor de necrosis tumoral alfa (TNF-alfa) tales como talidomida (o imida relacionada), (18) inhibidores de la quinasa Bcr/abl, (19) inhibidores de MEK1 y/o MEK 2 que son moléculas pequeñas, (20) inhibidores de IGF-1 y IGF-2 que son moléculas pequeñas, (21) inhibidores de moléculas pequeñas de quinasas RAF y BRAF, (22) inhibidores de moléculas pequeñas de quinasas dependientes del ciclo celular tales como CDK1, CDK2. CDK4 y CDK6, (23) agentes alquilantes, y (24) inhibidores de la farnesil transferasa de la proteína (también conocidos como inhibidores de FPT o FTI (es decir, inhibidores de transferencia de farnesilo)).

Esta invención provee, además, un método de tratamiento para el cáncer en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente cantidad terapéuticamente efectivas por lo menos un (por ej., 1, 2 o 3, o 1 o 2, o 1, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), y un agente anti-neoplásico seleccionado del grupo que consiste en: (1) inhibidores del FCE que son anticuerpos, (2) inhibidores del FCE que son moléculas pequeñas, (3) inhibidores de VEGF que son anticuerpos, y (4) inhibidores de VEGF que son moléculas pequeñas. También puede utilizarse terapia de rayos en conjunción con este tratamiento combinado anterior, es decir,

el método mencionado con anterioridad usando una combinación de compuestos de la invención y agente anti-neoplásico también pueden comprender la administración de una cantidad terapéuticamente efectiva de radiación.

Esta invención provee, además, un método de tratamiento de las leucemias (por ej., leucemia mieloide aguda (LMA), y leucemia mieloide crónica (CML)) en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente cantidad terapéuticamente efectivas por lo menos un (por ej., 1, 2 o 3, o 1 o 2, o 1, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), y: (1) Gleevec e interferón para tratar el CML; (2) Gleevec y interferón pegilado para tratar el CML; (3) Gleevec para tratar el CML; (4) un derivado de nucleósido anti-tumoral (por ej., Ara-C) para tratar el AML; o (5) un derivado de nucleósido anti-tumoral (por ej., Ara-C) en combinación con una antraciclina para tratar el AML.

Esta invención provee, además, un método para el tratamiento del linfoma de no Hodgkin en un paciente que necesita de dicho tratamiento, dicho método comprende administrar cantidad terapéuticamente efectivas por lo menos un (por ej., 1, 2 o 3, o 1 o 2, o 1, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) y: (1) un agente biológico (por ej., Rituxan); (2) un agente biológico (por ej., Rituxan) y un derivado de nucleósido anti-tumoral (por ej., Fludarabina); o (3) Genasense (antisentido para BCL-2).

Esta invención provee, además, un método para el tratamiento del mieloma múltiple en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente cantidades terapéuticamente efectivas de por lo menos un (por ej., 1, 2 o 3, o 1 o 2, o 1, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones

Nos. 1 hasta 143) y: (1) un inhibidor de proteosoma (por ej., PS-341 de Millenium); o (2) Talidomida (o imida relacionada).

Esta invención provee, además, un método de tratamiento para el cáncer en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente cantidades terapéuticamente efectivas de: (a) por lo menos un (por ej., 1, 2 o 3, o 1 o 2, o 1, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), y (b) por lo menos un (por ej., 1, 2 o 3, o 1 o 2, o 2, o 1) agente anti-neoplásico seleccionados del grupo que consiste en: (1) taxanos, (2) compuestos coordinadores de platino, (3) inhibidores del FCE que son anticuerpos, (4) inhibidores del FCE que son moléculas pequeñas, (5) inhibidores de VEGF que son anticuerpos, (6) inhibidores de quinasa de VEGF que son moléculas pequeñas, (7) antagonistas del receptor de estrógenos o moduladores selectivos del receptor de estrógenos, (8) derivados de nucleósidos anti-tumorales, (9) epotilonas, (10) inhibidores de topoisomerasa, (11) alcaloides vinca, y (12) anticuerpos que son inhibidores de αVβ3 integrinas.

Esta invención provee, además, un método para el tratamiento del cáncer de pulmón de células no pequeñas en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente cantidades terapéuticamente efectivas de: (a) por lo menos un (por ej., 1, 2 o 3, o 1 o 2, o 1, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), y (b) por lo menos un (por ej., 1, 2 o 3, o 1 o 2, o 2, o 1) agente anti-neoplásico seleccionados del grupo que consiste en: (1) taxanos, (2) compuestos coordinadores de platino, (3) inhibidores del FCE que son anticuerpos, (4) inhibidores del FCE que son moléculas pequeñas, (5) inhibidores de VEGF que son anticuerpos, (6) inhibidores de quinasa de VEGF que son moléculas pequeñas, (7) antagonistas del receptor de

estrógenos o moduladores selectivos del receptor de estrógenos, (8) derivados de nucleósidos anti-tumorales, (9) epotilonas, (10) inhibidores de topoisomerasa, (11) alcaloides vinca, y (12) anticuerpos que son inhibidores de αVβ3 integrinas.

Esta invención provee, además, un método para el tratamiento del cáncer de pulmón de células no pequeñas en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente cantidades terapéuticamente efectivas de: (a) por lo menos un (por ej., 1, 2 o 3, o 1 o 2, o 1, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), y (b) por lo menos un (por ej., 1, 2 o 3, o 1 o 2, o 2, o 1) agente anti-neoplásico seleccionados del grupo que consiste en: (1) taxanos, (2) compuestos coordinadores de platino, (3) derivados de nucleósidos anti-tumorales, (4) inhibidores de topoisomerasa, y (5) alcaloides vinca.

Esta invención provee, además, un método para el tratamiento del cáncer de pulmón de células no pequeñas en un paciente que necesita de dicho tratamiento, dicho método comprende administrar cantidades terapéuticamente efectivas de: (a) por lo menos un (por ej., 1, 2 o 3, o 1 o 2, o 1, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), (b) carboplatino, y (c) paclitaxel.

Esta invención provee, además, un método para el tratamiento del cáncer de pulmón de células no pequeñas en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente cantidades terapéuticamente efectivas de: (a) por lo menos un (por ej., 1, 2 o 3, o 1 o 2, o 1, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), (b) cisplatino, y (c) gemcitabina.

Esta invención provee, además, un método para el tratamiento del cáncer de pulmón de células no pequeñas en un paciente que necesita de dicho tratamiento, dicho método comprende administrar cantidades terapéuticamente efectivas de: (a) por lo menos un (por ej., 1, 2 o 3, o 1 o 2, o 1, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), (b) carboplatino, y (c) gemcitabina.

Esta invención provee, además, un método para el tratamiento del cáncer de pulmón de células no pequeñas en un paciente que necesita de dicho tratamiento, dicho método comprende administrar cantidades terapéuticamente efectivas de: (a) por lo menos un (por ej., 1, 2 o 3, o 1 o 2, o 1, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), (b) Carboplatino, y (c) Docetaxel.

Esta invención provee, además, un método de tratamiento para el cáncer en un paciente que necesita de dicho tratamiento, dicho método comprende administrar cantidades terapéuticamente efectivas de: (a) por lo menos un (por ej., 1, 2 o 3, o 1 o 2, o 1, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), y (b) un agente anti-neoplásico seleccionado del grupo que consiste en: (1) inhibidores del FCE que son anticuerpos, (2) inhibidores del FCE que son moléculas pequeñas, (3) inhibidores de VEGF que son anticuerpos, (4) inhibidores de quinasa de VEGF que son moléculas pequeñas.

Esta invención provee, además, un método de tratamiento para el cáncer de células escamosas de cuello y cabeza, en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente cantidades terapéuticamente efectivas de: (a) por lo menos un (por ej., 1, 2 o 3, o 1 o 2, o 1, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), y (b) por lo menos un (por ej.,

1, 2 o 3, o 1 o 2, o 2, o 1) agente anti-neoplásico seleccionados del grupo que consiste en: (1) taxanos, y (2) compuestos coordinadores de platino.

Esta invención provee, además, un método de tratamiento para el cáncer de células escamosas de cuello y cabeza, en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente cantidades terapéuticamente efectivas de: (a) por lo menos un (por ej., 1, 2 o 3, o 1 o 2, o 1, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), y (b) por lo menos un (por ej., 1, 2 o 3, o 1 o 2, o 2, o 1) agente anti-neoplásico seleccionados del grupo que consiste en: (1) taxanos, (2) compuestos coordinadores de platino, y (3) derivados de nucleósidos anti-tumorales (por ej., 5-Fluorouracilo).

Esta invención provee, además, un método para el tratamiento del CML en un paciente que necesita de dicho tratamiento, dicho método comprende administrar cantidades terapéuticamente efectivas de: (a) por lo menos un (por ej., 1, 2 o 3, o 1 o 2, o 1, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), (b) Gleevec, y (c) interferón (por ej., Intron-A).

Esta invención provee, además, un método para el tratamiento del CML en un paciente que necesita de dicho tratamiento que comprende administrar cantidades terapéuticamente efectivas de: (a) por lo menos un (por ej., 1, 2 o 3, o 1 o 2, o 1, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), (b) Gleevec; y (c) interferón pegilado (por ej., Peg-Intron, y Pegasys).

Esta invención provee, además, un método para el tratamiento del CML en un paciente que necesita de dicho tratamiento que comprende administrar cantidades terapéuticamente efectivas de: (a) por lo menos un (por ej., 1, 2 o 3, o

1 o 2, o 1, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) y (b) Gleevec.

Esta invención provee, además, un método para el tratamiento del CMML en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente cantidades terapéuticamente efectivas de por lo menos un (por ej., 1, 2 o 3, o 1 o 2, o 1, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143).

Esta invención provee, además, un método para el tratamiento de la AML en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente cantidades terapéuticamente efectivas de: (a) por lo menos un (por ej., 1, 2 o 3, o 1 o 2, o 1, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), y (b) un derivado de nucleósido anti-tumoral (por ej., Citarabina (es decir, Ara-C)).

Esta invención provee, además, un método para el tratamiento de AML en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente cantidades terapéuticamente efectivas de: (a) por lo menos un (por ej., 1, 2 o 3, o 1 o 2, o 1, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), (b) un derivado de nucleósido anti-tumoral (por ej., Citarabina (es decir, Ara-C)), y (c) una antraciclina.

Esta invención provee, además, un método para el tratamiento del linfoma de no Hodgkin en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente cantidades terapéuticamente efectivas de: (a) por lo menos un (por ej., 1, 2 o 3, o 1 o 2, o 1, y usualmente 1) compuesto

de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), y (b) Rituximab (Rituxan).

Esta invención provee, además, un método para el tratamiento del linfoma de no Hodgkin en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente cantidades terapéuticamente efectivas de: (a) por lo menos un (por ej., 1, 2 o 3, o 1 o 2, o 1, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), (b) Rituximab (Rituxan), y (c) un derivado de nucleósido anti-tumoral (por ej., Fludarabina (es decir, F-ara-A).

Esta invención provee, además, un método para el tratamiento del linfoma de no Hodgkin en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente cantidades terapéuticamente efectivas de: (a) por lo menos un (por ej., 1, 2 o 3, o 1 o 2, o 1, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), y (b) Genasense (antisentido para BCL-2).

Esta invención provee, además, un método para el tratamiento del mieloma múltiple en un paciente que necesita de dicho tratamiento, dicho método comprende administrar cantidades terapéuticamente efectivas de: (a) por lo menos un (por ej., 1, 2 o 3, o 1 o 2, o 1, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), y (b) un inhibidor de proteosoma (por ej., PS-341 (Millenium)).

Esta invención provee, además, un método para el tratamiento del mieloma múltiple en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente cantidades terapéuticamente efectivas de: (a) por lo menos un (por ej., 1, 2 o 3, o 1 o 2, o 1, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), y (b) Talidomida o imida relacionada.

Esta invención provee, además, un método para el tratamiento del mieloma múltiple en un paciente que necesita de dicho tratamiento, dicho método comprende administrar cantidades terapéuticamente efectivas de: (a) por lo menos un (por ej., 1, 2 o 3, o 1 o 2, o 1, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), y (b) Talidomida.

Esta invención se refiere, además, a los métodos de tratamiento para el cáncer descritos aquí, en particular aquellos que se describieron con anterioridad, en los cuales además de la administración del compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) y agentes anti-neoplásicos, la terapia de rayos se administra también antes de, durante o después del ciclo de tratamiento.

Esta invención provee, además, un método de tratamiento para el cáncer (por ej., cáncer de pulmón, cáncer de próstata y leucemias mieloides) en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente (1) una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, o 1 o 2, o 1, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), en combinación con (2) por lo menos un (por ej., 1, 2 o 3, o 1 o 2, o 2, o 1) agente anti-neoplásico, agente que afecta los microtúbulos y/o terapia de rayos.

Esta invención provee, además, un método de tratamiento para el cáncer en un paciente que necesita de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, o 1 o 2, o 1, y usualmente 1) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) en combinación con una cantidad efectiva de por lo menos un (por ej., 1, 2 o 3, o 1 o 2, o 1, y usualmente 1) inhibidor de transducción de señal.

De este modo, en un ejemplo (por ej., el tratamiento del cáncer de pulmón de células no pequeñas): (1) el compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) se administra en una cantidad de aproximadamente 50 mg hasta aproximadamente 200 mg dos veces por día, y en otro ejemplo aproximadamente 75 mg hasta aproximadamente 125 mg administrados dos veces por día, e incluso en otro ejemplo aproximadamente 100 mg administrados dos veces por día, (2) Paclitaxel (por ej., Taxol® se administra una vez por semana en una cantidad de aproximadamente 50 hasta aproximadamente 100 mg/m^2 y en otro ejemplo aproximadamente 60 hasta aproximadamente 80 mg/m^2 y (3) Carboplatino se administra una vez por semana en una cantidad para proporcionar un ABC de aproximadamente 2 hasta aproximadamente 3.

En otro ejemplo (por ej., el tratamiento del cáncer de pulmón de células no pequeñas): (1) el compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) se administra en una cantidad de aproximadamente 50 mg hasta aproximadamente 200 mg dos veces por día, y en otro ejemplo aproximadamente 75 mg hasta aproximadamente 125 mg administrados dos veces por día, e incluso en otro ejemplo aproximadamente 100 mg administrados dos veces por día, (2) Paclitaxel (por ej., Taxol® se administra una vez por semana en una cantidad de aproximadamente 50 hasta aproximadamente 100 mg/m^2 y en otro ejemplo aproximadamente 60 hasta aproximadamente 80 mg/m^2 y (3) Cisplatino se administra una vez por semana en una cantidad de aproximadamente 20 hasta aproximadamente 40 mg/m^2.

En otro ejemplo (por ej., el tratamiento del cáncer de pulmón de células no pequeñas): (1) el compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) se administra en una cantidad de aproximadamente 50 mg hasta aproximadamente 200 mg dos veces por día, y

en otro ejemplo aproximadamente 75 mg hasta aproximadamente 125 mg administrados dos veces por día, e incluso en otro ejemplo aproximadamente 100 mg administrados dos veces por día, (2) Docetaxel (por ej., Taxotere®) se administra una vez por semana en una cantidad de aproximadamente 10 hasta aproximadamente 45 mg/m^2, y (3) Carboplatino se administra una vez por semana en una cantidad para proporcionar un ABC de aproximadamente 2 hasta aproximadamente 3.

En otro ejemplo (por ej., el tratamiento del cáncer de pulmón de células no pequeñas): (1) el compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) se administra en una cantidad de aproximadamente 50 mg hasta aproximadamente 200 mg dos veces por día, y en otro ejemplo aproximadamente 75 mg hasta aproximadamente 125 mg administrados dos veces por día, e incluso en otro ejemplo aproximadamente 100 mg administrados dos veces por día, (2) Docetaxel (por ej., Taxotere®) se administra una vez por semana en una cantidad de aproximadamente 10 hasta aproximadamente 45 mg/m^2, y (3) Cisplatino se administra una vez por semana en una cantidad de aproximadamente 20 hasta aproximadamente 40 mg/m^2.

En otro ejemplo (por ej., el tratamiento del cáncer de pulmón de células no pequeñas): (1) el compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) se administra en una cantidad de aproximadamente 50 mg hasta aproximadamente 200 mg dos veces por día, y en otro ejemplo aproximadamente 75 mg hasta aproximadamente 125 mg administrados dos veces por día, e incluso en otro ejemplo aproximadamente 100 mg administrados dos veces por día, (2) Paclitaxel (por ej., Taxol® se administra una vez cada tres semanas en una cantidad de aproximadamente 150 hasta aproximadamente 250 mg/m^2, y en otro ejemplo aproximadamente 175 hasta aproximadamente 225 mg/m^2, e incluso en otro ejemplo 175 mg/m^2, y (3)

Carboplatino se administra una vez cada tres semanas en una cantidad para proporcionar un ABC de aproximadamente 5 hasta aproximadamente 8, y en otro ejemplo 6.

En otro ejemplo de el tratamiento del cáncer de pulmón de células no pequeñas: (1) el compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) se administra en una cantidad de 100 mg administrados dos veces por día, (2) Paclitaxel (por ej., Taxol® se administra una vez cada tres semanas en una cantidad de 175 mg/m^2 y (3) Carboplatino se administra una vez cada tres semanas en una cantidad para proporcionar un ABC de 6.

En otro ejemplo (por ej., el tratamiento del cáncer de pulmón de células no pequeñas): (1) el compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) se administra en una cantidad de aproximadamente 50 mg hasta aproximadamente 200 mg dos veces por día, y en otro ejemplo aproximadamente 75 mg hasta aproximadamente 125 mg administrados dos veces por día, e incluso en otro ejemplo aproximadamente 100 mg administrados dos veces por día, (2) Paclitaxel (por ej., Taxol® se administra una vez cada tres semanas en una cantidad de aproximadamente 150 hasta aproximadamente 250 mg/m^2 y en otro ejemplo aproximadamente 175 hasta aproximadamente 225 mg/m^2 y (3) Cisplatino se administra una vez cada tres semanas en una cantidad de aproximadamente 60 hasta aproximadamente 100 mg/m^2.

En otro ejemplo (por ej., el tratamiento del cáncer de pulmón de células no pequeñas): (1) el compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) se administra en una cantidad de aproximadamente 50 mg hasta aproximadamente 200 mg dos veces por día, y en otro ejemplo aproximadamente 75 mg hasta aproximadamente 125 mg

administrados dos veces por día, e incluso en otro ejemplo aproximadamente 100 mg administrados dos veces por día, (2) Docetaxel (por ej., Taxotere® se administra una vez cada tres semanas en una cantidad de aproximadamente 50 hasta aproximadamente 100 mg/m^2 y (3) Carboplatino se administra una vez cada tres semanas en una cantidad para proporcionar un ABC de aproximadamente 5 hasta aproximadamente 8.

En otro ejemplo (por ej., el tratamiento del cáncer de pulmón de células no pequeñas): (1) el compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) se administra en una cantidad de aproximadamente 50 mg hasta aproximadamente 200 mg dos veces por día, en otro ejemplo aproximadamente 75 mg hasta aproximadamente 125 mg administrados dos veces por día, e incluso en otro ejemplo aproximadamente 100 mg administrados dos veces por día, (2) Docetaxel (por ej., Taxotere® se administra una vez cada tres semanas en una cantidad de aproximadamente 50 hasta aproximadamente 100 mg/m^2 y (3) Cisplatino se administra una vez cada tres semanas en una cantidad de aproximadamente 60 hasta aproximadamente 100 mg/m^2.

En otro ejemplo para tratamiento del cáncer de pulmón de células no pequeñas usando los compuestos de fórmula 1.0, Docetaxel y Carboplatin: (1) el compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) se administra en una cantidad de aproximadamente 50 mg hasta aproximadamente 200 mg dos veces por día, y en otro ejemplo aproximadamente 75 mg hasta aproximadamente 125 mg administrados dos veces por día, e incluso en otro ejemplo aproximadamente 100 mg administrados dos veces por día, (2) Docetaxel (por ej., Taxotere® se administra una vez cada tres semanas en una cantidad de aproximadamente 75

mg/m^2, y (3) Carboplatino se administra una vez cada tres semanas en una cantidad para proporcionar un ABC de aproximadamente 6.

En otro ejemplo de los tratamientos de cáncer de pulmón de células no pequeñas descritos anteriormente el Docetaxel (por ej., Taxotere®) y Cisplatino, El Docetaxel (por ej., Taxotere®) y Carboplatino, el Paclitaxel (por ej., Taxol®) y Carboplatino, o el Paclitaxel (por ej., Taxol®) y Cisplatino se administran el mismo día.

En otro ejemplo (por ej., CML): (1) el compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) se administra en una cantidad de aproximadamente 100 mg hasta aproximadamente 200 mg administrados dos veces por día, (2) Gleevec se administra en una cantidad de aproximadamente 400 hasta aproximadamente 800 mg/día por vía oral, y (3) interferón (Intron-A) se administra en una cantidad de aproximadamente 5 hasta aproximadamente 20 millones de UI tres veces por semana.

En otro ejemplo (por ej., CML): (1) el compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) se administra en una cantidad de aproximadamente 100 mg hasta aproximadamente 200 mg administrados dos veces por día, (2) Gleevec se administra en una cantidad de aproximadamente 400 hasta aproximadamente 800 mg/día por vía oral, y (3) interferón pegilado (Peg-Intron o Pegasys) se administra en una cantidad de aproximadamente 3 hasta aproximadamente 6 microgramos/kg/día.

En otro ejemplo (por ej., linfoma de no Hodgkin): (1) el compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) se administra en una cantidad de aproximadamente 50 mg hasta aproximadamente 200 mg dos veces por día, y en otro ejemplo

aproximadamente 75 mg hasta aproximadamente 125 mg administrados dos veces por día, e incluso en otro ejemplo aproximadamente 100 mg administrados dos veces por día, y (2) Genasense (antisentido para BCL-2) se administra como infusión IV continua a una dosis de aproximadamente 2 hasta aproximadamente 5 mg/kg/día (por ej., 3 mg/kg/día) durante 5 hasta 7 días cada 3 hasta 4 semanas.

En otro ejemplo (por ej., mieloma múltiple): (1) el compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) se administra en una cantidad de aproximadamente 50 mg hasta aproximadamente 200 mg dos veces por día, y en otro ejemplo aproximadamente 75 mg hasta aproximadamente 125 mg administrados dos veces por día, e incluso en otro ejemplo aproximadamente 100 mg administrados dos veces por día, y (2) el inhibidor de proteosoma (por ej., PS-341 – Millenium) se administra en una cantidad de aproximadamente 1,5mg/m^2 dos veces por semana durante dos semanas consecutivas con un período de descanso de una semana.

En otro ejemplo (por ej., mieloma múltiple): (1) el compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) se administra en una cantidad de aproximadamente 50 mg hasta aproximadamente 200 mg dos veces por día, y en otro ejemplo aproximadamente 75 mg hasta aproximadamente 125 mg administrados dos veces por día, e incluso en otro ejemplo aproximadamente 100 mg administrados dos veces por día, y (2) la Talidomida (o imida relacionada) se administra por vía oral en una cantidad de aproximadamente 200 hasta aproximadamente 800 mg/día, donde la administración es continua hasta la recaída o toxicidad.

En una realización de los métodos de tratamiento para el cáncer de esta invención, los agentes quimioterapéuticos se seleccionan del grupo que consiste en: paclitaxel, docetaxel, carboplatino, cisplatino, gemcitabina, tamoxifeno,

Herceptina, Cetuximab, Tarceva, Iressa, bevacizumab, navelbina, IMC-1C11, SU5416 y SU6688.

En otra realización de los métodos de tratamiento para el cáncer de esta invención, los agentes quimioterapéuticos se seleccionan del grupo que consiste en: paclitaxel, docetaxel, carboplatino, cisplatino, navelbina, gemcitabina, y Herceptina.

De este modo, una realización de esta invención se refiere a un método de tratamiento para el cáncer que comprende administrar a un paciente que necesita de dicho tratamiento cantidades terapéuticamente efectivas del compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), un taxano, y un compuesto de coordinación de platino.

Otra realización de esta invención se refiere a un método de tratamiento para el cáncer que comprende administrar a un paciente que necesita de dicho tratamiento cantidades terapéuticamente efectivas del compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), un taxano, y un compuesto de coordinación de platino, donde dicho compuesto de fórmula 1.0 se administra todos los días, dicho taxano se administra una vez por semana por cada ciclo, y dicho compuesto coordinador de platino se administra una vez por semana por cada ciclo. En otra realización el tratamiento es durante una hasta cuatro semanas por cada ciclo.

Otra realización de esta invención se refiere a un método de tratamiento para el cáncer que comprende administrar a un paciente que necesita de dicho tratamiento cantidades terapéuticamente efectivas del compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), un taxano, y un compuesto de coordinación de platino, donde dicho compuesto de fórmula 1.0 se administra todos los días, dicho taxano se administra una vez cada tres semanas por cada ciclo, y dicho compuesto

coordinador de platino se administra una vez cada tres semanas por cada ciclo. En otra realización el tratamiento es para un período de una hasta tres semanas por cada ciclo.

Otra realización de esta invención se refiere a un método de tratamiento para el cáncer que comprende administrar a un paciente que necesita de dicho tratamiento cantidades terapéuticamente efectivas del compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), paclitaxel, y carboplatino. En otra realización, dicho compuesto de fórmula 1.0 se administra todos los días, dicho paclitaxel se administra una vez por semana por cada ciclo, y dicho Carboplatino se administra una vez por semana por cada ciclo. En otra realización el tratamiento es para un período de una hasta cuatro semanas por cada ciclo.

Otra realización de esta invención se refiere a un método de tratamiento para el cáncer que comprende administrar a un paciente que necesita de dicho tratamiento cantidades terapéuticamente efectivas del compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), paclitaxel, y carboplatino. En otra realización, dicho compuesto de fórmula 1.0 se administra todos los días, dicho paclitaxel se administra una vez cada tres semanas por cada ciclo, y dicho Carboplatino se administra una vez cada tres semanas por cada ciclo. En otra realización el tratamiento es para un período de una hasta tres semanas por cada ciclo.

Otra realización de esta invención se refiere a un método para tratamiento del cáncer de pulmón de células no pequeñas en un paciente que necesita de dicho tratamiento que comprende administrar diariamente una cantidad terapéuticamente efectiva del compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), administrar una cantidad terapéuticamente efectiva de Carboplatino una vez por semana por cada

ciclo, y administrar una cantidad terapéuticamente efectiva de paclitaxel una vez por semana por cada ciclo, en el cual el tratamiento se administra durante un período de una hasta cuatro semanas por cada ciclo. En otra realización dicho compuesto de fórmula 1.0 se administra dos veces por día. En otra realización dicho Carboplatino y dicho paclitaxel se administran el mismo día, y en otra realización dicho Carboplatino y dicho paclitaxel se administran en forma consecutiva, y en otra realización dicho Carboplatino se administra después de dicho paclitaxel.

Otra realización de esta invención se refiere a un método para tratamiento del cáncer de pulmón de células no pequeñas en un paciente que necesita de dicho tratamiento que comprende administrar diariamente una cantidad terapéuticamente efectiva de un compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), administrar una cantidad terapéuticamente efectiva de Carboplatino una vez cada tres semanas por cada ciclo, y administrar una cantidad terapéuticamente efectiva de paclitaxel una vez cada tres semanas por cada ciclo, en el cual el tratamiento se administra durante un período de una hasta tres semanas. En otra realización compuesto de fórmula 1.0 se administra dos veces por día. En otra realización dicho Carboplatino y dicho paclitaxel se administran el mismo día, y en otra realización dicho Carboplatino y dicho paclitaxel se administran en forma consecutiva, y en otra realización dicho Carboplatino se administra después de dicho paclitaxel.

Otra realización de esta invención se refiere a un método para tratamiento del cáncer de pulmón de células no pequeñas en un paciente que necesita de dicho tratamiento que comprende administrar aproximadamente 50 hasta aproximadamente 200 mg de un compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) dos veces por día, administrar Carboplatino una vez por semana por cada ciclo en una cantidad para

proporcionar un ABC de aproximadamente 2 hasta aproximadamente 8 (y en otra realización aproximadamente 2 hasta aproximadamente 3), y administrar una vez por semana por cada ciclo aproximadamente 60 hasta aproximadamente 300 mg/m^2 (y en otra realización aproximadamente 50 hasta 100 mg/m^2, e incluso en otra realización aproximadamente 60 hasta aproximadamente 80 mg/m^2) de paclitaxel, en el cual el tratamiento se administra durante un período de una hasta cuatro semanas por cada ciclo. En otra realización dicho compuesto de fórmula 1.0 se administra en una cantidad de aproximadamente 75 hasta aproximadamente 125 mg dos veces por día, y en otra realización aproximadamente 100 mg dos veces por día. En otra realización dicho Carboplatino y dicho paclitaxel se administran el mismo día, y en otra realización dicho Carboplatino y dicho paclitaxel se administran en forma consecutiva, y en otra realización dicho Carboplatino se administra después de dicho paclitaxel.

En otra realización, esta invención se refiere a un método para tratamiento del cáncer de pulmón de células no pequeñas en un paciente que necesita de dicho tratamiento que comprende administrar aproximadamente 50 hasta aproximadamente 200 mg de un compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) dos veces por día, administrar Carboplatino una vez cada tres semanas por cada ciclo en una cantidad para proporcionar un ABC de aproximadamente 2 hasta aproximadamente 8 (en otra realización aproximadamente 5 hasta aproximadamente 8, y en otra realización 6), y administrar una vez cada tres semanas por cada ciclo aproximadamente 150 hasta aproximadamente 250 mg/m^2 (y en otra realización aproximadamente 175 hasta aproximadamente 225 mg/m^2, y en otra realización 175 mg/m^2) de paclitaxel, en el cual el tratamiento se administra durante un período de una hasta tres semanas. En otra realización dicho compuesto de fórmula 1.0 se administra en una cantidad de

aproximadamente 75 hasta aproximadamente 125 mg dos veces por día, y en otra realización aproximadamente 100 mg dos veces por día. En otra realización dicho Carboplatino y dicho paclitaxel se administran el mismo día, y en otra realización dicho Carboplatino y dicho paclitaxel se administran en forma consecutiva, y en otra realización dicho Carboplatino se administra después de dicho paclitaxel.

Otras realizaciones de esta invención se refieren a métodos de tratamiento para el cáncer como se describió en las realizaciones anteriores (es decir, las realizaciones referidas al tratamiento del cáncer y al tratamiento del cáncer de pulmón de células no pequeñas con un taxano y compuesto coordinador de platino) excepto que en lugar de paclitaxel y Carboplatino los taxanos y compuestos coordinadores de platino usados juntos en los métodos son: (1) docetaxel (Taxotere®) y cisplatino; (2) paclitaxel y cisplatino; y (3) docetaxel y carboplatino. En otra realización de los métodos de esta invención Cisplatino se usa en cantidades de aproximadamente 30 hasta aproximadamente 100 mg/m^2. En otra realización de los métodos de esta invención docetaxel se usa en cantidades de aproximadamente 30 hasta aproximadamente 100 mg/m^2.

En otra realización esta invención se refiere a un método de tratamiento para el cáncer que comprende administrar a un paciente que necesita de dicho tratamiento cantidades terapéuticamente efectivas de un compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), un taxano, y un inhibidor de EGF que es un anticuerpo. En otra realización el taxano usado es paclitaxel, y el inhibidor de EGF es un anticuerpo HER2 (en una realización Herceptin) o Cetuximab, y en otra realización se usa Herceptin. La extensión del tratamiento, y las cantidades y administración de dicho compuesto de fórmula 1.0 y el taxano son como se describió en las realizaciones anteriores. El inhibidor de EGF que es un anticuerpo se administra

una vez por semana por cada ciclo, y en otra realización se administra el mismo día que el taxano, y en otra realización se administra en forma consecutiva con el taxano. Por ejemplo, Herceptin se administra en una dosis de carga de aproximadamente 3 hasta aproximadamente 5 mg/m^2 (en otra realización aproximadamente 4 mg/m^2), y luego se administra en una dosis de mantenimiento de aproximadamente 2 mg/m^2 una vez por semana por cada ciclo durante el resto del ciclo de tratamiento (usualmente el ciclo es de 1 hasta 4 semanas). En una realización el cáncer tratado es cáncer de mama.

En otra realización esta invención se refiere a un método de tratamiento para el cáncer que comprende administrar a un paciente que necesita de dicho tratamiento cantidades terapéuticamente efectivas de: (1) un compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), (2) un taxano, y (3) un agente anti-neoplásico seleccionado del grupo que consiste en: (a) un inhibidor de EGF que es una molécula pequeña, (b) un inhibidor de VEGF que es un anticuerpo, y (c) un inhibidor de VEGF quinasa que es una molécula pequeña. En otra realización, se usa el taxano paclitaxel o docetaxel. En otra realización el agente anti-neoplásico se selecciona del grupo que consiste en: tarceva, Iressa, bevacizumab, SU5416, SU6688 y BAY 43-9006. La extensión del tratamiento, y las cantidades y administración de dicho compuesto de fórmula 1.0 y el taxano son como se describió en las realizaciones anteriores. El inhibidor de VEGF quinasa que es un anticuerpo usualmente se administra una vez por semana por cada ciclo. Los inhibidores de EGF y VEGF que son moléculas pequeñas usualmente se administran diariamente por cada ciclo. En otra realización, el inhibidor de VEGF que es un anticuerpo se administra el mismo día que el taxano, y en otra realización se administra en forma concurrente con el taxano. En otra realización, cuando el inhibidor de EGF que es una molécula pequeña o el inhibidor de VEGF que es una molécula

pequeña se administra el mismo día que el taxano, la administración es en forma concurrente con el taxano. El inhibidor de quinasa EGF o VEGF se administra en general en una cantidad de aproximadamente 10 hasta aproximadamente 500 mg/m^2.

En otra realización esta invención se refiere a un método de tratamiento para el cáncer que comprende administrar a un paciente que necesita de dicho tratamiento cantidades terapéuticamente efectivas de un compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), un derivado de nucleósido anti-tumoral, y un compuesto de coordinación de platino.

Otra realización de esta invención se refiere a un método de tratamiento para el cáncer que comprende administrar a un paciente que necesita de dicho tratamiento cantidades terapéuticamente efectivas de un compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), un derivado de nucleósido anti-tumoral, y un compuesto de coordinación de platino, donde dicho compuesto de fórmula 1.0 se administra todos los días, dicho derivado de nucleósido anti-tumoral se administra una vez por semana por cada ciclo, y dicho compuesto coordinador de platino se administra una vez por semana por cada ciclo. Aunque el tratamiento puede ser durante un período de una hasta cuatro semanas por cada ciclo, en una realización el tratamiento es para un período de una hasta siete semanas por cada ciclo.

Otra realización de esta invención se refiere a un método de tratamiento para el cáncer que comprende administrar a un paciente que necesita de dicho tratamiento cantidades terapéuticamente efectivas de un compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), un derivado de nucleósido anti-tumoral, y un compuesto de

coordinación de platino, donde dicho compuesto de fórmula 1.0 se administra todos los días, dicho derivado de nucleósido anti-tumoral se administra una vez por semana por cada ciclo, y dicho compuesto coordinador de platino se administra una vez cada tres semanas por cada ciclo. Aunque el tratamiento puede ser durante un período de una hasta cuatro semanas por cada ciclo, en una realización el tratamiento es para un período de una hasta siete semanas por cada ciclo.

Otra realización de esta invención se refiere a un método de tratamiento para el cáncer que comprende administrar a un paciente que necesita de dicho tratamiento cantidades terapéuticamente efectivas de un compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), gemcitabina, y cisplatino. En otra realización, dicho compuesto de fórmula 1.0 se administra todos los días, dicha gemcitabina se administra una vez por semana por cada ciclo, y dicho Cisplatino se administra una vez por semana por cada ciclo. En una realización el tratamiento es para un período de una hasta siete semanas por cada ciclo.

Otra realización de esta invención se refiere a un método de tratamiento para el cáncer que comprende administrar a un paciente que necesita de dicho tratamiento cantidades terapéuticamente efectivas de un compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), gemcitabina, y cisplatino. En otra realización, dicho compuesto de fórmula 1.0 se administra todos los días, dicha gemcitabina se administra una vez por semana por cada ciclo, y dicho Cisplatino se administra una vez cada tres semanas por cada ciclo. En otra realización el tratamiento es para un período de una hasta siete semanas.

Otra realización de esta invención se refiere a un método de tratamiento para el cáncer que comprende administrar a un paciente que necesita de dicho

tratamiento cantidades terapéuticamente efectivas de un compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), gemcitabina, y carboplatino. En otra realización dicho compuesto de fórmula 1.0 se administra todos los días, dicha gemcitabina se administra una vez por semana por cada ciclo, y dicho Carboplatino se administra una vez por semana por cada ciclo. En otra realización el tratamiento es para un período de una hasta siete semanas por cada ciclo.

Otra realización de esta invención se refiere a un método de tratamiento para el cáncer que comprende administrar a un paciente que necesita de dicho tratamiento cantidades terapéuticamente efectivas de un compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), gemcitabina, y carboplatino. En otra realización dicho compuesto de fórmula 1.0 se administra todos los días, dicha gemcitabina se administra una vez por semana por cada ciclo, y dicho Carboplatino se administra una vez cada tres semanas por cada ciclo. En otra realización el tratamiento es para un período de una hasta siete semanas por cada ciclo.

En las realizaciones anteriores que utilizan gemcitabina, el compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) y el compuesto coordinador de platino se administran como se describió con anterioridad para las realizaciones que utilizan taxanos. Gemcitabina se administra en una cantidad de aproximadamente 500 hasta aproximadamente 1250 mg/m^2. En una realización the gemcitabina se administra el mismo día que el compuesto coordinador de platino, y en otra realización en forma consecutiva con el compuesto coordinador de platino, y en otra realización la gemcitabina se administra luego del compuesto coordinador de platino.

Otra realización de esta invención se refiere a un método de tratamiento para el cáncer en un paciente que necesita de dicho tratamiento que comprende

administrar a dicho paciente un compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) y un agente anti-neoplásico seleccionado de: (1) inhibidores del FCE que son anticuerpos, (2) inhibidores del FCE que son moléculas pequeñas, (3) inhibidores de VEGF que son anticuerpos, y (4) inhibidores de quinasa de VEGF que son moléculas pequeñas como las que se describieron con anterioridad. El tratamiento es para un período de una hasta siete semanas por cada ciclo, y en general para un período de una hasta cuatro semanas por cada ciclo. El compuesto de fórmula 1.0 se administra del mismo modo como se describió con anterioridad para las otras realizaciones de esta invención. El agente anti-neoplásico de molécula pequeña usualmente se administra diariamente, y el agentes anti-neoplásicos anticuerpo usualmente se administra una vez por semana por cada ciclo. En una realización los agentes anti-neoplásicos se seleccionan del grupo que consiste en: Herceptina, Cetuximab, Tarceva, Iressa, bevacizumab, IMC-1C11, SU5416, SU6688 y BAY 43-9006.

En las realizaciones de esta invención en las cuales se usa un compuesto inhibidor de platino como también por lo menos otro agente anti-neoplásico, y estas drogas se administran en forma consecutiva, el compuesto coordinador de platino se administra en general después de haber administrado el otro agente anti-neoplásico.

Otras realizaciones de esta invención incluyen la administración de una cantidad terapéuticamente efectiva de radiación al paciente además de la administración de un compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) y agentes anti-neoplásicos en las realizaciones descritas con anterioridad. La radiación se administra de acuerdo con técnicas y protocolos conocidos por aquellas personas con experiencia en el arte.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende por lo menos dos agentes quimioterapéuticos diferentes y un vehículo aceptable desde el punto de vista farmacéutico para administración endovenosa. Con preferencia el vehículo aceptable desde el punto de vista farmacéutico es una solución salina isotónica (NaCl al 0,9%) o una solución de dextrosa (por ej., dextrosa al 5%).

Otra realización de esta invención se refiere a una composición farmacéutica que comprende un compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) y por lo menos dos diferentes agentes anti-neoplásicos y un vehículo aceptable desde el punto de vista farmacéutico para administración endovenosa. Con preferencia el vehículo aceptable desde el punto de vista farmacéutico es una solución salina isotónica (NaCl al 0,9%) o una solución de dextrosa (por ej., dextrosa al 5%).

Otra realización de esta invención se refiere a una composición farmacéutica que comprende un compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) y por lo menos uno agente anti-neoplásico y un vehículo aceptable desde el punto de vista farmacéutico para administración endovenosa. Con preferencia el vehículo aceptable desde el punto de vista farmacéutico es una solución salina isotónica (NaCl al 0,9%) o una solución de dextrosa (por ej., dextrosa al 5%).

Otras realizaciones de esta invención se refieren a el uso de una combinación de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) y drogas para el tratamiento del cáncer de mama, es decir, esta invención se refiere a una terapia combinada para el tratamiento del cáncer de mama. Aquellas personas con experiencia en el arte apreciarán que los compuestos de fórmula 1.0 y las drogas se administran en general como composiciones farmacéuticas

individuales. El uso de una composición farmacéutica que comprende más de una droga se encuentra dentro del alcance de esta invención.

De este modo, otra realización de esta invención se refiere a un método para el tratamiento de (o prevenir) el cáncer de mama (es decir, cáncer de mama pre-menopáusico o post-menopáusico, por ej., cáncer de mama dependiente de hormonas) en un paciente que necesita de dicho tratamiento que comprende administrar a dicho paciente una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) y una cantidad terapéuticamente efectiva de por lo menos un agente anti-hormonal seleccionado del grupo que consiste en: (a) inhibidores de aromatasa, (b) anti-estrógenos, y (c) análogos de LHRH; y dicho tratamiento incluye en forma opcional la administración de por lo menos un agente quimioterapéutico.

El compuesto de fórmula 1.0 se administra con preferencia por vía oral, y en una realización se administra en forma de cápsula.

Ejemplos de inhibidores de aromatasa incluyen sin carácter limitativo: Anastrozol (por ej., Arimidex), Letrozol (por ej., Femara), Exemestano (Aromasin), Fadrozol y Formestano (por ej., Lentaron).

Ejemplos de anti-estrógenos incluyen sin carácter limitativo: Tamoxifeno (por ej., Nolvadex), Fulvestrant (por ej., Faslodex), Raloxifene (por ej., Evista), y Acolbifene.

Ejemplos de análogos de LHRH incluyen sin carácter limitativo: Goserelin (por ej., Zoladex) y Leuprolida (por ej., Acetato de Leuprolida, tales como Lupron o Lupron Depot).

Ejemplos de agentes quimioterapéuticos incluyen sin carácter limitativo: Trastuzumab (por ej., Herceptin), Gefitinib (por ej., Iressa), Erlotinib (por ej.,

Erlotinib HCl, tales como Tarceva), Bevacizumab (por ej., Avastin), Cetuximab (por ej., Erbitux), y Bortezomib (por ej., Velcade).

Con preferencia, cuando se usa más de un agente anti-hormonal, cada agente se selecciona de una categoría de agente diferente. Por ejemplo, un agente es un inhibidor de aromatasa (por ej., Anastrozol, Letrozol, o Exemestano) y un agente es un anti-estrógenos (por ej., Tamoxifeno o Fulvestrant).

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) y por lo menos un agente anti-hormonal seleccionado del grupo que consiste en: (a) inhibidores de aromatasa, (b) anti-estrógenos, y (c) análogos de LHRH; y administrar una cantidad efectiva de por lo menos un agente quimioterapéutico.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) y por lo menos un agente anti-hormonal seleccionado del grupo que consiste en: (a) inhibidores de aromatasa, (b) anti-estrógenos, y (c) análogos de LHRH.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula

1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) y por lo menos un agente anti-hormonal seleccionado del grupo que consiste en: (a) inhibidores de aromatasa, y (b) anti-estrógenos.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), por lo menos un agente anti-hormonal seleccionado del grupo que consiste en: (a) inhibidores de aromatasa y (b) anti-estrógenos; y por lo menos un agente quimioterapéutico.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) y por lo menos un inhibidor de aromatasa.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), por lo menos un inhibidor de aromatasa, y por lo menos un agente quimioterapéutico.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad

terapéuticamente efectiva de: (1) por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143); y (2) por lo menos un agente anti-hormonal seleccionado del grupo que consiste en: (a) inhibidores de aromatasa que se seleccionan del grupo que consiste en Anastrozol, Letrozol, Exemestano, Fadrozol y Formestano, (b) anti-estrógenos que se seleccionan del grupo que consiste en: Tamoxifeno, Fulvestrant, Raloxifeno, y Acolbifeno, y (c) análogos de LHRH que se seleccionan del grupo que consiste en: Goserelin y Leuprolida; y administrar una cantidad efectiva de por lo menos un agente quimioterapéutico seleccionado del grupo que consiste en: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, y Bortezomib.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de: (1) por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143); y (2) por lo menos un agente anti-hormonal seleccionado del grupo que consiste en: (a) inhibidores de aromatasa que se seleccionan del grupo que consiste en Anastrozol, Letrozol, Exemestano, Fadrozol y Formestano, (b) anti-estrógenos que se seleccionan del grupo que consiste en: Tamoxifeno, Fulvestrant, Raloxifeno, y Acolbifeno, y (c) análogos de LHRH que se seleccionan del grupo que consiste en: Goserelin y Leuprolida.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de: (1) por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones

Nos. 1 hasta 143); y (2) por lo menos un agente anti-hormonal seleccionado del grupo que consiste en: (a) inhibidores de aromatasa que se seleccionan del grupo que consiste en Anastrozol, Letrozol, Exemestano, Fadrozol y Formestano, y (b) anti-estrógenos que se seleccionan del grupo que consiste en: Tamoxifeno, Fulvestrant, Raloxifeno, y Acolbifeno.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de: (1) por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143); y (2) por lo menos un agente anti-hormonal seleccionado del grupo que consiste en: (a) inhibidores de aromatasa que se seleccionan del grupo que consiste en Anastrozol, Letrozol, Exemestano, Fadrozol y Formestano, (b) anti-estrógenos que se seleccionan del grupo que consiste en: Tamoxifeno, Fulvestrant, Raloxifeno, y Acolbifeno; y administrar una cantidad efectiva de por lo menos uno agentes quimioterapéuticos se seleccionan del grupo que consiste en: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, y Bortezomib.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de: (1) por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143); y (2) por lo menos un inhibidor de aromatasa seleccionados del grupo que consiste en Anastrozol, Letrozol, Exemestano, Fadrozol y Formestano.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad

terapéuticamente efectiva de: (1) por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143); (2) por lo menos un inhibidor de aromatasa que se selecciona del grupo que consiste en Anastrozol, Letrozol, Exemestano, Fadrozol y Formestano; y (3) administrar una cantidad efectiva de por lo menos un agente quimioterapéutico seleccionado del grupo que consiste en: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, y Bortezomib.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de: (1) por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143); (2) por lo menos un inhibidor de aromatasa; y (3) por lo menos un análogo de LHRH.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de:(1) por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143); (2) por lo menos un anti-estrógeno; y (3) por lo menos un análogo de LHRH.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de: (1) por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143); (2) por lo menos un inhibidor de aromatasa que se selecciona

del grupo que consiste en Anastrozol, Letrozol, Exemestano, Fadrozol y Formestano; y (3) por lo menos un análogo de LHRH que se selecciona del grupo que consiste en: Goserelin y Leuprolida.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de: (1) por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143); (2) por lo menos un anti-estrógeno que se selecciona del grupo que consiste en: Tamoxifeno, Fulvestrant, Raloxifeno, y Acolbifeno; y (3) por lo menos un análogo de LHRH que se selecciona del grupo que consiste en: Goserelin y Leuprolida.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) y Anastrozol.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) y Letrazol.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad

terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) y Exemestano.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) y Fadrozol.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) y Formestano.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) y Tamoxifeno.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) Fulvestrant.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) y Raloxifeno.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) y Acolbifeno.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) y Goserelin.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) y Leuprolida.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad

terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), Anastrozol, y un anti-estrógeno seleccionado del grupo que consiste en: Tamoxifeno, Fulvestrant, Raloxifeno, y Acolbifeno.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), Letrozol, y un anti-estrógeno seleccionado del grupo que consiste en: Tamoxifeno, Fulvestrant, Raloxifeno, y Acolbifeno.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), Exemestano, y un anti-estrógeno seleccionado del grupo que consiste en: Tamoxifeno, Fulvestrant, Raloxifeno, y Acolbifeno.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), Fadrozol, y un anti-estrógeno seleccionado del grupo que consiste en: Tamoxifeno, Fulvestrant, Raloxifeno, y Acolbifeno.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de

dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), Formestano, y un anti-estrógeno seleccionado del grupo que consiste en: Tamoxifeno, Fulvestrant, Raloxifeno, y Acolbifeno.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), Anastrozol, y Tamoxifeno.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), Letrozol, y Tamoxifeno.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), Exemestano, y Tamoxifeno.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula

1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), Fadrozol, y Tamoxifeno.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), Formestano, y Tamoxifeno.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), Anastrozol, y Fulvestrant.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), Letrozol, y Fulvestrant.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), Exemestano, y Fulvestrant.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), Fadrozol, y Fulvestrant.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), Formestano, y Fulvestrant.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), Anastrozol, y un agente quimioterapéutico seleccionado del grupo que consiste en: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, y Bortezomib.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), Letrozol, y un agente quimioterapéutico seleccionado del grupo que

consiste en: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, y Bortezomib.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), Exemestano, y un agente quimioterapéutico seleccionado del grupo que consiste en: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, y Bortezomib.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), Fadrozol, y un agente quimioterapéutico seleccionado del grupo que consiste en: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, y Bortezomib.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), Formestano, y un agente quimioterapéutico seleccionado del grupo que consiste en: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, y Bortezomib.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), Tamoxifeno, y un agente quimioterapéutico seleccionado del grupo que consiste en: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, y Bortezomib.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), Fulvestrant, y un agente quimioterapéutico seleccionado del grupo que consiste en: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, y Bortezomib.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), Raloxifeno, y un agente quimioterapéutico seleccionado del grupo que consiste en: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, y Bortezomib.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad

terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), Acolbifeno, y un agente quimioterapéutico seleccionado del grupo que consiste en: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, y Bortezomib.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), Goserelin, y un agente quimioterapéutico seleccionado del grupo que consiste en: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, y Bortezomib.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), Leuprolein, y un agente quimioterapéutico seleccionado del grupo que consiste en: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, y Bortezomib.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), Anastrozol, un anti-estrógeno seleccionado del grupo que consiste en:

Tamoxifeno, Fulvestrant, Raloxifeno, y Acolbifeno, y un agente quimioterapéutico seleccionado del grupo que consiste en: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, y Bortezomib.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), Letrozol, un anti-estrógeno seleccionado del grupo que consiste en: Tamoxifeno, Fulvestrant, Raloxifeno, y Acolbifeno, y un agente quimioterapéutico seleccionado del grupo que consiste en: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, y Bortezomib.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), Exemestano, un anti-estrógeno seleccionado del grupo que consiste en: Tamoxifeno, Fulvestrant, Raloxifeno, y Acolbifeno, y un agente quimioterapéutico seleccionado del grupo que consiste en: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, y Bortezomib.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), Fadrozol, un anti-estrógeno seleccionado del grupo que consiste en:

Tamoxifeno, Fulvestrant, Raloxifeno, y Acolbifeno, y un agente quimioterapéutico seleccionado del grupo que consiste en: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, y Bortezomib.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), Formestano, un anti-estrógeno seleccionado del grupo que consiste en: Tamoxifeno, Fulvestrant, Raloxifeno, y Acolbifeno, y un agente quimioterapéutico seleccionado del grupo que consiste en: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, y Bortezomib.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), Anastrozol, Tamoxifeno, y un agente quimioterapéutico seleccionado del grupo que consiste en: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, y Bortezomib.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), Letrozol, Tamoxifeno, y un agente quimioterapéutico seleccionado del

grupo que consiste en: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, y Bortezomib.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), Exemestano, Tamoxifeno, y un agente quimioterapéutico seleccionado del grupo que consiste en: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, y Bortezomib.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), Fadrozol, Tamoxifeno, y un agente quimioterapéutico seleccionado del grupo que consiste en: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, y Bortezomib.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), Formestano, Tamoxifeno, y un agente quimioterapéutico seleccionado del grupo que consiste en: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, y Bortezomib.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), Anastrozol, Fulvestrant, y un agente quimioterapéutico seleccionado del grupo que consiste en: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, y Bortezomib.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), Letrozol, Fulvestrant, y un agente quimioterapéutico seleccionado del grupo que consiste en: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, y Bortezomib.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), Exemestano, Fulvestrant, y un agente quimioterapéutico seleccionado del grupo que consiste en: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, y Bortezomib.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad

terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), Fadrozol, Fulvestrant, y un agente quimioterapéutico seleccionado del grupo que consiste en: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, y Bortezomib.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), Formestano, Fulvestrant, y un agente quimioterapéutico seleccionado del grupo que consiste en: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, y Bortezomib.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), Goserelin y Tamoxifeno.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), Goserelin, y Fulvestrant.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de

dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), Goserelin, y Raloxifeno.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), Goserelin y Acolbifeno.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), Leuprolida, y Tamoxifeno.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), Leuprolida, y Fulvestrant.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula

1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), Leuprolida, y Raloxifeno.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), Leuprolida y Acolbifeno.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), Goserelin y Anastrozol.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), Goserelin y Letrozol.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), Goserelin y Exemestano.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), Goserelin y Fadrozol.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), Goserelin y Formestano.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), Leuprolida y Anastrozol.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), Leuprolida y Letrozol.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad

terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), Leuprolida y Exemestano.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), Leuprolida y Fadrozol.

Otra realización de esta invención se refiere a un método para el tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), Leuprolida y Formestano.

Otra realización de esta invención se refiere al tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento, dicho tratamiento comprende la administración de una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) y Anastrozol.

Otra realización de esta invención se refiere al tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento, dicho tratamiento comprende la administración de una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) y Letrozol.

Otra realización de esta invención se refiere al tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento, dicho tratamiento comprende la administración de una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) y Exemestano.

Otra realización de esta invención se refiere al tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento, dicho tratamiento comprende la administración de una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) y Tamoxifeno.

Otra realización de esta invención se refiere al tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento, dicho tratamiento comprende la administración de una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) y Fulvestrant.

Otra realización de esta invención se refiere al tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento, dicho tratamiento comprende la administración de una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), Anastrozol, y Fulvestrant.

Otra realización de esta invención se refiere al tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento, dicho tratamiento comprende la administración de una cantidad terapéuticamente

efectiva de por lo menos uno compuesto de formula I (por ej., uno), Letrozol, y Fulvestrant.

Otra realización de esta invención se refiere al tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento, dicho tratamiento comprende la administración de una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), Exemestano, y Fulvestrant.

Otra realización de esta invención se refiere al tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento, dicho tratamiento comprende la administración de una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), Anastrozol, y Tamoxifeno.

Otra realización de esta invención se refiere al tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento, dicho tratamiento comprende la administración de una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), Letrozol, y Tamoxifeno.

Otra realización de esta invención se refiere al tratamiento o la prevención del cáncer de mama en un paciente que necesita de dicho tratamiento, dicho tratamiento comprende la administración de una cantidad terapéuticamente efectiva de por lo menos un (por ej., uno) compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), Exemestano, y Tamoxifeno.

Otras realizaciones de esta invención se refieren a cualquiera de las realizaciones mencionadas con anterioridad para el tratamiento del cáncer de mama en el cual el agente quimioterapéutico es Trastuzumab.

Otras realizaciones de esta invención se refieren a cualquiera de las realizaciones mencionadas con anterioridad para el tratamiento o la prevención del cáncer de mama donde el método se refiere al tratamiento del cáncer de mama.

El compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), agentes anti-hormonales y agentes quimioterapéuticos pueden administrarse en forma concurrente o secuencial.

Los agentes anti-hormonales y agentes quimioterapéuticos opcionales se administran de acuerdo con sus protocolos, cantidades de dosificación y formas de dosificación que son conocidas para aquellas personas con experiencia en el arte (por ej., el Physician's Desk Reference o bibliografía publicada). Por ejemplo, para Tamoxifeno, Fulvestrant, Raloxifeno, Anastrozol, Letrozol, Exemestano, Leuprolida y Goserelin, ver el Physician's Desk Reference, 57th Edition, 2003, publicado por Thomas PDR at Montvale, N.J. 07645-1742, cuya descripción se incorpora aquí a modo de referencia a ésta.

En general, en las realizaciones referidas a los métodos para el tratamiento del cáncer de mama: (1) el compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) pueden administrarse diariamente (por ej., una vez por día, y en una realización dos veces por día), (2) los inhibidores de aromatasa pueden administrarse de acuerdo con el protocolo conocido para el inhibidor de aromatasa usado (por ej., una vez por día), (3) los anti-estrógenos pueden administrarse de acuerdo con el protocolo conocido para el anti-estrógeno usado (por ej., desde una vez por día hasta una vez por mes), (4) el análogo de LHRH puede administrarse de acuerdo con el

protocolo conocido para el análogo de LHRH usado (por ej., una vez por mes hasta una vez cada tres meses), y (5) el agente quimioterapéutico pueden administrarse de acuerdo con el protocolo conocido para el agente quimioterapéutico usado (por ej., desde una vez por día hasta una vez por semana).

La terapia de rayos, si se administra en los tratamientos anteriores para el cáncer de mama, se administra en general de acuerdo con protocolos conocidos antes de la administración del compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), agentes anti-hormonales y agentes quimioterapéuticos opcionales.

El tratamiento de acuerdo con los métodos para el tratamiento del cáncer de mama es continuo (es decir, se sigue un cronograma de administración continua). El tratamiento continúa hasta que hay una completa respuesta, o hasta que el médico con experiencia determine que el paciente ya no se beneficia con el tratamiento (por ejemplo, cuando hay progresión de la enfermedad).

El protocolo de tratamiento continuo para el cáncer de mama puede cambiarse por un cronograma de tratamiento discontinuo si, a criterio del médico con experiencia, el paciente se beneficiaría con un cronograma de tratamiento discontinuo con uno o más de los medicamentos administrados. Por ejemplo, el compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) puede administrarse usando un cronograma de tratamiento discontinuo mientras que el resto de los medicamentos usados en el tratamiento se administran como se describe aquí. Un ejemplo de un protocolo de tratamiento discontinuo para el compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) es un ciclo reiterado de tres semanas con el compuesto de fórmula 1.0 seguido de una semana sin el compuesto de fórmula 1.0.

Luego de lograr una respuesta completa con el tratamiento para el cáncer de mama, la terapia de mantenimiento con el compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) puede continuarse usando la dosificación descrita en los métodos de esta invención. La terapia de mantenimiento también puede incluir la administración de los agentes anti-hormonales usando la posología descrita en los métodos de esta invención. La terapia de mantenimiento puede ser sólo con los agentes anti-hormonales. Por ejemplo, luego de lograr una respuesta completa, un inhibidor de aromatasa (por ej., Anastrozol, Letrozol o Exemestano) puede continuarse durante hasta cinco años. O, por ejemplo, un anti-estrógeno, por ej., Tamoxifeno, puede usarse durante hasta cinco años después de lograr una respuesta completa. O, por ejemplo, un anti-estrógeno (por ej., Tamoxifen) puede usarse durante hasta cinco años después de lograr una respuesta completa seguido del uso de un inhibidor de aromatasa (por ej., Anastrozol, Letrozol o Exemestano) durante hasta cinco años.

En las realizaciones referidas al tratamiento del cáncer de mama descrito con anterioridad, el compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) se administra en forma continua en una dosis diaria total de aproximadamente 100 mg hasta aproximadamente 600 mg. Usualmente esta cantidad se administra en dosis divididas, y en una realización esta cantidad se administra dos veces por día. En una realización el compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) se administra dos veces por día en una cantidad de aproximadamente 50 mg hasta aproximadamente 300 mg por cada dosis. En otra realización el compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) se administra dos veces por día en una cantidad de aproximadamente 100 mg hasta

aproximadamente 200 mg por cada dosis. Ejemplos incluyen el compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) que se administran dos veces por día a razón de 100 mg por cada dosis. Ejemplos también incluyen el compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) que se administran dos veces por día a razón de 200 mg por cada dosis.

Anastrozol se administra p.o. y se administra una vez por día en cantidades de aproximadamente 0,5 hasta aproximadamente 10 mg por cada dosis, y en una realización en una cantidad de aproximadamente 1.0 mg por cada dosis.

Letrozol se administra p.o. y se administra una vez por día en cantidades de aproximadamente 1.0 hasta aproximadamente 10 mg por cada dosis, y en una realización en una cantidad de aproximadamente 2,5 mg por cada dosis.

Exemestano se administra p.o. y se administra una vez por día en cantidades de aproximadamente 10 hasta aproximadamente 50 mg por cada dosis, y en una realización en una cantidad de aproximadamente 25 mg por cada dosis.

Fadrozol se administra p.o. y se administra dos veces por día en cantidades de aproximadamente 0,5 hasta aproximadamente 10 mg por cada dosis, y en una realización en una cantidad de aproximadamente 2.0 mg por cada dosis.

Formestano se administra i.m. y se administra una vez cada dos semanas en cantidades de aproximadamente 100 hasta aproximadamente 500 mg por cada dosis, y en una realización en una cantidad de aproximadamente 250 mg por cada dosis.

Tamoxifeno se administra p.o. y se administra una vez por día en cantidades de aproximadamente 10 hasta aproximadamente 100 mg por cada

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dosis, y en una realización en una cantidad de aproximadamente 20 mg por cada dosis.

Fulvestrant se administra i.m. y se administra una vez por mes en cantidades de aproximadamente 100 hasta aproximadamente 1000 mg por cada dosis, y en una realización en una cantidad de aproximadamente 250 mg por cada dosis.

Raloxifeno se administra p.o. y se administra una vez por día en cantidades de aproximadamente 10 hasta aproximadamente 120 mg por cada dosis, y en una realización en una cantidad de aproximadamente 60 mg por cada dosis.

Acolbifeno se administra p.o. y se administra una vez por día en cantidades de aproximadamente 5 hasta aproximadamente 20 mg por cada dosis, y en una realización en una cantidad de aproximadamente 20 mg por cada dosis.

Goserelin se administra s.c. y se administra una vez por mes, o una vez cada tres meses, en cantidades de aproximadamente 2 hasta aproximadamente 20 mg por cada dosis, y en una realización en una cantidad de aproximadamente 3,6 mg por cada dosis cuando se administra una vez por mes, y en otra realización en una cantidad de aproximadamente 10,8 mg por cada dosis cuando se administra una vez cada tres meses.

Leuprolida se administra s.c. y se administra una vez por mes, o una vez cada tres meses, en cantidades de aproximadamente 2 hasta aproximadamente 20 mg por cada dosis, y en una realización en una cantidad de aproximadamente 3,75 mg por cada dosis cuando se administra una vez por mes, y en otra realización en una cantidad de aproximadamente 11.25 mg por cada dosis cuando se administra una vez cada tres meses.

Trastuzumab se administra por i.v. y se administra una vez por semana en cantidades de aproximadamente 2 hasta aproximadamente 20 mpk por cada dosis, y en una realización en una cantidad de aproximadamente 2 mpk por cada

dosis. Trastuzumab se administra inicialmente, en general en una dosis de carga que es en general dos veces la dosis de la dosis semanal. De este modo, por ejemplo, una dosis de carga de 4 mpk se administra y luego la administración es de 2 mpk por cada dosis por semana.

Gefitinib se administra p.o. y se administra una vez por día en cantidades de aproximadamente 100 hasta aproximadamente 1000 mg por cada dosis, y en una realización en una cantidad de aproximadamente 250 mg por cada dosis.

Erlotinib se administra p.o. y se administra una vez por día en cantidades de aproximadamente 100 hasta aproximadamente 500 mg por cada dosis, y en una realización en una cantidad de aproximadamente 150 mg por cada dosis.

Bevacizumab se administra i.v. y se administra una vez cada dos semanas en cantidades de aproximadamente 2,5 hasta aproximadamente 15 mg por kilogramo de peso corporal por cada dosis, y en una realización en una cantidad de aproximadamente 10 mg por kilogramo por cada dosis.

Cetuximab se administra i.v. y se administra una vez por semana en cantidades de aproximadamente 200 hasta aproximadamente 500 mg por dosis por metro cuadrado, y en una realización en una cantidad de aproximadamente 250 mg por metro cuadrado por cada dosis.

Bortezomib se administra i.v. y se administra dos veces por semana durante 2 semanas seguido de un período de descanso de 10 días (ciclo de tratamiento de 21 días) durante un máximo de 8 ciclos de tratamiento en cantidades de aproximadamente 1.0 hasta aproximadamente 2,5 mg por metro cuadrado por cada dosis, y en una realización en una cantidad de aproximadamente 1,3 mg por metro cuadrado por cada dosis.

De este modo en una realización de esta invención el cáncer de mama se trata (o se previene) en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar a dicho paciente: (1) el compuesto de

fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) por vía oral en una cantidad de aproximadamente 50 mg hasta aproximadamente 300 mg por cada dosis donde cada dosis se administra dos veces por día, y (2) Anastrozol p.o. en una cantidad de aproximadamente 0,5 hasta aproximadamente 10 mg por cada dosis donde cada dosis se administra una vez por día.

En otra realización de esta invención el cáncer de mama se trata (o se previene) en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar a dicho paciente: (1) el compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) por vía oral en una cantidad de aproximadamente 100 hasta 200 mg por cada dosis, donde cada dosis se administra dos veces por día, y (2) Anastrozol en una cantidad de aproximadamente 1.0 mg por cada dosis donde cada dosis se administra una vez por día.

En otra realización de esta invención el cáncer de mama se trata (o se previene) en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar a dicho paciente: (1) el compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) por vía oral en una cantidad de aproximadamente 50 mg hasta aproximadamente 300 mg por cada dosis donde cada dosis se administra dos veces por día, y (2) Letrozol p.o. en una cantidad de aproximadamente 1.0 hasta aproximadamente 10 mg por cada dosis donde cada dosis se administra una vez por día.

En otra realización de esta invención el cáncer de mama se trata (o se previene) en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar a dicho paciente: (1) el compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1

hasta 143) por vía oral en una cantidad de aproximadamente 100 hasta 200 mg por cada dosis, donde cada dosis se administra dos veces por día, y (2) Letrozol p.o. en una cantidad de aproximadamente 2,5 mg por cada dosis donde cada dosis se administra una vez por día.

En otra realización de esta invención el cáncer de mama se trata (o se previene) en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar a dicho paciente: (1) el compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) por vía oral en una cantidad de aproximadamente 50 mg hasta aproximadamente 300 mg por cada dosis donde cada dosis se administra dos veces por día, y (2) Exemestano p.o. en una cantidad de aproximadamente 10 hasta aproximadamente 50 mg por cada dosis donde cada dosis se administra una vez por día.

En otra realización de esta invención el cáncer de mama se trata (o se previene) en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar a dicho paciente: (1) el compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) por vía oral en una cantidad de aproximadamente 100 hasta 200 mg por cada dosis, donde cada dosis se administra dos veces por día, y (2) Exemestano en una cantidad de aproximadamente 25 mg por cada dosis donde cada dosis se administra una vez por día.

En otra realización de esta invención el cáncer de mama se trata (o se previene) en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar a dicho paciente: (1) el compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) por vía oral en una cantidad de aproximadamente 50 mg hasta aproximadamente 300 mg por cada dosis donde cada dosis se administra dos

veces por día, y (2) Fulvestrant i.m. en una cantidad de aproximadamente 100 hasta aproximadamente 1000 mg por cada dosis donde cada dosis se administra una vez por mes.

En otra realización de esta invención el cáncer de mama se trata (o se previene) en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar a dicho paciente: (1) el compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) por vía oral en una cantidad de aproximadamente 100 hasta 200 mg por cada dosis, donde cada dosis se administra dos veces por día, y (2) Fulvestrant i.m. en una cantidad de aproximadamente 250 mg por cada dosis donde cada dosis se administra una vez por mes.

En otra realización de esta invención el cáncer de mama se trata (o se previene) en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar a dicho paciente: (1) el compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) p.o. en una cantidad de aproximadamente 50 mg hasta aproximadamente 300 mg por cada dosis donde cada dosis se administra dos veces por día, y (2) Tamoxifeno p.o. en una cantidad de aproximadamente 10 hasta aproximadamente 100 mg por cada dosis donde cada dosis se administra una vez por día.

En otra realización de esta invención el cáncer de mama se trata (o se previene) en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar a dicho paciente: (1) el compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) p.o. en una cantidad de aproximadamente 100 hasta 200 mg por cada dosis, donde cada dosis se administra dos veces por día, y (2) Tamoxifeno p.o. en

una cantidad de aproximadamente 20 mg por cada dosis donde cada dosis se administra una vez por día.

En otras realizaciones de la invención el cáncer de mama se trata en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende la administración del compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), uno de los inhibidores de aromatasa (por ej., Anastrozol, Letrozol, o Exemestano, y en una realización Anastrozol), y uno de los anti-estrógenos (por ej., Fulvestrant o Tamoxifeno), donde el compuesto de fórmula 1.0, inhibidor de aromatasa y anti-estrógeno se administran en las descripciones descritas con anterioridad.

De este modo, por ejemplo en otra realización de esta invención el cáncer de mama se trata (o se previene) en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar a dicho paciente : (1) el compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) p.o. en una cantidad de aproximadamente 50 mg hasta aproximadamente 300 mg por cada dosis donde cada dosis se administra dos veces por día, (2) Anastrozol p.o. en una cantidad de aproximadamente 0,5 hasta aproximadamente 10 mg por cada dosis donde cada dosis se administra una vez por día, y (3) Fulvestrant i.m. en una cantidad de aproximadamente 100 hasta aproximadamente 1000 mg por cada dosis donde cada dosis se administra una vez por mes.

En otra realización de esta invención el cáncer de mama se trata (o se previene) en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar a dicho paciente: (1) el compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) p.o en una cantidad de aproximadamente 100 hasta 200 mg por cada dosis, donde cada dosis se administra dos veces por día, (2) Anastrozol p.o. en

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una cantidad de aproximadamente 1.0 mg por cada dosis donde cada dosis se administra una vez por día, y (3) Fulvestrant i.m. en una cantidad de aproximadamente 250 mg por cada dosis donde cada dosis se administra una vez por mes.

En otra realización de esta invención el cáncer de mama se trata (o se previene) en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar a dicho paciente: (1) el compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) p.o. en una cantidad de aproximadamente 50 mg hasta aproximadamente 300 mg por cada dosis donde cada dosis se administra dos veces por día, (2) Letrozol p.o en una cantidad de aproximadamente 1.0 hasta aproximadamente 10 mg por cada dosis donde cada dosis se administra una vez por día, y (3) Fulvestrant en una cantidad de aproximadamente 100 hasta aproximadamente 1000 mg por cada dosis donde cada dosis se administra una vez por mes.

En otra realización de esta invención el cáncer de mama se trata (o se previene) en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar a dicho paciente: (1) el compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) p.o. en una cantidad de aproximadamente 100 hasta 200 mg por cada dosis, donde cada dosis se administra dos veces por día, (2) Letrozol p.o. en una cantidad de aproximadamente 2,5 mg por cada dosis donde cada dosis se administra una vez por día, y (3) Fulvestrant i.m. en una cantidad de aproximadamente 250 mg por cada dosis donde cada dosis se administra una vez por mes.

En otra realización de esta invención el cáncer de mama se trata (o se previene) en un paciente que necesita de dicho tratamiento donde dicho

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tratamiento comprende administrar a dicho paciente: (1) el compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) p.o. en una cantidad de aproximadamente 50 mg hasta aproximadamente 300 mg por cada dosis donde cada dosis se administra dos veces por día, (2) Exemestano p.o. en una cantidad de aproximadamente 10 hasta aproximadamente 50 mg por cada dosis donde cada dosis se administra una vez por día, y (3) Fulvestrant i.m. en una cantidad de aproximadamente 100 hasta aproximadamente 1000 mg por cada dosis donde cada dosis se administra una vez por mes.

En otra realización de esta invención el cáncer de mama se trata (o se previene) en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar a dicho paciente: (1) el compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) p.o. en una cantidad de aproximadamente 100 hasta 200 mg por cada dosis, donde cada dosis se administra dos veces por día, (2) Exemestano p.o. en una cantidad de aproximadamente 25 mg por cada dosis donde cada dosis se administra una vez por día, y (3) Fulvestrant i.m. en una cantidad de aproximadamente 250 mg por cada dosis donde cada dosis se administra una vez por mes.

En otra realización de esta invención el cáncer de mama se trata (o se previene) en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar a dicho paciente: (1) el compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) p.o. en una cantidad de aproximadamente 50 mg hasta aproximadamente 300 mg por cada dosis donde cada dosis se administra dos veces por día, (2) Anastrozol p.o. en una cantidad de aproximadamente 0,5 hasta aproximadamente 10 mg por cada dosis donde cada dosis se administra una vez

por día, y (3) Tamoxifeno p.o. en una cantidad de aproximadamente 10 hasta aproximadamente 100 mg por cada dosis donde cada dosis se administra una vez por día.

En otra realización de esta invención el cáncer de mama se trata (o se previene) en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar a dicho paciente: (1) el compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) p.o. en una cantidad de aproximadamente 100 hasta 200 mg por cada dosis, donde cada dosis se administra dos veces por día, (2) Anastrozol p.o. en una cantidad de aproximadamente 1.0 mg por cada dosis donde cada dosis se administra una vez por día, y (3) Tamoxifeno p.o. en una cantidad de aproximadamente 20 mg por cada dosis donde cada dosis se administra una vez por día.

En otra realización de esta invención el cáncer de mama se trata (o se previene) en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar a dicho paciente: (1) el compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) p.o. en una cantidad de aproximadamente 50 mg hasta aproximadamente 300 mg por cada dosis donde cada dosis se administra dos veces por día, (2) Letrozol p.o. en una cantidad de aproximadamente 1.0 hasta aproximadamente 10 mg por cada dosis donde cada dosis se administra una vez por día, y (3) Tamoxifeno p.o. en una cantidad de aproximadamente 10 hasta aproximadamente 100 mg por cada dosis donde cada dosis se administra una vez por día.

En otra realización de esta invención el cáncer de mama se trata (o se previene) en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar a dicho paciente: (1) el compuesto de fórmula

1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) p.o. en una cantidad de aproximadamente 100 hasta 200 mg por cada dosis, donde cada dosis se administra dos veces por día, (2) Letrozol p.o. en una cantidad de aproximadamente 2,5 mg por cada dosis donde cada dosis se administra una vez por día, y (3) Tamoxifeno p.o. en una cantidad de aproximadamente 20 mg por cada dosis donde cada dosis se administra una vez por día.

En otra realización de esta invención el cáncer de mama se trata (o se previene) en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar a dicho paciente: (1) el compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) p.o. en una cantidad de aproximadamente 50 mg hasta aproximadamente 300 mg por cada dosis donde cada dosis se administra dos veces por día, (2) Exemestano p.o. en una cantidad de aproximadamente 10 hasta aproximadamente 50 mg por cada dosis donde cada dosis se administra una vez por día, y (3) Tamoxifeno p.o. en una cantidad de aproximadamente 10 hasta aproximadamente 100 mg por cada dosis donde cada dosis se administra una vez por día.

En otra realización de esta invención el cáncer de mama se trata (o se previene) en un paciente que necesita de dicho tratamiento donde dicho tratamiento comprende administrar a dicho paciente: (1) el compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) p.o. en una cantidad de aproximadamente 100 hasta 200 mg por cada dosis, donde cada dosis se administra dos veces por día, (2) Exemestano p.o. en una cantidad de aproximadamente 25 mg por cada dosis donde cada dosis se administra una vez por día, y (3) Tamoxifeno p.o. en una cantidad de

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aproximadamente 20 mg por cada dosis donde cada dosis se administra una vez por día.

Aquellas personas con experiencia en el arte apreciarán que cuando se usan otras combinaciones de agentes anti-hormonales, el agente anti-hormonal individual se usa en las cantidades especificadas con anterioridad para ese agente anti-hormonal individual.

Otras realizaciones del tratamiento del cáncer de mama se refieren a los métodos para el tratamiento del cáncer de mama descritos con anterioridad donde el compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) se administra dos veces por día en una cantidad de aproximadamente 100 mg por cada dosis.

Otras realizaciones del tratamiento del cáncer de mama se refieren a los métodos para el tratamiento del cáncer de mama descritos con anterioridad donde el compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) se administra dos veces por día en una cantidad de aproximadamente 200 mg por cada dosis.

Otras realizaciones del tratamiento del cáncer de mama se refieren a los métodos para el tratamiento del cáncer de mama descritos con anterioridad en los cuales un agente quimioterapéutico se administra además del compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) y agente anti-hormonal (o agentes anti-hormonales). En estas realizaciones los rangos de dosificación del compuesto de fórmula 1.0 y agentes anti-hormonales son como aquellos que se describieron con anterioridad en las terapias combinadas, o aquellos que se describieron con anterioridad para el compuesto individual de formula I y agentes anti-hormonales, y las dosificaciones de los agentes quimioterapéuticos son aquellos que se describieron con

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anterioridad para el agente quimioterapéutico individual. Las dosificaciones para los agentes quimioterapéuticos se conocen muy bien en el arte.

Otras realizaciones de esta invención se refieren a composiciones farmacéuticas que comprenden el compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143) y por lo menos uno agente anti-hormonal y un vehículo aceptable desde el punto de vista farmacéutico.

Otras realizaciones de esta invención se refieren a composiciones farmacéuticas que comprenden el compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), por lo menos uno agente anti-hormonal, por lo menos un agente quimioterapéutico, y un vehículo aceptable desde el punto de vista farmacéutico.

Otras realizaciones de esta invención se refieren a composiciones farmacéuticas que comprenden el compuesto de fórmula 1.0 (por ejemplo, como se describe en cualquiera de las Realizaciones Nos. 1 hasta 143), por lo menos un agente quimioterapéutico, y un vehículo aceptable desde el punto de vista farmacéutico.

Aquellas personas con experiencia en el arte apreciarán que los compuestos (drogas) usados en los métodos de esta invención se encuentran disponibles para el médico con experiencia en composiciones farmacéuticas (formas de dosificación) del fabricante y se usan en esas composiciones. Así, la mención del compuesto o clase de compuestos in en los métodos descritos con anterioridad puede reemplazarse con una mención de una composición farmacéutica que comprende ese compuesto o clase de compuestos en particular. Por ejemplo, la realización referida a un método de tratamiento para el cáncer que comprende administrar a un paciente que necesita de dicho tratamiento cantidades terapéuticamente efectivas del compuesto de fórmula 1.0, un taxano, y

un compuesto de coordinación de platino, incluye dentro de su alcance un método de tratamiento para el cáncer que comprende administrar a un paciente que necesita de dicho tratamiento cantidades terapéuticamente efectivas de una composición farmacéutica que comprende el compuesto de fórmula 1.0, una composición farmacéutica que comprende un taxano, y una composición farmacéutica que comprende un compuesto de coordinación de platino.

Aquellas personas con experiencia en el arte reconocerán que las dosificaciones reales y protocolos para administración empleados en los métodos de esta invención pueden variarse de acuerdo con el criterio del médico con experiencia. La dosificación real empleada puede variarse dependiendo de los requerimientos del paciente y la severidad de la afección sometida a tratamiento. La determinación de la dosificación apropiada para una situación particular se encuentra dentro de la experiencia en el arte. Una determinación para variar las dosificaciones y los protocolos de administración puede realizarse después de que el médico con experiencia tenga en cuenta factores tales como la edad del paciente, la condición y el tamaño, como también la severidad del cáncer tratado y la respuesta del paciente al tratamiento.

La cantidad y la frecuencia de administración del compuesto de fórmula 1.0 y los agentes quimioterapéuticos se regularán de acuerdo con el criterio del médico (clínico) a cargo considerando factores tales como la edad, la condición y el tamaño del paciente como también la severidad del cáncer tratado.

El agente quimioterapéutico puede administrarse de acuerdo con protocolos terapéuticos conocidos en el arte. Aquellas personas con experiencia en el arte apreciarán que la administración del agente quimioterapéutico puede variarse dependiendo del cáncer sometido a tratamiento y los efectos conocidos del agente quimioterapéutico sobre esa enfermedad. Además, de acuerdo con el conocimiento del médico con experiencia, los protocolos terapéuticos (por ej., las

cantidades de dosificación y los horarios de administración) pueden variarse en vista de los efectos observados de los agentes terapéuticos administrados sobre el paciente, y en vista de las respuestas observadas del cáncer a los agentes terapéuticos administrados.

La administración inicial puede realizarse de acuerdo con protocolos establecidos conocidos en el arte, y luego, en base a los efectos observados, la dosificación, los modos de administración y los horarios de administración pueden ser modificados por el médico con experiencia.

La elección particular del agente quimioterapéutico dependerá del diagnóstico de los médicos tratantes y su criterio de la condición del paciente y el protocolo del tratamiento apropiado.

La determinación del orden de administración, y el número de repeticiones de administración del agente quimioterapéutico durante un protocolo de tratamiento, se encuentra dentro del conocimiento del médico con experiencia luego de la evaluación del cáncer sometido a tratamiento y la afección del paciente.

De este modo, de acuerdo con la experiencia y el conocimiento, el médico prácticamente puede modificar cada protocolo para la administración de un agente quimioterapéutico de acuerdo con las necesidades individuales del paciente, a medida que avanza el tratamiento. Todas dichas modificaciones se encuentran dentro del alcance de la presente invención.

La elección particular de los agentes anti-hormonales, agentes quimioterapéuticos opcionales y radiación opcional dependerá del diagnóstico de los médicos tratantes y su criterio de la afección del paciente y el protocolo de tratamiento apropiado.

La determinación del orden de administración y el número de repeticiones de administración de los agentes anti-hormonales, agentes quimioterapéuticos

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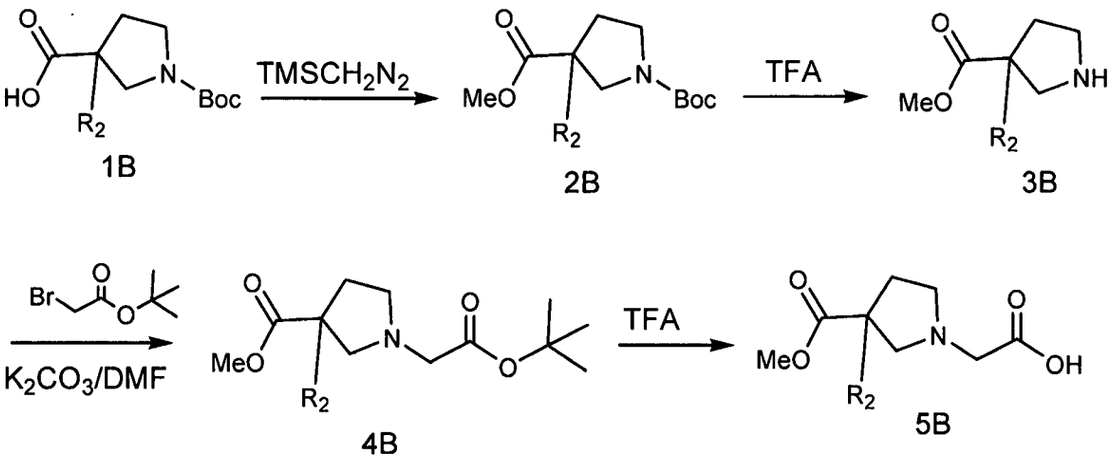
opcionales y radiación opcional durante un protocolo de tratamiento, se encuentra dentro del conocimiento del médico experimentado luego de la evaluación del cáncer de mama sometido a tratamiento y la condición del paciente.

De este modo, de acuerdo con la experiencia y el conocimiento, el médico practicante puede modificar cada protocolo para la administración de agentes anti-hormonales, agentes quimioterapéuticos opcionales y radiación opcional de acuerdo con the las necesidades individuales del paciente, a medida que avanza el tratamiento. Todas dichas modificaciones se encuentran dentro del alcance de la presente invención.

El médico tratante, al juzgar si el tratamiento es efectivo en la dosis administrada, considerará el bienestar general del paciente como también signos más definidos tales como el alivio de los síntomas relacionados con el cáncer (por ej., dolor, tos (para el cáncer de pulmón), y dificultad respiratoria (para el cáncer de pulmón)), inhibición del crecimiento del tumor, encogimiento real del tumor, o inhibición de la metástasis. El tamaño del tumor puede medirse por métodos estándar tales como estudios radiológicos, por ej., TAC o barrido por RMI, y pueden usarse mediciones sucesivas para juzgar si el crecimiento del tumor se ha retrasado o incluso revertido o no. El alivio de los síntomas relacionados con la enfermedad tales como dolor y mejora de la condición general también puede utilizarse para ayudar a juzgar sobre la efectividad del tratamiento.

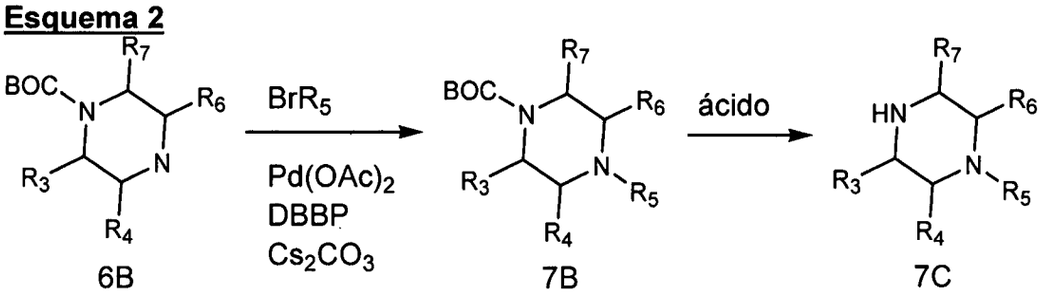
Los compuestos de esta invención pueden realizarse de acuerdo con los procesos descritos en WO2007/070398 publicada el 21 de junio de 2007, y los compuestos de la invención pueden realizarse de acuerdo con los procesos descritos a continuación.

Esquema 1



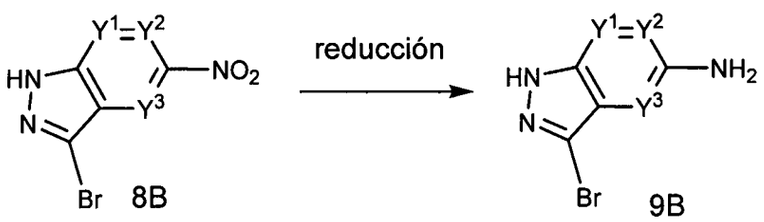
La pirrolidina sustituida en forma apropiada se prepara de la siguiente manera. El metil éster de la pirrolidina 1B se prepara por reacción con TMSdiazometano. Luego de eliminar el grupo protector BOC, el compuesto 3B se hace reaccionar con bromo-ter-butilacetato para obtener 4B. El ter-butil éster luego se elimina para obtener el intermediario 5B.

Esquema 2



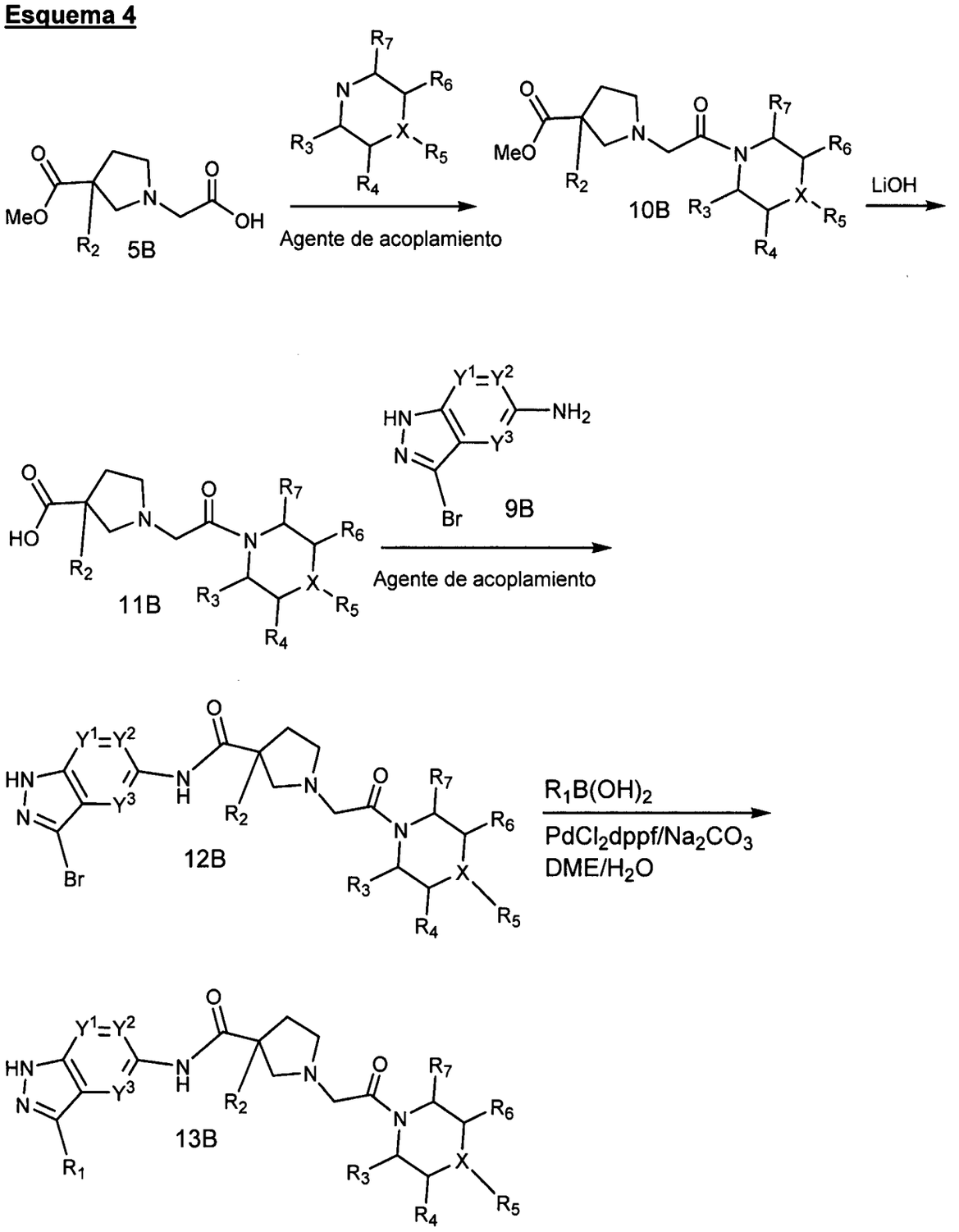
La piperazina sustituida R^5 se prepara por acoplamiento tipo Buchwald de la piperazina 6B con un aril bromuro en presencia de paladio para obtener la piperazina 7B. El grupo BOC se retira usando condiciones ácidas (por ej., TFA) para dar la piperazina 7C.

Esquema 3



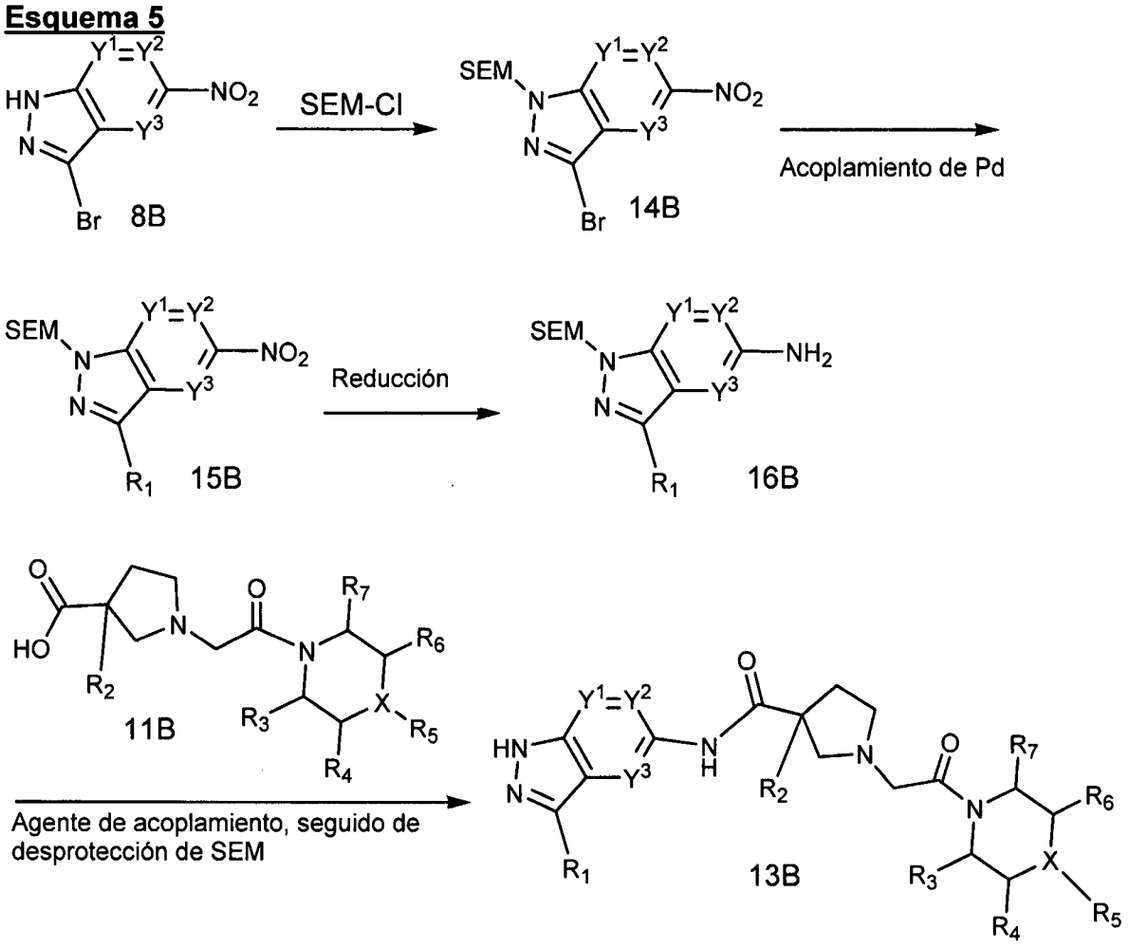
El bromuro de indazol 9B se prepara por reducción del compuesto nitro indazol 8B usando condiciones de reducción como paladio sobre carbono en presencia de atmósfera de hidrógeno.

Esquema 4



La molécula final se arma por acoplamiento de la pirrolidina 5B con la piperazina (X es N, ver compuesto 7C del Esquema 2), o con la piperidina (X es C, preparado en los Esquemas 11 o 12, o preparado de acuerdo con los Ejemplos descritos aquí, o preparado de acuerdo con métodos conocidos para aquellas personas con experiencia en el arte), usando condiciones de acoplamiento estándar tales como HATU en DMF para obtener 10B. Luego de la hidrólisis del metil éster para obtener 11B, el intermediario indazol 9B se acopla entonces usando condiciones de acoplamiento estándar tales como HATU en DMF para obtener 12B. El indazol se deriva luego en la posición 3 por acoplamiento de Suzuki con un ácido borónico para obtener el producto final 13B.

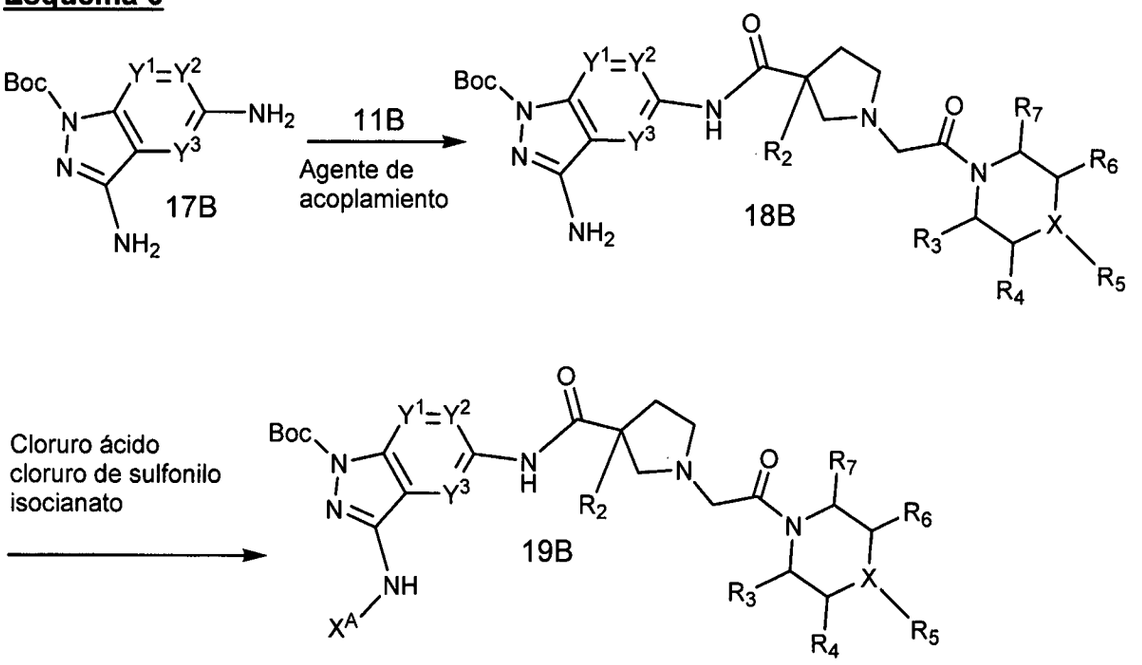
Esquema 5



En forma alternativa, el producto final 13B puede prepararse protegiendo el

indazol 8B como el derivado de SEM (o tritilo) seguido de acoplamiento de Suzuki para dar el intermediario indazol sustituido en forma apropiada 15B. Luego de la reducción usando condiciones de reducción tales como paladio sobre carbono en presencia de atmósfera de hidrógeno para obtener 16B, la amina 16B puede acoplarse a 11B usando condiciones de acoplamiento estándar tales como HATU en DMF para obtener 13B.

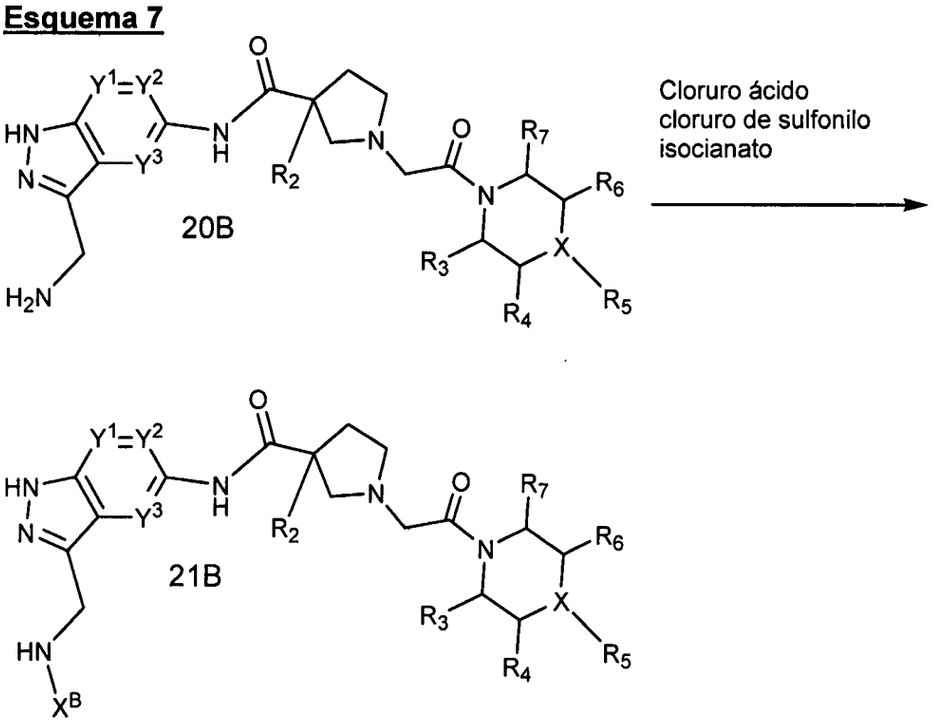
Esquema 6



Un derivado indazol 3-amino sustituido puede prepararse de acuerdo con el Esquema general 6 a través del acoplamiento del 3,5-diamino indazol Boc protegido 17B con 11B en condiciones de acoplamiento estándar tales como HATU en DMF para obtener 18B. El grupo 3-amino luego puede hacerse reaccionar con cloruros ácidos, cloruros de sulfonilo e isocianatos para preparar las correspondientes amidas, sulfonamidas y ureas 19B respectivamente.

Aquellas personas con experiencia en el arte apreciarán que el resto – NHX^A representa los grupos R^1 amino sustituidos, tales como, $-N(R^{10})_2$. $-NR^{32}-C(O)-R^{14}$, $-N(R^{10})C(O)N(R^{10})_2$. y $-N(R^{10})S(O)_tR^{10}$.

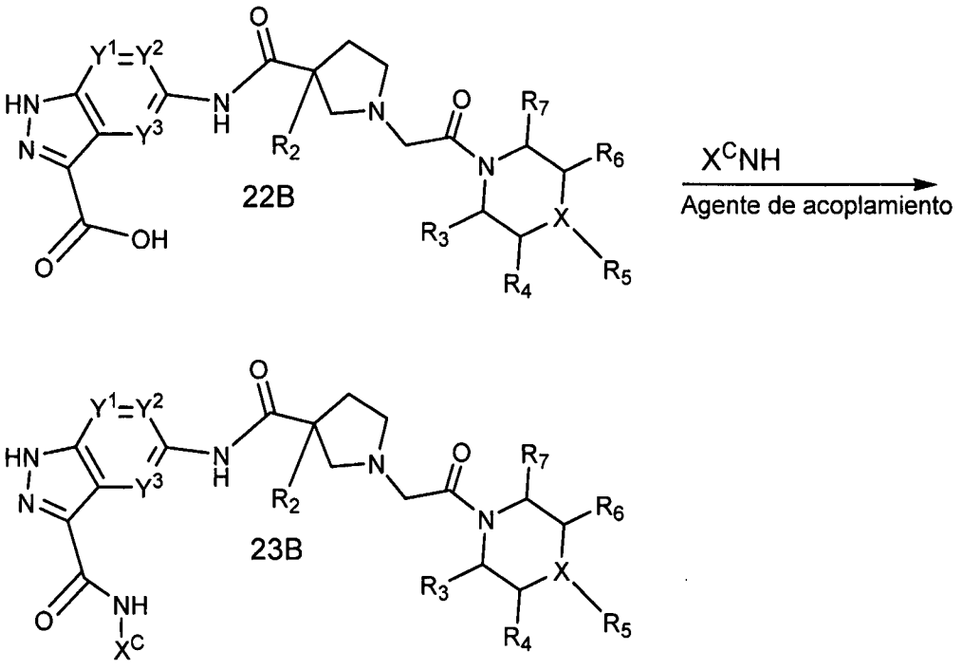
Esquema 7



El derivado amino metil indazol 20B puede prepararse de acuerdo con Ejemplo 76 paso 1 hasta 4 por la sustitución de los anillos sustituidos en forma apropiada. El grupo 3-aminometilo luego puede hacerse reaccionar con cloruros ácidos, cloruros de sulfonilo e isocianatos para preparar las correspondientes amidas, sulfonamidas y ureas 21B respectivamente.

Aquellas personas con experiencia en el arte apreciarán que el resto – CH_2NHX^B representa los grupos amino metilo sustituidos R^1, tales como, $-(C(R^{30})_2)_n-NR^{32}-C(O)-R^{10}$ (donde n es 1 y cada R^{30} es H), $-(C(R^{30})_2)_n-NR^{32}-S(O)_t-R^{10}$ (donde n es 1 y cada R^{30} es H), $-(C(R^{30})_2)_n-NR^{32}-C(O)-N(R^{32})-R^{10}$ (donde n es 1 y cada R^{30} es H), $-(C(R^{30})_2)_nR^{13}$ (donde n es 1, cada R^{30} es H y R^{13} es $-N(R^{10})_2$),

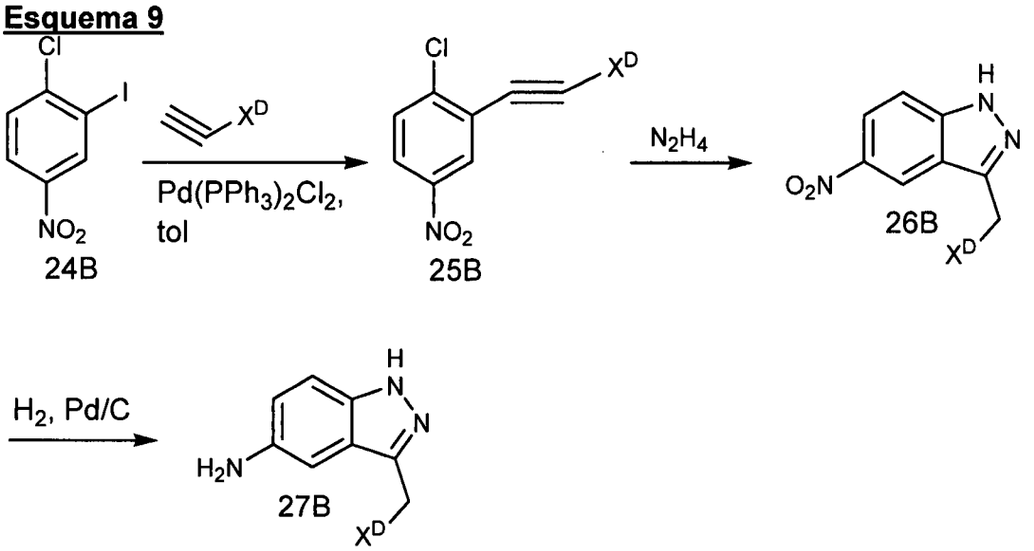
Esquema 8

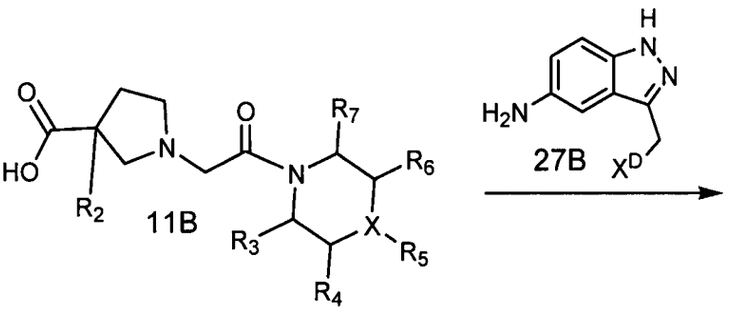


El compuesto amida 23B puede prepararse siguiendo el Ejemplo 87 sustituyendo el compuesto apropiado11B (Esquema general 4). El ácido resultante 22B luego se acopla a la amina apropiada en condiciones de acoplamiento estándar tales como en presencia de EDC/HOBt para obtener 23B.

Aquellas personas con experiencia en el arte apreciarán que el resto – $C(O)NHX^C$ representa los grupos R^1, tales como, $-C(O)N(R^{10})_2$ y $-C(O)-NR^{32}-C(R^{18})_3$

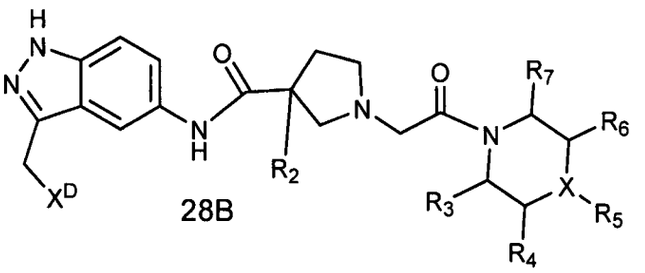
Esquema 9





11B

27B



28B

Los indazoles del tipo 27B pueden prepararse haciendo reaccionar 24B con el acetileno sustituido en forma apropiada en presencia de $Pd(PPh_3)_2Cl_2$ en tolueno para obtener 25B. Luego de calentar con hidrazina para obtener 26B, 27B se obtiene después de la hidrogenación. El acoplamiento de 27B con 11B en condiciones de acoplamiento estándar tales como HATU o EDC/HOBt da 28B.

El resto $-CH_2X^D$ representa R^1 grupos que son un sustituyente R^{10}, tales como, alquilo, heteroarilalquilo, y arilalquilo.

Esquema 10



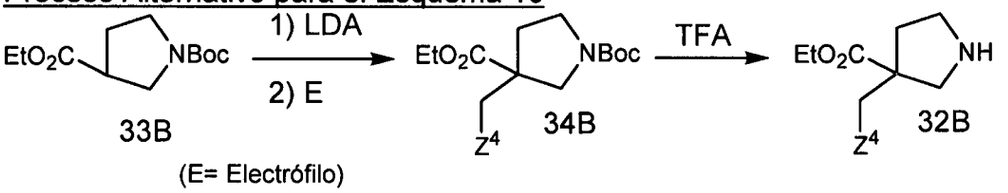
29B 30B 31B 32B

$$—\overset{H_2}{C}—Z^4 = R^2$$

La pirrolidina sustituida en forma apropiada 32B puede obtenerse haciendo reaccionar 29B con el compuesto sustituido en forma apropiada 30B en presencia

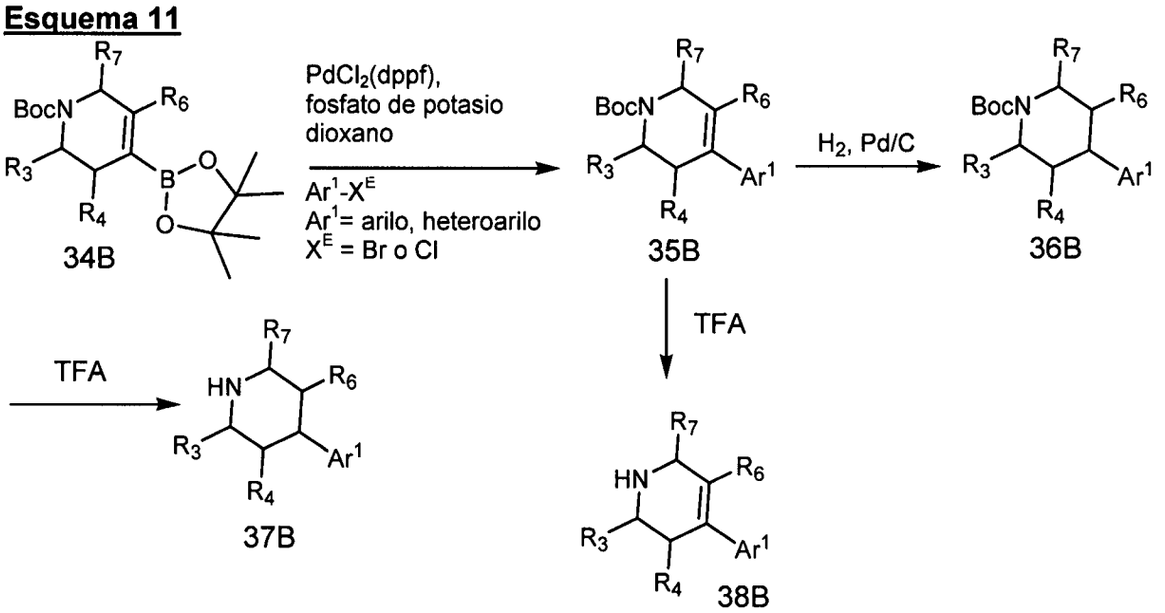
de ácido trifluoroacético para obtener 31B. El Compuesto 31B luego puede desprotegerse usando condiciones de hidrogenación (Pd/C, H_2 para obtener 32B).

Proceso Alternativo para el Esquema 10



En forma alternativa, 32B se puede obtener por reacción de 33B con LDA seguido de la incorporación de un electrófilo apropiado tal como alil bromuro, como en el ejemplo 127, para obtener 34B. El tratamiento de 34B con ácido trifluoroacético produce 32B.

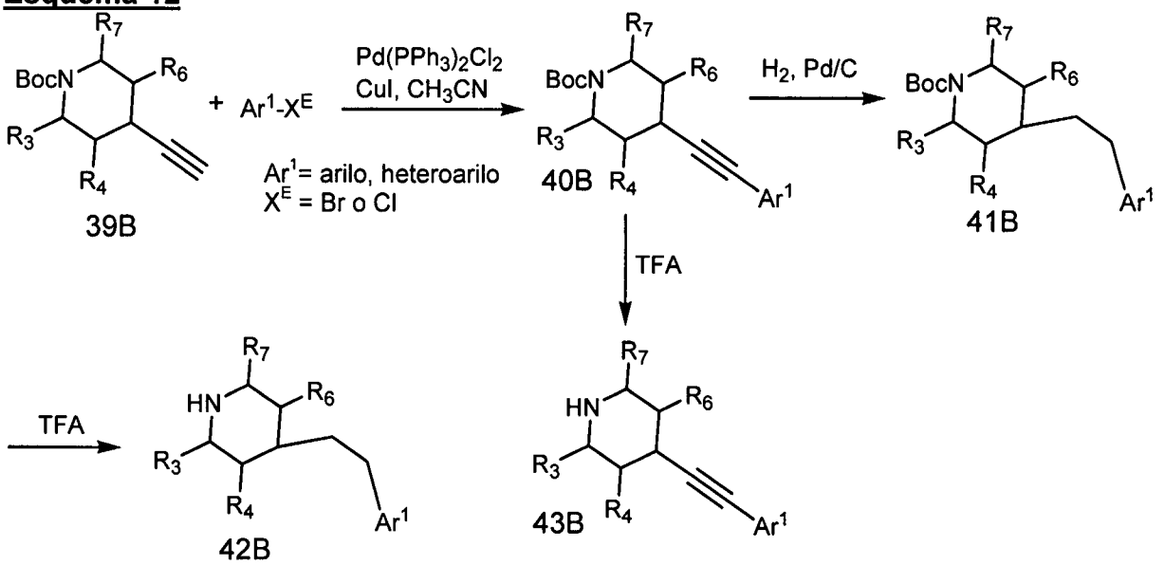
Esquema 11



Las piperidinas aril o heteroaril sustituidas pueden prepararse por acoplamiento de Suzuki de un haluro de arilo o heteroarilo con el pinicolboronato 34B para obtener 35B. El enlace doble del anillo puede hidrogenarse luego obtener 36B seguido de la eliminación del grupo protector BOC en condiciones de

ácido trifluoroacético. En forma alternativa el enlace doble puede retenerse y retirarse el grupo BOC para dar 38B.

Esquema 12



De manera similar las piperazinas aril o heteroaril sustituidas con un espaciador de carbono 2 puede prepararse como se muestra en el Esquema 12 a través del acoplamiento un arilo o heteroaril haluro con un derivado acetileno 39B que puede prepararse de acuerdo con procedimientos conocidos en el arte para obtener 40B. 40B puede reducirse en 41B seguido de la eliminación del grupo protector BOC en condiciones de ácido trifluoroacético. En forma alternativa el grupo protector BOC de 40B puede eliminarse en condiciones de ácido trifluoroacético para dar 43B.

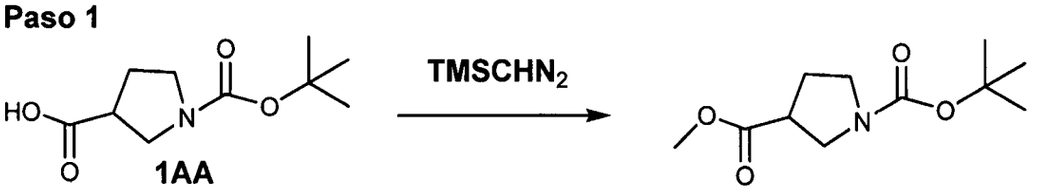
Los Compuestos de esta invención se ejemplifican en los siguientes ejemplos, que no deben construirse como límite del alcance de la invención. Las vías mecánicas alternativas y estructuras análogas dentro del alcance de la invención pueden resultar obvias para aquellas personas con experiencia en el arte.

Las condiciones de LCMS son: (1) columna: C-18 fase inversa, 5um, 4,6 x 50 mm, (2) MS:PE Sciex API-150EX, y (3) HPLC: Shimadzu LC-10 ADvp, 1ml/min, gradiente lineal 10% acetonitrilo en agua a 95% acetonitrilo en agua, ambos contienen 0,05% TFA

Los Ejemplos 1 hasta 611 se describen en la WO2007/070398 (publicada el 21 de junio de 2007) en la página 188 aproximadamente renglón 15 hasta la página 453 aproximadamente renglón 10, cuyas páginas se copian aquí en su totalidad y deben considerarse parte de la presente invención, aunque dichas páginas publicadas no se reproducen con el objetivo de ser breves.

EJEMPLO 612

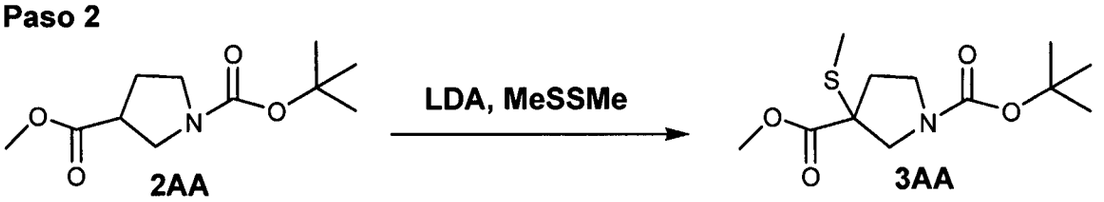
Paso 1



1AA **2AA**

1—ter—butil éster del ácido pirrolidin—1,3—dicarboxílico **1AA** (4,3 gm, 20 mmol) se disolvió en 28 ml de tolueno y 3,5 ml de metanol. Se agregó solución 2N de trimetilsilildiazometano en hexanos (13 ml, 26 mmol) gota a gota a 0°C y la mezcla de reacción se agitó durante 10 min a temperatura ambiente. La mezcla se evaporó para obtener 4,3 g de aceite.

Paso 2

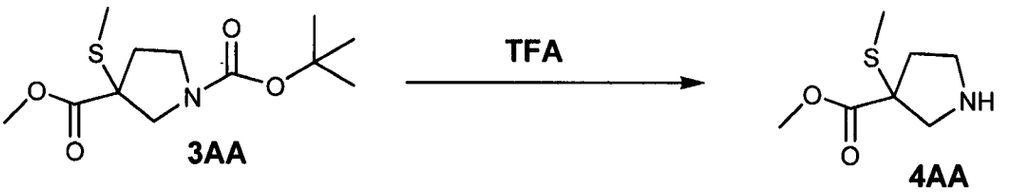


2AA **3AA**

Al aceite **2** (0,5 gm, 2.1 mmol) disuelto en tetrahidrofurano (15 ml) 1,2 ml de solución 2N de diisopropilamida de litio en hexanos se agregó gota a gota y la mezcla de reacción se agitó durante 1 hr a -78°C. Sulfuro de dimetilo (0,48 ml, 5,4 mmol) se agregó lentamente y se dejó entibiar hasta la temperatura ambiente en forma gradual. La mezcla de reacción se agitó durante 18 hrs. Se agregó una

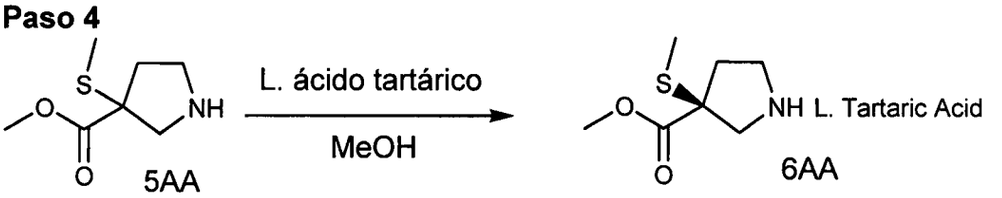
solución saturada de Cloruro de amonio (25 ml) y la mezcla de reacción se agitó durante 5 min. La mezcla de reacción se extrajo con acetato de etilo tres veces (3x25 ml), se secó sobre sulfato de magnesio, se filtró y se evaporó para dar 0,386 g del producto del título **3AA** luego de la cromatografía en columna.

Paso 3



3-metil éster 3-Metilsulfanil-1-ter-butil éster del ácido pirrolidin-1,3-dicarboxílico **3AA** (2,15 g, 8,8 mmol) se disolvió en 20 ml de ácido trifluoroacético al 50%/diclorometano y se agitó durante 2 hrs. La mezcla de reacción se evaporó hasta obtener un aceite y se cambió con ácido clorhídrico por disolución en 20 ml de diclorometano y agregando 10 ml de HCl 1N en éter para obtener 3,35 g **4AA** como un sólido gomoso.

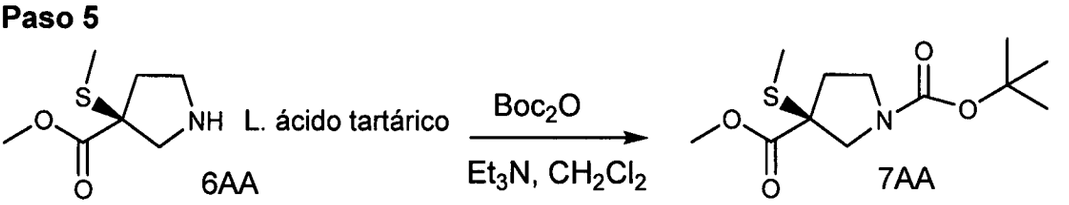
Paso 4



El Compuesto A (42.9g, 244,8 mmol) y 1 eq. de ácido L-tartárico se colocaron en un balón de 1 l y se disolvió con 250 ml de MeOH. El matraz se adhirió luego a un rotavapor a 75°C. La mezcla se dejó centrifugar suavemente a esta temperatura durante aproximadamente 20 min., para asegurar la completa disolución. Luego de la formación de una solución, aproximadamente 10 mg de cristales puros se agregaron (para ayudar a la formación de cristales) se dejó decantar suavemente para la formación de cristales. Luego de 3 días, se recuperaron 19,4 g de cristales que luego se lavó con MeOH frío para dar 18,2g de cristales.

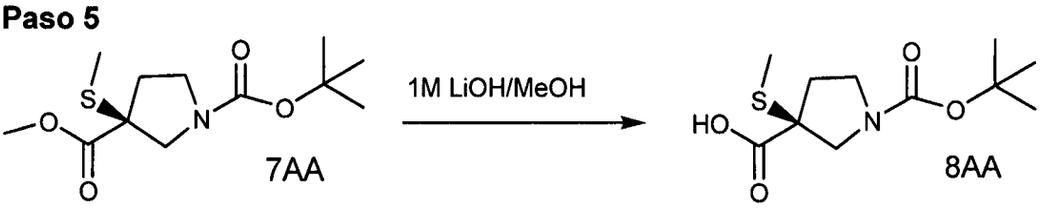
La pureza quiral de los cristales se determinó derivando con cloroformiato de 4-nitrobencilo sometiéndolos a HPLC en las condiciones de la columna quiral AD, sistema solvente de 20% isopropanol/hexano y un caudal de flujo de 1 ml/min. Se encontró que la pureza era ~ 99,9% con un tiempo de retención de 16,58 min.

Paso 5



El Compuesto 6AA (3,0g, 9,2 mmol) se disolvió en 100 ml de CH_2Cl_2 a temperatura ambiente. Se agregó 2,5 eq. de Et_3N seguido de 1,2 eq. de Boc_2O. La mezcla de reacción se dejó agitar durante 1 día luego de que se diluyó con CH_2Cl_2 y se lavó con $NaHCO_3$ sat. seguido de NaCl sat.. La fase orgánica se secó sobre MgSO4 anhidro y se evaporó hasta la sequedad. El producto en bruto se purificó en columna (20% EtAOc/Hex) y se evaporó para dar 2,43g de producto puro en el rendimiento de ~ 96%.

Paso 5



$C_{12}H_{21}NO_4S$
Masa exacta: 275,12
Peso Mol.: 375,36

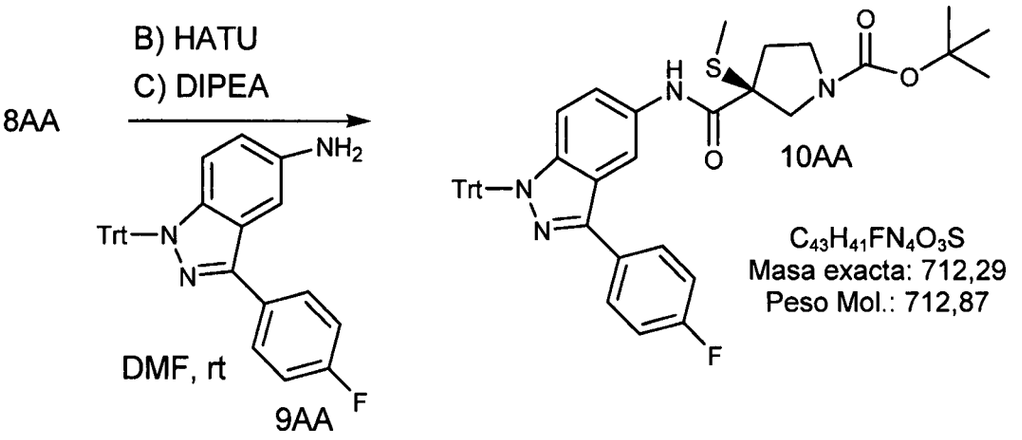
$C_{11}H_{19}NO_4S$
Masa exacta: 261,10
Peso Mol.: 261,34

El Compuesto 7AA (0,75g, 2.73 mmol) se disolvió en 20 ml de MeOH. Se agregó 6 ml de LiOH 1M al matraz de reacción y la solución resultante se dejó agitar a temperatura ambiente durante 1 hasta la mañana siguiente. Luego de la finalización de la reacción (determinada por TLC), se agregó 6 ml de HCl 1N para neutralizar el LiOH presente en la mezcla de reacción. La mezcla luego se

712

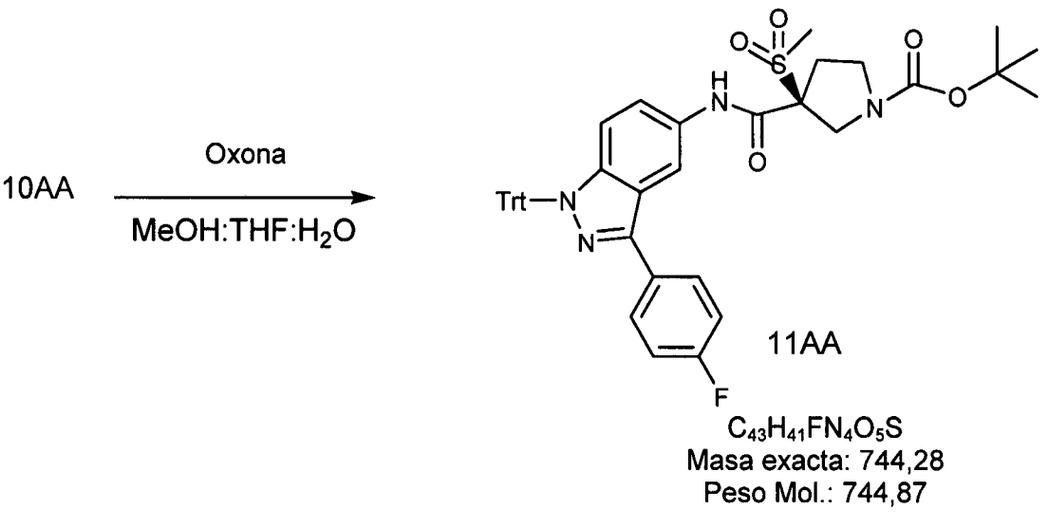
evaporó hasta la sequedad y se hizo azeotrópico con dioxano para dar 1,6 g de 8AA como un sólido blanco.

Paso 7



En un balón equipado con entrada de tabique se colocó 0,26 g de 8AA (0,994 mMol) y 0,467g de 9AA (0,994 mMol). Estos 2 componentes se disolvieron en DMF. Se agregó DIPEA a la mezcla de reacción seguido de HATU. La mezcla se agitó a temperatura ambiente bajo un chorro de nitrógeno durante 2 días. El producto en bruto luego se desactivó con 50 ml de $NaHCO_3$ sat. y se extrajo (3x50 ml) con EtOAc. Los extractos orgánicos combinados se lavaron con salmuera y se secaron sobre Na_2SO_4. Luego se filtró y se evaporó hasta la sequedad para dar un producto en bruto que se purificó en columna (30% E/H) para dar 0,605 de producto.

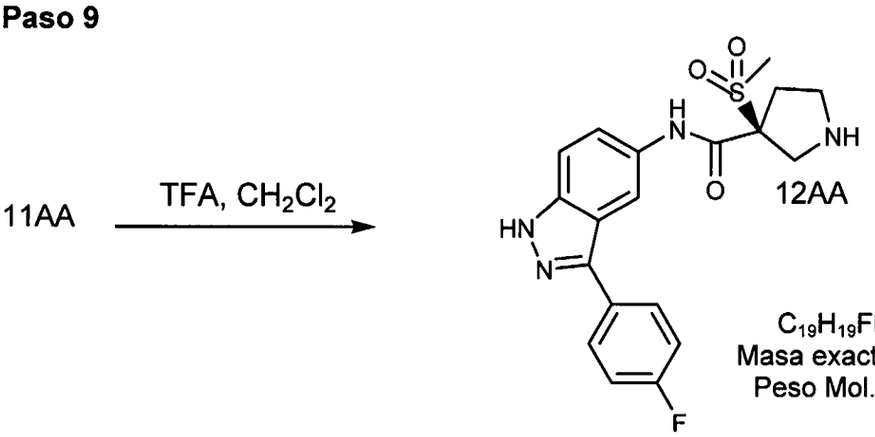
Paso 8



$C_{43}H_{41}FN_4O_5S$
Masa exacta: 744,28
Peso Mol.: 744,87

El Compuesto 10AA (0,9g, 1.26 mMol) se disolvió en 6 ml cada uno de MeOH:THF:H_2O. Se agregó oxona y la mezcla resultante se dejó agitar hasta la mañana siguiente. Luego de la finalización, la mezcla se filtró a través de una fritura de vidrio y se lavó con MeOH. El filtrado luego se concentró para dar un producto en bruto que luego se sometió al siguiente paso.

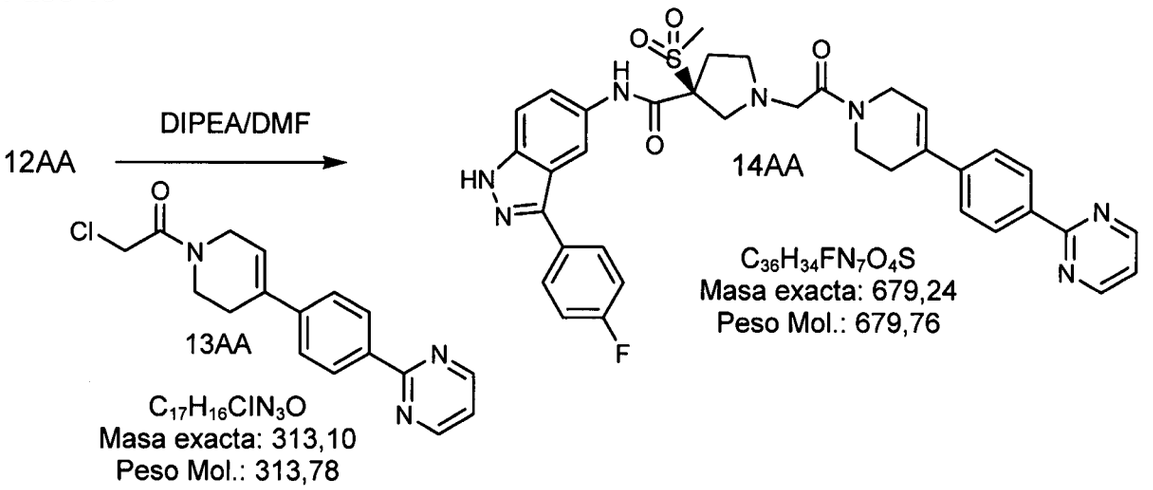
Paso 9



$C_{19}H_{19}FN_4O_3S$
Masa exacta: 402,12
Peso Mol.: 402,44

Este material de partida 11AA (0,64g, 0,858 mmol) se disolvió en 20 ml de CH_2Cl_2 anhidro. Se agregó 2,5 ml de TFA lentamente y se dejó agitar a temperatura ambiente bajo un chorro de nitrógeno durante 1 hasta la mañana siguiente. La mezcla se evaporó hasta la sequedad y se purificó en columna (7% $NH_3$2N, MeOH/CH_2Cl_2) para dar 0,31g de producto en el rendimiento de 91%.

Paso 10



$C_{17}H_{16}ClN_3O$
Masa exacta: 313,10
Peso Mol.: 313,78

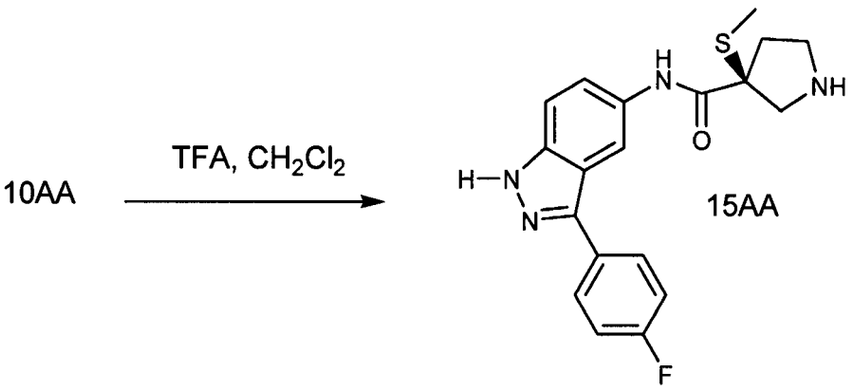
$C_{36}H_{34}FN_7O_4S$
Masa exacta: 679,24
Peso Mol.: 679,76

El Compuesto 12AA (0,105g, 0,261 mmol) se disolvió en 5 ml de DMF. Se agregó 3 eq. de DIPEA seguido de 1.1 eq. de 13AA. La mezcla de reacción se agitó durante 3 días a temperatura ambiente bajo un chorro de nitrógeno. Luego de la finalización, se agregó 25 ml de salmuera a la mezcla de reacción que luego se extrajo 3 veces con EtOAc. Los extractos orgánicos combinados se secaron sobre MgSO4 anhidro, se filtró y se evaporó para obtener el producto del título en bruto. El producto en bruto se purificó por PTLC (6% 2N NH_3, MeOH/CH_2Cl_2) para dar 132 mg de producto puro.

EJEMPLO 613

Paso 1

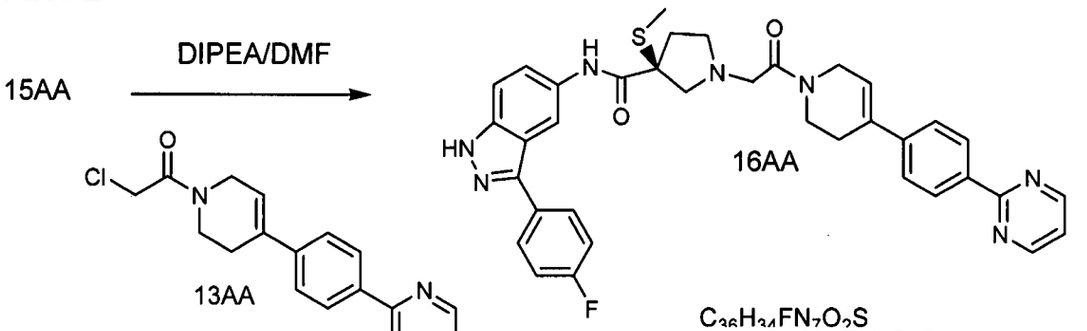
215



$C_{19}H_{19}FN_4OS$
Masa exacta: 370,12636
Peso Mol.: 370,44376

Este material de partida 10AA (ver Ejemplo 612. Paso 8) (0,712g, 1,0 mmol) se disolvió en 20 ml de CH_2Cl_2 anhidro. Se agregó 2 ml de TFA lentamente y se dejó agitar a temperatura ambiente bajo un chorro de nitrógeno durante 1 hasta la mañana siguiente. La mezcla se evaporó hasta la sequedad y se trató con 30 ml de 2% NH_3 2N, MeOH para dar 0,612 g de producto.

Paso 2



$C_{17}H_{16}ClN_3O$
Masa exacta: 313,10
Peso Mol.: 313,78

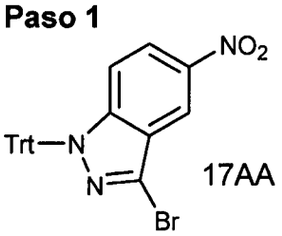
$C_{36}H_{34}FN_7O_2S$
Masa exacta: 647,24787
Peso Mol.: 647,76426

E ,300g, 0,81 mmol) se disolvió en 5 ml de DMF. Se agregó 3 eq. de DIPEA seguido de 1,1 eq. de 13AA. La mezcla de reacción se agitó durante 2 días a temperatura ambiente bajo un chorro de nitrógeno. Luego de la finalización, se agregó 25 ml de salmuera a la mezcla de reacción que luego se extrajo 3 veces con EtOAc. Los extractos orgánicos combinados se secaron sobre MgSO4 anhidro, se filtró y se evaporó para obtener el producto del título en

bruto. El producto en bruto se purificó por PTLC (6% NH_3 2N, $MeOH/CH_2Cl_2$) para dar 431 mg de producto puro.

Preparación 46

Paso 1

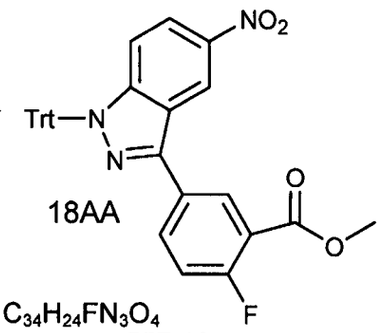


17AA

$C_{26}H_{18}BrB_3O_2$
Masa exacta: 483,06
Peso Mol.: 484,34

2) ácido borónico 3) $PddppCl_2$

4) K_3PO_4
Dioxano, H_2O, 80°C

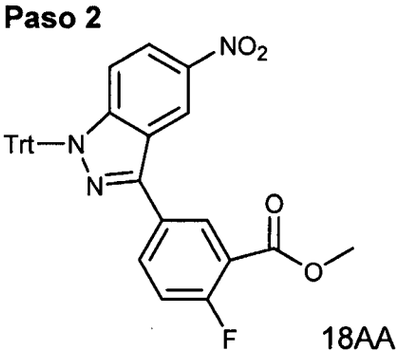


18AA

$C_{34}H_{24}FN_3O_4$
Masa exacta: 557,18
Peso Mol.: 557,57

En un tubo sellado seco con llama se colocó 3,0 g de compuesto 17AA (6,19 mMol). 1,5 eq. de 2. 0,1 eq. de 3 y también se agregaron 2,5 eq. de 4. Se agregaron 65 ml de dioxano y 30 ml de H_2O a la mezcla. La mezcla se desgasificó bajo nitrógeno y luego se calentó hasta 80°C durante 1 día. Luego de la finalización, se diluyó la mezcla con EtOAc y se filtró a través de celite. La fase de acetato de etilo se lavó con agua, se secó sobre Mg SO_4 anhidro y se evaporó hasta la sequedad. El producto en bruto se purificó en columna (5%E/H) para dar 1,1 g de producto.

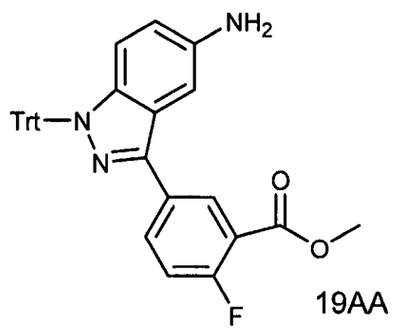
Paso 2



18AA

$C_{34}H_{24}FN_3O_4$
Masa exacta: 557,18
Peso Mol.: 557,57

10% Pd/C, H_2

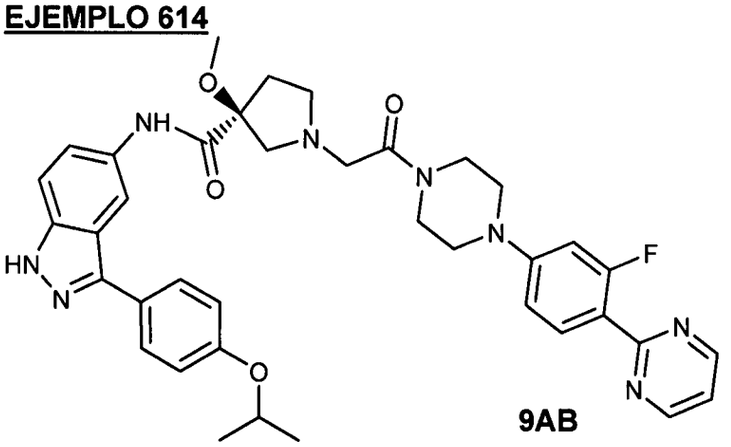


19AA

$C_{34}H_{26}FN_3O_2$
Masa exacta: 527,20
Peso Mol.: 527,59

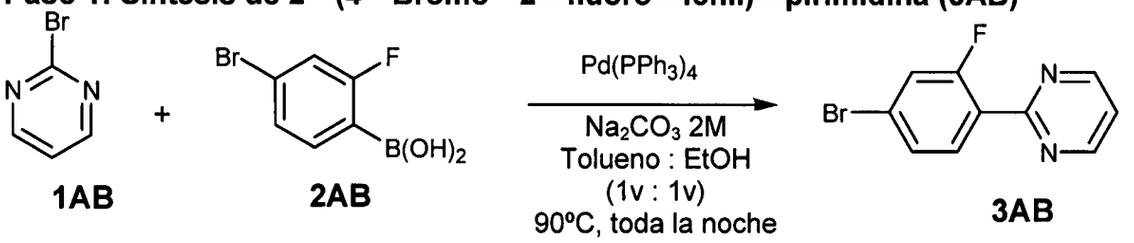
El Compuesto 18AA (1.2g, 2.15 mmol) se disolvió en 20 ml cada uno de MeOH:Tolueno. Se agregó 20% de catalizador de Pd/C al 10% y la mezcla se sometió a H_2 en la forma de balón. Luego de desgasificar durante un número de veces, la mezcla se dejó agitar durante 1 día. Luego de la finalización, la mezcla se diluyó con CH_2Cl_2 y se filtró a través de celite. Luego se lavó con 50% E/H. El filtrado se evaporó hasta la sequedad para dar 1,18 g del producto del título.

EJEMPLO 614



9AB

Paso 1: Síntesis de 2—(4—Bromo—2—fluoro—fenil)—pirimidina (3AB)



1AB **2AB** **3AB**

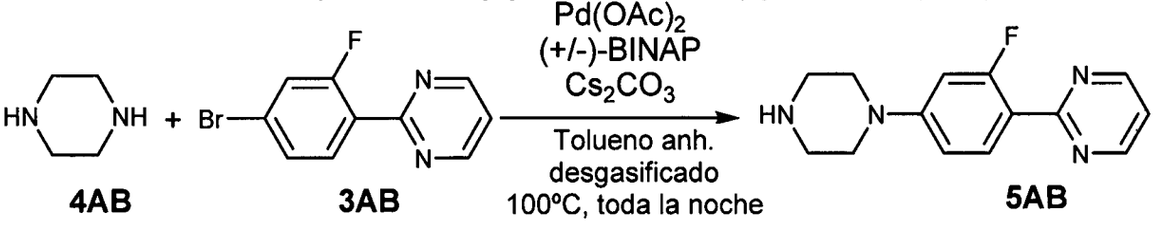
Se agregaron ácido 4-bromo-2-fluorofenil borónico **(2AB)** (3,0g, 13,71 mmol, 1 equiv), 2-bromopirimidina **(1AB)** (6,54 g, 41.13 mmol, 3 equiv), y carbonato de sodio 2M (34 ml) en un recipiente de presión (350 ml) y se agregó una mezcla (1v : 1v) de tolueno y etanol (45 ml : 45 ml). La mezcla luego se burbujeó con nitrógeno gaseoso durante aproximadamente 10 minutos. Se agregó tetrakistrifenilfosfin paladio (0) (793 mg, 0,686 mmol, 0,05 equiv) a la mezcla. El

recipiente de reacción se tapó herméticamente, se colocó en un baño de aceite a 90°C y se agitó hasta la mañana siguiente.

La mezcla de reacción se enfrió hasta la temperatura ambiente y el contenido se filtró en un matraz y la mezcla de solventes se evaporó en el rotovap. El residuo se absorbió luego en una mezcla uno a uno de tolueno y acetato de etilo y se lavó con mezcla (3v : 1v) de salmuera y agua DI dos veces. La fase orgánica se separó y se combinó y se secó sobre sulfato de magnesio. El producto en bruto luego se filtró en un matraz y el solvente se eliminó en rotovap. El residuo se absorbió en tan poca cantidad de diclorometano como sea posible y se purificó por cromatografía en columna usando sistema de purificación Analogix con las siguientes condiciones: Solvente A: Hexanos; Solvente B: Acetato de etilo. Caudal de Flujo: 65 ml/min. Gradiente: 0% Solvente B a 50% Solvente B en 60 minutos.

Rendimiento = 2.79 g (80,4%)

Paso 2: Síntesis de 2-(2-Fluoro-4-piperazin-1-il-fenil)-pirimidina (5AB)



4AB **3AB** **5AB**

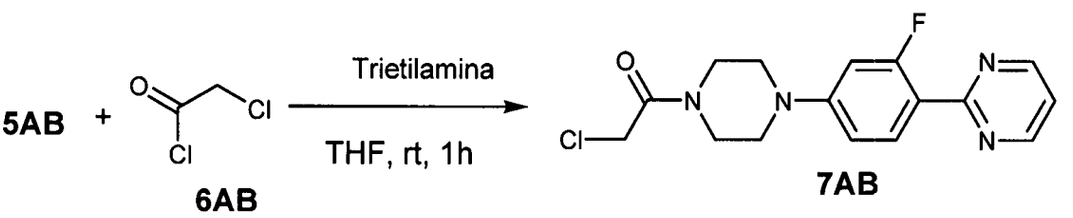
2-(4-Bromo-2-fluoro-fenil)-pirimidina **(3AB)** (2.0 g, 7,9 mmol, 1 equiv), piperazina **(4AB)** (2.72 g, 31,6 mmol, 4 equiv), carbonato de cesio (20,6 g, 63,2 mmol, 8 equiv), (+/-) BINAP racémico (492 mg, 0,79 mmol, 0,1 equiv), y acetato de paladio (II) (89 mg, 0,395 mmol, 0,05 equiv) se pesaron todos en un recipiente de presión secado con llama y el recipiente se selló con un tabique de goma y el contenido del recipiente de reacción se mantuvo con vacío durante 2 horas. Se agregó tolueno anhidro desgasificado (100 ml) al recipiente de reacción usando una cánula. El tabique de goma se reemplazó con una tapa de Teflón y el

recipiente se selló herméticamente y se colocó en un baño de aceite a 100°C para agitar el contenido hasta la mañana siguiente.

El recipiente de reacción se enfrió hasta la temperatura ambiente y el contenido se transfirió en un matraz. Se agregó algo de agua para solubilizar el exceso de base inorgánica junto con algo de acetato de etilo. La fase orgánica luego se lavó con agua y salmuera dos veces, y se separó y se secó sobre sulfato de magnesio. El producto en bruto luego se filtró en un matraz y el solvente se eliminó en rotovap. El residuo se absorbió en tan poca cantidad de diclorometano como sea posible y se purificó por cromatografía en columna usando sistema de purificación Analogix con las siguientes condiciones: Solvente A: Diclorometano; Solvente B: 40% NH_3 7N en Metanol. Caudal de Flujo: 65 ml/min. Gradiente: 0% Solvente B a 30% Solvente B en 52 minutos y se dejó a 30% Solvente B durante 10 minutos.

Rendimiento = 889 mg (44%).

Paso 3: Síntesis de 2—Cloro—1—[4—(3—fluoro—4—pirimidin—2—il—fenil)—piperazin—1—il]—etanona (7AB)

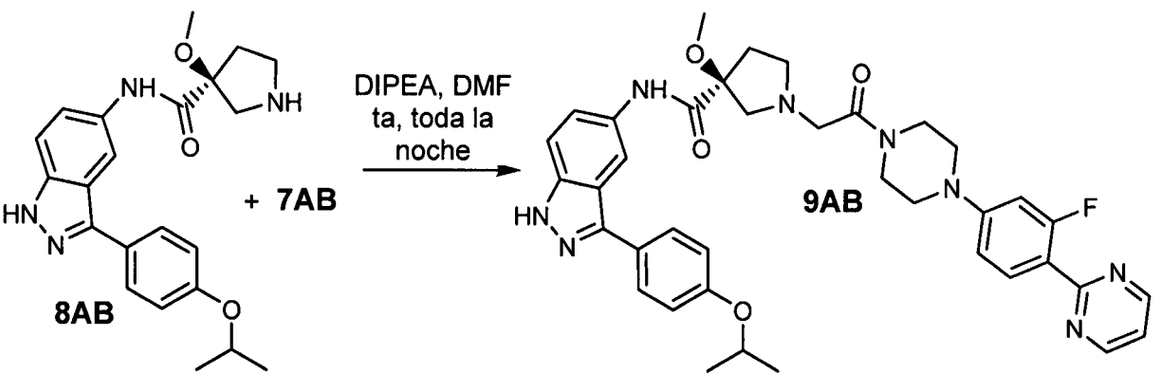


2—(2—Fluoro—4—piperazin—1—il—fenil)—pirimidina **(5AB)** (889 mg, 3,442 mmol, 1 equiv) se disolvió en tetrahidrofurano anhidro (5 ml) y trietilamina (697 mg, 959 µl, 6,884 mmol, 2 equiv) se agregó, seguido de la lenta incorporación de una solución de cloruro de cloroacetilo **(6AB)** (466,5 mg, 330 µl, 4,13 mmol, 1,2 equiv) en tetrahidrofurano a temperatura ambiente. La mezcla se agitó luego durante aproximadamente 1 hora a temperatura ambiente.

Luego de finalizar de la reacción, el solvente se eliminó en rotovap y el residuo se absorbió en diclorometano y se lavó con una mezcla (1v : 1v) de salmuera y agua en un embudo de decantación. La fase orgánica se separó, se concentró y se secó en un bombeador. El residuo en bruto se absorbió en diclorometano y se purificó por cromatografía en columna usando sistema de purificación Analogix con las siguientes condiciones: Solvente A: Diclorometano; Solvente B: 40% 7N NH_3 en Metanol. Caudal de Flujo: 65 ml/min. Gradiente: 0% Solvente B a 30% Solvente B en 52 minutos y se dejó a 30% Solvente B durante 10 minutos.

Rendimiento = 1.05 g (91.1%)

Paso 4: Síntesis de [3—(4—isopropoxi—fenil)—1H—indazol—5—il]—amida del ácido 1—{2—[4—(3—Fluoro—4—pirimidin—2—il—fenil)—piperazin—1—il]—2—oxo—etil}—3—metoxi—pirrolidin—3—carboxílico (9AB)

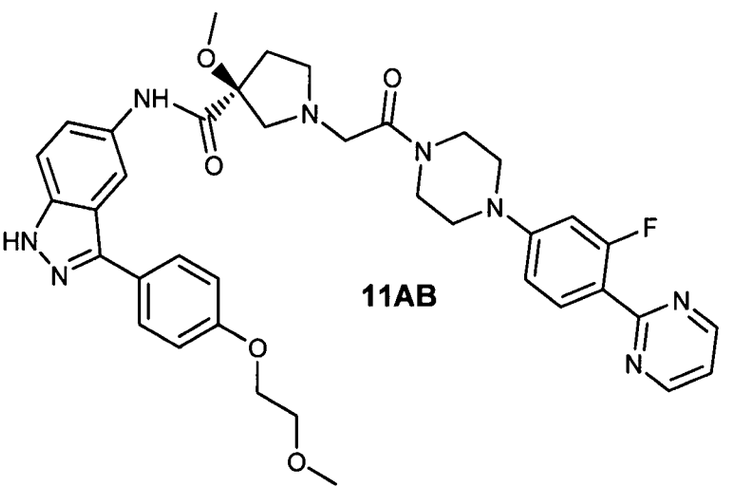


[3—(4—isopropoxi—fenil)—1H—indazol—5—il]—amida del ácido 3—Metoxi—pirrolidina—3—carboxílico **(8AB)** (40 mg, 0,086 mmol, 1 equiv) y 2—Cloro—1—[4—(3—fluoro—4—pirimidin—2—il—fenil)—piperazin—1—il]—etanona **(7AB)** (35 mg, 0,103 mmol, 1,2 equiv) se pesaron en un matraz, y a esto se agregó N,N-dimetilformamida (3 ml) y diisopropiletilamina (22 mg, 30 µl, 0,172 mmol, 2 equiv). El contenido de la reacción se agitó a temperatura ambiente, hasta la mañana siguiente.

La reacción en bruto se diluyó con suficiente cantidad de acetato de etilo y la fase orgánica se lavó con una mezcla (1v : 1v) de salmuera y agua dos veces. La fase orgánica se separó y se concentró en rotovap hasta la sequedad, y se secó en forma adicional en un bombeador de alto vacío. El residuo se absorbió en tan poca cantidad de diclorometano como sea posible y se purificó por cromatografía en columna usando sistema de purificación Analogix con las siguientes condiciones: Solvente A: Diclorometano; Solvente B: 40% 7N NH_3 en Metanol. Caudal de Flujo: 30 ml/min. Gradiente: 0% Solvente B a 20% Solvente B en 30 minutos. Las fracciones limpias se combinaron en un matraz y se concentraron en rotovap. El residuo luego se disolvió en Metanol y se acidificó con HCl 4N en 1,4-dioxano (80 ul) para transformarlo en forma de sal de HCl antes de someterlo al ensayo biológico.

Rendimiento = 46,4 mg, LCMS [M+H$^+$] = 693,4.

EJEMPLO 615



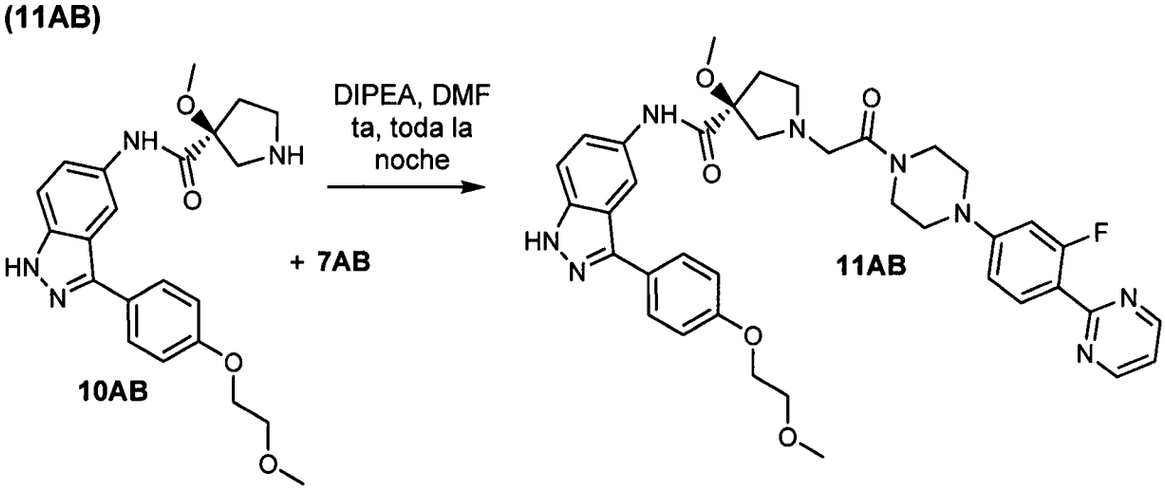
11AB

Pasos 1 hasta 3

Los Pasos 1 hasta 3 son similares a los Pasos 1 hasta 3 del Ejemplo 614.

Paso 4: Síntesis de {3—[4—(2—metoxi—etoxi)—fenil]—1H—indazol—5—il}—amida del ácido 1—{2—[4—(3—Fluoro—4—pirimidin—2—il—fenil)—

piperazin—1—il]—2—oxo—etil}—3—metoxi—pirrolidina—3—carboxílico (11AB)



{3—[4—(2—metoxi—etoxi)—fenil]—1H—indazol—5—il}—amida del ácido 3—Metoxi—pirrolidin—3—carboxílico **(10AB)** (50 mg, 0,103 mmol, 1 equiv) y 2—Cloro—1—[4—(3—fluoro—4—pirimidin—2—il—fenil)—piperazin—1—il]—etanona **(7AB)** (42 mg, 0,124 mmol, 1,2 equiv) se pesaron en un matraz y a esto se agregó N,N-dimetilformamida (3 ml) y diisopropiletilamina (26,6 mg, 36 µl, 0,206 mmol, 2 equiv). El contenido de la reacción se agitó a temperatura ambiente, hasta la mañana siguiente.

La mezcla de reacción en bruto se diluyó con suficiente cantidad de acetato de etilo y la fase orgánica se lavó con una mezcla (1v : 1v) de salmuera y agua dos veces. La fase orgánica se separó y se concentró en rotovap hasta la sequedad, y se secó en forma adicional en un bombeador de alto vacío. El residuo se absorbió en tan poca cantidad de diclorometano como sea posible y se purificó por cromatografía en columna usando sistema de purificación Analogix con las siguientes condiciones: Solvente A: Diclorometano; Solvente B: 40% 7N NH_3 en Metanol. Caudal de Flujo: 30 ml/min. Gradiente: 0% Solvente B a 20% Solvente B en 30 minutos. Las fracciones limpias se combinaron en un matraz y se concentró en rotovap. El residuo luego se disolvió en Metanol y se acidificó con

HCl 4N en 1,4-dioxano (100 ul) para transformarlo en forma de sal de HCl antes de someterlo al ensayo biológico.

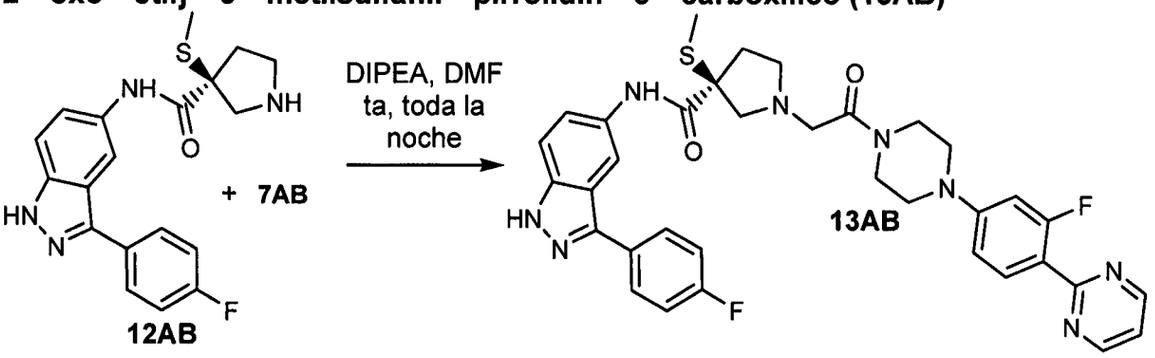
Rendimiento = 46,4 mg, LCMS [M+H$^+$] = 709,4.

EJEMPLO 616

Pasos 1 hasta 3

Pasos 1 hasta 3 son similares a los Pasos 1 hasta 3 del Ejemplo 614. .

Paso 4: Síntesis de [3—(4—fluoro—fenil)—1H—indazol—5—il]—amida del ácido 1—{2—[4—(3—Fluoro—4—pirimidin—2—il—fenil)—piperazin—1—il]—2—oxo—etil}—3—metilsulfanil—pirrolidin—3—carboxílico (13AB)



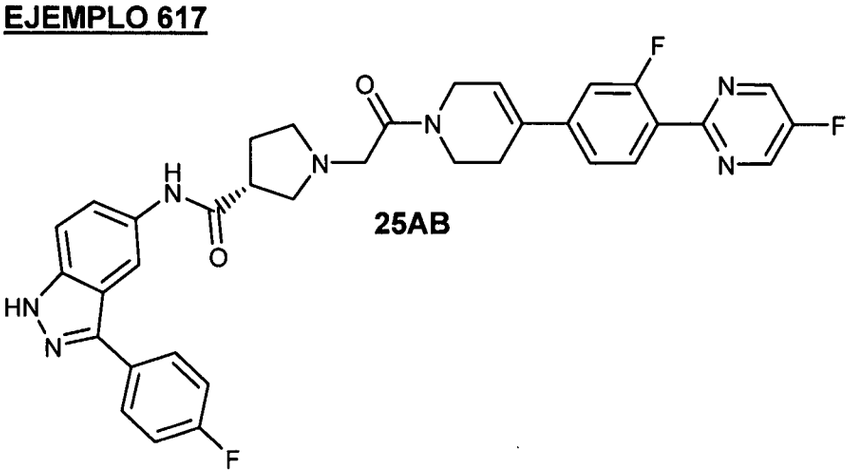
[3—(4—fluoro—fenil)—1H—indazol—5—il]—amida del ácido 3—Metilsulfanil—pirrolidin—3—carboxílico **(12AB)** (40 mg, 0,09 mmol, 1 equiv) y 2—Cloro—1—[4—(3—fluoro—4—pirimidin—2—il—fenil)—piperazin—1—il]—etanona **(7AB)** (37 mg, 0,11 mmol, 1,2 equiv) se pesaron en un matraz, y a esto se agregó N,N-dimetilformamida (3 ml) y diisopropiletilamina (23 mg, 32 µl, 0,18 mmol, 2 equiv). El contenido de la reacción se agitó a temperatura ambiente hasta la mañana siguiente.

La mezcla de reacción en bruto se diluyó con suficiente cantidad de acetato de etilo y la fase orgánica se lavó con una mezcla (1v : 1v) de salmuera y agua dos veces. La fase orgánica se separó y se concentró en rotovap hasta la sequedad, y se secó en forma adicional en un bombeador de alto vacío. El residuo se absorbió en tan poca cantidad de diclorometano como sea posible y se

purificó por cromatografía en columna usando sistema de purificación Analogix con las siguientes condiciones: Solvente A: Diclorometano; Solvente B: 40% 7N NH_3 en Metanol. Caudal de Flujo: 30 ml/min. Gradiente: 0% Solvente B a 20% Solvente B en 30 minutos. Las fracciones limpias se combinaron en un matraz y se concentró en rotovap. El residuo luego se disolvió en Metanol y se acidificó con HCl 4N en 1,4-dioxano (100 ul) para transformarlo en forma de sal de HCl antes de someterlo al ensayo biológico.

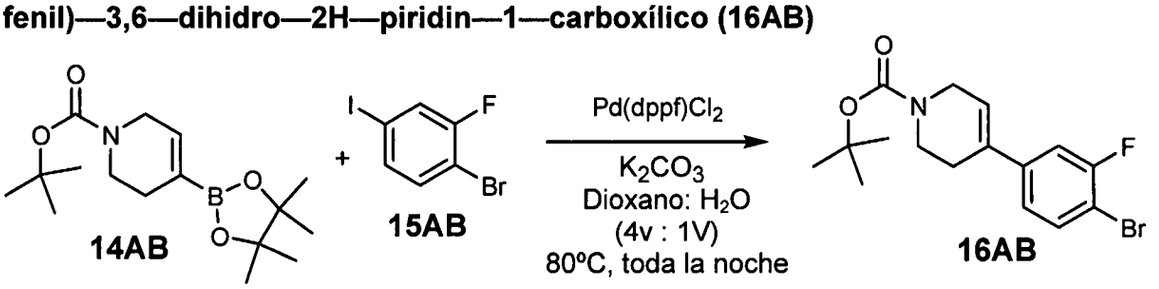
Rendimiento = 58 mg, LCMS $[M+H^+]$ = 669,4.

EJEMPLO 617



25AB

Paso 1: Síntesis de ter—butil éster del ácido 4—(4—Bromo—3—fluoro—fenil)—3,6—dihidro—2H—piridin—1—carboxílico (16AB)



14AB **15AB** **16AB**

Ter—butil éster del ácido 4—(4,4,5,5—Tetrametil—[1.3,2]dioxaborolan—2—il)—3,6—dihidro—2H—piridin—1—carboxílico **(14AB)** (4,0 g, 12,9 mmol, 1

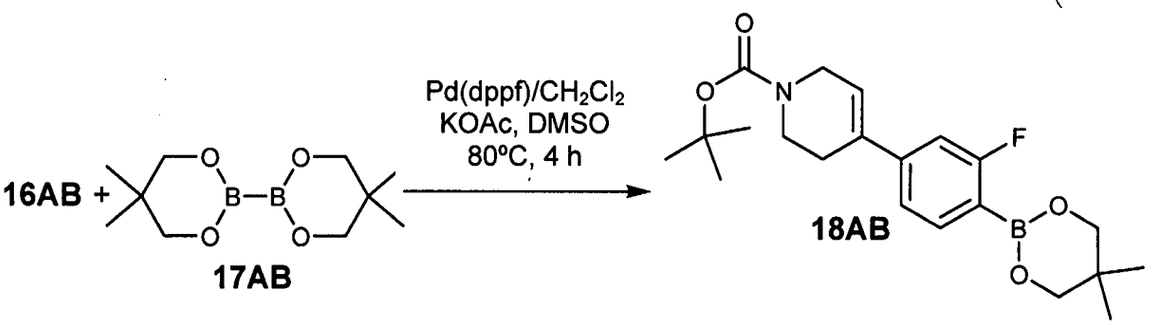
equiv), 1—Bromo—2—fluoro—4—yodo—benceno **(15AB)** (5,84 g, 19,4 mmol, 1,5 equiv), carbonato de potasio (5,4 g, 38,8 mmol, 3 equiv), y a (4v : 1 v) mezcla de 1,4-dioxano y agua (120 ml : 30 ml) se agregaron todos en un recipiente de presión (350 ml) y la mezcla se burbujeó con nitrógeno gaseoso durante aproximadamente 10 minutos. A esta mezcla se agregó aducto de dicloro[1,1'-bis(difenilfosfin)ferroceno] paladio (II)/diclorometano (1,05 g, 1,29 mmol, 0,1 equiv), y el recipiente de reacción se tapó herméticamente, se colocó en un baño de aceite a 80°C, y se agitó hasta la mañana siguiente.

La mezcla de reacción se enfrió hasta la temperatura ambiente y el contenido se transfirió en un matraz y se concentró en rotovap. El residuo se absorbió luego en acetato de etilo y, en un embudo de decantación; la mezcla en bruto se lavó con agua, carbonato de sodio al 10% y salmuera. La fase orgánica se secó sobre sulfato de magnesio y se pasó a través de un taco de Celite. El filtrado luego se trató con carbón activado a 65°C en un Erlenmeyer en un baño de agua durante aproximadamente 10 minutos para decolorar la solución. El carbón activado se separó por un taco de Celite. El solvente se eliminó en rotovap y el residuo se secó en bombeador hasta la mañana siguiente. El residuo se absorbió en tan poca cantidad de diclorometano como sea posible y se purificó por cromatografía en columna usando sistema de purificación Analogix con las siguientes condiciones: Solvente A: Hexanos; Solvente B: Acetato de etilo. Caudal de Flujo: 65 ml/min. Gradiente: 0% Solvente B a 50% Solvente B en 60 minutos.

Rendimiento = 3,12 g (68%)

Paso 2: Síntesis de ter—butil éster del ácido 4—[4—(5,5—Dimetil—[1.3,2]dioxaborinan—2—il)—3—fluoro—fenil]—3,6—dihidro—2H—piridin—1—carboxílico (18AB):

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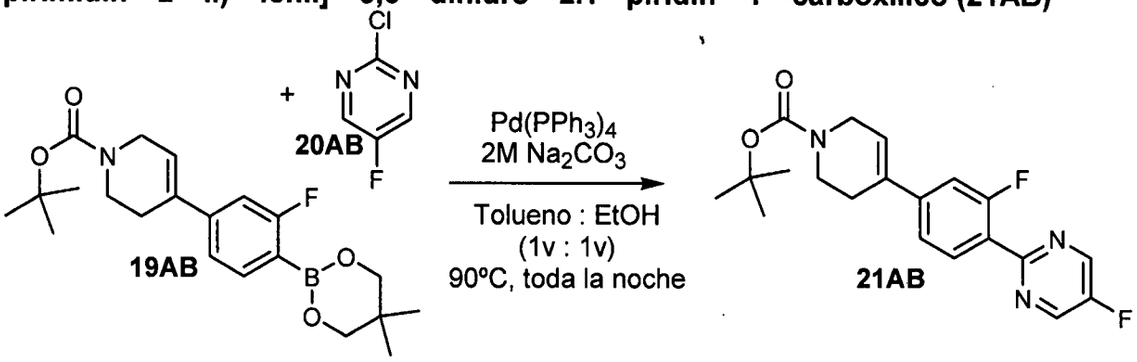


Ter—butil éster del ácido 4—(4—Bromo—3—fluoro—fenil)—3,6—dihidro—2H—piridin—1—carboxílico **(16AB)** (2,3 g, 6,59 mmol, 1 equiv), bis(neopentilglicolato)diboro **(17AB)**(1,79 g, 7,91 mmol, 1,2 equiv), y acetato de potasio (1,94 g, 19,77 mmol, 3 equiv) se pesaron todos en un recipiente de presión seco y se disolvieron en dimetilsulfóxido (50 ml). La mezcla se burbujeó con nitrógeno gaseoso durante 10 minutos. Aducto de dicloro[1,1'-bis(difenilfosfin) ferroceno]paladio (II)/diclorometano (540 mg, 0,66 mmol, 0,1 equiv) se agregó y el recipiente de reacción se selló herméticamente con una tapa y se colocó en un baño de aceite a 80°C durante 4 horas.

Luego de finalizar de 4 horas, el recipiente de reacción se enfrió hasta la temperatura ambiente y el contenido se transfirió en un matraz. Se agregó algo de agua para solubilizar el exceso de base inorgánica junto con algo de acetato de etilo. La fase orgánica luego se lavó con agua y salmuera dos veces, y se separó y se secó sobre sulfato de magnesio. La fase orgánica se concentró en rotovap y se absorbió con diclorometano. En un Erlenmeyer el compuesto en bruto se trató con carbón activado a 65°C en un baño de agua durante aproximadamente 10 minutos para decolorar la solución. El carbón activado se separó por un taco de Celite. El solvente se eliminó en rotovap y el residuo se secó en bombeador hasta la mañana siguiente. El residuo se absorbió en tan poca cantidad de diclorometano como sea posible y se purificó por cromatografía en columna usando sistema de purificación Analogix con las siguientes condiciones: Solvente

A: Hexanos; Solvente B: Acetato de etilo. Caudal de Flujo: 65 ml/min. Gradiente: 0% Solvente B a 50% Solvente B en 60 minutos. Las fracciones relativamente limpias se combinaron y el Solvente se concentró. La mancha de producto sobre TLC fue notoria; esto probablemente se debe a que durante la purificación de este compuesto sobre una columna de gel de sílice algo del éster del ácido borónico se hidrolizó en ácido borónico. Por lo tanto, aunque la separación no fue deseable, el compuesto se usó como está en la siguiente reacción luego del paso de purificación.

Paso 3: Síntesis ter—butil éster del ácido 4—[3—Fluoro—4—(5—fluoro—pirimidin—2—il)—fenil]—3,6—dihidro—2H—piridin—1—carboxílico (21AB)

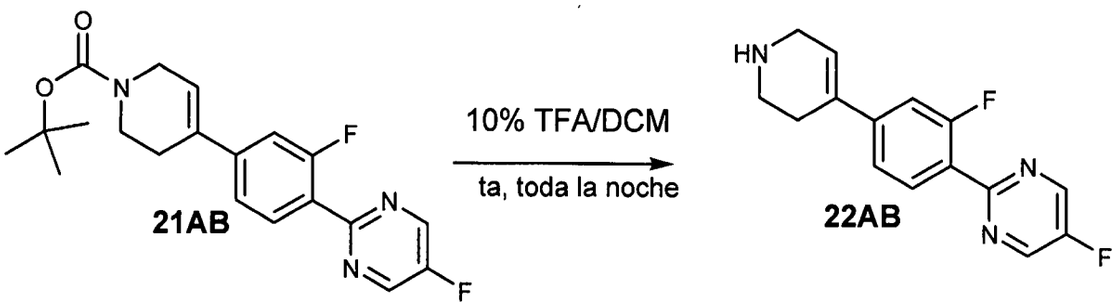


Ter—butil éster del ácido 4—[4—(5,5—Dimetil—[1.3,2]dioxaborinan—2—il)—3—fluoro—fenil]—3,6—dihidro—2H—piridin—1—carboxílico **(19AB)**(1,55g, 3,98 mmol, 1 equiv), 2—Cloro—5—fluoro—pirimidina **(20AB)**(634 mg, 591 µl, 4,78 mmol, 1,2 equiv), y carbonato de sodio 2M (9,95 ml) se agregaron en un recipiente de presión (350 ml) y una mezcla (1v : 1v) de tolueno y se agregó etanol (25 ml : 25 ml). La mezcla luego se burbujeó con nitrógeno gaseoso durante aproximadamente 10 minutos. Se agregó tetrakis(trifenilfosfin) paladio (0) (462 mg, 0,4 mmol, 0,1 equiv) a la mezcla. El recipiente de reacción se tapó herméticamente, se colocó en un baño de aceite a 90°C, y se agitó hasta la mañana siguiente.

La mezcla de reacción se enfrió hasta la temperatura ambiente y se diluyó con acetato de etilo. La mezcla en bruto se transfirió en un embudo de decantación y se lavó con a (1v : 1v) salmuera y agua mezcla. La fase orgánica se separó y se combinó y se secó sobre sulfato de magnesio. El producto en bruto luego se filtró en un matraz y el solvente se eliminó en rotovap. El residuo se absorbió en tan poca cantidad de diclorometano como sea posible y se purificó por cromatografía en columna usando sistema de purificación Analogix con las siguientes condiciones: Solvente A: Diclorometano; Solvente B: Metanol. Caudal de Flujo: 45 ml/min. Gradiente: 0% Solvente B a 10% Solvente B en 60 minutos.

Rendimiento = 677 mg (46%)

Paso 4: Síntesis de 5—Fluoro—2—[2—fluoro—4—(1.2.3,6—tetrahidro—piridin—4—il)—fenil]—pirimidina (22AB)

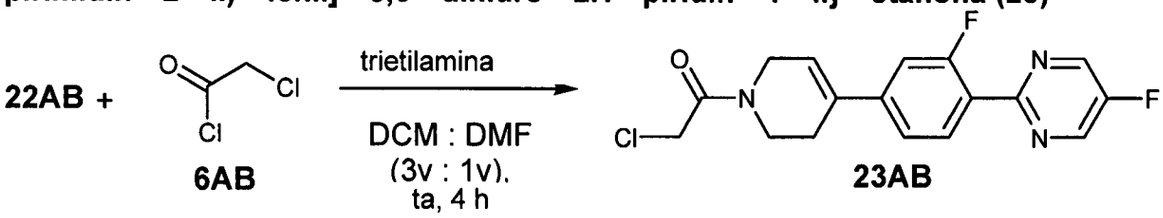


Ter—butil éster del ácido 4—[3—Fluoro—4—(5—fluoro—pirimidin—2—il)—fenil]—3,6—dihidro—2H—piridin—1—carboxílico **(21AB)** (717 mg, 1,92 mmol, 1 equiv) se trató con solución de ácido trifluoroacético al 10% en diclorometano a temperatura ambiente hasta la mañana siguiente.

El Solvente se concentró y el residuo se absorbió en acetato de etilo y se lavó solución de bicarbonato de sodio acuoso al 10% dos veces. Se combinaron las fases de agua y se saturaron con cloruro de sodio y el producto restante en la fase de agua se extrajo de este modo con acetato de etilo. Las fases orgánicas se combinaron y se evaporaron hasta la sequedad en un rotovap. El residuo se

absorbió en tan poca cantidad de diclorometano como sea posible y se purificó por cromatografía en columna usando sistema de purificación Analogix con las siguientes condiciones: Solvente A: Diclorometano; Solvente B: 40% 7N NH_3 en Metanol. Caudal de Flujo: 65 ml/min. Gradiente: 0% Solvente B a 30% Solvente B en 60 minutos y se dejó a 30% Solvente B durante 10 minutos. LCMS $[M+H^+]$ = 274,2.

PASO 5: Síntesis de 2—Cloro—1—{4—[3—fluoro—4—(5—fluoro—pirimidin—2—il)—fenil]—3,6—dihidro—2H—piridin—1—il}—etanona (23)



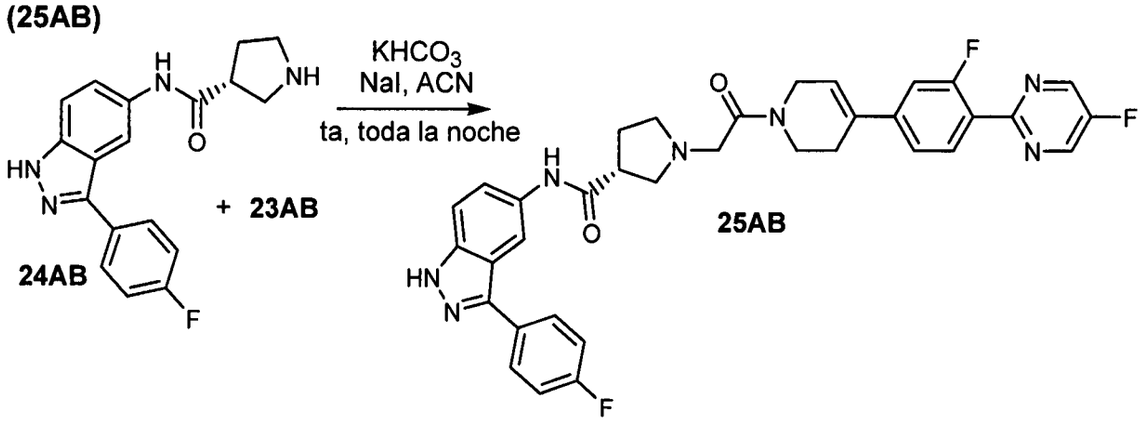
Se disolvió 5—Fluoro—2—[2—fluoro—4—(1.2.3,6—tetrahidro—piridin—4—il)—fenil]—pirimidina **(22AB)** (1,94 g, 7,1 mmol, 1 equiv) en una mezcla (3v : 1v) de diclorometano (30 ml) y N,N-dimetil formamida (10 ml) y trietilamina (862 mg, 1.19 ml, 8,52 mmol, 1,2 equiv) se agregó, seguido de la lenta incorporación de cloruro de cloroacetilo (962 mg, 678 µl, 8,52 mmol, 1,2 equiv) a temperatura ambiente. La mezcla se agitó luego durante aproximadamente 4 horas a temperatura ambiente.

Luego de finalizar de la reacción, la mezcla de solventes se eliminó en rotovap y el residuo se absorbió en diclorometano y se lavó con solución saturada de bicarbonato de sodio y una mezcla (1v : 1v) de salmuera y agua en un embudo de decantación. La fase orgánica se separó, se concentró y se secó en un bombeador. El residuo en bruto se absorbió en diclorometano y se purificó por cromatografía en columna usando sistema de purificación Analogix con las siguientes condiciones: Solvente A: Diclorometano; Solvente B: 40% NH_3 7N en

Metanol. Caudal de Flujo: 65 ml/min. Gradiente: 0% Solvente B a 30% Solvente B en 52 minutos y se dejó a 30% Solvente B durante 10 minutos.

Rendimiento = 851 mg (34%)

Paso 6: Síntesis de [3—(4—fluoro—fenil)—1H—indazol—5—il]—amida del ácido 1—(2—{4—[3—Fluoro—4—(5—fluoro—pirimidin—2—il)—fenil]—3,6—dihidro—2H—piridin—1—il}—2—oxo—etil)—pirrolidin—3—carboxílico (25AB)



[3—(4—fluoro—fenil)—1H—indazol—5—il]—amida del ácido pirrolidin—3—carboxílico **(24AB)** (30 mg, 0,093 mmol, 1 equiv), 2—Cloro—1—{4—[3—fluoro—4—(5—fluoro—pirimidin—2—il)—fenil]—3,6—dihidro—2H—piridin—1—il}—etanona **(23AB)** (36 mg, 0,102 mmol, 1,1 equiv), bicarbonato de potasio (47 mg, 0,465 mmol, 5 equiv), y yoduro de sodio (3 mg, 0,019 mmol, 0,2 equiv) se pesaron todos en un matraz y a esto se agregó acetonitrilo (3 ml). El contenido de la reacción se agitó a temperatura ambiente hasta la mañana siguiente.

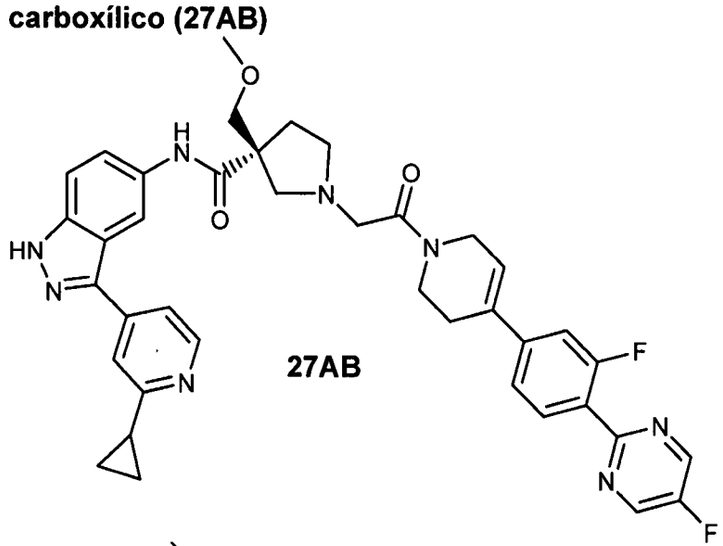
La reacción en bruto mezcla se concentró en rotovap y el residuo se absorbió en acetato de etilo. En un embudo de decantación, la fase orgánica se lavó con una mezcla (1v : 1v) de salmuera y agua dos veces. La fase orgánica se separó y se concentró en rotovap hasta la sequedad, y se secó en forma adicional en un bombeador de alto vacío. El residuo se absorbió en tan poca cantidad de diclorometano como sea posible y se purificó por cromatografía en columna usando sistema de purificación Analogix con las siguientes condiciones: Solvente

A: Diclorometano; Solvente B: 40% NH_3 7N en Metanol. Caudal de Flujo: 30 ml/min. Gradiente: 0% Solvente B a 20% Solvente B en 30 minutos. Las fracciones limpias se combinaron en un matraz y se concentró en rotovap. El residuo luego se disolvió en Metanol y se acidificó con HCl 4N en 1,4-dioxano (100 ul) para transformarlo en forma de sal de HCl antes de someterlo al ensayo biológico.

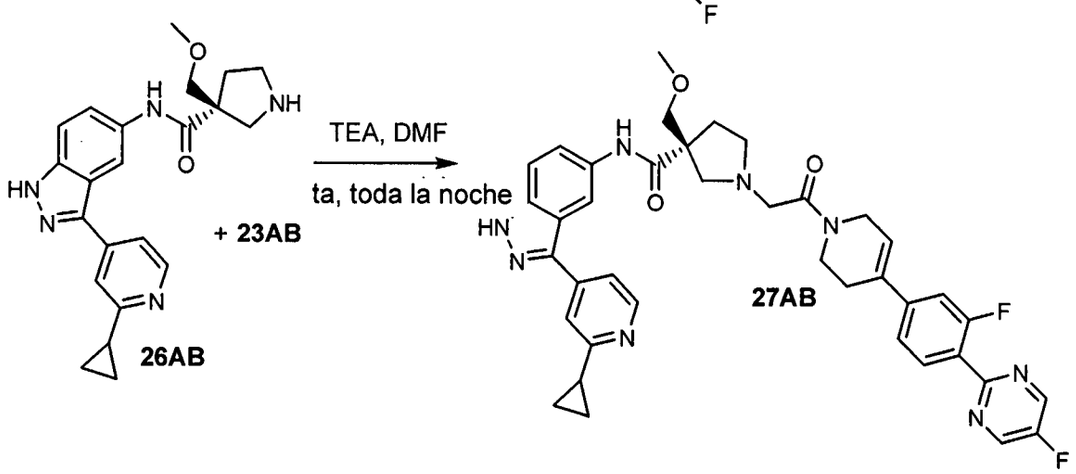
Rendimiento = 16,9 mg, LCMS $[M+H^+]$ = 638,4.

Ejemplo 618

Síntesis de [3—(2—ciclopropil—piridin—4—il)—1H—indazol—5—il]—amida del 1—(2—{4—[3—Fluoro—4—(5—fluoro—pirimidin—2—il)—fenil]—3,6—dihidro—2H—piridin—1—il}—2—oxo—etil)—3—metoximetil—pirrolidin—3—carboxílico (27AB)



27AB



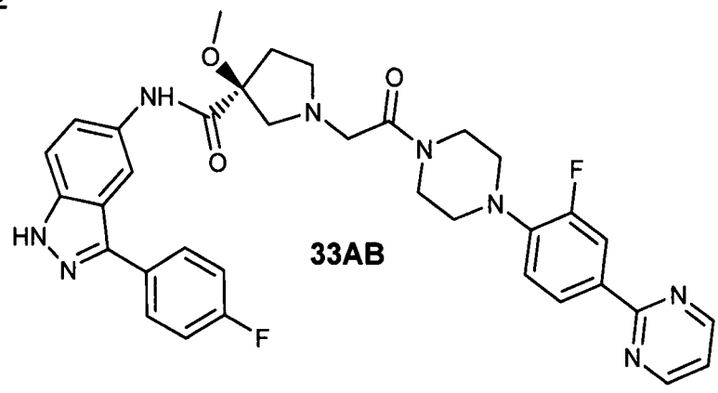
232

[3—(2—ciclopropil—piridin—4—il)—1H—indazol—5—il]—amida del ácido 3—Metoximetil—pirrolidin—3—carboxílico **(26AB)** (85 mg, 0,217 mmol, 1 equiv) y 2—Cloro—1—{4—[3—fluoro—4—(5—fluoro—pirimidin—2—il)—fenil]—3,6—dihidro—2H—piridin—1—il}—etanona **(23AB)** (84 mg, 0,239 mmol, 1,1 equiv) se pesaron en un matraz y se disolvieron en N,N-dimetilformamida anhidra (5 ml). Se agregó trietil amina (33 mg, 46 µl, 0,326 mmol, 1,5 equiv) a la mezcla de reacción y el contenido de la reacción se agitó a temperatura ambiente hasta la mañana siguiente.

La mezcla de reacción en bruto se diluyó con suficiente cantidad de acetato de etilo y la fase orgánica se lavó con una solución saturada de bicarbonato de sodio y una mezcla (1v : 1v) de (salmuera : agua) dos veces. La fase orgánica se separó y se concentró en rotovap hasta la sequedad, y se secó en forma adicional en un bombeador de alto vacío. El residuo se absorbió en tan poca cantidad de diclorometano como sea posible y se purificó por cromatografía en columna usando sistema de purificación Analogix con las siguientes condiciones: Solvente A: Diclorometano; Solvente B: 40% NH_3 7N en Metanol. Caudal de Flujo: 30 ml/min. Gradiente: 0% Solvente B a 20% Solvente B en 30 minutos. Las fracciones limpias se combinaron en un matraz y se concentró en rotovap. El residuo luego se disolvió en Metanol y se acidificó con HCl 4N en 1,4-dioxano (100 ul) para transformarlo en forma de sal de HCl antes de someterlo al ensayo biológico.

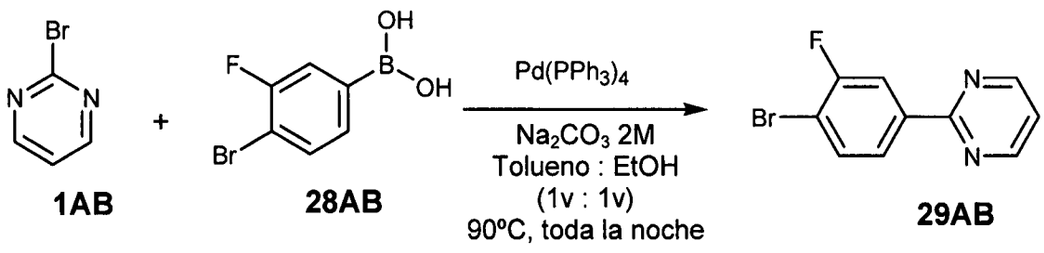
Rendimiento = 75 mg (49%), LCMS $[M+H^+]$ = 705,4.

Ejemplo 619



33AB

Paso 1: Síntesis de 2—(4—Bromo—3—fluoro—fenil)—pirimidina (29AB)



1AB **28AB** **29AB**

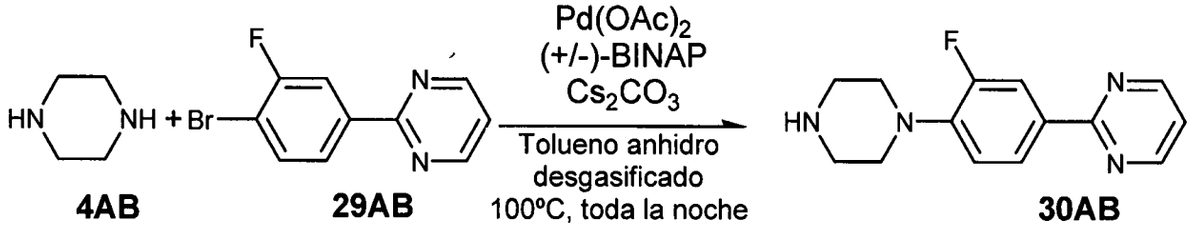
Ácido 4-bromo-3-fluorofenil borónico **(28AB)** (1.0g, 4,57 mmol, 1 equiv), 2-bromopirimidina **(1AB)** (2.18 g, 13,7 mmol, 3 equiv), y carbonato de sodio 2M (12 ml) se agregaron en un recipiente de presión (150 ml) y se agregó una mezcla (1v : 1v) de tolueno y etanol (25 ml : 25 ml). La mezcla luego se burbujeó con nitrógeno gaseoso durante aproximadamente 10 minutos. Se agregó a la mezcla tetrakistrifenilfosfin paladio (0) (266 mg, 0,23 mmol, 0,05 equiv). El recipiente de reacción se tapó herméticamente, se colocó en un baño de aceite a 90°C, y se agitó hasta la mañana siguiente.

La mezcla de reacción se enfrió hasta la temperatura ambiente y el contenido se filtró en un matraz y la mezcla de solventes se evaporó en el rotovap. El residuo se absorbió luego en una mezcla uno a uno de tolueno y acetato de etilo y se lavó con (3v : 1v) mezcla de salmuera : agua DI dos veces. La fase orgánica se separó y se combinó y se secó sobre sulfato de magnesio. El

producto en bruto luego se filtró en un matraz y el solvente se eliminó en rotovap. El residuo se absorbió en tan poca cantidad de diclorometano como sea posible y se purificó por cromatografía en columna usando sistema de purificación Analogix con las siguientes condiciones: Solvente A: Hexanos; Solvente B: Acetato de etilo. Caudal de Flujo: 65 ml/min. Gradiente: 0% Solvente B a 50% Solvente B en 60 minutos.

Rendimiento = 1,08 g (94%)

Paso 2: Síntesis de 2—(3—Fluoro—4—piperazin—1—il—fenil)—pirimidina (30AB)



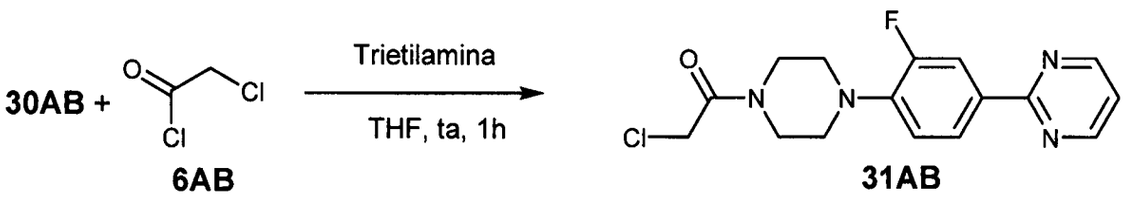
4AB **29AB** **30AB**

2-(4-Bromo-3-fluoro-fenil)-pirimidina **(29AB)** (874 mg, 3,45 mmol, 1 equiv), piperazina (1,19 g, 13,8 mmol, 4 equiv), carbonato de cesio (9,0 g, 27,6 mmol, 8 equiv), (+/-) BINAP racémico (215 mg, 0,345 mmol, 0,1 equiv), y acetato de paladio (II) (38,8 mg, 0,173 mmol, 0,05 equiv) se pesaron todos en un recipiente de presión secado con llama y el recipiente se selló con un tabique de goma y la mezcla de todos los sólidos se mantuvo con vacío durante 2 horas. Se agregó tolueno anhidro desgasificado (30 ml) al recipiente de reacción usando una cánula. El tabique de goma se reemplazó con una tapa de Teflón y el recipiente se selló herméticamente y se colocó en un baño de aceite a 100°C para agitar el contenido hasta la mañana siguiente.

El recipiente de reacción se enfrió hasta la temperatura ambiente y el contenido se transfirió en un matraz. Se agregó algo de agua para solubilizar el exceso de base inorgánica junto con algo de acetato de etilo. La fase orgánica luego se lavó con agua y salmuera dos veces, y se separó y se secó sobre sulfato de magnesio. El producto en bruto luego se filtró en un matraz y el solvente se eliminó en rotovap. El residuo se absorbió en tan poca cantidad de diclorometano como sea posible y se purificó por cromatografía en columna usando sistema de purificación Analogix con las siguientes condiciones: Solvente A: Diclorometano; Solvente B: 40% NH_3 7N en Metanol. Caudal de Flujo: 40 ml/min. Gradiente: 0% Solvente B a 30% Solvente B en 52 minutos y se dejó a 30% Solvente B durante 10 minutos.

Rendimiento = 675 mg (76%)

Paso 3: Síntesis de 2—Cloro—1—[4—(2—fluoro—4—pirimidin—2—il—fenil)—piperazin—1—il]—etanona (31AB)



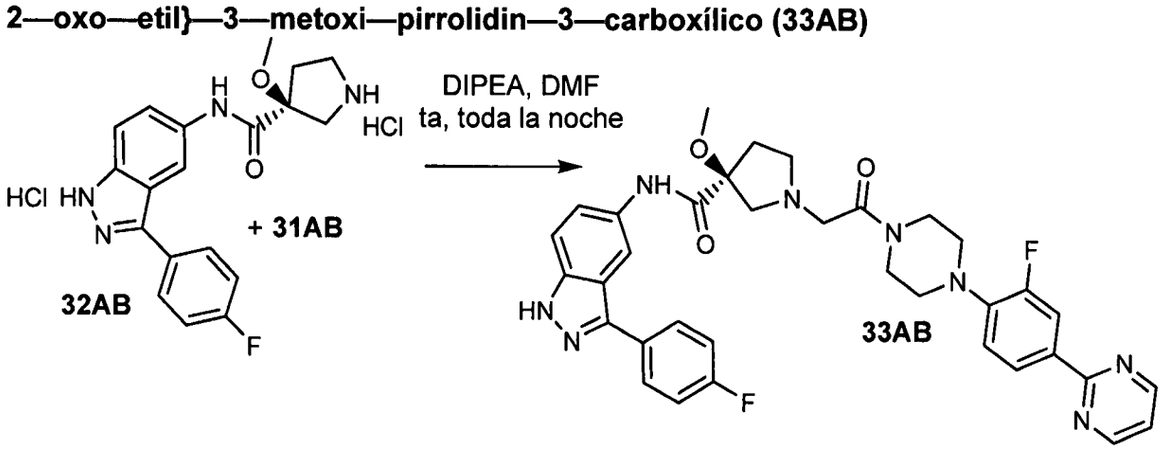
6AB **31AB**

Se disolvió 2-(3-fluoro-4-piperazin-1-il-fenil)-pirimidina **(29AB)** (675 mg, 2.61 mmol, 1 equiv) en tetrahidrofurano anhidro (5 ml), y se agregó trietilamina (1.32 mg, 1,82 ml, 13,05 mmol, 5 equiv), seguido de la lenta incorporación de una solución de cloruro de cloroacetilo (591 mg, 417 µl, 5,23 mmol, 2 equiv) en tetrahidrofurano a temperatura ambiente. La mezcla se agitó luego durante aproximadamente 1 hora a temperatura ambiente.

Luego de finalizar de la reacción, el solvente se eliminó en rotovap y el residuo se absorbió en diclorometano y se lavó con una mezcla (1v : 1v) de salmuera y agua en un embudo de decantación. La fase orgánica se separó, se concentró y se secó en un bombeador. El residuo en bruto se absorbió en diclorometano y se purificó por cromatografía en columna usando sistema de purificación Analogix con las siguientes condiciones: Solvente A: Diclorometano; Solvente B: 40% 7N NH_3 en Metanol. Caudal de Flujo: 40 ml/min. Gradiente: 0% Solvente B a 30% Solvente B en 52 minutos y se dejó a 30% Solvente B durante 10 minutos.

Rendimiento = 821 mg (94%)

Paso 4: Síntesis de [3—(4—fluoro—fenil)—1H—indazol—5—il]—amida del ácido 1—{2—[4—(2—Fluoro—4—pirimidin—2—il—fenil)—piperazin—1—il]—2—oxo—etil}—3—metoxi—pirrolidin—3—carboxílico (33AB)



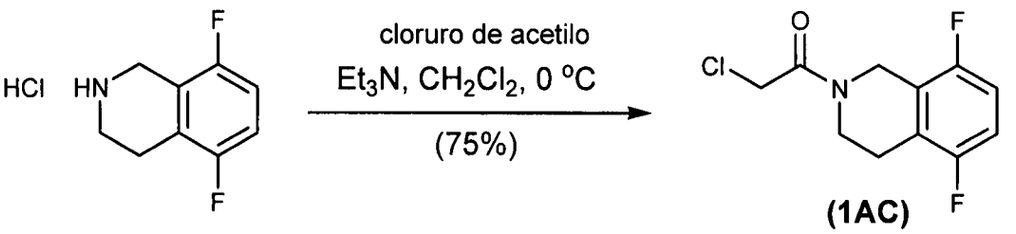
[3—(4—fluoro—fenil)—1H—indazol—5—il]—amida del ácido 3—Metoxi—pirrolidin—3—carboxílico 2, sal de HCl **(32AB)** (30 mg, 0,07 mmol, 1 equiv) y 2—Cloro—1—[4—(2—fluoro—4—pirimidin—2—il—fenil)—piperazin—1—il]—etanona **(31AB)** (28 mg, 0,08 mmol, 1,2 equiv) se pesaron en un matraz y a esto se agregó N,N-dimetilformamida (3 ml) y diisopropiletilamina (54,3 mg, 73 µl, 0,42 mmol, 6 equiv). El contenido de la reacción se agitó a temperatura ambiente hasta la mañana siguiente.

La mezcla de reacción en bruto se diluyó con suficiente cantidad de acetato de etilo y la fase orgánica se lavó con una mezcla (1v : 1v) de salmuera y agua dos veces. La fase orgánica se separó y se concentró en rotovap hasta la sequedad, y se secó en forma adicional en un bombeador de alto vacío. El residuo se absorbió en tan poca cantidad de diclorometano como sea posible y se purificó por cromatografía en columna usando sistema de purificación Analogix con las siguientes condiciones: Solvente A: Diclorometano; Solvente B: 40% 7N NH_3 en Metanol. Caudal de Flujo: 30 ml/min. Gradiente: 0% Solvente B a 15% Solvente B en 30 minutos. Las fracciones limpias se combinaron en un matraz y se concentró en rotovap. El residuo luego se disolvió en Metanol y se acidificó con HCl 4N en 1,4-dioxano (100 ul) para transformarlo en forma de sal de HCl antes de someterlo al ensayo biológico.

Rendimiento = 41 mg (90%), LCMS $[M+H^+]$ = 653,4.

Preparación 47

Preparación de 2—Cloro—1—(5,8—dicloro—3,4—dihidro—1*H*—isoquinolin—2—il)—etanona



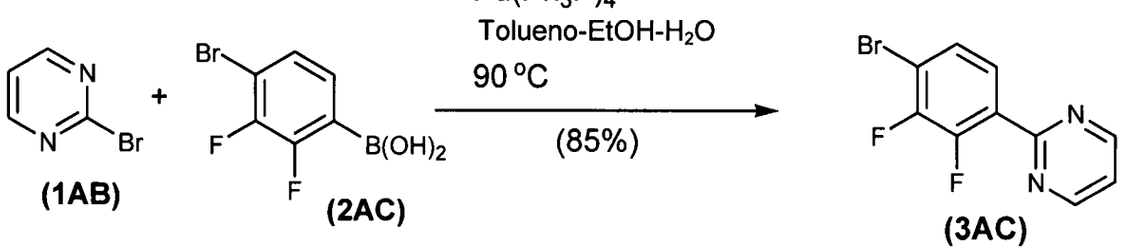
(1AC)

A una suspensión agitada de 5, clorhidrato de 8—di—fluoro—1,2,3,4—tetrahidroisoquinolina (0. 69g, 3,36 mmol) en diclorometano (20 ml) a 0°C bajo nitrógeno, se agregaron diisopropiletilamina (1,40 ml, 8,05 mmol) seguido de cloruro de cloroacetilo (0,32 ml, 4,03 mmol). La mezcla se agitó a 0°C durante 2 hr. Luego de desactivarse con solución saturada de carbonato de sodio, se agregaron agua y diclorometano. Las fases se separaron y la fase acuosa

separada se extrajo con diclorometano. Las fases orgánicas combinadas se secaron ($MgSO_4$), se filtraron y los solventes se eliminaron al vacío. La purificación en columna [Hexanos – Acetato de etilo, 4:1 (v/v)] dio el cloruro **1AC** (619 mg, 75%) como un aceite incoloro.

Preparación 48

PASO 1: Preparación de 2—(4—Bromo—2.3—difluoro—fenil)—pirimidina

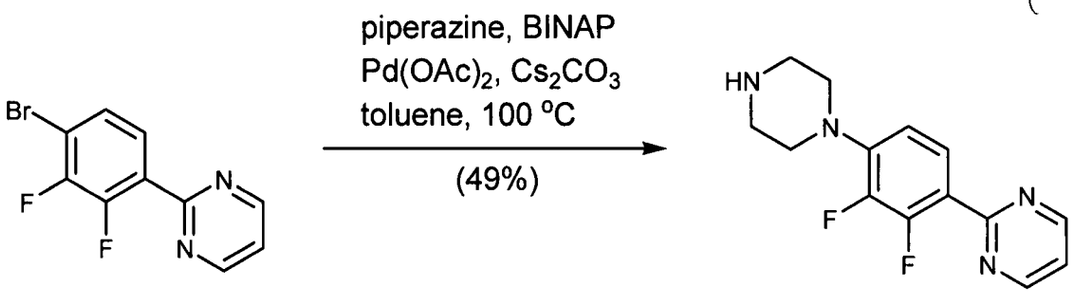


(1AB) **(2AC)** **(3AC)**

Una mezcla de 2-bromopirimidina (2,0 g, 12.7 mmol) , ácido 4-bromo-2.3-difluorobencenoborónico (1.0g, 4,22 mmol), carbonato de potasio (2.93 g, 21.1 mmol) en una mezcla de tolueno (30 ml) /etanol (30 ml) /agua (15 ml) se purgaron con nitrógeno durante 15 min. Se agregó tetrakis(trifenilfosfin)paladio(0) (488 mg, 0,42 mmol) y la mezcla se agitó a 90°C en un tubo sellado hasta la mañana siguiente. La mezcla se enfrió hasta la temperatura ambiente y se diluyó con agua y acetato de etilo. Las fases se separaron. La fase orgánica separada se secó ($MgSO_4$), se filtró y los solventes se eliminaron al vacío. La purificación en columna [Hexanos – Acetato de etilo, 2:1 (v/v)] dio el bromuro **3AC** (0,97 g, 85%) como un sólido blanco.

Paso 2: Preparación de 2—(2,3—Difluoro—4—piperazin—1—il—fenil)—pirimidina

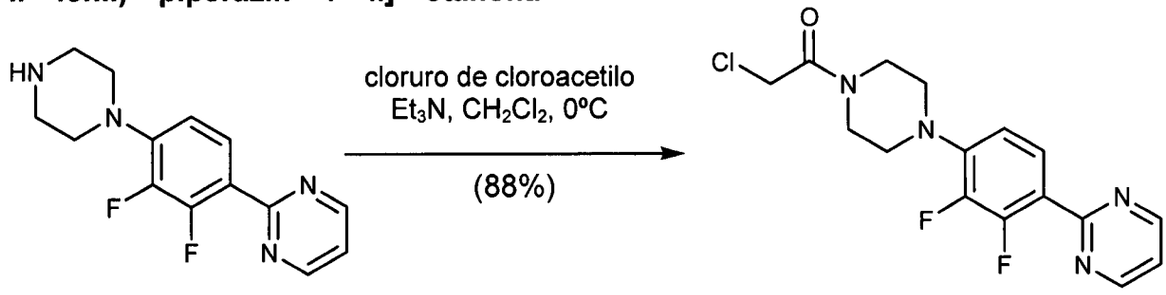
piperazina, BINAP
$Pd(OAc)_2$, Cs_2CO_3
Tolueno, 100°C



(3AC) **(5AC)**

A mezcla del bromuro **3AC** (300 mg, 1.11 mmol), piperazina (286 mg, 3,32 mmol), BINAP (69 mg, 0,11 mmol), carbonato de cesio (721 mg, 2.21 mmol) en tolueno (10 ml) se purgaron con nitrógeno durante 15 min. Se agregó acetato de paladio (II) (13 mg, 0,055 mmol) y la mezcla se agitó a 100°C en un tubo sellado hasta la mañana siguiente. La mezcla se enfrió hasta la temperatura ambiente y se diluyó con agua y acetato de etilo. Las fases se separaron. La fase orgánica separada se secó ($MgSO_4$), se filtró y los solventes se eliminaron al vacío. La purificación en columna [Metanol – Acetato de etilo, 1:1 (v/v)] dio la piperazina **5AC** (150 mg, 49%) como un sólido blanco.

Paso 3: Preparación de 2—Cloro—1—[4—(2.3—Difluoro—4—pirimidin—2—il—fenil)—piperazin—1—il]—etanona



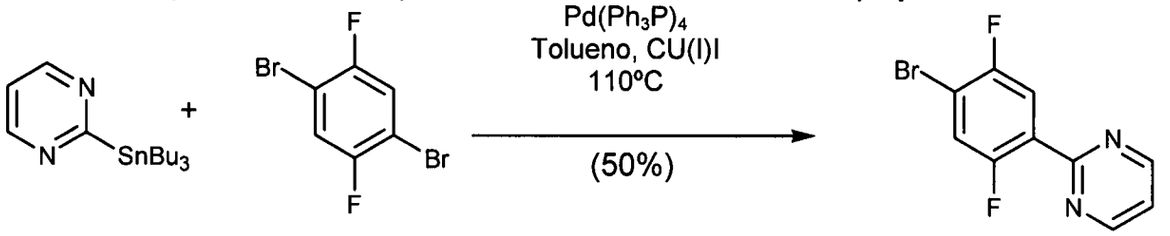
(5AC) **(7AC)**

A una solución agitada de piperazina **5AC** (150 mg, 0,54 mmol) en diclorometano (5 ml) a 0°C bajo nitrógeno, se agregaron trietilamina (0,076 ml, 0,54 mmol) seguido de cloruro de cloroacetilo (0,043 ml, 0,54 mmol). La mezcla

se agitó a 0°C durante 2 hr. Luego de desactivarse con solución saturada de carbonato de sodio, se agregaron agua y diclorometano. Las fases se separaron y la fase acuosa separada se extrajo con diclorometano. Las fases orgánicas combinadas se secaron ($MgSO_4$), se filtraron y los solventes se eliminaron al vacío. La purificación en columna [Hexanos – Acetato de etilo, 1:1 (v/v)] dio el cloruro **7AC** (169 mg, 88%) como un sólido blanco.

Preparación 49

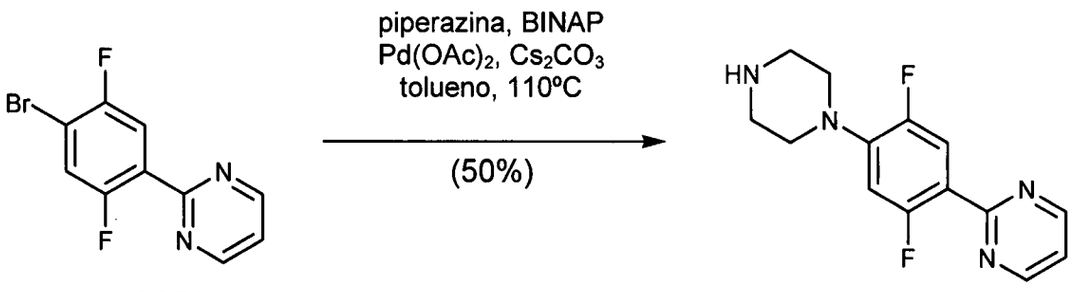
Paso 1: Preparación de 2—(4—Bromo—2,5—difluoro—fenil)—pirimidina



(2AD)

A mezcla de 1, 4-dibromobenceno (4,4 g, 16,3 mmol), 2-(tributilestanil)pirimidina (3,0 g, 8,13 mmol), yoduro de cobre (I) (154 mg, 0,81 mmol) en tolueno (50 ml) se purgaron con nitrógeno durante 15 min. Se agregó tetrakis(trifenilfosfin)paladio(0) (939 mg, 0,81 mmol) y la mezcla se agitó a 110°C en un tubo sellado durante 1 día. La mezcla se enfrió hasta la temperatura ambiente y se diluyó con agua y acetato de etilo. Las fases se separaron. La fase orgánica separada se secó ($MgSO_4$), se filtraron y los solventes se eliminaron al vacío. La purificación en columna [Hexanos – Acetato de etilo, 2:1 (v/v)] dio el bromuro **2AD** (1.09 g, 50%) como un sólido blanco.

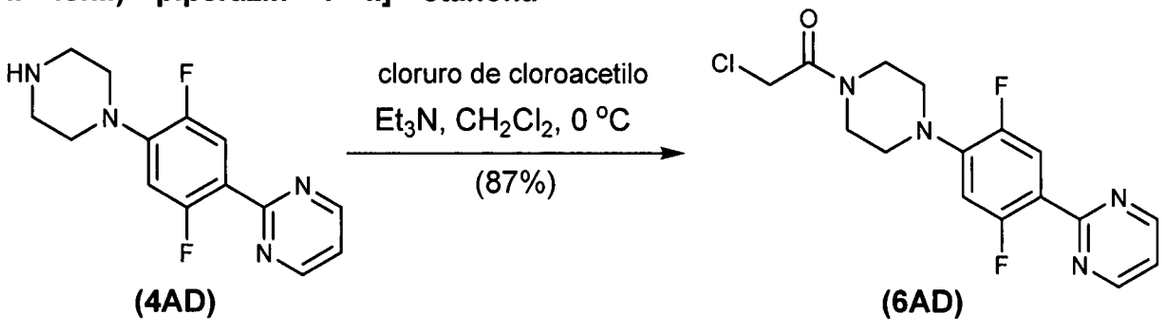
Paso 2: Preparación de 2—(2,5—Difluoro—4—piperazin—1—il—fenil)—pirimidina



(2AD) **(4AD)**

Una mezcla de bromuro **2AD** (850 mg, 3,14 mmol), piperazina (810 mg, 9,41 mmol), BINAP (196 mg, 0,31 mmol), carbonato de cesio (2.0 g, 6,27 mmol) en tolueno (30 ml) se purgaron con nitrógeno durante 15 min. Se agregó acetato de paladio (II) (35 mg, 0,16 mmol) y la mezcla se agitó a 100°C en un tubo sellado hasta la mañana siguiente. La mezcla se enfrió hasta la temperatura ambiente y se diluyó con agua y acetato de etilo. Las fases se separaron. La fase orgánica separada se secó ($MgSO_4$), se filtraron y los solventes se eliminaron al vacío. La purificación en columna [Metanol – Acetato de etilo, 1:1 (v/v)] dio la piperazina **4AD** (393 mg, 43%) como un sólido blanco.

Paso 3: Preparación de 2—Cloro—1—[4—(2,5—Difluoro—4—pirimidin—2—il—fenil)—piperazin—1—il]—etanona



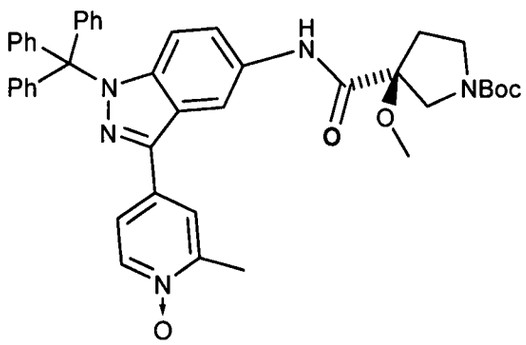
(4AD) **(6AD)**

A una solución agitada de piperazina **4AD** (255 mg, 0,92 mmol) en diclorometano (5 ml) a 0°C bajo nitrógeno, se agregaron trietilamina (0,13 ml, 0,92 mmol) seguido de cloruro de cloroacetilo (0,074 ml, 0,92 mmol). La mezcla se agitó a 0°C durante 2 hr. Luego de desactivarse con solución saturada de carbonato de sodio, se agregaron agua y diclorometano. Las fases se separaron y la fase acuosa separada se extrajo con diclorometano. Las fases orgánicas

combinadas se secaron ($MgSO_4$), se filtraron y los solventes se eliminaron al vacío. La purificación en columna [Hexanos – Acetato de etilo, 1:1 (v/v)] dio el cloruro **6AD** (283 mg, 87%) como un sólido blanco.

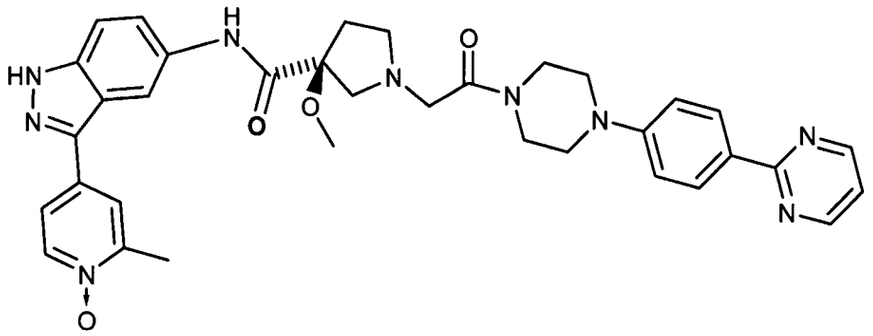
Ejemplo 620

PASO 1: Preparación de ter—butil éster del ácido 3—Metoxi—3—[3—(2—metil—1—oxi—piridin—4—il)—1—tritil—1H—indazol—5—ilcarbamoil]—pirrolidin—1—carboxílico



Ter—butil éster del ácido 3—metoxi—3—[3—(2—metil—piridin—4—il)—1—tritil—1H—indazol—5—ilcarbamoil]—pirrolidin—1—carboxílico (2.9 g, 4,2 mmol) se disolvió en CH_2Cl_2 (80 ml) a temperatura ambiente seguido la incorporación de mCPBA (2.0 g, max. 77%). Luego de agitar durante 24 hrs, la solución de reacción se concentró hasta un pequeño volumen *al vacío* y se purificó usando columna de gel de sílice eluyendo con 2%, 5% y 10% metanol en CH_2Cl_2 para producir un sólido marrón (1,94 g).

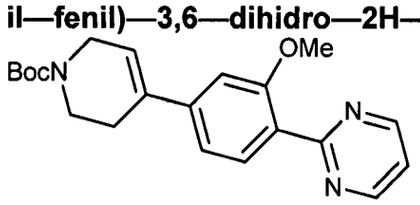
PASO 2: Preparación de [3—(2—metil—1—oxi—piridin—4—il)—1H—indazol—5—il]—amida del ácido 3—Metoxi—1—{2—oxo—2—[4—(4—pirimidin—2—il—fenil)—piperazin—1—il]—etil}—pirrolidin—3—carboxílico



Se disolvieron ter—butil éster del ácido 3—Metoxi—3—[3—(2—metil—1—oxi—piridin—4—il)—1—tritil—1H—indazol—5—ilcarbamoil]—pirrolidin—1—carboxílico (170 mg) y trietilsilano (0,1 ml) en CH_2Cl_2 (5 ml) a temperatura ambiente seguido la incorporación de TFA (1 ml). Luego de 2 hrs, la mezcla de reacción se concentró hasta la sequedad *al vacío*. A esto, se agregaron DMF (5 ml), trietil amina (0,1 ml) y 2—cloro—1—[4—(4—pirimidin—2—il—fenil)—piperazin—1—il]—etanona (170 mg). La mezcla resultante se calentó a 70°C durante 16 hrs. Luego de enfriar hasta la temperatura ambiente, la mezcla de reacción se concentró hasta la sequedad. El producto en bruto resultante se purificó a través de HPLC de fase inversa (ACN/H2O/0,1% HCOOH) para producir un sólido amarillo (70,0 mg). LCMS (M+1) 648,4 (rt 2.12)

Preparación 50

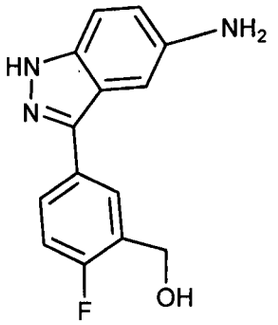
Preparación de ter—butil éster del ácido 4—(3—Metoxi—4—pirimidin—2—il—fenil)—3,6—dihidro—2H—piridin—1—carboxílico



Se preparó ter-butil éster del ácido 4-(3-Metoxi-4-pirimidin-2-il-fenil)-3,6-dihidro-2H-piridin-1-carboxílico usando esencialmente el mismo esquema para la Preparación 38 comenzando con 1—bromo—4—yodo—2—metoxi—benceno.

Preparación 51

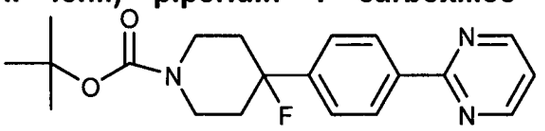
Preparación de [5—(5—Amino—1H—indazol—3—il)—2—fluoro—fenil]—metanol



Se preparó [5—(5—Amino—1H—indazol—3—il)—2—fluoro—fenil]—metanol usando esencialmente el mismo esquema para preparar 10H (ver Preparación 17 Paso 3). El ácido borónico para el primer paso fue ácido 4-fluoro-3-hidroxilmetilfenilborónico.

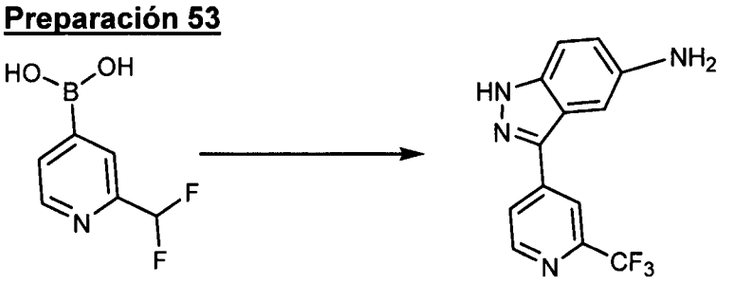
Preparación 52

Preparación de ter—butil éster del ácido 4—Fluoro—4—(4—pirimidin—2—il—fenil)—piperidin—1—carboxílico



El compuesto anterior se preparó usando un procedimiento similar al de la Preparación 54 Paso 4 por el uso de ter-butil éster del ácido 4-(4-Bromo-fenil)-4-fluoro-piperidin-1-carboxílico en lugar de **3AE**.

Preparación 53

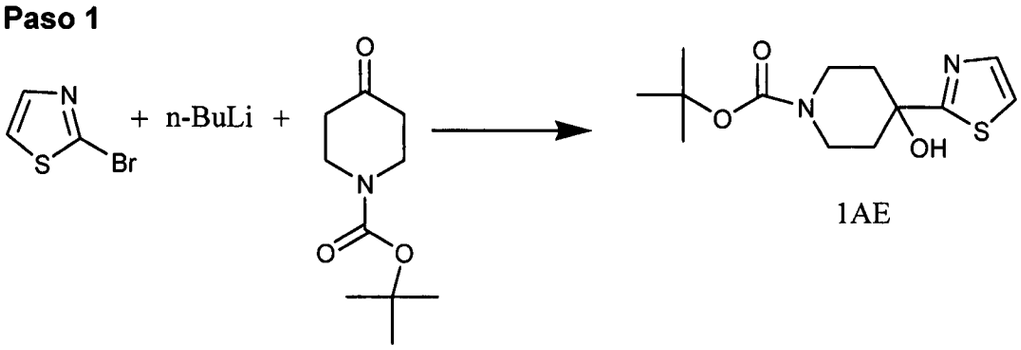


3—(2—Trifluorometil—piridin—4—il)—1H—indazol—5—ilamina se preparó por un procedimiento similar al de la Preparación 25 por la sustitución de

CF_3CO_2Et con CF_2CO_2Et en la Preparación 25 (Chem. Het. Cpds, 1997, p995) y utilizando el procedimiento similar al del Ejemplo 98 Pasos 2 y 3.

Preparación 54

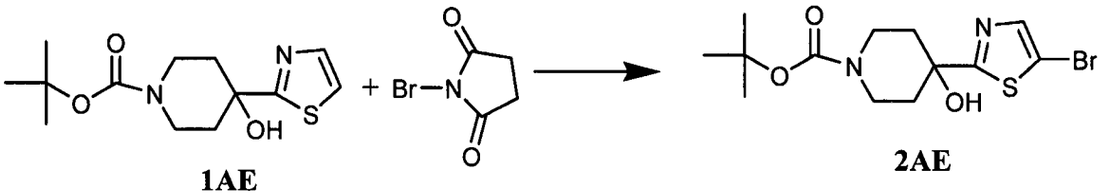
Paso 1



1AE

El Compuesto 1AE se preparó siguiendo un procedimiento similar al del Ejemplo 132.

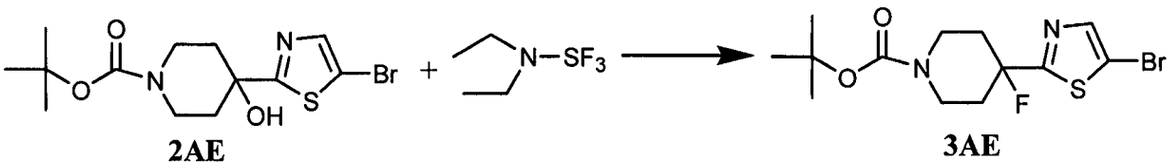
Paso 2



1AE **2AE**

Se disolvió 4,03 g (14,18 mmoles) **1AE** en 50 ml de CH_3CN anhidro a temperatura ambiente bajo N2 anhidro gaseoso. A esto se agregó 2,524 g (14,18 mmoles) de N-Bromosuccinimida a temperatura ambiente y mezcla se calentó a 40-50°C bajo N2 anhidro gaseoso durante 3 hrs.. La mezcla se evaporó hasta la sequedad. El residuo se repartió entre 100 ml de EtOAc y 100 ml de solución saturada de $NaHCO_3$. La fase orgánica se secó sobre $MgSO_4$ y se evaporó hasta la sequedad. La goma marrón resultante se purificó sobre gel de sílice (Hexano-30% EtOAc/ Hexano) dio 1,3 g (25%) de sólido amarillo.

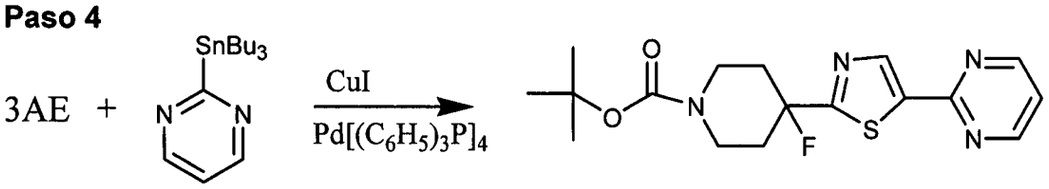
Paso 3



2AE 3AE

Se disolvió 2,38 g (6,55 mmoles) de 3 en 30 ml Diclorometano anhidro a temperatura ambiente bajo N2 anhidro gaseoso. La mezcla se enfrió hasta 0°C en un baño de hielo y 2,112g (13,1 mmoles) de DAST se agregó gota a gota a 0°C bajo N_2 anhidro. La mezcla se agitó a 0ºC durante 1 hr. La mezcla de reacción se alcalinizó cuidadosamente (evolución de CO_2 gaseoso) con solución saturada de $NaHCO_3$ a 0°C. La mezcla se transfirió a un embudo de decantación y se agitó bien. La fase orgánica se eliminó y la fase acuosa se extrajo con 2X50 ml de diclorometano. Las fases orgánicas combinadas se secaron sobre $MgSO_4$ y se evaporaron hasta la sequedad, dio 2,368 (99%) de sólido blancuzco de bajo punto de fusión.

Paso 4

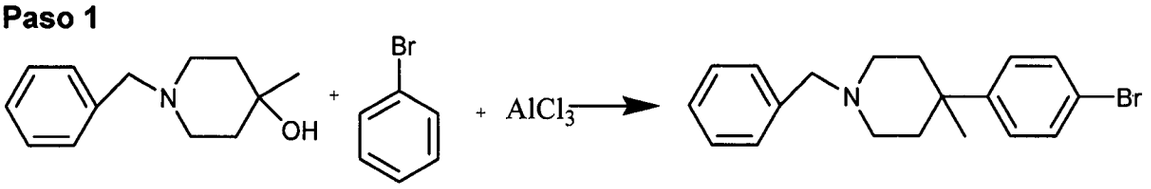


4AE

Se disolvió 1,7g (4,65 mmoles) de **4AE** en 15 ml DMF anhidra a temperatura ambiente bajo N2 anhidro gaseoso. A esta mezcla se agregaron CuI 0,93g (4,88 mmoles), Tetrakis(trifenilfosfin) paladio 0,537g (0,465 mmoles) y 2-Tributilestanilpirimidina 1,762g (5,2 mmoles) y la mezcla se agitó a 60°C bajo N2 anhidro gaseoso durante 24 hrs. La mezcla se concentró hasta un pequeño volumen, se diluyó con 50 ml EtOAc y se filtró a través de un taco de celite. El filtrado se lavó con salmuera y se secó sobre $MgSO_4$. La evaporación del Solvente dio una goma marrón oscuro que se purificó sobre gel de sílice (Hexano-25% EtOAc/ Hexano) dio 0,300g (17%) de sólido marrón.

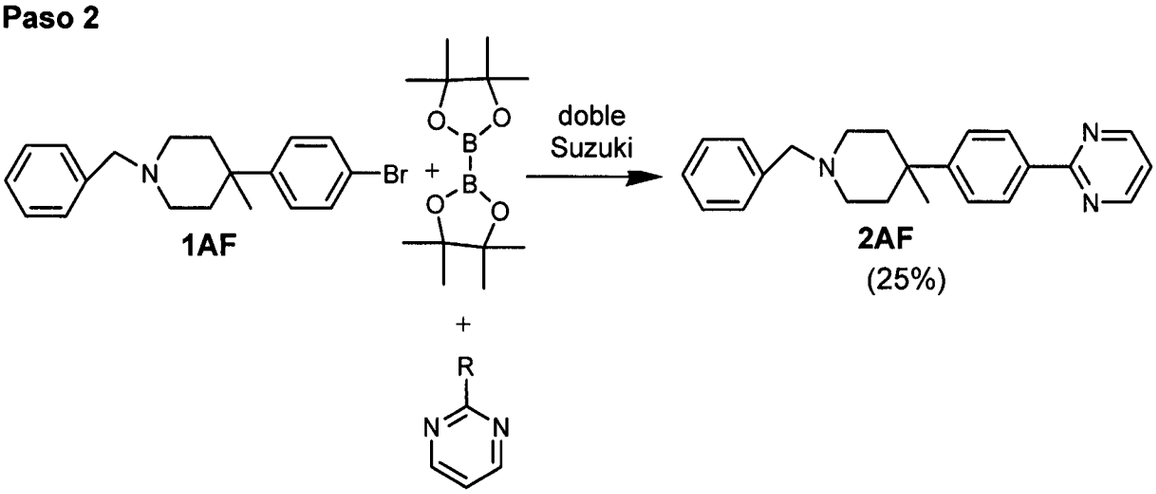
Preparación 55

Paso 1



Se disolvió 1-bencil-4-hidroxi-4-metil piperidina (4,927g, 24mmoles) en Bromobenceno(12ml, 114mmoles) a temperatura ambiente bajo N2 anhidro gaseoso. Se agregó $AlCl_3$ (4,81g, 36 mmoles) como sólido a la mezcla anterior a temperatura ambiente bajo N2 anhidro gaseoso. Hubo una leve reacción exotérmica. La solución marrón oscuro resultante se calentó a 100°C durante el fin de semana. La reacción se dejó enfriar hasta la temperatura ambiente y se vertió en agua helada. Se agregó $NaHCO_3$ acuoso saturado hasta que el pH fue 7. La mezcla se extrajo con 3X100 ml EtOAc. El extracto orgánico combinado se secó sobre $MgSO_4$ y se evaporó hasta la sequedad. La goma marrón oscuro resultante se purificó sobre sílice y se eluyó con (Hexano-25%EtOAc/Hexano), dio 4,43g (53%) como aceite espeso claro violeta.

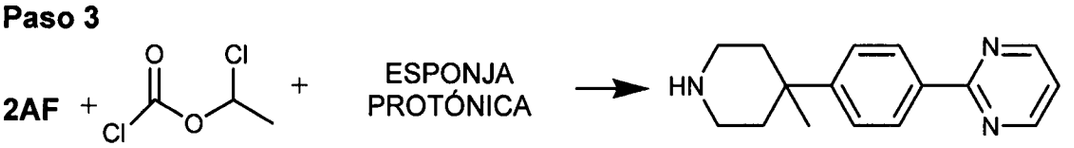
Paso 2



A una solución de 4,43 g (12,87 mmoles) de **1AF** en 100 ml de DMSO anhidro se agregaron 4,903 g (19,31 mmoles) de Bis(pinacolato)diboro, 3,784 g (38,61 mmoles) de Acetato de potasio y 1.051 g (1.287 mmoles) de $Pd(dppf)Cl_2$ a temperatura ambiente bajo N2 anhidro gaseoso. Los contenidos se desgasificaron

un par de veces con N_2 gas y se agitó a 100°C durante 2 hrs. La mezcla se dejó enfriar hasta la temperatura ambiente y se agregó 50 ml de agua seguido de 2,455 g (15,44 mmoles) de 2-Bromopirimidina, 8,894 g (64,35 mmoles) de Carbonato de potasio y 1,49 g (1.29 mmoles) de Tetrakis(trifenilfosfin)paladio. Los contenidos se desgasificaron un par de veces con N2 gas y se agitó a 100°C durante 2 hrs. La mezcla se dejó enfriar hasta la temperatura ambiente. Se agregaron 100 ml de agua y 100 ml de EtOAc a la mezcla de reacción y se filtró a través de un taco de celite y se lavó con EtOAc. Los contenidos se transfirieron a un embudo de decantación y la fase orgánica se separó y la fase acuosa se extrajo con EtOAC. Las fases orgánicas se combinaron y se lavó con agua y se secaron sobre MgSO4. El Solvente se evaporó hasta la sequedad y la goma marrón oscuro se purificó sobre gel de sílice (Hexano-25% EtOAC/Hexano), dio 1,00 de sólido blancuzco.

Paso 3

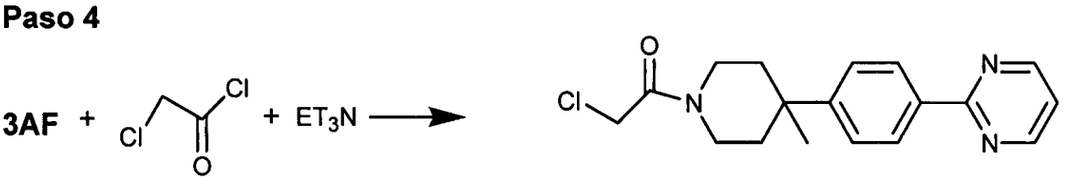


3AF

Se agregó 1,00 g (2,9 mmoles) de **2AF** 20 ml de diclorometano anhidro a temperatura ambiente bajo N2 anhidro gaseoso. A esta solución se agregó 0,178 g (0,83 mmoles) de Esponja Protónica a temperatura ambiente seguido de la incorporación gota a gota de 0,713g (4,99 mmoles) de cloroformiato de 2-cloroetilo. La mezcla de reacción se agitó a temperatura ambiente bajo N2 anhidro gaseoso durante 4 hrs. La mezcla se evaporó hasta la sequedad y se secó con alto vacío durante 15 minutos. El residuo resultante se disolvió en 20 ml de MeOH anhidro bajo N2 anhidro gaseoso y se agitó a reflujo bajo N2 anhidro gaseoso durante 4 hrs. La mezcla se dejó enfriar hasta la temperatura ambiente y se

evaporó hasta la sequedad. El producto en bruto se purificó sobre gel de sílice (CH_2Cl_2-25%MeOH/CH_2Cl_2) y dio 0,606g (82%) de sólido blanco.

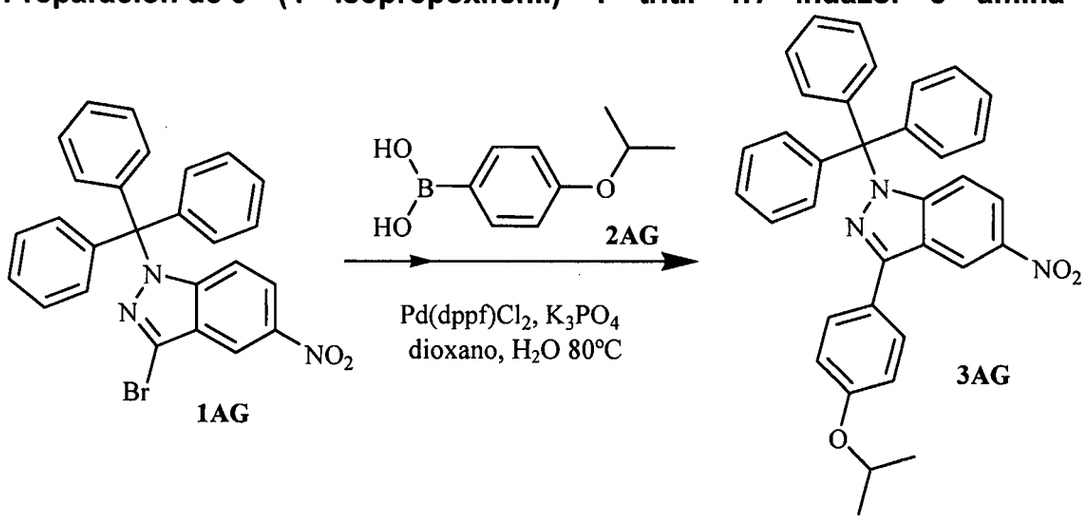
Paso 4



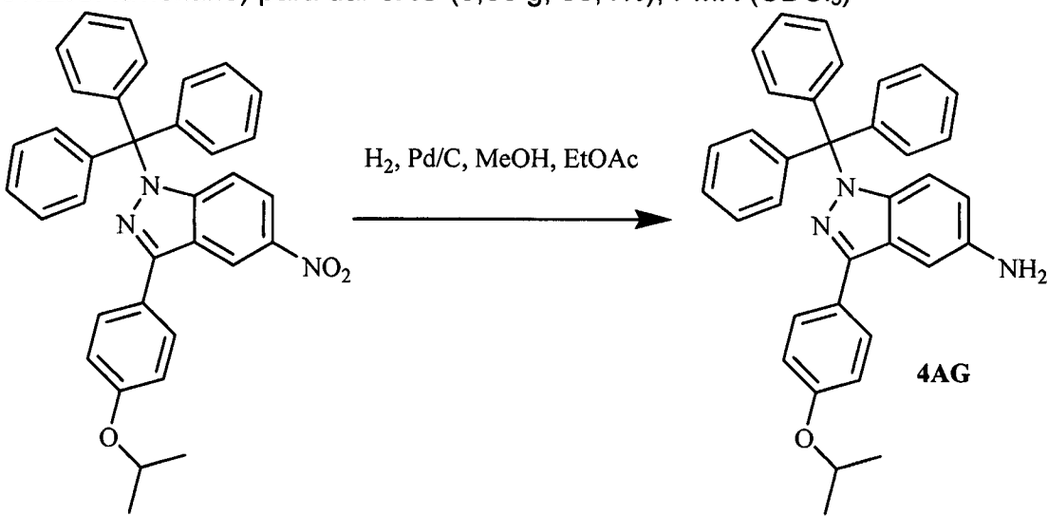
A una solución agitada de 0,60 g (2,37 mmoles) de **3AF** en 15 ml de diclorometano anhidro 1,20 g (11,85 mmoles) de Trietilamina se agregó a temperatura ambiente bajo N2 anhidro gaseoso. La mezcla se enfrió hasta 0°C en baño de agua y se agregó 0,321 g (2.84 mmoles) de cloruro de cloroacetilo gota a gota a 0°C bajo N2 anhidro gaseoso. La mezcla se agitó a 0°C durante media hora 25 ml de CH_2Cl_2 y solución acuosa saturada de $NaHCO_3$ se agregaron a 0°C. Los contenidos se transfirieron a un embudo de decantación y se agitó bien. La fase orgánica se separó, se secó sobre $MgSO_4$ y se evaporó hasta la sequedad, dio un sólido marrón. Este sólido se usó sin purificación para la posterior reacción.

Preparación 56

Preparación de 3—(4—isopropoxifenil)—1—tritil—1*H*—indazol—5—amina



En un tubo sellado que contiene **1AG** (1,21 g, 2,50 mmol), **2AG** (0,67 g, 3,75 mmol), $Pd(dppf)Cl_2$ (0,21g, 0,25 mmol) y K_3PO_4 (1,31 g, 6,25 mmol) se agregó dioxano (25 ml) y agua (12 ml) y se desgasificó bajo atmósfera de nitrógeno tres veces. Esta mezcla de reacción se agitó a 80°C durante 18 horas. La mezcla de reacción se diluyó con agua y EtOAc, luego se filtró a través de celite. La fase orgánica se lavó con agua, se secó sobre $MgSO_4$, se filtró y rotovap hasta la sequedad. El producto en bruto se cromatografió (Biotage, 40 L, 5%EtOAc/hexano) para dar **3AG** (0,68 g, 50,4%), PMR ($CDCl_3$)

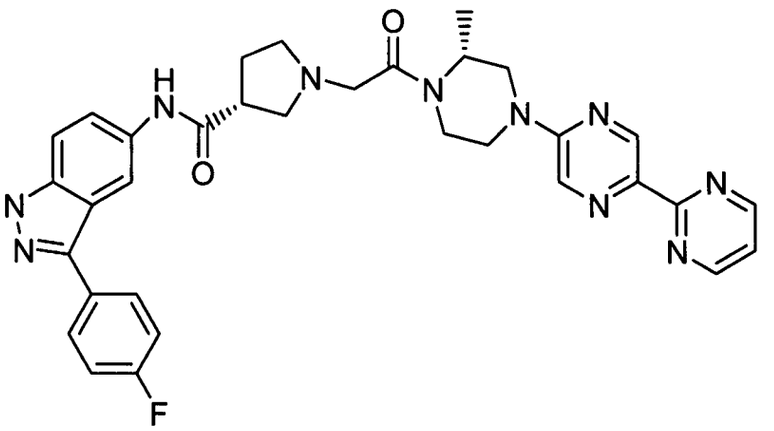


4AG

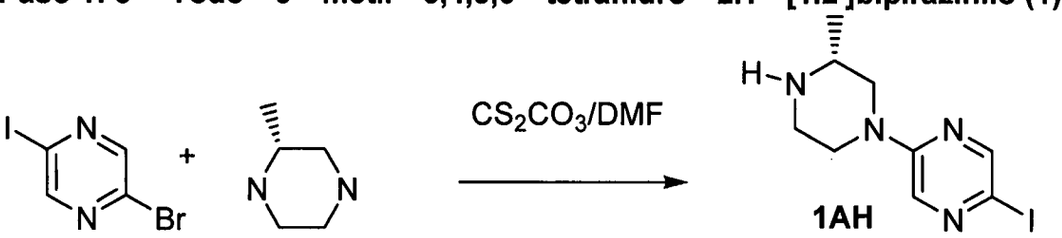
En un compuesto de RB **3AG** (0,6 g, 1.11 mmol) agitado en una mezcla de MeOH y EtOAc (10 ml cada uno) se agregó 0,2 g de Pd/C (10%, 50% agua). La mezcla de reacción se desgasificó bajo atmósfera de hidrógeno (globo) y se agitó hasta la mañana siguiente. La MS de la mezcla de reacción mostró (M+H) a 510. La mezcla de reacción se filtró (Celite) y rotovap hasta la sequedad para dar un producto en bruto **4AG**, usado como estaba para la siguiente reacción.

Ejemplo 621

[3—(4—fluoro—fenil)—1H—indazol—5—il]—amida del ácido 1—[2—(3—Metil—5'—pirimidin—2—il—2.3,5,6—tetrahidro—[1.2']bipirazinil—4—il)—2—oxo—etil]—pirrolidin—3—carboxílico

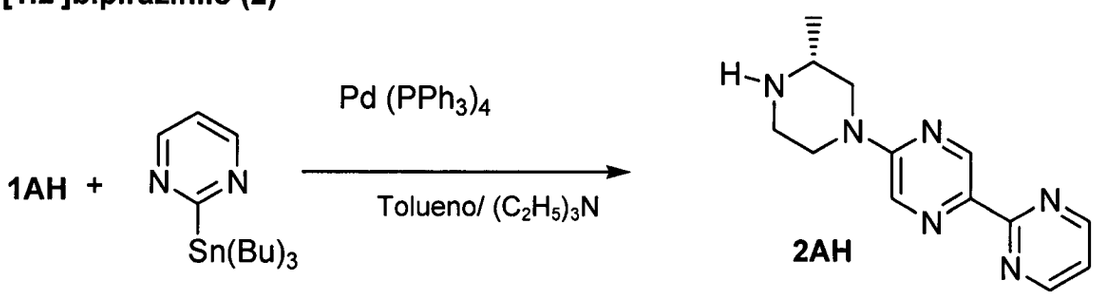


Paso 1: 5'—Yodo—3—metil—3,4,5,6—tetrahidro—2H—[1.2']bipirazinilo (1)



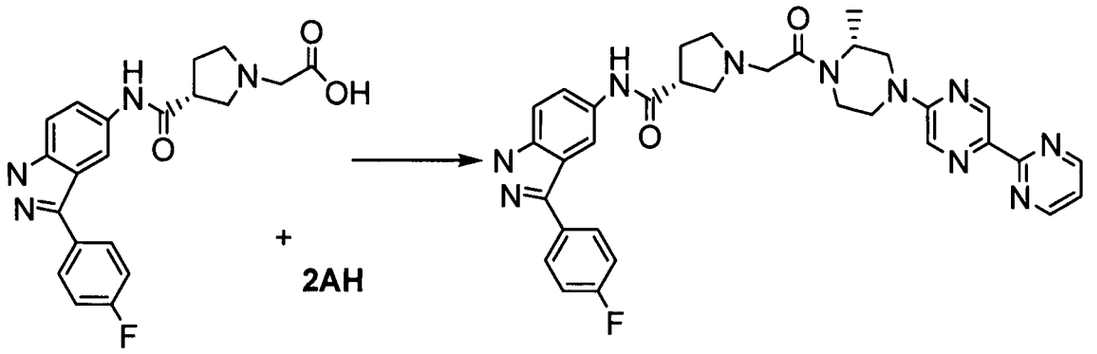
A mezcla de 2-bromo-5-yodopirazina (200 mg, 0,704 mmol), carbonato de cesio (400 mg, 1,23 mmol) y 2R metil piperazina (85 mg, 0,85 mmol) en DMF (10 ml) se agitó a 100^{0}C hasta la mañana siguiente. La reacción se enfrió y el solvente se evaporó. Se agregó agua (100 ml) y el sólido insoluble se filtró, luego se disolvió en $MeCl_2$ (100 ml), se secó sobre Na_2SO_4, se filtró y el solvente se evaporó generando producto (205mg, 95%) Espec. de Masa (MH, 305)

Paso 2: 3—Metil—5'—pirimidin—2—il—3,4,5,6—tetrahidro—2H—[1.2']bipirazinilo (2)



Se agregó $Pd(PPh_3)_4$ (30 mg, 0,025 mmol) a una mezcla de **5'—Yodo—3—metil—3,4,5,6—tetrahidro—2H—[1.2']bipirazinilo (1AH)** (50 mg, 0,164 mmol), 2-tributil estanil pirimidina (0,2 ml), trietilamina (0,2 ml, 1,43 mmol) en tolueno (3 ml) a temperatura ambiente luego se agitó 100°C durante 5 horas. La reacción se enfrió, se diluyó con EtOAc (50 ml) y agua (20 ml). La fase orgánica se separó, se secó (Na_2SO_4) se filtró y el solvente se evaporó. El residuo se purificó sobre TLC prep eluyendo con 10% MeOH:$MeCl_2$:NH_4OH generando el producto (10 mg,24%) Espec. de Masa MH 256

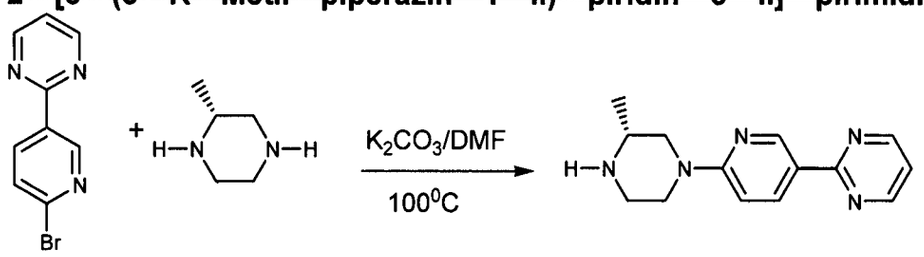
Paso 3: [3—(4—fluoro—fenil)—1H—indazol—5—il]—amida ácido del 1—[2—(3—Metil—5'—pirimidin—2—il—2.3,5,6—tetrahidro—[1.2']bipirazinil—4—il)—2—oxo—etil]—pirrolidin—3—carboxílico



A mezcla del ácido (20 mg, 0,044mmol); **3—Metil—5'—pirimidin—2—il—3,4,5,6—tetrahidro—2H—[1.2']bipirazinilo (2AH)** (10 mg, 0,039 mmol) EDCI (10 mg, 0,052 mmol); HOBT (7 mg, 0,052 mmol) y NMM (0,1 ml) se agitó en DMF (3 ml) a temperatura ambiente hasta la mañana siguiente. La reacción se diluyó con EtOAc (20 ml) y agua (10 ml) y la fase orgánica se separó. Los productos orgánicos se lavaron con salmuera (10 ml) se secaron sobre Na_2SO_4 se filtraron y el solvente se evaporó produciendo un residuo que se purificó sobre gel de sílice eluyendo con 10% MeOH; $MeCl_2$;NH_4OH generando el producto del título como sólido (10 mg,31%) Espec. de Masa (MH, 621)

Preparación 57

2—[6—(3—R—Metil—piperazin—1—il)—piridin—3—il]—pirimidina

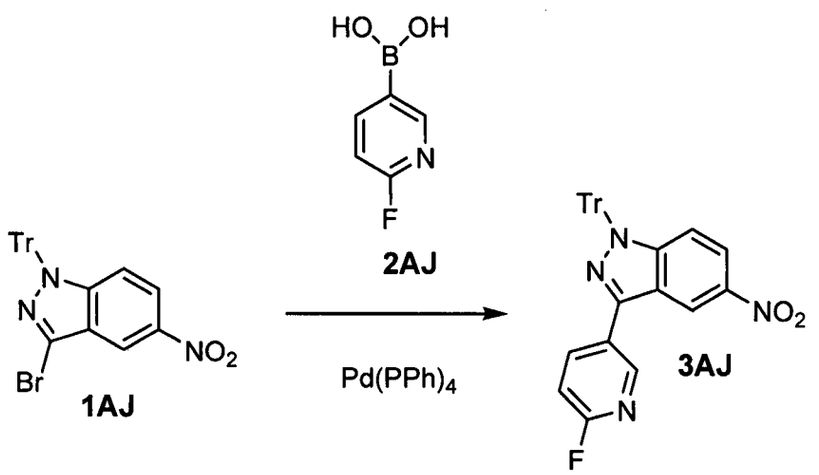


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Siguiendo el procedimiento descrito en el Ejemplo 98 Paso 7, pero sustituyendo una cantidad equivalente de 2-R-Metil piperazina en lugar de piperazina, se obtiene el compuesto del título como un sólido blanco (ESMS MH, 256) 95% de Rendimiento.

Preparación 58

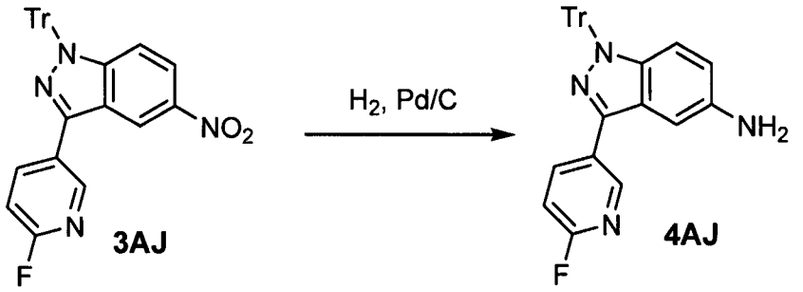
Paso 1: Preparación de 1—N—Tritil—3—(6—Fluoro—piridin—3—il)—1—metil—5—nitro—1H—indazol



A mezcla de compuesto **1AJ** (8 g, 16,53 mmol), el compuesto **2AJ** (2.33 g, 16,53 mmol), $Pd(PPh_3)_4$ (1,9 g, 1,653 mmol) y 1:1 dioxano/Na_2CO_3 (2M) (60 ml) se desgasificó durante 15 min. Luego se calentó a 120 °C durante hasta la mañana siguiente. Se enfrió hasta la temperatura ambiente y se diluyó con DCM

(300 ml). La fase orgánica se lavó con agua (200 ml), se secó sobre Na_2SO_4, se filtró y se concentró. El residuo se purificó por Biotage para dar el producto deseado **3AJ** (6 g, 58%).

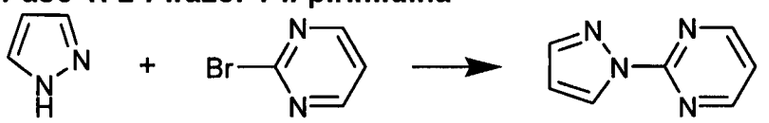
Paso 2: Preparación de 1—N—Tritil—3—(6—Fluoro—piridin—3—il)—1—metil—5—amino—1H—indazol



A mezcla de compuesto **3AJ** (6 g) y Pd/C (10%, 200 mg) en EtOAc (200 ml) se agitó durante hasta la mañana siguiente. Se filtró y se concentró. El residuo se purificó por Biotage para dar el producto deseado **4AJ** (5 g, 83%).

Preparación 59

Paso 1: 2-Pirazol-1-il-pirimidina



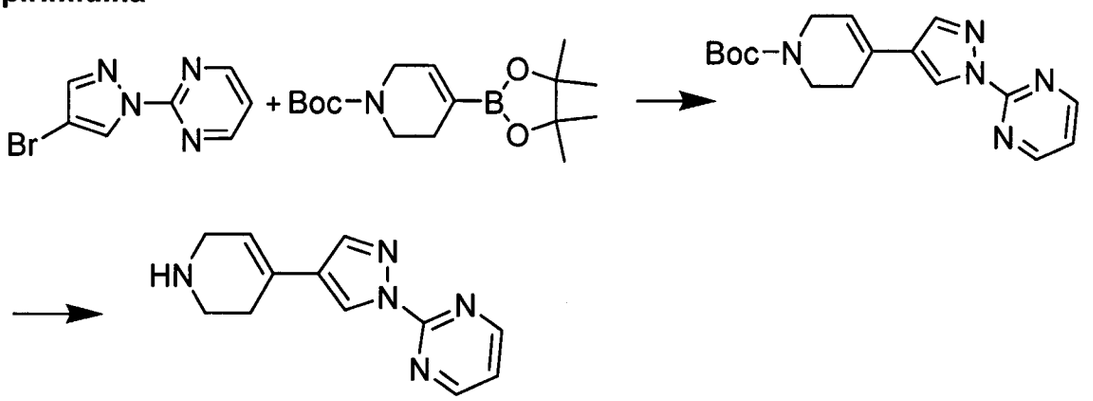
Una mezcla de reacción que contiene pirazol (2 g, 29 mmol), 2-bromopirimidina (3,8 g, 24 mmol), yoduro de cobre (I) (0,91 g, 4,8 mmol) y 1,10-fenantrolina (1,7 g, 9,6 mmol) en DMA se calentó a 140°C en un tubo sellado durante 6 horas. Luego de la reacción, se agregó acetato de etilo (30 ml), seguido de agua. La fase acuosa se extrajo tres veces (20 ml) y la fase orgánica se recolectó, se secó sobre sulfato de sodio. Luego de la concentración al vacío, el producto en bruto se purificó usando cromatografía en columna (10% acetato de etilo en diclorometano) para dar 0,55 g de producto puro. 15% de Rendimiento. MS (ESMS, M+H 146).

Paso 2: 2—(4—Bromo—pirazol—1—il)—pirimidina



A una solución de 2-pirazol-1-il-pirimidina (0,55 g, 3,7 mmol) en ácido acético (5 ml) se agregó bromo (1.2 g, 7,5 mmol) en ácido acético (3 ml) gota a gota. Luego de la incorporación, la mezcla de reacción se agitó a temperatura ambiente hasta la mañana siguiente. Luego de eliminar el ácido acético, el producto en bruto se purificó usando cromatografía en columna (2% metanol en diclorometano) para dar 0,7 g de producto puro en un 85% de Rendimiento. MS (ESMS, M+H 225).

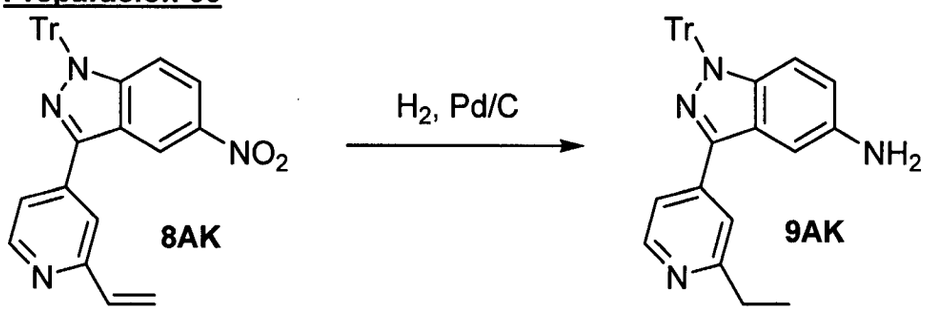
Paso 3: 2—[4—(1,2,3,6—Tetrahidro—piridin—4—il)—pirazol—1—il]—pirimidina



Una solución que contiene 2—(4—bromo—pirazol—1—il)—pirimidina (300 mg, 1.34 mmol), ter—butil éster del ácido 4—(4,4,5,5—tetrametil—[1.3,2]dioxaborolan—2—il)—3,6—dihidro—2H—piridin—1—carboxílico (280 mg, 1.34 mmol), $PdCl_2$(dppf) (95 mg, 0,13 mmol) y fosfato de potasio (800 mg, 4 mmol) en dioxano se calentó a 80°C bajo argón hasta la mañana siguiente. Luego de eliminar el solvente, se agregó acetato de etilo y se filtró la mezcla, se lavó con agua. Luego de la concentración al vacío, se encontró que el producto era difícil de separar de la impureza y el producto en bruto se trató con 90% de TFA durante 20 min y TFA se eliminó al vacío. El producto en bruto luego se

purificó usando HPLC prep para dar el producto deseado como sal de TFA (120 mg, 0,37 mmol) en un 27% de rendimiento general. MS (ESMS, M+H 228)

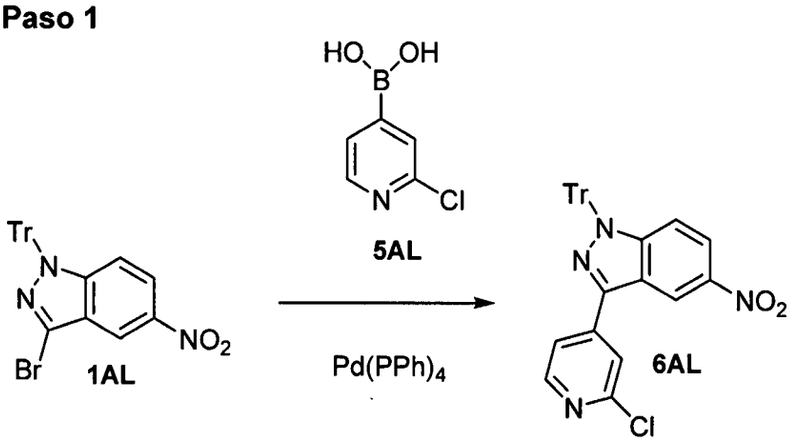
Preparación 60

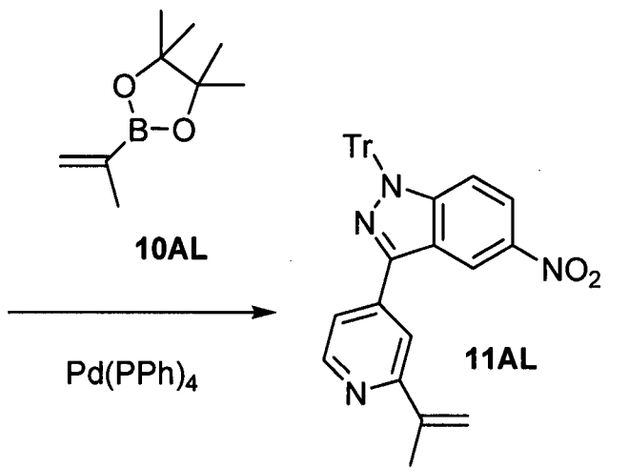


Una mezcla de compuesto **8AK** (5 g) y Pd/C (10%, 200 mg) en EtOAc (200 ml) se agitó durante hasta la mañana siguiente. Se filtró y se concentró. El residuo se purificó por Biotage para dar el producto deseado **9AK** (4,6 g, 92%).

Preparación 61

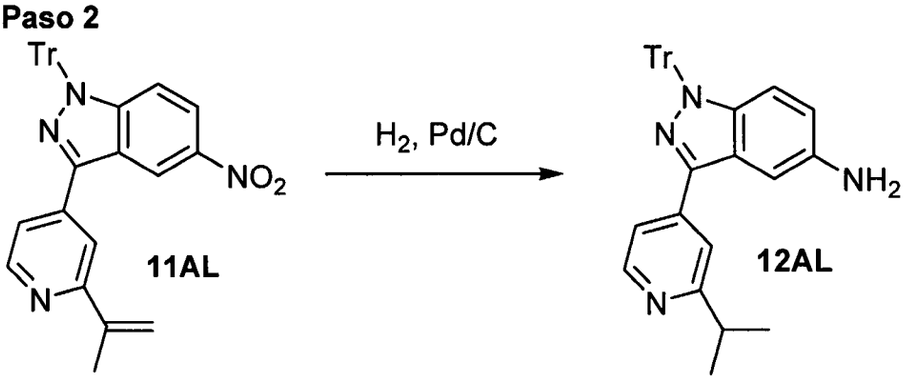
Paso 1





Una mezcla de compuesto **1AL** (10 g, 20,66 mmol), el compuesto **5AL** (3,23 g, 20,66 mmol), $Pd(PPh_3)_4$ (2,3 g, 2 mmol) y 1:1 dioxano/Na_2CO_3 (2M) (70 ml) se desgasificó durante 15 min. Luego se calentó a 120°C durante hasta la mañana siguiente. Se enfrió hasta la temperatura ambiente y se agregó compuesto **10AL** (3,47 g, 20,66 mmol), luego se calentó a 120°C durante hasta la mañana siguiente. Se enfrió hasta la temperatura ambiente y se diluyó con DCM (400 ml). La fase orgánica se lavó con agua (250 ml), se secó sobre Na_2SO_4, se filtró y se concentró. El residuo se purificó por Biotage para dar el producto deseado **11AL** (6 g, 50%).

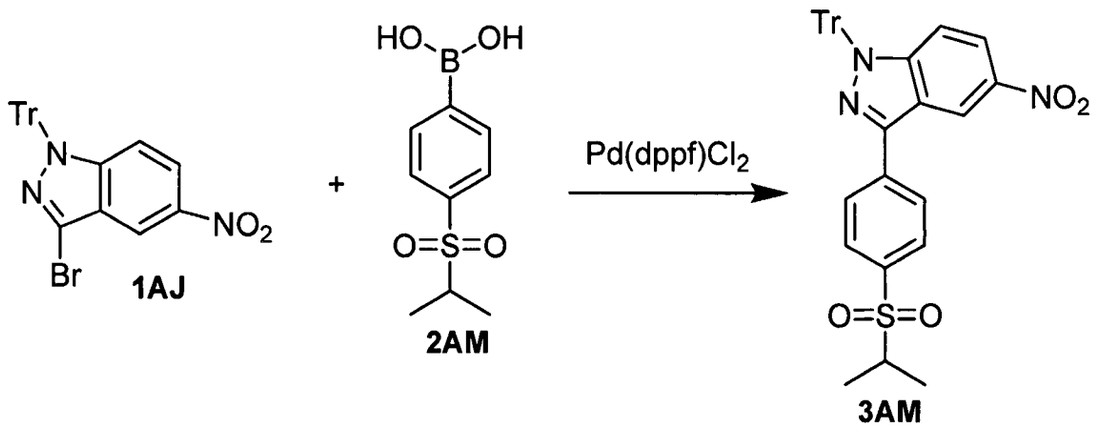
Paso 2



Una mezcla de compuesto **11AL** (6 g) y Pd/C (10%, 200 mg) en EtOAc (200 ml) se agitó durante hasta la mañana siguiente. Se filtró y se concentró. El residuo se purificó por Biotage para dar el producto deseado **12AL** (5 g, 83%).

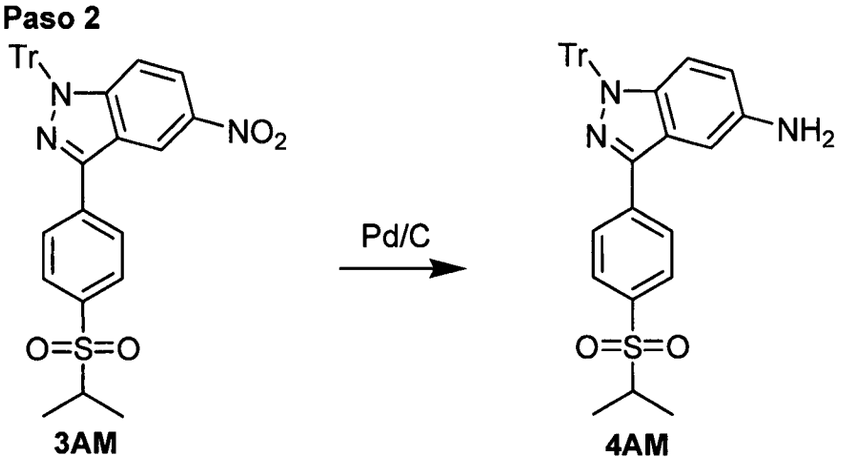
Preparación 62

Paso 1



Una mezcla de 3—bromo—5—nitro—1—tritil—1*H*—indazol **1AJ** (0,43 g, 0,9 mmol), ácido 4—(propane—2—sulfonil)—fenil borónico **2AM** (0,3 g, 1,35 mmol), carbonato de potasio (0,38 g, 2,7 mmol), $Pd(dppf)Cl_2$ (0,07g, 0,09 mmol) y 4/1 /dioxano/agua (5 ml) se desgasificó durante 5 minutos. Luego se calentó a 80°C durante hasta la mañana siguiente. Se enfrió hasta temperatura ambiente y se diluyó con EtOAc (60 ml). La fase orgánica se lavó con agua (20 ml), se secó sobre $MgSO_4$, se filtró y se concentró. El residuo se purificó sobre gel de sílice eluyendo con 1/2 EtOAc/Hexano para dar el producto deseado **3AM** (0,4g, 76%).

Paso 2

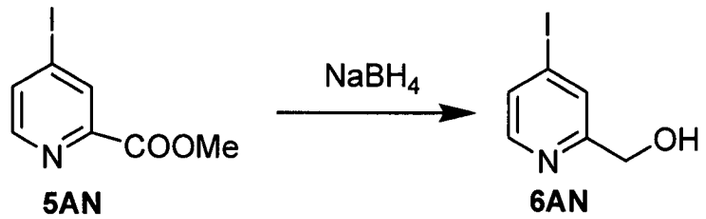


Una solución de 5—nitro—3—[4—(propan—2—sulfonil)—fenil]—1—tritil—1*H*—indazol **3AM** (0,4 g, 0,68 mmol) en EtOAc (18 ml) y MeOH (9 ml) se

desgasificó durante 5 minutos. A esta solución se agregó Pd/C al 10% (38 mg). Luego de agitar durante hasta la mañana siguiente a 40°C, se enfrió y se filtró en un taco de celite. El filtrado se concentró para dar el producto deseado **4AM** (0,36 g, 99%).

Preparación 63

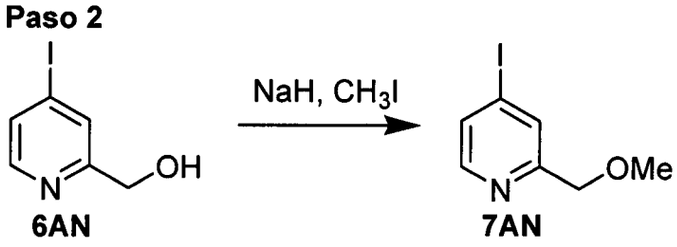
Paso 1



5AN **6AN**

A una solución de 4-yodopicolinato de metilo **5AN** (2.83g, 10,78mmol) en MeOH (30 ml) se agregó $NaBH_4$ (1,59 g, 43,12 mmol) en porciones a 0°C. Se dejó entibiar la mezcla de reacción hasta la temperatura ambiente. Luego de agitar durante 3 días a temperatura ambiente, se desactivó con 14 ml de NaOH 1N. La reacción se diluyó la mezcla con DCM (200 ml). La fase orgánica se lavó con agua (2 x 30 ml), se secó sobre $MgSO_4$, se filtró y se concentró. El residuo se purificó sobre gel de sílice eluyendo con 3/1 EtOAc/Hexano para dar el producto deseado (4-yodo-piridin-2-il)-metanol **6AN** (2.27g, 90%).

Paso 2

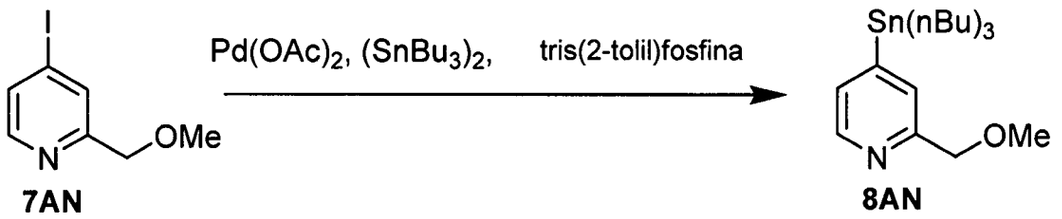


6AN **7AN**

Una solución de (4-yodo-piridin-2-il)-metanol **6AN** (0,51 g, 2,16 mmol) en THF (7,5ml) se agregó en NaH anhidro (0,17g, 4,32mmol). La mezcla de reacción se agitó durante 20 min a temperatura ambiente. Se enfrió hasta 0°C y se agregó CH_3I 0,16 ml, 2,59 mmol) gota a gota. Luego de 30 min. a 0°C, se entibió hasta la

temperatura ambiente y se agitó en forma adicional durante 2 hr. Luego se diluyó con EtOAc (50 ml) y se lavó con agua (2 x 10 ml) y salmuera (1 x 15ml). Los extractos orgánicos se secaron sobre $MgSO_4$, se filtraron y se concentraron. El residuo se purificó sobre gel de sílice eluyendo con 1/2 EtOAc/Hexano para dar el producto deseado 4-Yodo-2-metoximetil-piridina **7AN** (0,39, 72%).

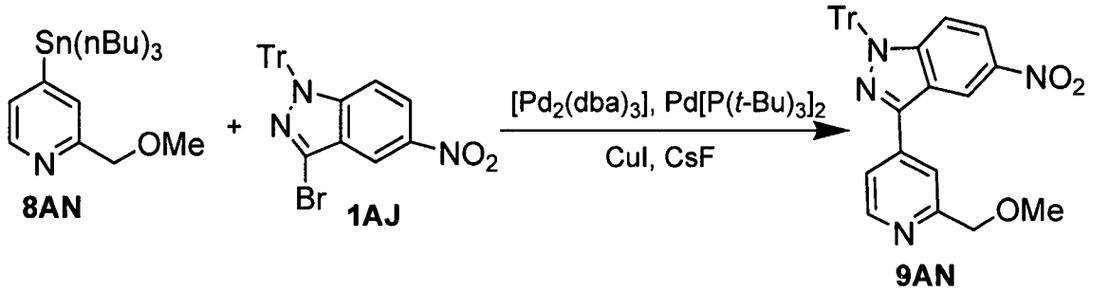
Paso 3



7AN **8AN**

A una mezcla de 4-yodo-2-metoximetil-piridina **7AN** (0,22 g, 0,89 mmol), $Pd(OAc)_2$ (9 mg, 0,04 mmol) y tris (2-tolil)fosfina (72 mg, 0,23 mmol) en ACN (7 ml) se agregó TEA (0,27 ml, 1,78 mmol) y bis(tributilestaño) (0,53 ml, 1,07 mmol). Se desgasificó durante 5 minutos. Luego se calentó a 85**°C durante** 2hr. Se enfrió hasta temperatura ambiente y se diluyó con EtOAc (50 ml). La fase orgánica se lavó con agua (15 ml), se secó sobre $MgSO_4$, se filtró sobre un taco de celite y se concentró. El residuo se purificó sobre gel de sílice eluyendo con 1/2 EtOAc/Hexano para dar el producto deseado 2-metoximetil-4-tributilestanil-piridina **8AN** (0,36g, 80%).

Paso 4

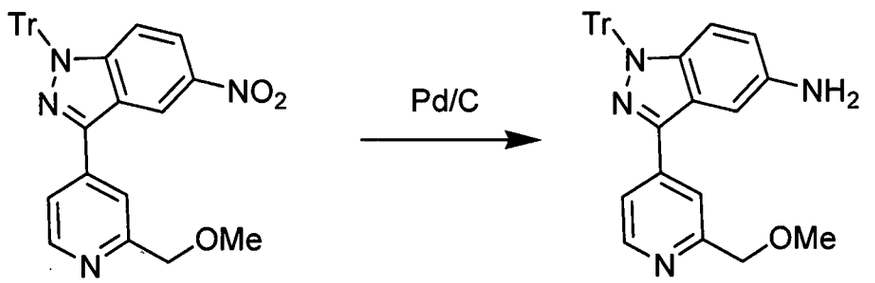


8AN **1AJ** **9AN**

A mezcla de 2—metoximetil—4—tributilestanil—piridina **8AN** (0,1 g, 0,24 mmol), 3—bromo—5—nitro—1—tritil—1*H*—indazol **1AJ** (0,12g, 0,24 mmol), CsF (0,08g, 0,53 mmol), $[Pd_2(dba)_3]$ (5 mg, 0,005 mmol), $Pd[P(t\text{-}Bu)_3)_2$. y CuI (4 mg,

0,024 mmol) en DMF (2 ml) se desgasificó durante 5 minutos. Luego se calentó a 120°C durante dos horas. Se enfrió hasta temperatura ambiente y se diluyó con EtOAc (10 ml). Luego se filtró sobre un taco de celite. El filtrado se lavó con agua (3 ml) y los extractos orgánicos se secaron sobre $MgSO_4$. Se filtró nuevamente sobre un taco de celite y se concentró. El residuo se purificó sobre gel de sílice eluyendo con 2/1 EtOAc/Hexano para dar el producto deseado 3—(2—metoximetil—piridin—4—il)—5—nitro—1—tritil—1*H*—indazol **9AN** (0,095 g, 76%).

Paso 5

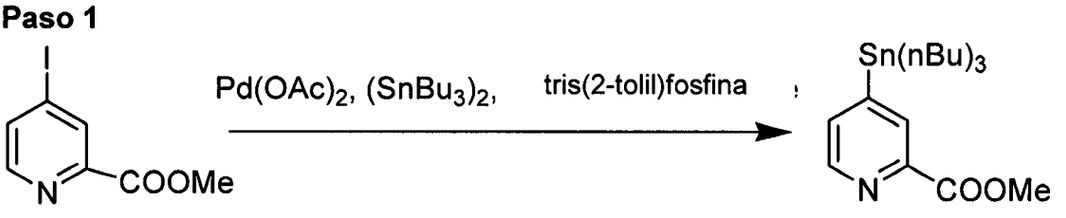


9AN **10AN**

Una solución de 3—(2—metoximetil—piridin—4—il)—5—nitro—1—tritil—1*H*—indazol **9AN** (0,095 g 0,18 mmol) en EtOAc (5 ml) se desgasificó durante 5 minutos. A esta solución se agregó Pd/C al 10% (20 mg). Luego de agitar durante hasta la mañana siguiente a temperatura ambiente, se enfrió y se filtró sobre un taco de celite. El filtrado se concentró para dar el producto deseado 3—(2—metoximetil—piridin—4—il)—1—tritil—1*H*—indazol—5—ilamina **10AN** (0,086g, 96%).

Preparación 64

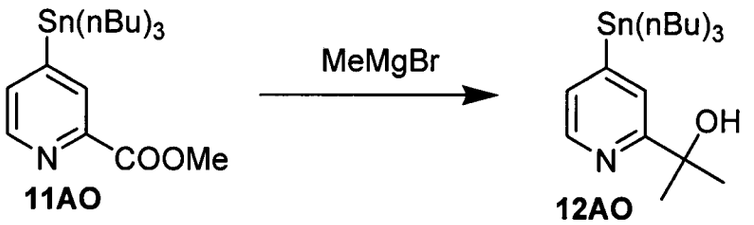
Paso 1



5AN **11AO**

A una mezcla de 4-yodopicolinato de metilo **5AN** (2,6g, 9,89 mmol), $Pd(OAc)_2$ (0,1 g, 0,45 mmol) y tris (2-tolil)fosfina (0,79 g, 2,58 mmol) en ACN (20 ml) se agregó TEA (2,8 ml, 19,89 mmol) y bis(tributilestaño) (6 ml, 11,93 mmol). Se desgasificó durante 5 minutos. Luego se calentó a 85**°C durante** 2hr. Se enfrió hasta temperatura ambiente y se diluyó con EtOAc (200 ml). La fase orgánica se lavó con agua (50 ml), se secó sobre $MgSO_4$, se filtró sobre un taco de celite y se concentró. El residuo se purificó sobre gel de sílice eluyendo con 1/2 EtOAc/Hexano para dar el producto deseado metil éster del ácido 4-tributilestanil-piridin-2-carboxílico **11AO** (3,48g, 82%).

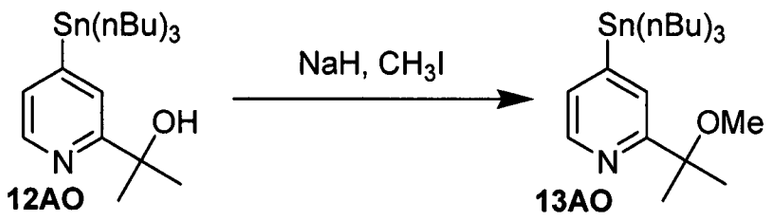
Paso 2



11AO **12AO**

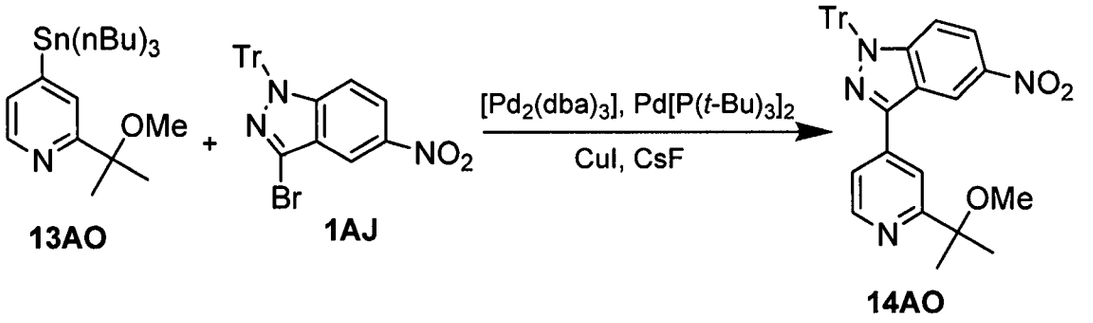
En una solución de metil éster del ácido 4-tributilestanil-piridin-2-carboxílico **11AO** (0,34g, 0,8 mmol) en THF (7 ml) a -78°C se agregó MeMgBr (1,15 ml, 1,6 mmol, 1,4M en tolueno/THF) gota a gota. Se agitó a -78^0C durante 30 mins. La mezcla de reacción se entibió hasta la temperatura ambiente. Luego de 1,5 hr, se enfrió nuevamente hasta 0°C y se desactivó con 5 ml de NH_4Cl saturado. Los extractos orgánicos se lavaron con agua (3 ml) y salmuera (3 ml) y se secaron sobre $MgSO_4$. El residuo se purificó sobre gel de sílice eluyendo con 1/2 EtOAc/Hexano para dar el producto deseado 2—(4—tributilestanil—piridin—2—il)—propan—2—ol **12AO** (012 g, 77%).

Paso 3



Una solución de 2—(4—tributilestanil—piridin—2—il)—propan—2—ol **12AO** (0,12g, 0,27 mmol) en THF (2 ml) se agregó en un NaH anhidro (0,02g, 0,54 mmol). La mezcla de reacción se agitó durante 20 min a temperatura ambiente. Se enfrió hasta 0 ^{0}C y se agregó CH_3I (0,02 ml, 0,32 mmol) gota a gota. Luego de 30 min. a 0°C, la mezcla de reacción se entibió hasta la temperatura ambiente. Se diluyó con EtOAc (15 ml) luego de 2 hr y se lavó con agua (2 x 3 ml) y salmuera (5 ml). Los extractos orgánicos se secaron sobre $MgSO_4$, se filtró y se concentró. El residuo se purificó sobre gel de sílice eluyendo con 1/4 EtOAc/Hexano para dar el producto deseado 2—(1—metoxi—1—metil—etil)—4—tributilestanil—piridina **13AO** (0,1g, 88%).

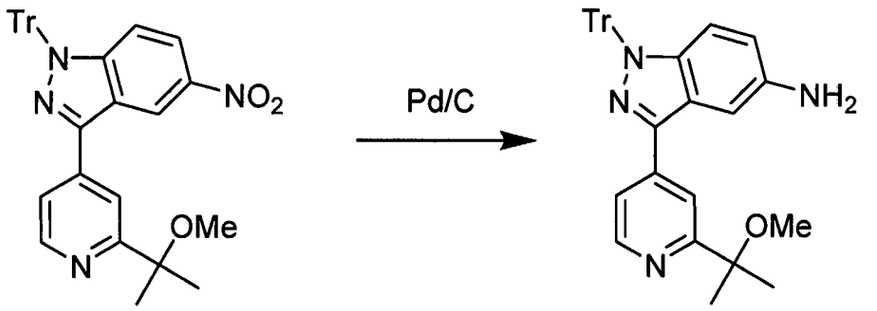
Paso 4



2—(1—metoxi—1—metil—etil)—4—tributilestanil—piridina **13AO** (0,1 g, 0,24 mmol), 3—bromo—5—nitro—1—tritil—1*H*—indazol **1AJ** (0,12 g, 0,24 mmol), CsF (0,08g, 0,53 mmol), $[Pd_2(dba)_3]$ (5 mg, 0,005 mmol), $Pd[P(t\text{-}Bu)_3)_2$. y CuI (4 mg, 0,024 mmol) en DMF (2 ml) se desgasificó durante 5 minutos. Luego se calentó a 120°C durante dos horas. Se enfrió hasta temperatura ambiente y se diluyó con EtOAc (10 ml). Luego se filtró sobre un taco de celite. El filtrado se lavó con agua (3 ml) y los extractos orgánicos se secaron sobre $MgSO_4$. Se filtró nuevamente sobre un taco de celite y se concentró. El residuo se purificó sobre

gel de sílice eluyendo con 1/3 EtOAc/Hexano para dar el producto deseado 3—[2—(1—metoxi—1—metil—etil)—piridin—4—il]—5—nitro—1—tritil—1*H*—indazol **14AO** (0,05 g, 39%).

Paso 5

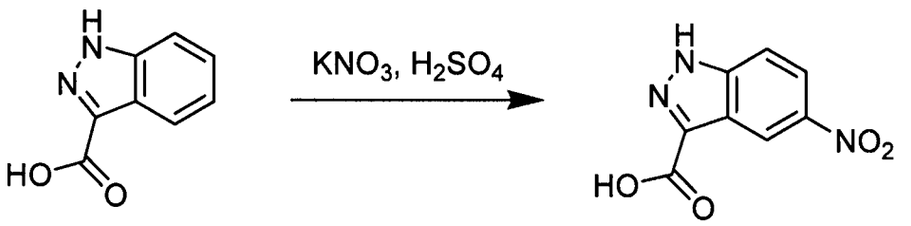


14AO **15AO**

Una solución de 33—[2—(1—metoxi—1—metil—etil)—piridin—4—il]—5—nitro—1—tritil—1*H*—indazol **14AO** (0,05 g, 0,09 mmol) en EtOAc (5 ml) se desgasificó durante 5 minutos. A esta solución se agregó Pd/C al 10% (10 mg). Luego de agitar durante hasta la mañana siguiente a temperatura ambiente, se enfrió y se filtró sobre un taco de celite. El filtrado se concentró para dar el producto deseado 3—[2—(1—metoxi—1—metil—etil)—piridin—4—il]—1—tritil—1*H*—indazol—5—ilamina **15AO** (0,046g, 97%).

Procedimiento 65

Paso 1

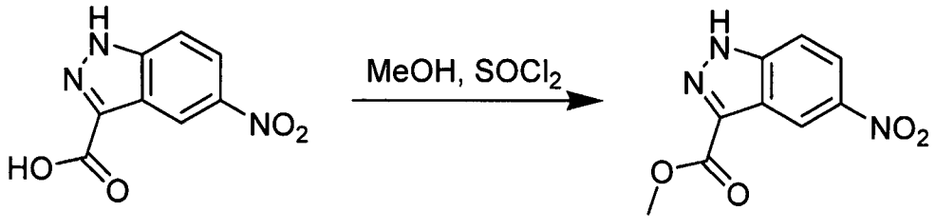


16AP **17AP**

A una suspensión de ácido indazol—3—carboxílico **16AP** (10,5 g, 64,8 mmol) en ácido sulfúrico concentrado (125 ml) a 0°C se agregó KNO_3 (64,8 mmol, 6,55 g). La mezcla de reacción se entibió hasta la temperatura ambiente. Luego de agitar durante 4hr a temperatura ambiente, se vertió en 525 ml de hielo/agua.

El sólido se recolectó por filtración y se lavó con agua para dar el ácido 5—nitro—1*H*—indazol—3—carboxílico deseado **17AP** (10,74g, 80%).

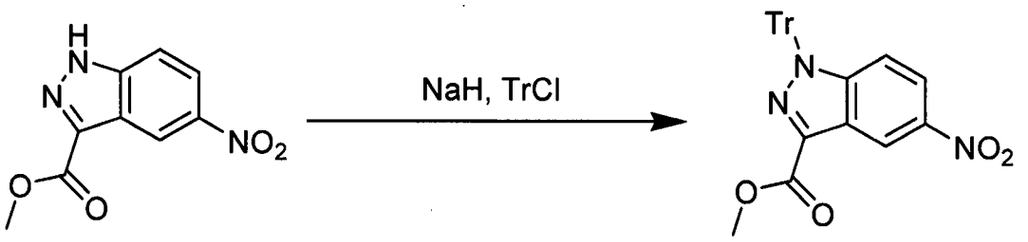
Paso 2



17AP **18AP**

A una suspensión de ácido 5—nitro—1*H*—indazol—3—carboxílico **17AP** (10,74g, 51,88 mmol) en MeOH (145 ml) a 0°C se agregó $SOCl_2$ (35 ml) gota a gota. Luego de agitar durante 10 min a 0°C, la mezcla de reacción se reflujó hasta la mañana siguiente. Evolucionó HCl gaseoso (El condensador se equipó con globo vacío para atrapar el HCl). Luego se enfrió hasta temperatura ambiente, se recolectó el sólido por filtración y se lavó con MeOH para dar el metil éster del ácido 5—nitro—1*H*—indazol—3—carboxílico deseado **18AP** (7g, 61%).

Paso 3

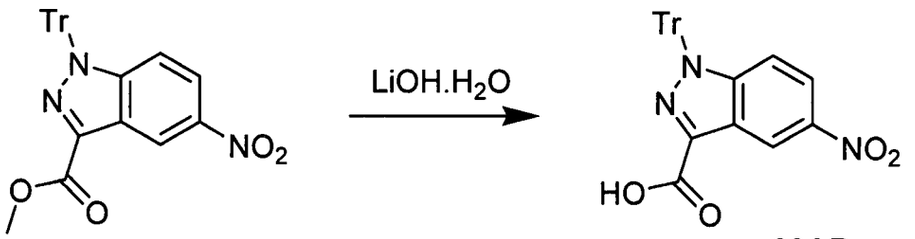


18AP **19AP**

La suspensión de metil éster del ácido 5—nitro—1*H*—indazol—3—carboxílico **18AP** (7g, 31,67 mmol) en THF (130 ml) y DCM (15 ml) se agregó a NaH (60% en aceite mineral, 1,61g, 41,17 mmol) a 0°C. Evolucionó H_2 gaseoso. Se agregó clorotrifenil metano (8,83g, 31,67 mmol) luego de agitar durante 20 min a 0°C. La mezcla de reacción se sometió a calor a 60°C durante hasta la mañana siguiente. Luego se enfrió hasta temperatura ambiente y se concentró bajo presión reducida. El sólido se re-disolvió en DCM y se filtró. El filtrado se

concentró bajo presión reducida para dar el metil éster del ácido 5—nitro—1—tritil—1*H*—indazol—3—carboxílico deseado **19AP** (12.95 g, 88%).

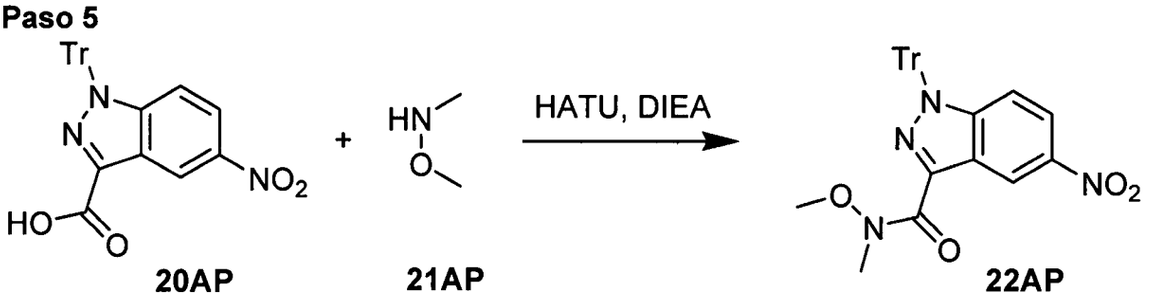
Paso 4



19AP **20AP**

A una solución de metil éster del ácido 5—nitro—1—tritil—1*H*—indazol—3—carboxílico **19AP** (12,95 g, 27,96 mmol) en THF (270 ml) y H_2O (135 ml) se agregó $LiOH{\cdot}H_2O$ (2.34g, 55,92 mmol) a temperatura ambiente. Luego de agitar durante hasta la mañana siguiente a temperatura ambiente, se enfrió hasta 0°C y se acidificó con la lenta incorporación de HCl 1N (55,9 ml, 55,92 mmol). La mezcla de reacción se concentró bajo presión reducida. El sólido se recolectó por filtración y se lavó con agua para dar el ácido 5—nitro—1—tritil—1*H*—indazol—3—carboxílico deseado **20AP** (12,06 g, 96%).

Paso 5

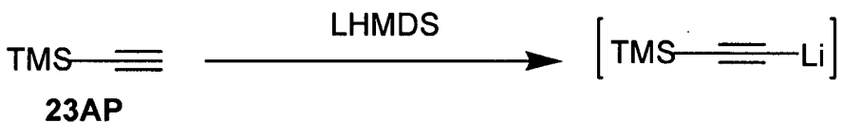


20AP **21AP** **22AP**

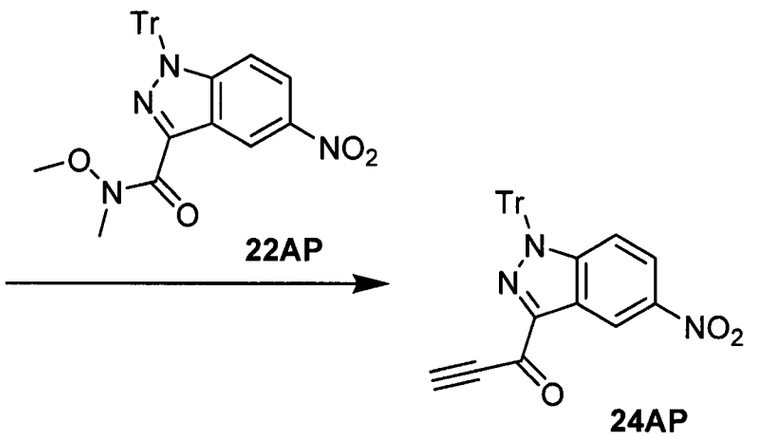
Se disolvió ácido 5—nitro—1—tritil—1*H*—indazol—3—carboxílico **20AP** (12.06g, 26,85 mmol) y HATU (10,2g, 26,85 mmol) en DMF (100 ml). Luego de agitar durante 10 min a temperatura ambiente, se agregó *N,O*—dimetilhidroxil amina, clorhidrato **21AP** (2,62g, 26,85 mmol) y DIEA (14,1 ml, 80,55 mmol). Se agitó un adicional de 1 hr a temperatura ambiente. La mezcla de reacción se

vertió en 300 ml de agua. El sólido se recolectó por filtración. Este sólido se disolvió nuevamente en EtOAc (300 ml) y se agregó 75 ml de $NaHCO_3$ sat.. La fracción orgánica se lavó con agua (2 X 75 ml), salmuera (75 ml) y se secó sobre $MgSO_4$. El solvente se eliminó bajo presión reducida para dar la metoxi—metil—amida del ácido 5—nitro—1—tritil—1*H*—indazol—3—carboxílico deseada **22AP** (12,56g, 95%).

Paso 6



23AP

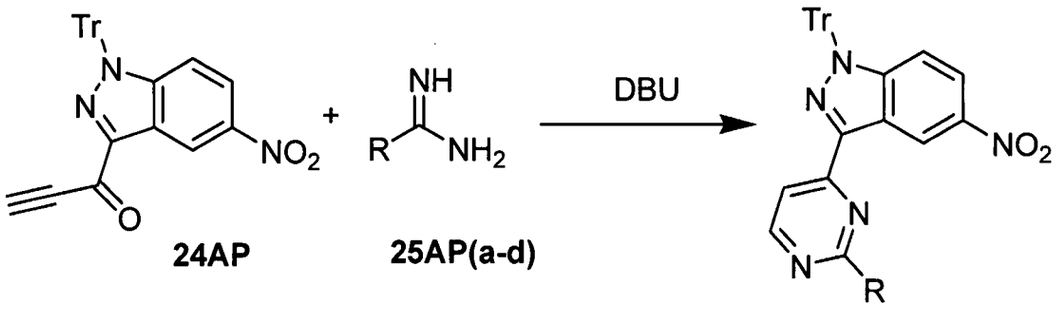


24AP

A una solución enfriada (-20°C) de TMS-acetileno **23AP** (5,5 ml, 38,28 mmol) en tolueno (23 ml) se agregó LHMDS (33,2 ml, 1M en THF, 33,2 mmol) gota a gota durante 5 min manteniendo la T < -5°C. La mezcla se agitó a 0°C durante 30 min, luego se transfirió a la mezcla de reacción fría (-10°C) que contiene metoxi—metil—amida del ácido 5—nitro—1—tritil—1*H*—indazol—3—carboxílico **22AP** (12,56g, 25,52 mmol) en THF (120 ml) a una velocidad que mantuvo la T < -5°C. La mezcla resultante se agitó durante 20 min a -5°C luego 1,5hr a temperatura ambiente. La mezcla de reacción se enfrió hasta 0°C y se desactivó por la lenta incorporación de HCl 1N (40 ml) bajo N_2. Se agitó un adicional de 5 min. La reacción se diluyó la mezcla con EtOAc (500 ml). La

fracción orgánica se separó y se lavó con agua (2 x 100 ml) y salmuera (1 x 125 ml). Se secó sobre $MgSO_4$, se filtró y se concentró. El residuo se purificó sobre gel de sílice eluyendo con 2/1 EtOAc/Hexano para dar la 1—(5—nitro—1—tritil—1*H*—indazol—3—ilo—)—propinona deseada **24AP** (6,99g, 60%).

Paso 7

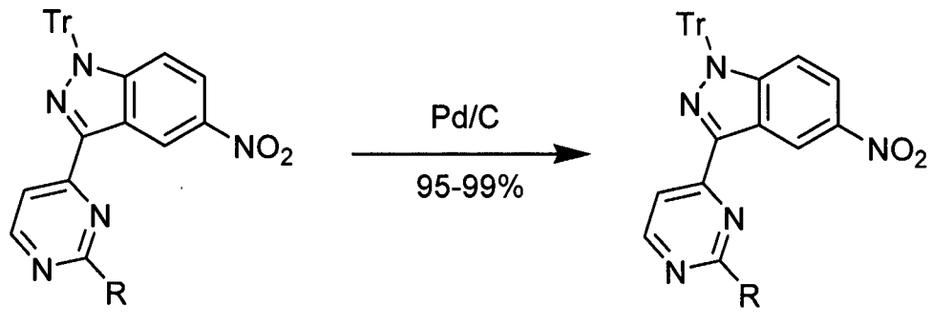


24AP **25AP(a-d)** **26AP(a-d)**

a. R = metilo (60%)
b. R = etilo (58%)
c. R = isopropilo (54%)
d. R = t-butilo (43%)

A mezcla de 1—(5—nitro—1—tritil—1*H*—indazol—3—ilo—)—propinona **24AP** (0,5 g, 1,09 mmol), clorhidrato de amidina **25AP** (1,75 mmol) y DBU (1,6 ml, 10,9 mmol) en acetonitrilo (10 ml) se calentó a 120**°C durante** 50 minutos con microondas. Luego se enfrió hasta temperatura ambiente y se diluyó con DCM (60 ml). La fase orgánica se lavó con agua (10 ml), se secó sobre $MgSO_4$, se filtró y se concentró. El residuo se purificó sobre gel de sílice eluyendo con 1/1 EtOAc/Hexano para dar el producto deseado **26AP**.

Paso 8



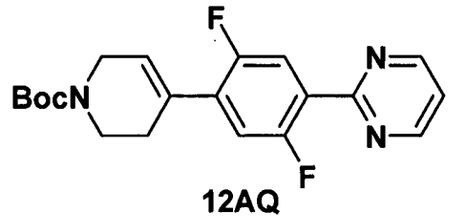
26AP(a-d) **27AP(a-d)**

a. R = metilo
b. R = etilo
c. R = isopropilo
d. R = t-butilo

Una solución de **26AP** (0,96 mmol) en EtOAc (20 ml) y MeOH (5 ml) se desgasificó durante 5 minutos. A esta solución se agregó Pd/C al 10% (0,08g). Luego de agitar durante hasta la mañana siguiente at 40°C, se enfrió y se filtró sobre un taco de celite. El filtrado se concentró para dar el **27AP** deseado.

Preparación 66

Preparación de ter—butil éster del ácido 4—(2,5—Difluoro—4—pirimidin—2—il—fenil)—3,6—dihidro—2H—piridin—1—carboxílico (Compuesto 12AQ)

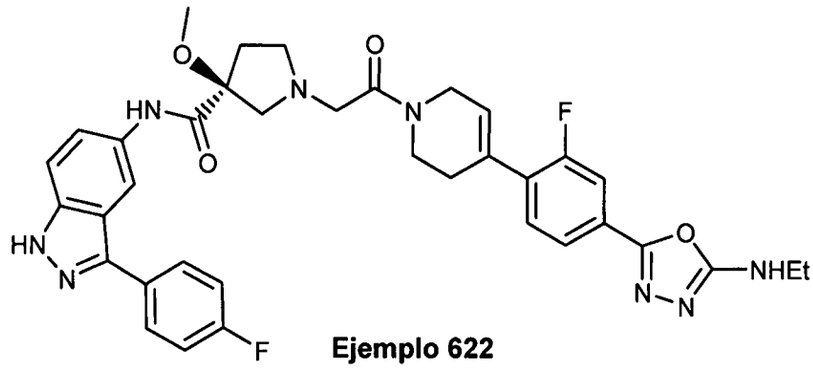


12AQ

El compuesto **12AQ** se preparó a partir de ter—butil éster del ácido 4—(4,4,5,5—tetrametil—[1.3,2]dioxaborolan—2—il)—3,6—dihidro—2*H*—piridin—1—carboxílico usando el procedimiento como el que se describió para la preparación del Compuesto ter—butil éster del ácido 4—(2—fluoro—4—pirimidin—2—il—fenil)—3,6—dihidro—2*H*—piridin—1—carboxílico pero usando 1,4—dibromo—2,5—difluoro—benceno en lugar de 4—bromo—2—fluoro—1—yodobenceno.

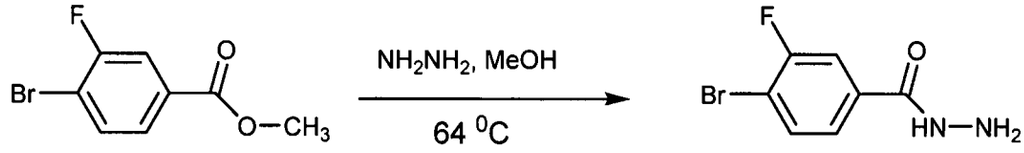
Ejemplo 622

Preparación de [3—(4—fluoro—fenil)—1*H*—indazol—5—il]—amida del ácido 1—(2—{4—[4—(5—Etilamino—[1.3,4]oxadiazol—2—il)—2—fluoro—fenil]—3,6—dihidro—2*H*—piridin—1—il}—2—oxo—etil)—3—metoxi—pirrolidin—3—carboxílico



Ejemplo 622

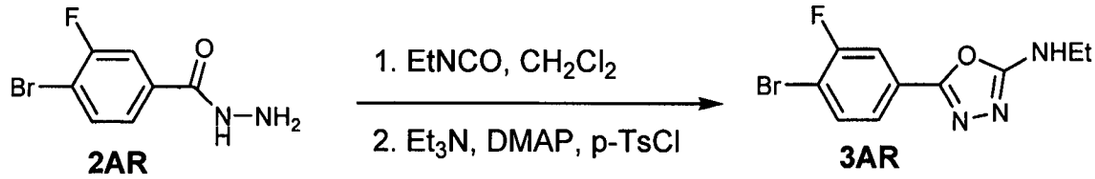
Paso 1: Preparación de hidrazida del ácido 4—Bromo—3—fluoro—benzoico



1AR **2AR**

Una mezcla del Compuesto metil éster del ácido 4—bromo—3—fluoro—benzoico (1 g, 4,29 mmol), hidrato de hidrazina (2,2 ml, 42,9 mmol) y MeOH (20 ml) se calentó a 70 °C durante hasta la mañana siguiente. Se concentró, se diluyó con EtOAc (300 ml) y se lavó con agua (100 ml). La fase orgánica se secó sobre Na_2SO_4, se filtró y se concentró para dar el producto deseado **2AR** (0,9 g, 90%).

Paso 2: Preparación de [5—(4—Bromo—3—fluoro—fenil)—[1.3,4]oxadiazol—2—il]—etil—amina

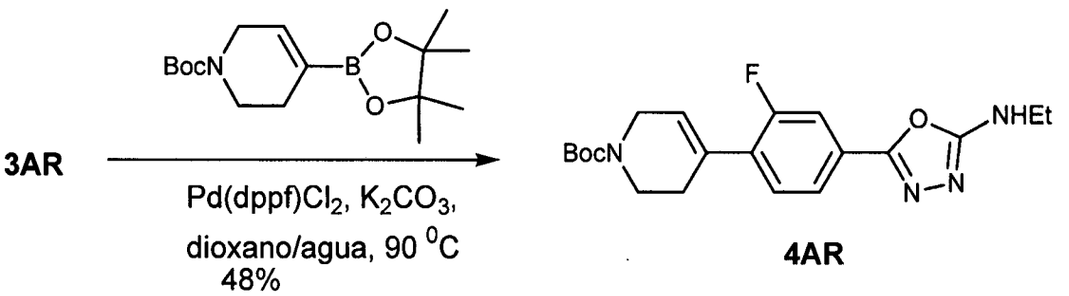


2AR **3AR**

Una mezcla del Compuesto **2AR** (0,9 g, 2,53 mmol), CH_2Cl_2 (5 ml) e isocianato de etilo (0,34 ml, 4,35 mmol) se agitó a temperatura ambiente durante

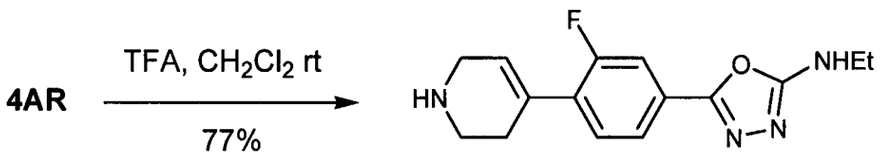
3 horas. A la mezcla de reacción se agregó trietilamina (0,94 ml, 6,7 mmol), DMAP (0,205 g, 1,675 mmol) y una solución de cloruro de p—toluensulfonilo (0,83 g, 4,36 mmol) en CH_2Cl_2 (10 ml). La mezcla de reacción se agitó a temperatura ambiente durante 18 horas. Se diluyó con CH_2Cl_2 (200 ml) y se lavó con agua (100 ml). La fase orgánica se secó sobre Na_2SO_4, se filtró y se concentró. El residuo se purificó sobre gel de sílice eluyendo con 3% MeOH/ CH_2Cl_2 para dar el producto deseado **3AR** (0,56 g, 58%).

Paso 3: Preparación de ter—butil éster del ácido 4—[4—(5—Etilamino—[1.3,4]oxadiazol—2—il)—2—fluoro—fenil]—3,6—dihidro—2*H*—piridin—1—carboxílico



A mezcla del Compuesto **3AR** (0,56 g, 1,96 mmol), ter—butil éster del ácido 4—(4,4,5,5—tetrametil—[1.3,2]dioxaborolan—2—il)—3,6—dihidro—2*H*—piridin—1—carboxílico (0,73 g, 2.35 mmol), carbonato de potasio (0,81 g, 5,88 mmol), $Pd(dppf)Cl_2$ (0,192 g, 0,235 mmol) y 4/1 /dioxano/agua (10 ml) se desgasificó durante 15 minutos. Luego se calentó a 80°C durante hasta la mañana siguiente. Se enfrió hasta temperatura ambiente y se diluyó con EtOAc (200 ml). La fase orgánica se lavó con agua (100 ml), se secó sobre Na_2SO_4, se filtró y se concentró. El residuo se purificó sobre gel de sílice eluyendo con 5% MeOH/CH_2Cl_2 para dar el producto deseado **4AR** (0,44 g, 48%).

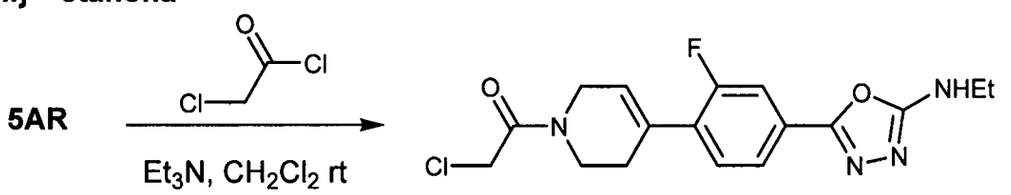
Paso 4: Preparación de Etil—{5—[3—fluoro—4—(1,2,3,6—tetrahidro—piridin—4—il]—[1.3,4]oxadiazol—2il}—amina



5AR

Una mezcla del Compuesto **4AR** (0,44 g, 1.13 mmol), CH_2Cl_2 (20 ml) y TFA (2 ml) se agitó a temperatura ambiente durante 18 horas. Se concentró y se purificó sobre gel de sílice eluyendo con 5% MeOH (NH_3)/ CH_2Cl_2 para dar el producto deseado **5AR** (0,25 g, 77%).

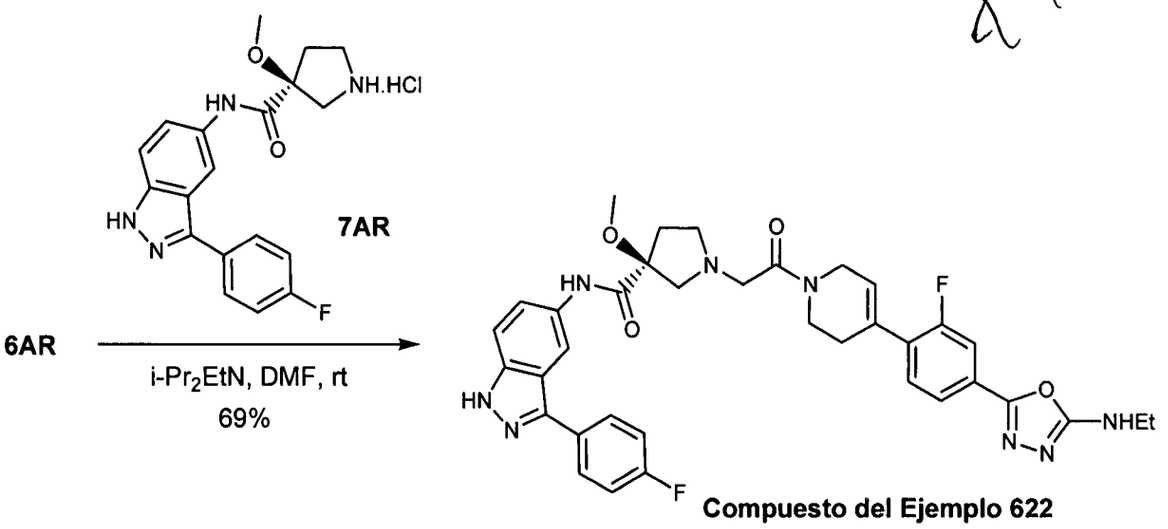
Paso 5: Preparación de 2—Cloro—1—{4—[4—(5—etilamino—[1.3,4]oxadiazol—2—il)—2—fluoro—fenil]—3,6—dihidro—2*H*—piridin—1—il}—etanona



6AR

A una mezcla del Compuesto **5AR** (0,1 g, 0,35 mmol), CH_2Cl_2 (5 ml), MeOH (1 ml) y trietil amina (0,041 ml, 0,29 mmol) a -78°C se agregó cloruro de cloroacetilo (0,021 ml, 0,264 mmol). La mezcla de reacción se agitó a -78°C durante 10 minutos luego se entibió hasta 0°C y se agitó durante 1 hora. Se diluyó con CH_2Cl_2 (100 ml) y se lavó con $NaHCO_3$ acuoso saturado (100 ml). La fase orgánica se secó sobre Na_2SO_4, se filtró y se concentró. El residuo se purificó sobre gel de sílice eluyendo con 2% MeOH/ CH_2Cl_2 para dar el producto deseado **6AR** (0,09 g, 70%).

Paso 6

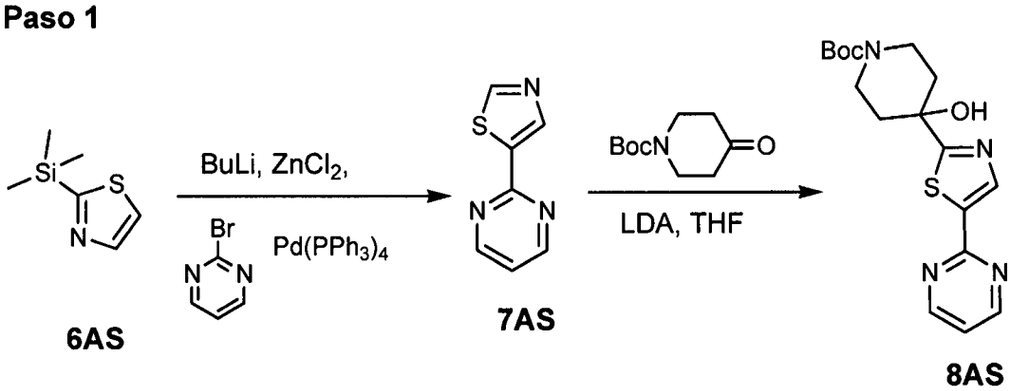


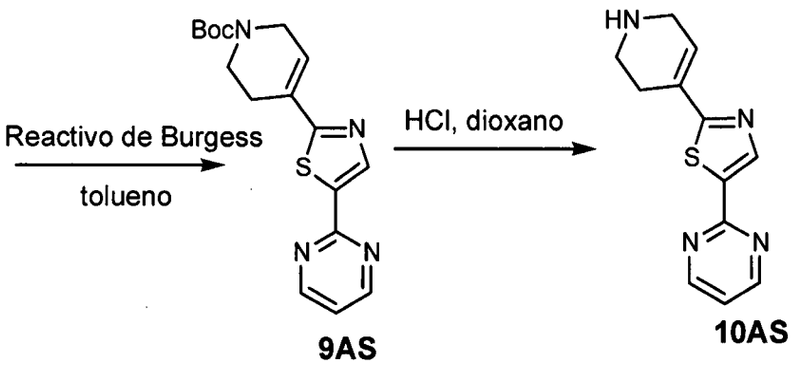
Compuesto del Ejemplo 622

Una mezcla del Compuesto **6AR** (0,09 g, 0,247 mmol), el compuesto **7AR** (0,073 g, 0,2 mmol), DMF (2 ml) y N,N—diisopropiletilamina (0,131 ml, 0,74 mmol) se agitó a temperatura ambiente durante 18 horas. Se diluyó con EtOAc (100 ml) y se lavó con agua (2 x 100 ml). La fase orgánica se secó sobre Na_2SO_4, se filtró y se concentró. El residuo se purificó sobre gel de sílice eluyendo con 5% MeOH (NH_3)/ CH_2Cl_2 para dar el compuesto deseado del Ejemplo **622** (0,11 g, 69%).

Preparación 67

Paso 1





9AS **10AS**

En un balón de 250 ml se colocó butil litio (6,1 ml, 2,5 M en hexanos, 15,2 mmol) en THF a -78°C bajo Ar. A esto se agregó 6 (2.0 g, 12.7 mmol), se agitó durante 15 min y se agregó cloruro de Zinc (38,1 ml, 0,5 M en THF, 19,1 mmol). La mezcla se entibió hasta la temperatura ambiente y se agitó durante 1 hr. A esto se agregó 2—bromopirimidina (2.4 g, 15,2 mmol) y $Pd(PPh_3)_4$ (293 mg, 0,252 mmol). La reacción se calentó hasta el reflujo hasta la mañana siguiente, se enfrió hasta temperatura ambiente y se filtró. El filtrado se repartió entre salmuera y acetato de etilo. La fase orgánica se secó sobre sulfato de sodio y se concentró. La mezcla resultante se purificó por biotage cromatografía en columna para obtener **7AS** (936 mg, 54,2%)

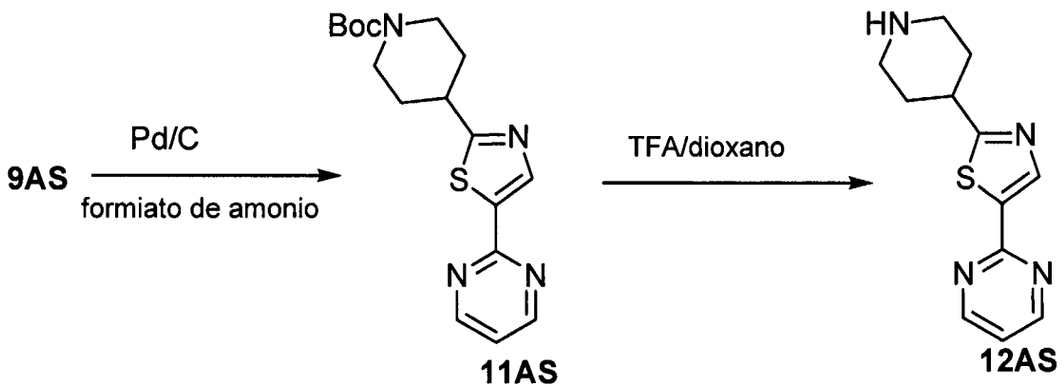
A una solución de **7AS** (710 mg, 4,35 mmol) en THF a -78°C se agregó LDA (2,61 ml, 2.0 M, 5,22 mmol), y luego Boc—4—piperidona (1,04 g, 5,22 mmol). La reacción se agitó a -78°C durante 1 hr, se entibió hasta alcanzar la temperatura ambiente y se desactivó con solución de cloruro de amonio. La mezcla se extrajo con acetato de etilo. La fase orgánica combinada se secó sobre sulfato de sodio y se concentró. El aceite resultante se purificó por cromatografía en columna biotage para obtener **8AS** (1.08 g, 68%)

A una solución de **8AS** (800 mg, 2.21 mmol) en tolueno se agregó reactivo de Burgess (1.09 g, 4,58 mmol). La mezcla se calentó hasta 100°C, se agitó durante 2 hrs, se enfrió hasta temperatura ambiente y se concentró. El residuo se purificó biotage cromatografía en columna para obtener **9AS** (562 mg, 74%)

Paso 2

A **9AS** (560 mg, 1,63 mmol) en un vial de 20 ml se agregó 4 ml de HCl en dioxano (4 M). La reacción se agitó a temperatura ambiente durante 4 hrs y el precipitado se filtró. El sólido resultante se filtró con bomba para obtener **10** (350 mg, 88%)

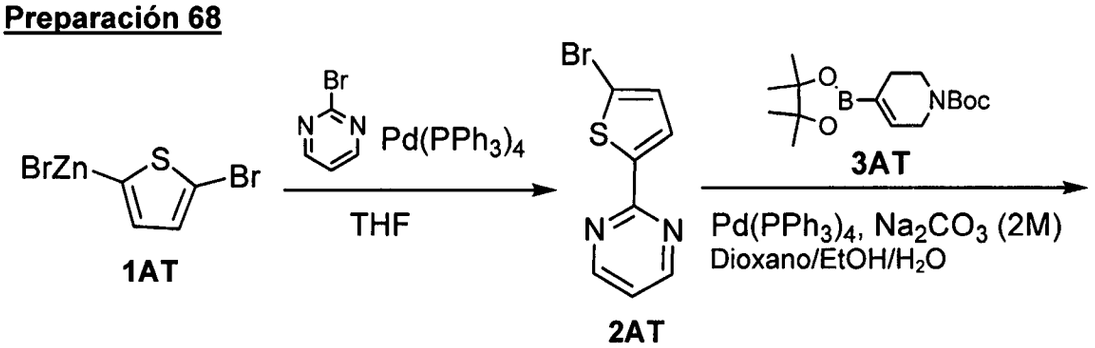
Paso 3

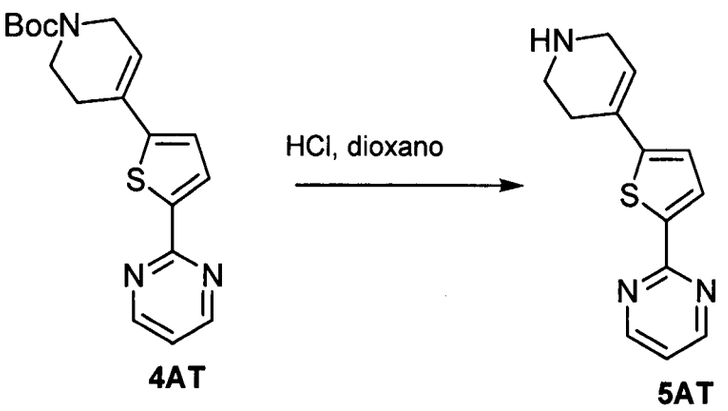


A una solución de **9AS** (100 mg, 0,291 mmol) y formiato de amonio (183 mg, 2.91 mmol) en Metanol se agregó una cantidad catalítica de 10 % Paladio sobre carbono. La mezcla se calentó hasta el reflujo hasta la mañana siguiente, se enfrió hasta temperatura ambiente y se filtró. El filtrado se concentró y el residuo se purificó por cromatografía en columna biotage para obtener **11AS** (52 mg, 52%) y se recuperó 9 (18 mg, 18%)

A **11AS** (52 mg, 0,15 mmol) en 1 ml de DCM se agregó 1 ml de TFA. La reacción se agitó a temperatura ambiente durante 2 hrs y se concentró para obtener el **12AS** en bruto.

Preparación 68





4AT **5AT**

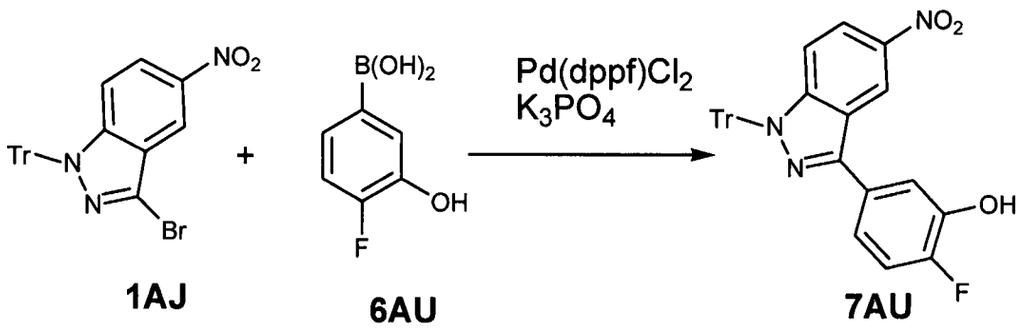
En un balón de 250 ml se colocó **1AT** (0,5 M en THF, 20,0 ml, 10,0 mol). A esto se agregó 2—bromopirimidina (2.00 g, 12.6 mol) y $Pd(PPh_3)_4$ (346 mg, 0,3 mmol). La mezcla se calentó hasta el reflujo bajo Ar hasta la mañana siguiente y se enfrió hasta alcanzar la temperatura ambiente. La reacción se desactivó con solución de cloruro de amonio y se extrajo con acetato de etilo. La fase orgánica combinada se secó sobre sulfato de sodio y se concentró. El aceite resultante se purificó por cromatografía en columna biotage para obtener **2AT** (1,62 g, 69%)

En un recipiente para microondas biotage de 5 ml se colocó **2AT** (136 mg, 0,568 mmol), pinacol éster **3AT** (193 mg, 0,625 mmol), $Pd(PPh_3)_4$ (32.8 mg, 0,0284 mmol) y solución de carbonato de sodio (0,85 ml, 2 M) en dioxano/EtOH/H2O (7:3:2. 2,5 ml) bajo Ar. El recipiente se selló y se calentó en un reactor de microondas a 150°C durante 10 minutos. La reacción se repartió entre acetato de etilo y agua. La fase orgánica se secó sobre sulfato de sodio y se concentró. El aceite resultante se purificó por cromatografía en columna biotage para obtener **4AT** (149 mg, 76%).

A **4AT** (144 mg, 0,420 mmol) en un vial de 20 ml se agregó 2 ml de HCl en dioxano (4 M). La reacción se agitó a temperatura ambiente durante 4 hrs y el precipitado se filtró. El sólido resultante se filtró con bomba para obtener **5AT** (83 mg, 82%)

Preparación 69

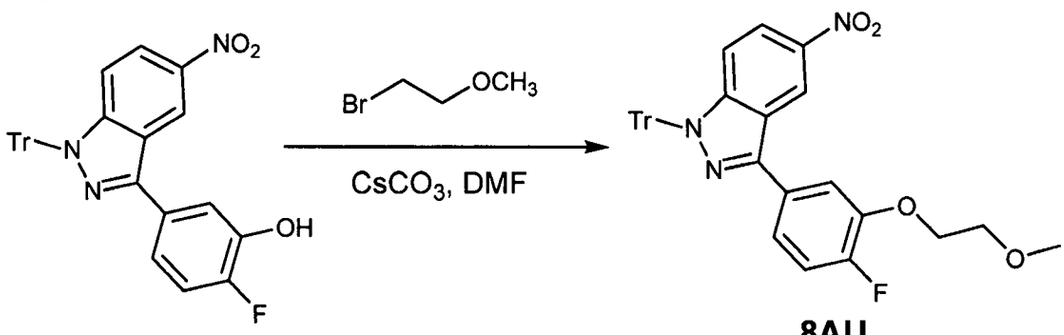
Paso 1: Preparación de 3—(4—Fluoro—3—hidroxifenil)—5—nitro—1—tritil—1H—indazol



1AJ **6AU** **7AU**

Una suspensión de ácido 3—bromo—5—nitro—1—tritil—1H—indazol **1AJ** (10,0 g, 20,68 mmol), 4—fluoro—3—hidroxifenilborónico **6AU** (3,55 g, 22.78 mmol), $Pd(dppf)Cl_2$ (1,6 mg, 1,96 mmol) y K_3PO_4 (10,6 g, 4,99 mmol) en 200 ml de dioxano/H_2O (4/1) se calentó hasta 75°C durante hasta la mañana siguiente. Luego de la eliminación de la mayor parte del solvente, el residuo blanco se diluyó con EtOAc (250 ml) y H2O (60 ml). La mezcla resultante se filtró a través de un taco de Celite. Un adicional de 150 ml de EtOAc se usó para lavar la torta de Celite. Los filtrados se combinaron. La fase acuosa se separó y la fase orgánica se lavó con salmuera, se secó ($MgSO_4$) y se concentró para dar un sólido verde, que se recristalizó a partir de CH_2Cl_2/hexano para dar 3—(4—fluoro—3—hidroxifenil)—5—nitro—1—tritil—1H—indazol **7AU** (8,1 g).

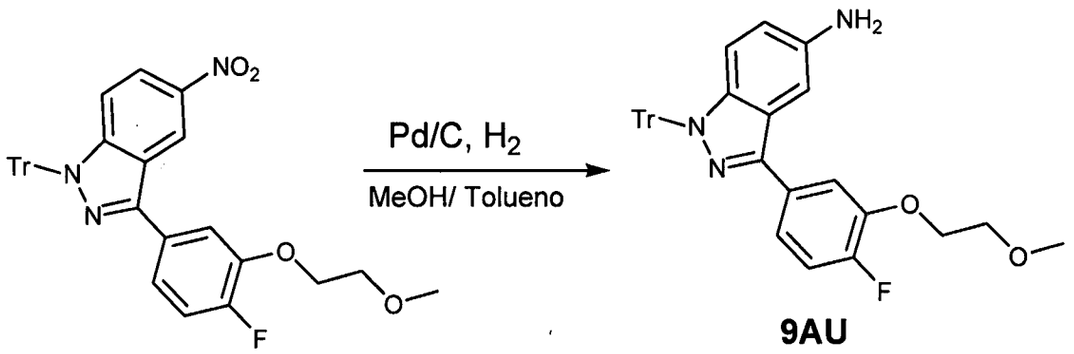
Paso 2: Preparación de 3—[4—Fluoro—3—(2—metoxi—etoxi)—fenil]—1—tritil—5—nitro—1H—indazol



7AU **8AU**

A una mezcla agitada de 3—(4—fluoro—3—hidroxifenil)—5—nitro—1—tritil—1H—indazol **7AU** (2 g, 3,88 mmol) en DMF (25 ml) se agregó $CsCO_3$ 1,9 g, 5,82 mmol) y bromoetilmetil éter (474 µL, 5,04 mmol). La mezcla resultante se agitó a temperatura ambiente durante hasta la mañana siguiente luego se diluyó con EtOAc (300 ml), el cual se lavó con salmuera, se secó ($MgSO_4$) y se concentró. La cromatografía sobre gel de sílice (2:1, hexanos/EtOAc) dio 3—[4—fluoro—3—(2—metoxi—etoxi)—fenil]—1—tritil—5—nitro—1H—indazol **8AU** (1,8 g) como un sólido amarillo.

Paso 3: Preparación de 3—[4—Fluoro—3—(2—metoxi—etoxi)—fenil]—1—tritil—1H—indazol—5—ilamina

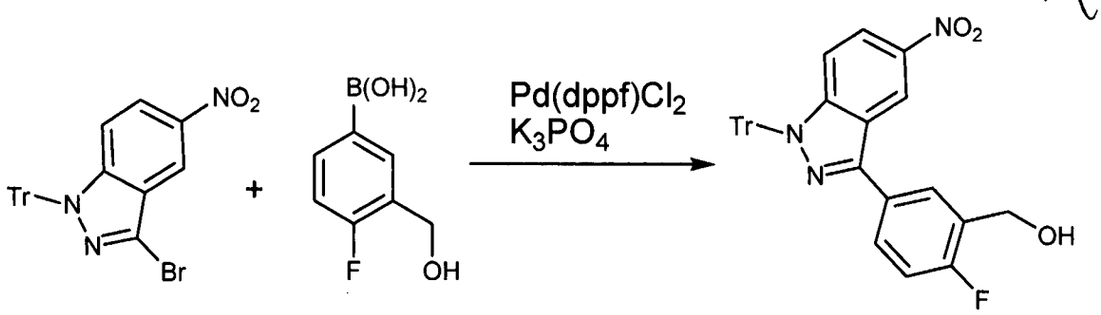


8AU **9AU**

Una suspensión de **8AU** (890 mg, 1,55 mmol) y Cantidad catalítica de Pd sobre carbón (5% en peso, 180 mg) en 45 ml de metanol/tolueno/CH_2Cl_2 (4:4:1) se agitó bajo una atmósfera de hidrógeno durante 2 d y se filtró a través de celite. El filtrado se concentró y se purificó sobre columna de gel de sílice (1:1, hexanos/EtOAc) para dar 3—[4—fluoro—3—(2—metoxi—etoxi)—fenil]—1—tritil—1H—indazol—5—ilamina **9AU** (680 mg) como un sólido blanco.

Preparación 70

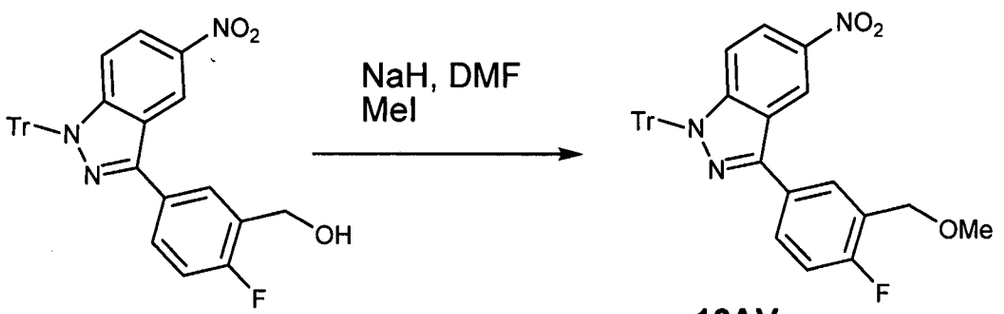
Paso 1: Preparación de 3—(4—Fluoro—3—hidroximetilfenil)—5—nitro—1—tritil—1H—indazol



1AJ **10AV** **11AV**

Una suspensión de 3—bromo—5—nitro—1—tritil—1H—indazol **1** (6 g, 12.41 mmol), ácido 4—fluoro—3—hidroximetilfenilborónico **10AV** (2 g, 12.87 mmol), $Pd(dppf)Cl_2$ (800 mg, 0,98 mmol) y K_3PO_4 (6 g, 28,30 mmol) en 124 ml de dioxano/H_2O (25:6) se calentó hasta 80°C durante hasta la mañana siguiente. Luego de la eliminación de la mayor parte del solvente, el residuo negro se diluyó con EtOAc (250 ml) y H_2O (60 ml). La mezcla resultante se filtró a través de un taco de Celite. Un adicional de 150 ml de EtOAc se usó para lavar la torta de Celite. Los filtrados se combinaron. La fase acuosa se separó y la fase orgánica se lavó con salmuera, se secó ($MgSO_4$) y se concentró para dar 3—(4—fluoro—3—hidroximetilfenil)—5—nitro—1—tritil—1H—indazol **11AV** (8,2 g) en bruto como un sólido amarillo verdoso.

Paso 2: Preparación de 3—[4—Fluoro—3—(2—metoximetil)—fenil]—1—tritil—5—nitro—1H—indazol

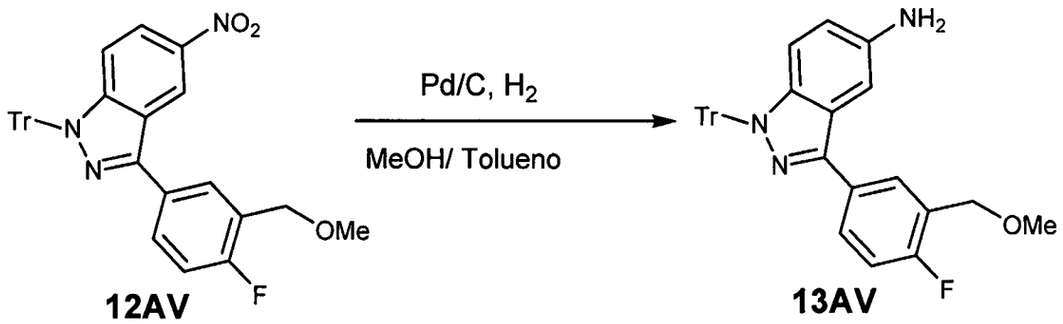


11AV **12AV**

A una solución agitada de 3—(4—fluoro—3—hidroximetilfenil)—5—nitro—1—tritil—1H—indazol **11AV** (5,5 g, 10,4 mmol) en DMF (120 ml) a 0°C bajo N_2 se agregó NaH (60% en aceite mineral, 500 mg, 12,5 mmol) en porciones

durante 10 min. Luego de 15 min, MeI (1 ml, 16,06 mmol) se agregó gota a gota. La mezcla de reacción se agitó a 0°C hasta la ta hasta la mañana siguiente y se desactivó con H_2O. La mezcla resultante se extrajo con EtOAc, se lavó con salmuera, se secó ($MgSO_4$) y se concentró para dar el 3—[4—fluoro—3—(2—metoximetil)—fenil]—1—tritil—5—nitro—1H—indazol en bruto **12AV** (7,2 g) como un sólido amarillo.

Paso 3: Preparación de 3—[4—Fluoro—3—(2—metoximetil)—fenil]—1—tritil—1H—indazol—5—ilamina

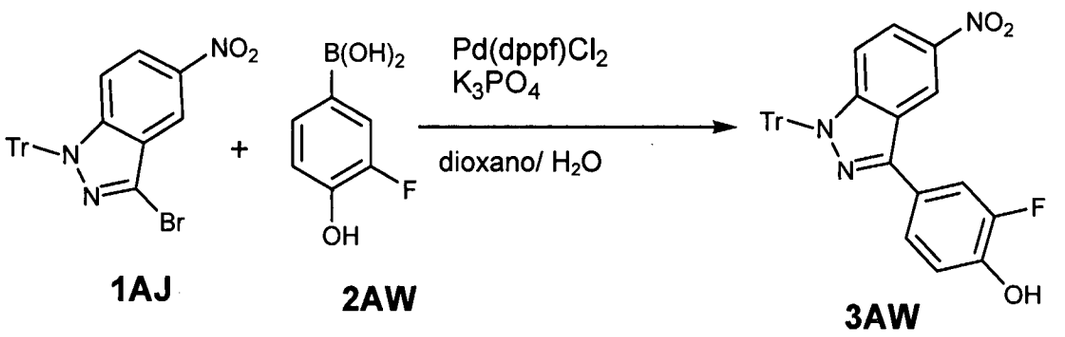


12AV **13AV**

Una suspensión del 3—[4—fluoro—3—(2—metoximetil)—fenil]—1—tritil—5—nitro—1H—indazol en bruto **12AV** (7,2 g) a partir del paso 2 y cantidad catalítica de Pd sobre carbón (5% en peso, 1.3 g) en 150 ml de metanol/tolueno (1:1) se agitó bajo una atmósfera de hidrógeno hasta la mañana siguiente y se filtró a través de celite. El filtrado se concentró y se purificó sobre columna de gel de sílice (4:1, hexanos/EtOAc) para dar 3—[4—fluoro—3—(2—metoximetil)—fenil]—1—tritil—1H—indazol—5—ilamina **13AV** (5 g) como un sólido blanco.

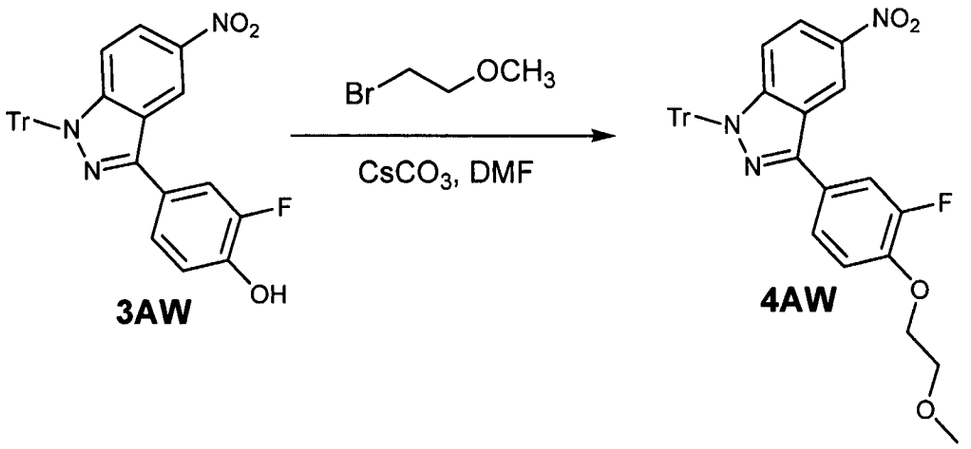
Preparación 71

Paso 1: Preparación de 3—(3—Fluoro—4—hidroxifenil)—5—nitro—1—tritil—1H—indazol



Una suspensión de 3—bromo—5—nitro—1—tritil—1H—indazol **1AJ** (10,0 g, 20,68 mmol), 3—fluoro—4—hidroxifenilborónico ácido **2AW** (3,55 g, 22.78 mmol), $Pd(dppf)Cl_2$ (1,6 g, 1,96 mmol) y K_3PO_4 (10,6 g, 4,99 mmol) in 200 ml de dioxano/H_2O (4/1) se calentó hasta 75°C durante hasta la mañana siguiente. Luego de la eliminación de la mayor parte del solvente, el residuo negro se diluyó con EtOAc (250 ml) y H_2O (60 ml). La mezcla resultante se filtró a través un taco de Celite. Se usó un adicional de 150 ml de EtOAc para lavar la torta de Celite. Los filtrados se combinaron. La fase acuosa se separó y la fase orgánica se lavó con salmuera, se secó ($MgSO_4$) y se concentró para dar un sólido verde, que se recristalizó a partir de CH_2Cl_2/hexano para dar 3—(3—fluoro—4—hidroxifenil)—5—nitro—1—tritil—1H—indazol **3AW** (8,1 g).

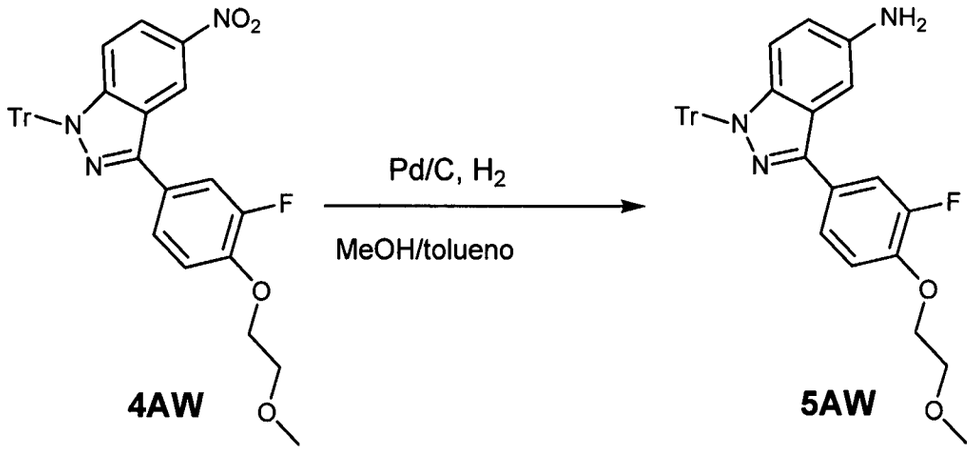
Paso 2: Preparación de 3—[3—Fluoro—4—(2—metoxi—etoxi)—fenil]—1—tritil—5—nitro—1H—indazol



A una mezcla agitada de 3—(3—fluoro—4—hidroxifenil)—5—nitro—1—tritil—1H—indazol **3AW** (3 g, 5,82 mmol) en DMF (40 ml) se agregó $CsCO_3$ (2.85

g, 8,75 mmol) y bromoetilmetil éter (711 µL, 7,57 mmol). La mezcla resultante se agitó a temperatura ambiente durante hasta la mañana siguiente luego se diluyó con EtOAc (300 ml), que se lavó con salmuera, se secó ($MgSO_4$) y se concentró. La cromatografía sobre gel de sílice (2:1, hexanos/EtOAc) dio 3—[3—fluoro—4—(2—metoxi—etoxi)—fenil]—1—tritil—5—nitro—1H—indazol **4AW** (2.8 g).

Paso 3: Preparación de 3—[3—Fluoro—4—(2—metoxi—etoxi)—fenil]—1—tritil—1H—indazol—5—ilamina

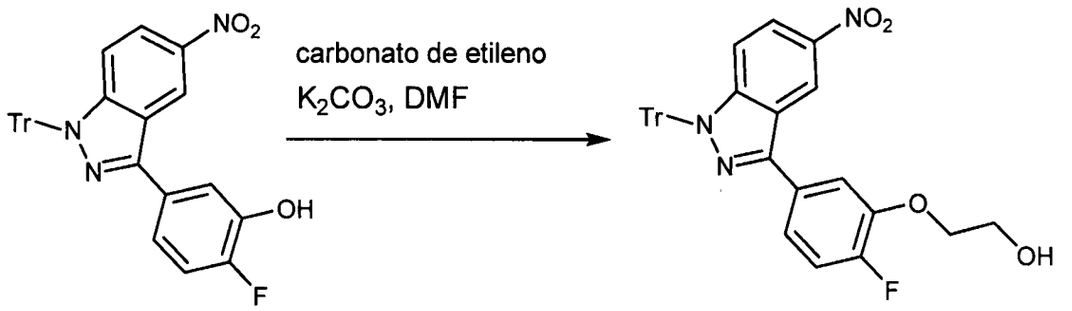


4AW **5AW**

Una suspensión de 3—[3—fluoro—4—(2—metoxi—etoxi)—fenil]—1—tritil—5—nitro—1H—indazol **4** (2.8 g, 4,88 mmol) y cantidad catalítica de Pd sobre carbón (5% en peso, 0,5 g) en 120 ml de metanol/tolueno (1:1) se agitó bajo a atmósfera de hidrógeno durante 6 h y se filtró a través de celite. El filtrado se concentró para proveer 3—[3—fluoro—4—(2—metoxi—etoxi)—fenil]—1—tritil—1H—indazol—5—ilamina **5** (2.6 g) como un sólido blancuzco.

Preparación 72

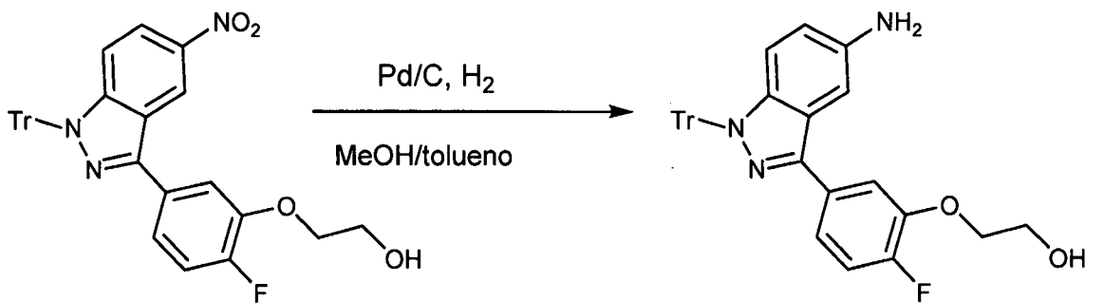
Paso 1: Preparación de 3—[4—Fluoro—3—(2—hidroxi—etoxi)—fenil]—1—tritil—5—nitro—1H—indazol



7AU **14AX**

Una mezcla de 3—(4—fluoro—3—hidroxifenil)—5—nitro—1—tritil—1H—indazol **7AU** (1,25 g, 2.42 mmol), K_2CO_3 (402 mg, 2.91 mmol) y carbonato de etileno (2,6 ml, 24,00 mmol) en DMF (10 ml) se agitó en un tubo sellado a 160°C durante 4 h y se enfrió hasta rt. Se agregó H_2O para desactivar la reacción. La mezcla resultante se extrajo con EtOAc, la cual se lavó con H_2O, salmuera, se secó ($MgSO_4$) y se concentró para dar un aceite amarillo. La cromatografía sobre gel de sílice (4:1, hexanos/EtOAc) dio 3—[4—fluoro—3—(2—hidroxi—etoxi)—fenil]—1—tritil—5—nitro—1H—indazol **14AX** (1,4 g) como un aceite amarillo.

Paso 2: Preparación de 3—[4—Fluoro—3—(2—hidroxi—etoxi)—fenil]—1—tritil—1H—indazol—5—ilamina

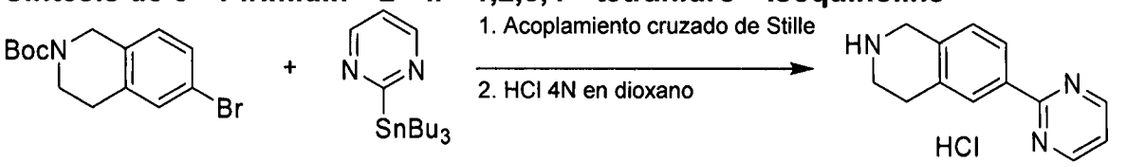


14AX **15AX**

Una suspensión de 3—[4—fluoro—3—(2—hidroxi—etoxi)—fenil]—1—tritil—5—nitro—1H—indazol **14AX** (1,5 g) y cantidad catalítica de Pd sobre carbón (5% en peso, 300 mg) in 40 ml de metanol/tolueno (1:1) se agitó bajo a atmósfera de hidrógeno durante 1 d y se filtró a través de celite. El filtrado se concentró para proveer 3—[4—fluoro—3—(2—hidroxi—etoxi)—fenil]—1—tritil—1H—indazol—5—ilamina **15AX** (1,4 g) como un sólido blancuzco.

Preparación 73

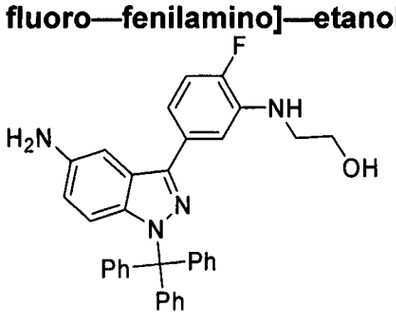
Síntesis de 6—Pirimidin—2—il—1,2,3,4—tetrahidro—isoquinoline



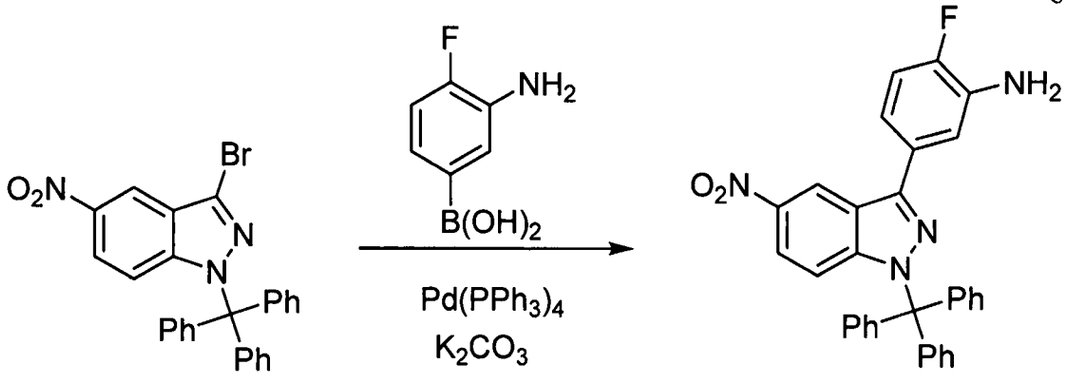
A un tubo de Schlenk se cargaron $Pd_2(dba)_3$ (10 mg, 0,01 mmol), bis(tri—*ter*—butilfosfin)paladio (20 mg, 0,04 mmol), CuI (16 mg, 0,08 mmol) y CsF (334 mg, 2.2 mmol). El tubo se evacuó bajo alto vacío y se llenó nuevamente con nitrógeno durante tres ciclos. Se introdujo DMF (2 ml), seguido de 2—tributilestanilpirimidina (537 mg, 1,4 mmol). El tubo se selló con una tapa de Teflón y la mezcla de reacción se calentó con agitación a 120^0C durante 2 horas. Luego de enfriar, la mezcla se filtró a través de Celite, se lavó con acetato de etilo. El filtrado se lavó con agua tres veces, salmuera y se secó ($MgSO_4$). Luego de la concentración el residuo se purificó sobre gel de sílice eluyendo con acetato de etilo en hexanos (0—100%) para dar ter—butil éster del ácido 6—pirimidin—2—il—3, 4—dihidro—1*H*—isoquinolin—2—carboxílico (28 mg). El compuesto se trató con HCl 4N en dioxano durante 30 minutos. Luego de la concentración se obtuvo el compuesto del título como una sal de clorhidrato.

Preparación 74

Preparación de 2—[5—(5—amino—1—tritil—1*H*—indazol—3—il)—2—fluoro—fenilamino]—etanol



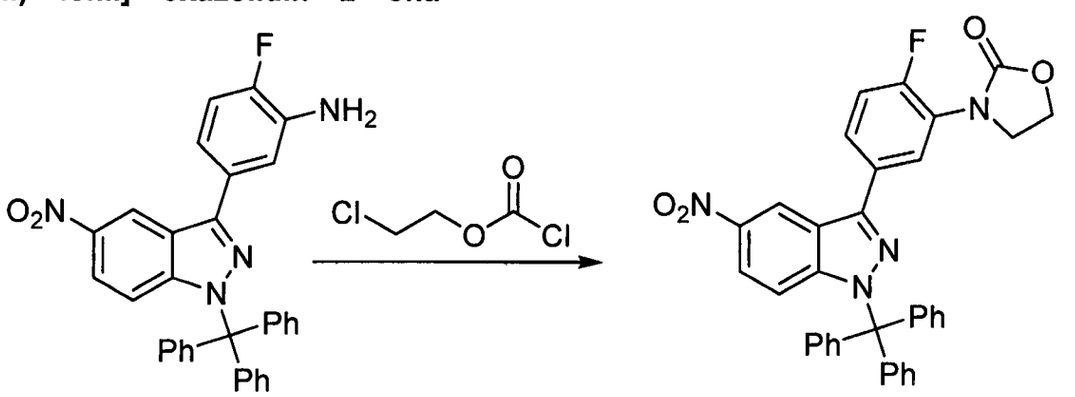
Paso 1: Preparación de 2—fluoro—5—(5—nitro—1—tritil—1*H*—indazol—3—il)—fenilamina



1AJ **2AY**

A un tubo de presión se cargaron compuesto **1AJ** (1g, 2.1 mmol), ácido 3—amino—4—fluoro—fenilborónico (448 mg, 2.89 mmol), $Pd(PPh_3)_4$ (120 mg, 0,1 mmol), K_2CO_3 (1,4 g, 10,1 mmol), DME (8 ml) y agua (2 ml). La mezcla resultante se desgasificó con nitrógeno durante 20 segundos y el tubo se selló con una tapa de Teflón, y se calentó a 100°C con agitación hasta la mañana siguiente. Luego de enfriar la mezcla de reacción se diluyó con acetato de etilo, la fase orgánica se aisló, se lavó con salmuera. Luego de la concentración, el residuo se purificó sobre gel de sílice. La elución con acetato de etilo en hexanos (0—70%) dio el compuesto **2AJ** (1g).

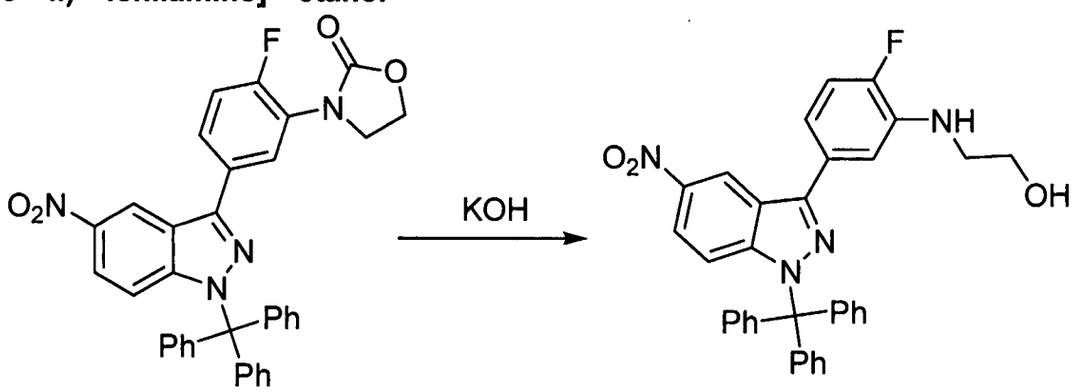
Paso 2: Síntesis de 3—[2—fluoro—5—(5—nitro—1—tritil—1*H*—indazol—3—il)—fenil]—oxazolidin—2—ona



2AY **3AY**

A una mezcla del Compuesto **2AY** (1g, 1,95 mmol), Cs_2CO_3 (1.2 g, 3,68 mmol) in acetonitrilo (20 ml) se agregó cloroformiato de 2—cloroetilo (200 µl, 1,94 mmol) y la mezcla resultante se reflujó durante 20 minutos. Luego la incorporación de cloroformiato de 2—cloroetilo (150 µl) la mezcla de reacción se dejó reflujar hasta la mañana siguiente. Se agregó una solución de 40% KOH y la mezcla se reflujó un adicional de 2 horas. Luego de enfriar la mezcla de reacción se diluyó con acetato de etilo y agua, y la fase acuosa se separó y se extrajo con acetato de etilo dos veces. Las fases orgánicas combinadas se lavaron con salmuera y se secaron ($MgSO_4$). Luego de la concentración el residuo se purificó sobre gel de sílice eluyendo con acetato de etilo en hexanos (0-40%) para dar compuesto **3AY** (1g).

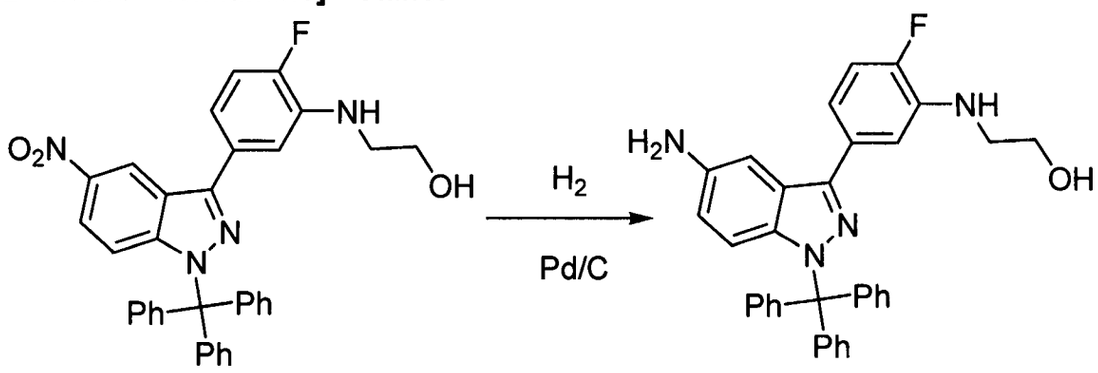
Paso 3: Preparación de 2—[2—fluoro—5—(5—nitro—1—tritil—1*H*—indazol—3—il)—fenilamino]—etanol



3AY **4AY**

Una mezcla del Compuesto **3AY** (658 mg) en DME (15 ml), MeOH (6 ml) y 40% KOH (4 ml) se reflujó hasta la mañana siguiente. Luego de enfriar, la mezcla se diluyó con acetato de etilo, la fase orgánica se separó, se lavó con salmuera y se secó ($MgSO_4$). Luego de la concentración el residuo se purificó sobre gel de sílice eluyendo con acetato de etilo en hexanos (0—100%) para dar compuesto **4AY** (559 mg).

Paso 4: Preparación de 2—[5—(5—amino—1—tritil—1*H*—indazol—3—il)—2—fluoro—fenilamino]—etanol

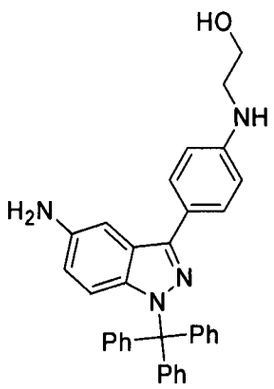


4AY **5AY**

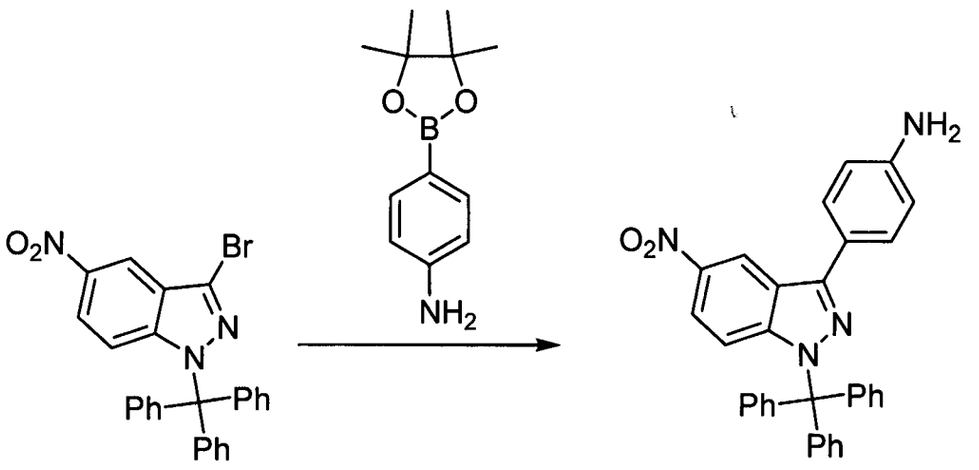
Una mezcla del Compuesto **4AY** (173 mg), Pd/C al 10% (50 mg) en acetato de etilo (10 ml) se agitó bajo hidrógeno (presión en globo) hasta la mañana siguiente. Luego de la filtración y concentración, el residuo se purificó sobre sílice eluyendo con acetato de etilo para proveer el Compuesto **5AY** (81 mg).

Preparación 75

Síntesis de 2—[4—(5—amino—1—tritil—1*H*—indazol—3—il)—fenilamino]—etanol



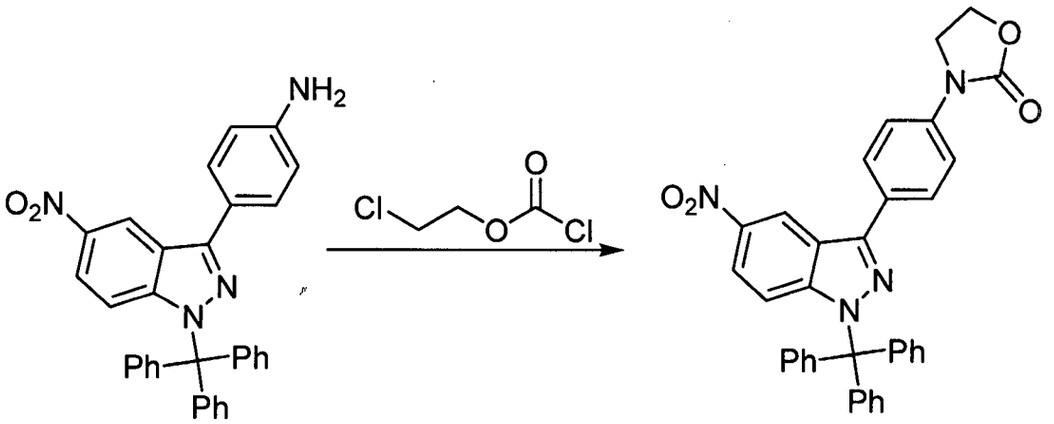
Paso 1: Preparación de 4—(5—nitro—1—tritil—1*H*—indazol—3—il)—fenilamina



1AJ **2AZ**

A un tubo de presión se cargaron con compuesto **1AJ** (1g, 2.1 mmol), 4—(4,4,5,5—tetrametil—[1.3,2]dioxaborolan—2—il)—fenilamina (0,635 g, 2.9 mmol), $Pd(PPh_3)_4$ (0,12 g, 0,1 mmol), K_2CO_3 (1,4 g, 10,1 mmol), DME (8 ml) y agua (2 ml). La mezcla resultante se desgasificó con nitrógeno brevemente y el tubo se selló con una tapa de Teflón, y se calentó a 100ºC con agitación hasta la mañana siguiente. Luego de enfriar, la mezcla de reacción se diluyó con acetato de etilo, la fase orgánica se aisló, se lavó con salmuera. Luego de la concentración, el residuo se purificó sobre gel de sílice. La elución con acetato de etilo en hexanos (0—70%) dio compuesto **2AZ** (0,956 g).

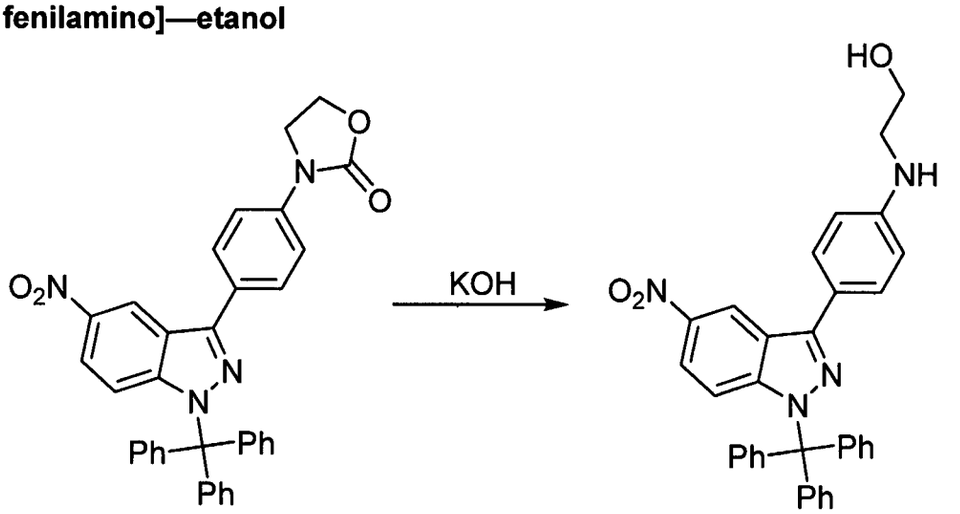
Paso 2: Preparación de 3—[4—(5—nitro—1—tritil—1*H*—indazol—3—il)—fenil]—oxazolidin—2—ona



2AZ **3AZ**

A una mezcla del Compuesto **2AZ** (409 mg, 0,82 mmol), 10% NaOH (2 ml) in DME (8 ml) se agregó cloroformiato de 2—cloroetilo (102 µl, 1 mmol) y la mezcla resultante se agitó a temperatura ambiente durante hasta la mañana siguiente. La mezcla se diluyó con acetato de etilo y agua, y la fase acuosa se separó y se extrajo con acetato de etilo dos veces. Las fases orgánicas combinadas se lavaron con salmuera y se secaron ($MgSO_4$). Luego de la concentración el residuo se purificó sobre gel de sílice eluyendo con acetato de etilo en hexanos (0—80%) para dar compuesto **3AZ** (340 mg).

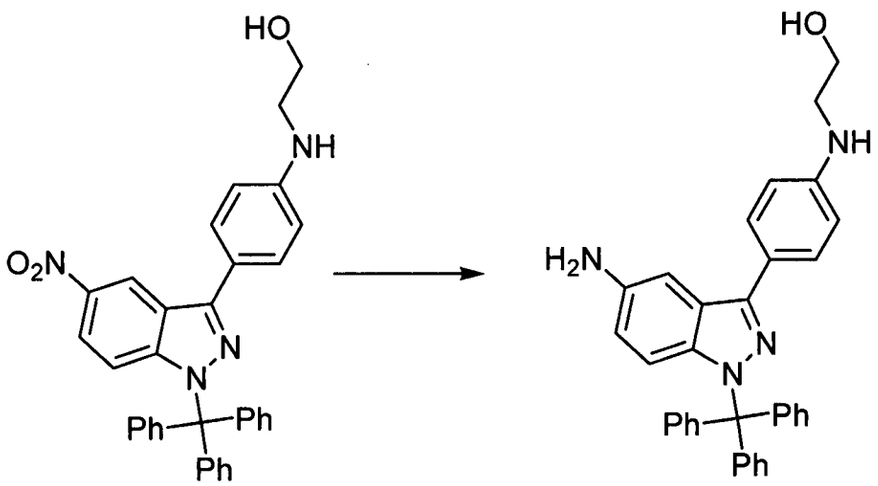
Paso 3: Preparación de 2—[4—(5—nitro—1—tritil—1*H*—indazol—3—il)—fenilamino]—etanol



3AZ **4AZ**

Una mezcla del Compuesto **3AZ** (340 mg) in DME (6 ml), MeOH (4 ml) y 40% KOH (2 ml) se reflujó durante dos horas. Luego de enfriar, solventes se eliminaron, se diluyeron con agua, se extrajeron con diclorometano tres veces, las fases orgánicas combinadas se lavaron con salmuera y se secaron ($MgSO_4$). Luego de la concentración el residuo se purificó sobre gel de sílice eluyendo con acetato de etilo en hexanos (0—100%) para dar el compuesto **4AZ** (280 mg).

Paso 4: Preparación de 2—[4—(5—amino—1—tritil—1*H*—indazol—3—il)—fenilamino]—etanol

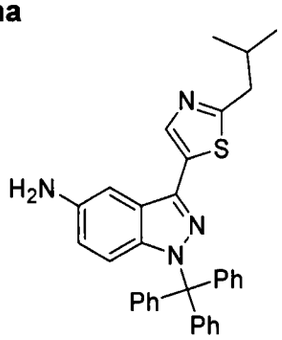


4AZ **5AZ**

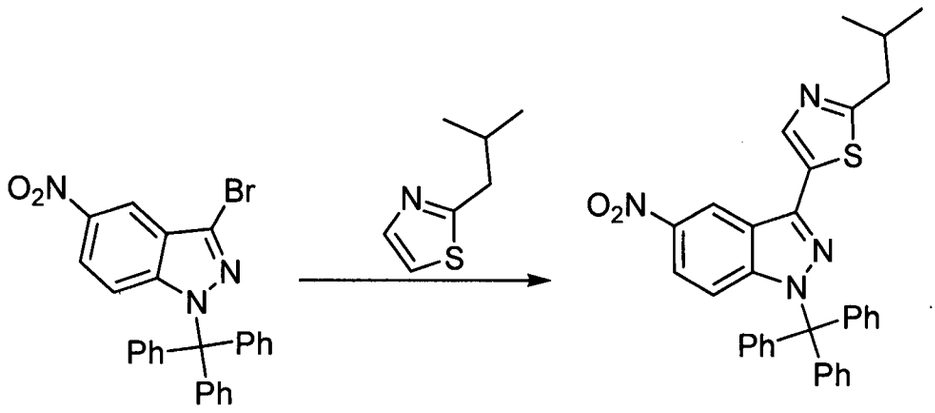
Una mezcla del Compuesto **4AZ** (280 mg), Pd/C al 10% (70 mg) in etanol (10 ml) se agitó a 45^{0}C bajo hidrógeno (presión en globo) hasta la mañana siguiente. Luego de la filtración y concentración, el residuo se purificó sobre sílice eluyendo con acetato de etilo para proveer el Compuesto **5AZ** (224 mg).

Preparación 76

Síntesis de 3—(2—Isobutil—tiazol—5—il)—1—tritil—1*H*—indazol—5—ilamina



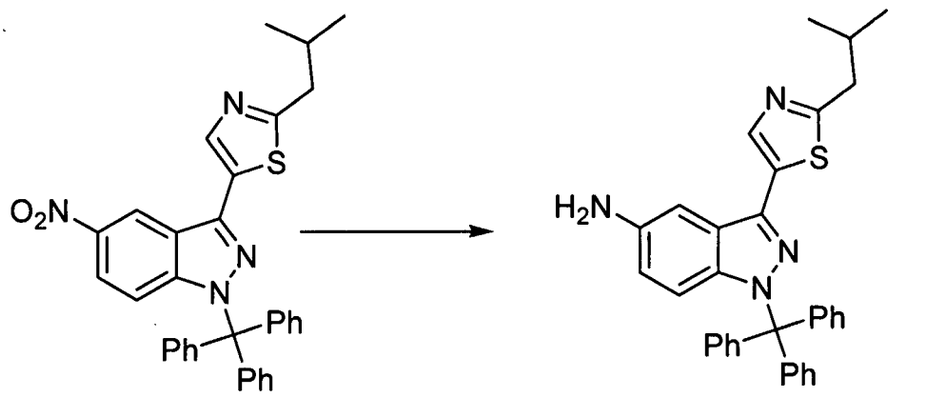
Paso 1: Preparación de 3—(2—Isobutil—tiazol—5—il)—5—nitro—1—tritil—1*H*—indazol



1AJ **2BA**

A un tubo de presión se cargaron compuesto **1AJ** (194 mg, 0,4 mmol), $Pd(OAc)_2$ (90 mg, 0,4 mmol), (2—bifenil)—di—*ter*—butilfosfina (12 mg, 0,1 mmol), C_2CO_3 (313 mg, 0,96 mmol) y el tubo se evacuó con vacío y se llenó nuevamente con nitrógeno. Se introdujo dioxano (4 ml), seguido de 2—isobutiltiazol (114 µl, 0,8 mmol). El tubo se selló y se calentó a 100 ^{0}C con agitación hasta la mañana siguiente. Luego de enfriar la mezcla de reacción se filtró a través de Celite, se lavó con acetato de etilo varias veces. El filtrado se concentró y el residuo se purificó sobre gel de sílice. La elución con acetato de etilo en hexanos (0—30%) dio compuesto **2BA** (124 mg).

Paso 2: Preparación de 3—(2—Isobutil—tiazol—5—il)—1—tritil—1*H*—indazol—5—ilamina



2BA **3BA**

Organización y
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PATENTE DE INVENCIÓN

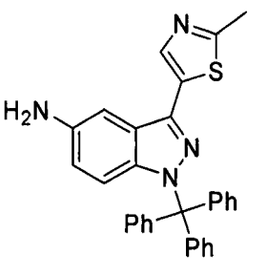
09-139231

A/A

Una mezcla del Compuesto **2BA** (180 mg), Pd/C al 10% (50 mg) en acetato de etilo (8 ml) se agitó a 45^{0}C bajo hidrógeno (presión en globo) hasta la mañana siguiente. Luego de la filtración y concentración, el residuo se purificó sobre sílice eluyendo con acetato de etilo para proveer el Compuesto **3BA** (75 mg).

Preparación 77

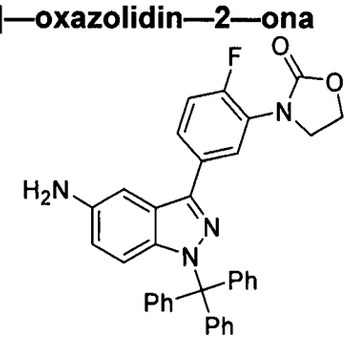
Síntesis de 3—(2—metil—tiazol—5—il)—1—tritil—1*H*—indazol—5—ilamina

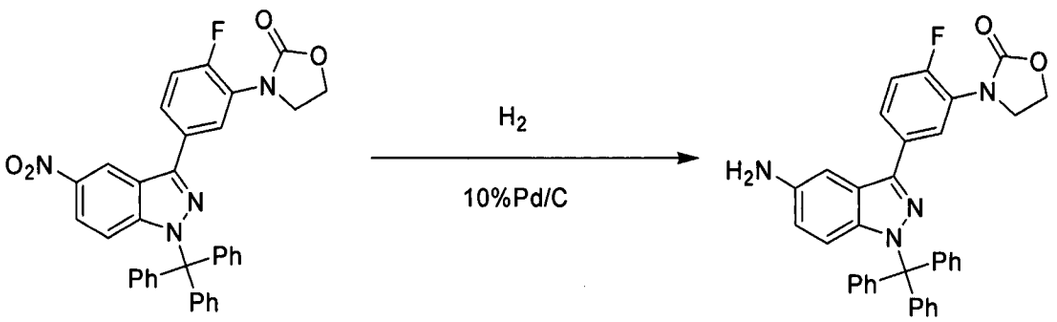


La Preparación de 3—(2—metil—tiazol—5—il)—1—tritil—1*H*—indazol—5—ilamina fue similar a la de 3—(2—isobutil—tiazol—5—il)—1—tritil—1*H*—indazol—5—ilamina como se ilustró con anterioridad excepto que usando 2—metiltiazol en la reacción de acoplamiento cruzado.

Preparación 78

Síntesis de 3—[5—(5—amino—1—tritil—1H—indazol—3—il)—2—fluoro—fenil]—oxazolidin—2—ona

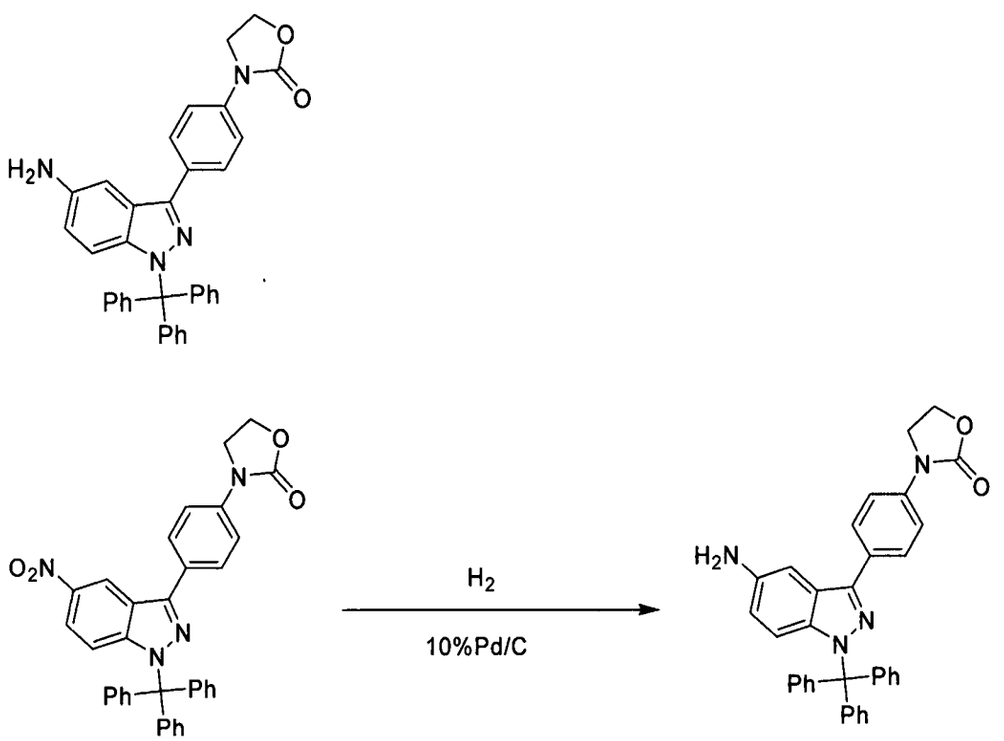




La hidrogenación de 3—[2—fluoro—5—(5—nitro—1—tritil—1*H*—indazol—3—il)—fenil]—oxazolidin—2—ona se condujo en un modo similar a los otros ejemplos ilustrados anteriormente.

Preparación 79

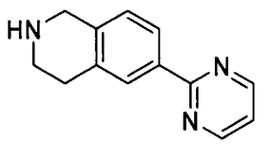
Síntesis de 3—[4—(5—amino—1—tritil—1*H*—indazol—3—il)—fenil]—oxazolidin—2—ona

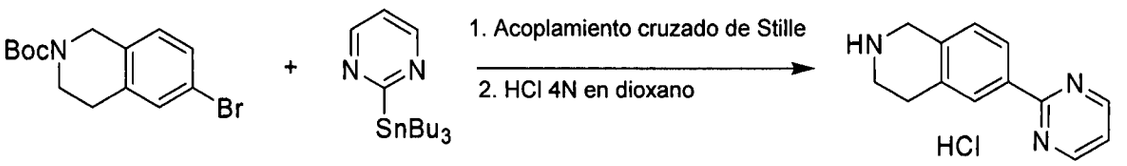


La hidrogenación de 3—[4—(5—nitro—1—tritil—1*H*—indazol—3—il)—fenil]—oxazolidin—2—ona se condujo en un modo similar a los otros ejemplos ilustrados anteriormente.

Preparación 80

Síntesis de 6—Pirimidin—2—il—1,2,3,4—tetrahidro—isoquinolina

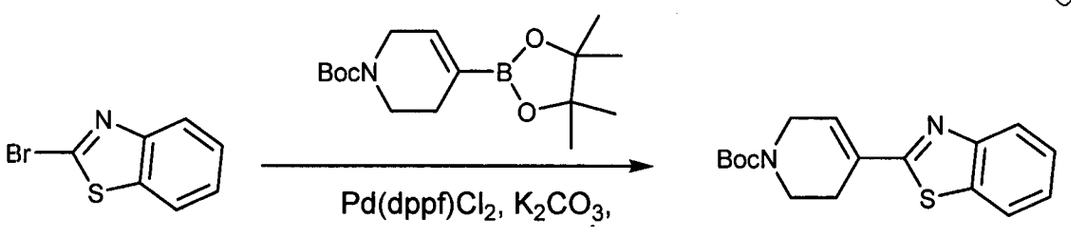




A un tubo de Shernk se cargaron $Pd_2(dba)_3$ (10 mg, 0,01 mmol), bis(tri—*ter*—butilfosfin)paladio (20 mg, 0,04 mmol), CuI (16 mg, 0,08 mmol) y CsF (334 mg, 2.2 mmol). El tubo se evacuó bajo alto vacío y se llenó nuevamente con nitrógeno durante tres ciclos. Se introdujo DMF (2 ml), seguido de 2—tributilestanilpirimidina (537 mg, 1,4 mmol). El tubo se selló con una tapa de Teflón y la mezcla de reacción se calentó con agitación a 120°C durante 2 horas. Luego de enfriar, la mezcla se filtró a través de Celite, se lavó con acetato de etilo. El filtrado se lavó con agua tres veces, salmuera y se secó ($MgSO_4$). Luego de la concentración el residuo se purificó sobre gel de sílice eluyendo con acetato de etilo en hexanos (0—100%) para dar ter—butil éster del ácido 6—pirimidin—2—il—3, 4—dihidro—1*H*—isoquinolina—2—carboxílico (28 mg). El compuesto se trató con HCl 4N en dioxano durante 30 minutos. Luego de la concentración se obtuvo el compuesto del título como la sal de clorhidrato.

Preparación 81

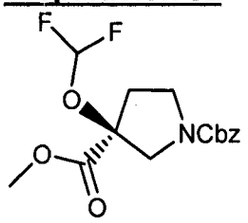
Preparación de ter—butil éster del ácido 4—Benzotiazol—2—il—3,6—dihidro—2*H*—piridin—1—carboxílico (Compuesto 21BB)



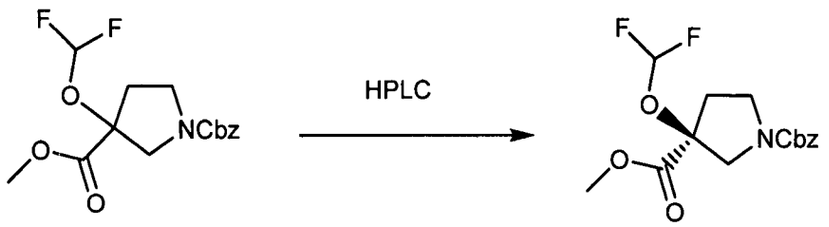
22BB **21BB**

A mezcla de 2—bromo—benzotiazol (0,38 g, 1.1 mmol), 4—(4,4,5,5—tetrametil—[1.3,2]dioxaborolan—2—il)—3,6—dihidro—2*H*—piridin—1—carboxílico ter—butil éster del ácido (0,5 g, 1,62 mmol), carbonato de potasio (0,67 g, 4,85 mmol), $Pd(dppf)Cl_2$ (0,132 g, 0,16 mmol) y 4/1 /dioxano/agua (10 ml) se desgasificó durante 15 minutos. Luego se calentó a 90°C durante hasta la mañana siguiente. Se enfrió hasta temperatura ambiente y se diluyó con EtOAc (200 ml). La fase orgánica se lavó con agua (100 ml), se secó sobre Na_2SO_4, se filtró y se concentró. El residuo se purificó sobre gel de sílice para dar el producto deseado **21BB** (0,4 g, 78%).

Preparación 82



16BC



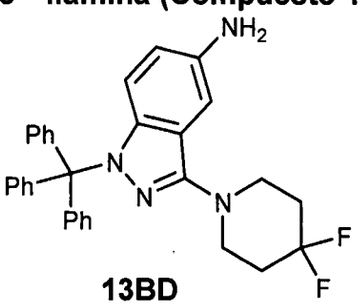
17BC **16BC**

El compuesto **17BC** se prepara siguiendo un procedimiento similar al de la Preparación 37 Pasos 1 hasta 4 por la sustitución de bencil éster del ácido 3—oxo—pirrolidin—1—carboxílico en lugar de ter—butil éster del ácido 3—oxo—

pirrolidin—1—carboxílico en el Paso 1 de la preparación 37. El Compuesto **17BC** se separó en HPLC usando columna ChiralCel AS eluyendo con 25% isopropanol/ 75% hexano. El primer pico (tiempo de retención 46 minutos) fue el producto deseado **16BC**.

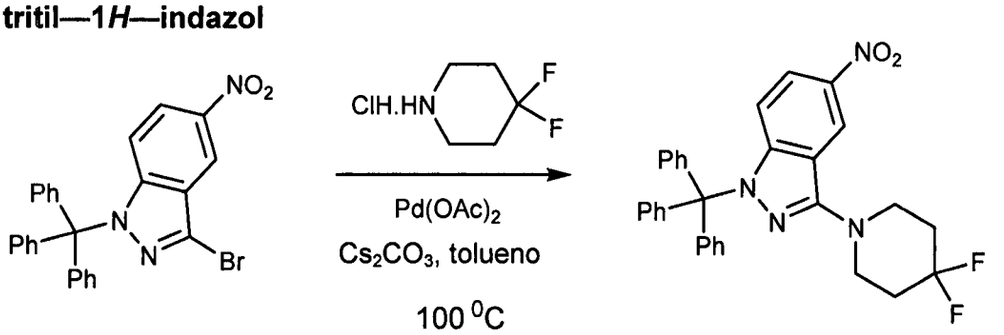
Preparación 83

Preparación de 3—(4,4—Difluoro—piperidin—1—il)—1—tritil—1*H*—indazol—5—ilamina (Compuesto 13BD)



13BD

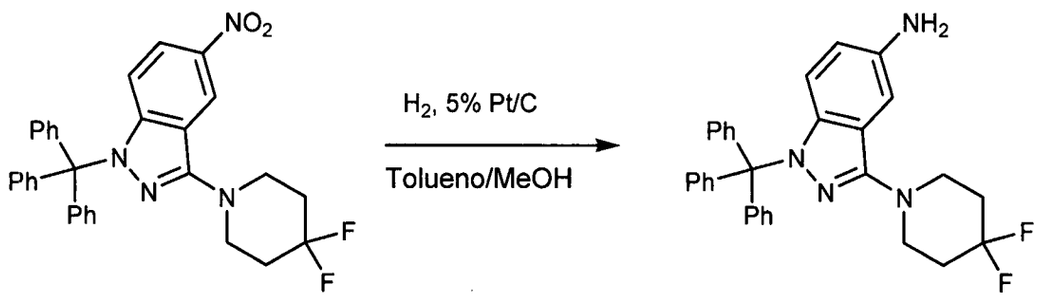
Paso 1: Preparación de 3—(4,4—Difluoro—piperidin—1—il)—5—nitro—1—tritil—1*H*—indazol



14BD **15BD**

El compuesto 14BD se convirtió en el Compuesto 15BD usando el procedimiento como el que se describió para la preparación del Compuesto 4AD (Preparación 49 Paso 2) a partir del Compuesto 2AD (Preparación 49 Paso 2).

Paso 2

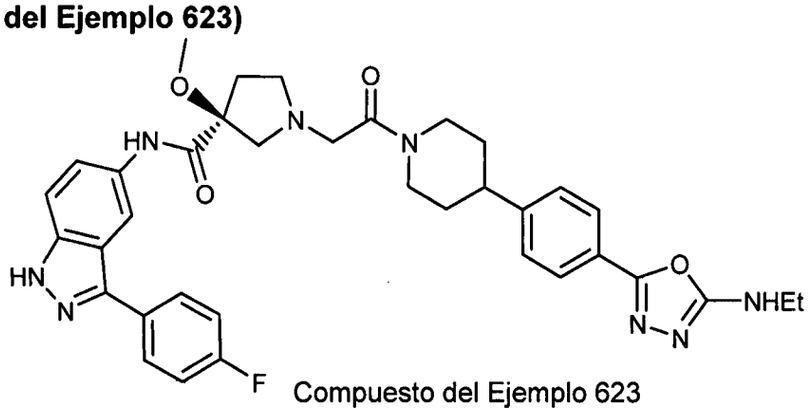


15BD **13BD**

Una mezcla del Compuesto **15BD** (1,6 g, 3,1 mmol), 1/1 tolueno/MeOH (25 ml) y 5% Pt/C (0,726 mg) se agitó bajo hidrógeno a temperatura ambiente durante 18 horas. La mezcla de reacción se filtró sobre celite y el filtrado se concentró. El residuo se purificó sobre gel de sílice eluyendo con 5% $MeOH/CH_2Cl_2$ para dar el producto deseado **13BD** (1.38 g, 91%).

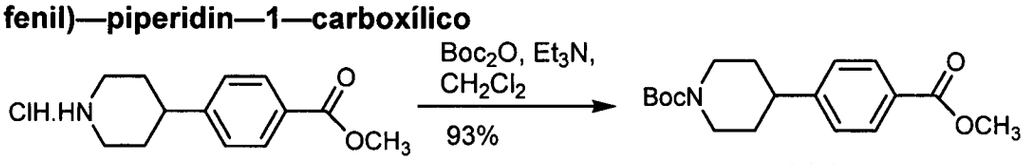
Ejemplo 623

Preparación de 3—(4—fluoro—fenil)—1*H*—indazol—5—il]—amida del ácido 1—(2—{4—[4—(5—Etilamino—[1.3,4]oxadiazol—2—il)—fenil]—piperidin—1—il}—2—oxo—etil)—3—metoxi—pirrolidin—3—carboxílico [(Compuesto del Ejemplo 623)



Compuesto del Ejemplo 623

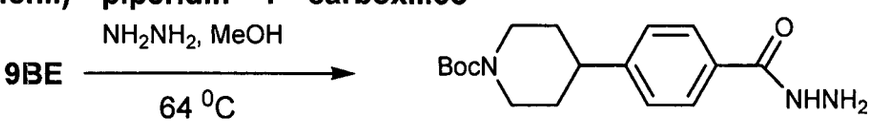
Paso 1: Preparación de ter—butil éster del ácido 4—(4—Metoxicarbonil—fenil)—piperidin—1—carboxílico



8BE **9BE**

Una mezcla del Compuesto **8BE** (3 g, 11,73 mmol), CH_2Cl_2 (30 ml), trietilo amina (4,9 ml, 35,19 mmol) y dicarbonato de di—*ter*—butilo (3,83 g, 17,55 mmol) se agitó a temperatura ambiente durante 3 horas. Se diluyó con CH_2Cl_2 (100 ml) y se lavó con agua (100 ml). La fase orgánica se secó sobre Na_2SO_4, se filtró y se concentró. El residuo se purificó sobre gel de sílice eluyendo con 100% EtOAc para dar el producto deseado **9BE** (3,5 g, 93%).

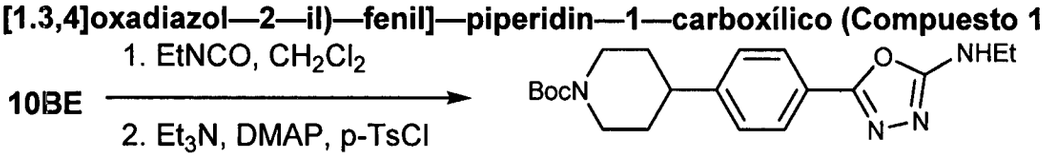
Paso 2: Preparación de ter—butil éster del ácido 4—(4—Hidrazinocarbonil—fenil)—piperidin—1—carboxílico



10BE

El compuesto **9BE** se convirtió en el Compuesto **10BE** usando el procedimiento como el que se describió para la preparación del Compuesto **2AR** a partir del Compuesto **1AR** (Ejemplo 622 Paso 1).

Paso 3: Preparación de ter—butil éster del ácido 4—[4—(5—Etilamino—[1.3,4]oxadiazol—2—il)—fenil]—piperidin—1—carboxílico (Compuesto 11BE)



11BE

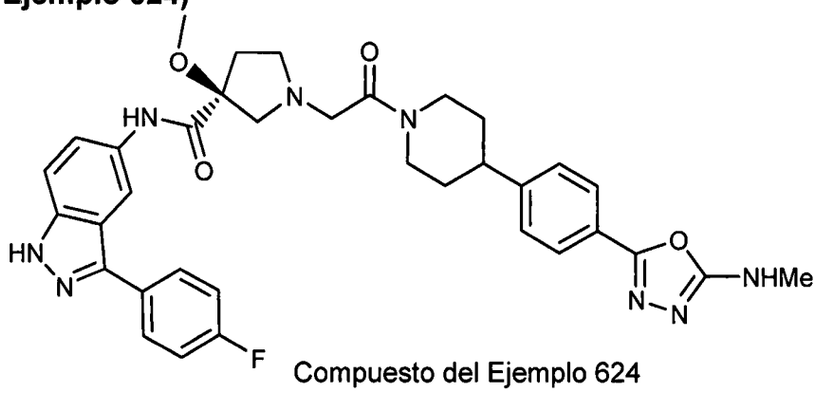
El compuesto **10BE** se convirtió en el Compuesto **11BE** usando el procedimiento como el que se describió para la preparación del Compuesto **3AR** a partir del Compuesto **2AR** (Ejemplo 622 Paso 2).

Paso 4:

El compuesto **11BE** se convirtió en el compuesto del Ejemplo **623** usando el procedimiento como el que se describió para la preparación del compuesto del Ejemplo **622** a partir del Compuesto **4AR**.

Ejemplo 624

Preparación de [3—(4—fluoro—fenil)—1*H*—indazol—5—il]—amida del ácido 1—(2—{4—[4—(5—metilamino—[1.3,4]oxadiazol—2—il)—fenil]—piperidin—1—il}—2—oxo—etil)—3—metoxi—pirrolidin—3—carboxílico (Compuesto del Ejemplo 624)

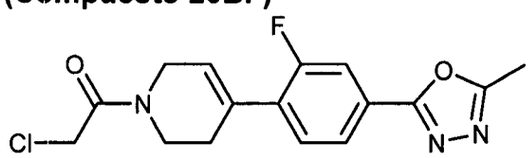


Compuesto del Ejemplo 624

El compuesto del Ejemplo **624** se preparó a partir del Compuesto **10BE** (Ejemplo 623 Paso 3) usando el procedimiento como el que se describió para la preparación del compuesto del Ejemplo **623** a partir del Compuesto **10BE** pero usando isocianato de metilo en lugar de isocianato de etilo.

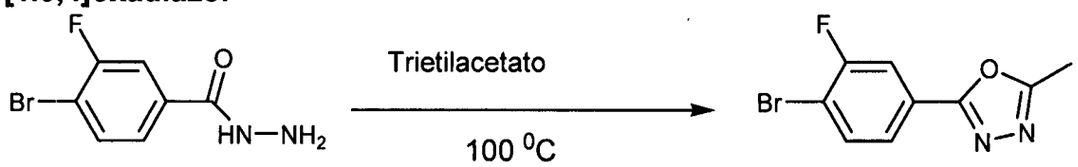
Preparación 84

Preparación de 2—Cloro—1—{4—[2—Fluoro—4—(5—metil—[1.3,4]oxadiazol—2—il)—fenil]—3,6—dihidro—2*H*—piridin—1—il}—etanona (Compuesto 20BF)



Compuesto 20BF

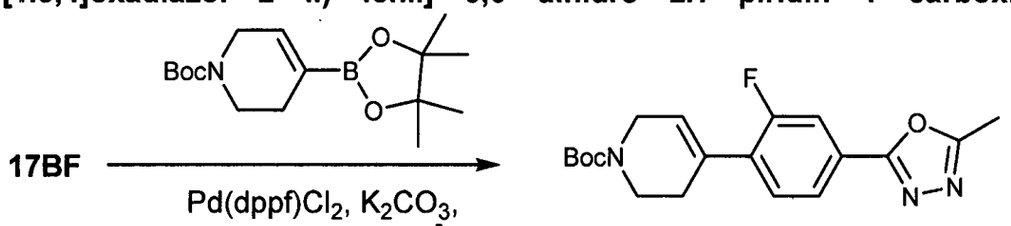
Paso 1: Preparación de de 2—(4—Bromo—3—fluoro—fenil)—5—metil—[1.3,4]oxadiazol



2BF 32% **17BF**

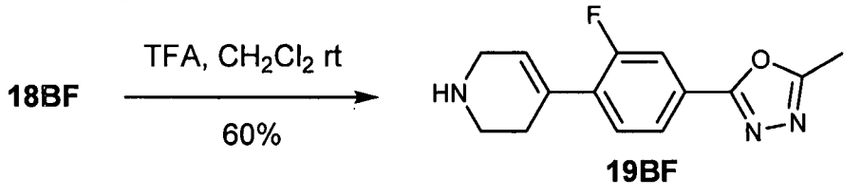
Una mezcla del Compuesto **2BF** (0,9 g, 2,53 mmol) y triacetato de etilo (5 ml) se calentó a 100 °C durante 18 horas. Se enfrió hasta temperatura ambiente y se vertió en agua (100 ml). Se extrajo con EtOAc (100 ml). La fase orgánica se secó (Na_2SO_4), se filtró y se concentró. El residuo se purificó sobre gel de sílice eluyendo con 20% EtOAc/ hexano para dar el producto deseado **17BF** (0,36 g, 32%).

Paso 2: Preparación de *ter*—butil ácido 4—[2—Fluoro—4—(5—metil—[1.3,4]oxadiazol—2—il)—fenil]—3,6—dihidro—2*H*—piridin—1—carboxílico



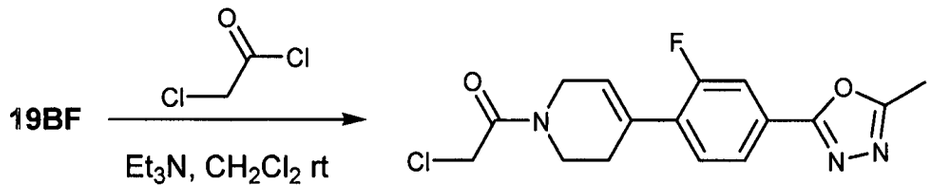
Una mezcla del Compuesto **17BF** (0,34 g, 0,99 mmol), 4—(4,4,5,5—tetrametil—[1.3,2]dioxaborolan—2—il)—3,6—dihidro—2*H*—piridin—1—carboxílico ter—butil éster del ácido (0,37 g, 1.19 mmol), carbonato de potasio (0,41 g, 2.97 mmol), $Pd(dppf)Cl_2$ (0,081 g, 0,099 mmol) y 4/1 /dioxano/agua (10 ml) se desgasificó durante 15 minutos. Luego se calentó a 90°C durante hasta la mañana siguiente. Se enfrió hasta temperatura ambiente y se diluyó con EtOAc (200 ml). La fase orgánica se lavó con agua (100 ml), se secó sobre Na_2SO_4, se filtró y se concentró. El residuo se purificó sobre gel de sílice para dar el producto deseado **18BF** (0,35 g, 98%).

Paso 3: Preparación de 4—[2—Fluoro—4—(5—metil—[1.3,4]oxadiazol—2—il)—fenil]—1,2,3,6—tetrahidro—piridina



El compuesto **18BF** (0,44 g, 1.13 mmol) se convirtió en Compuesto **19BF** usando el procedimiento como el que se describió para la preparación del Compuesto **5AR** a partir del Compuesto **4AR** (Ejemplo 622 Paso 4).

Paso 4:

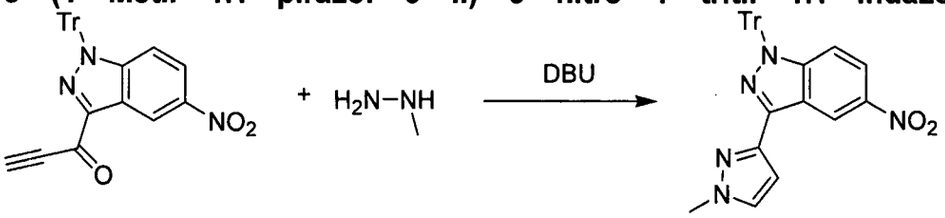


20BF

El compuesto **19BF** (0,44 g, 1.13 mmol) se convirtió en Compuesto **20BF** usando el procedimiento como el que se describió para la preparación del Compuesto **6AR** a partir del Compuesto **5AR** (Ejemplo 622 Paso 5).

Preparación 85

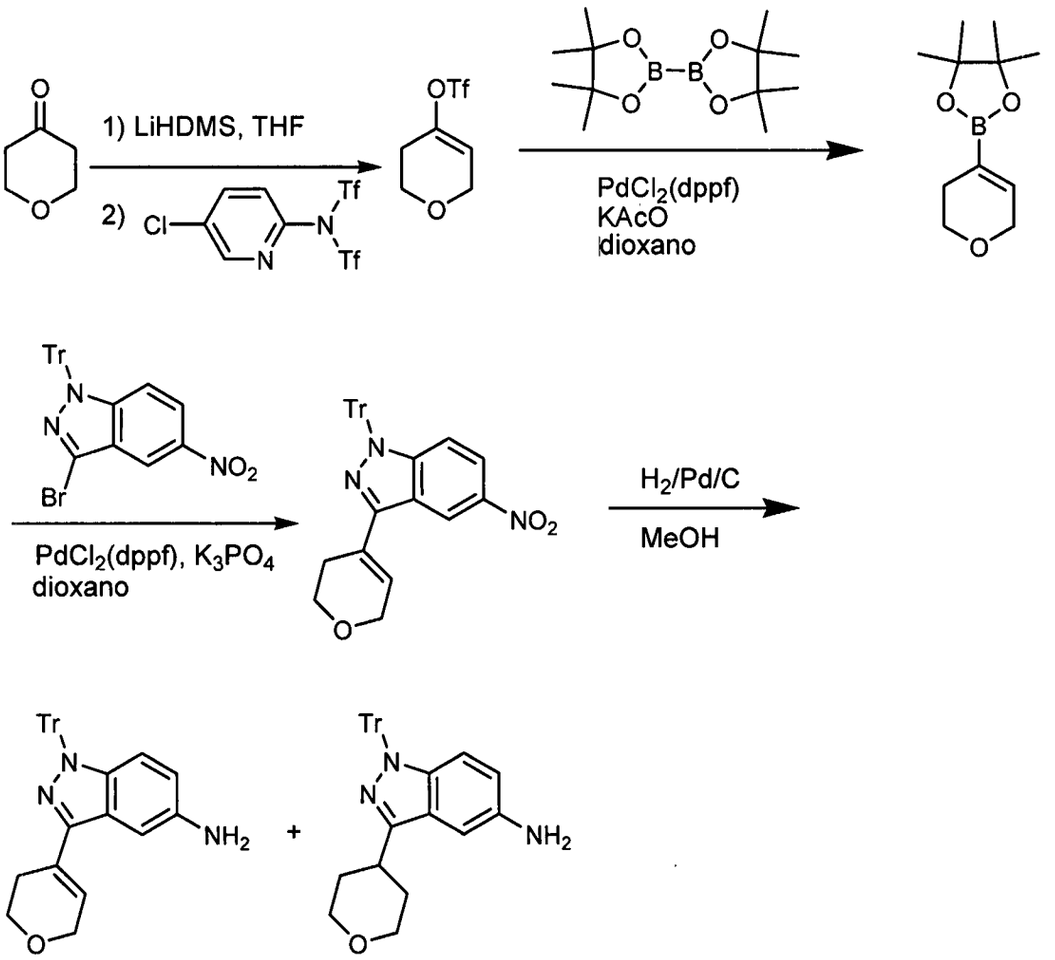
3—(1—Metil—1H—pirazol—3—il)—5—nitro—1—tritil—1H—indazol



A mezcla de 1—(5—nitro—1—tritil—1*H*—indazol—3—ilo—)—propinona (0,5 g, 1.09 mmol), metil hidrazina clorhidrato (1,75 mmol) y DBU (1,6 ml, 10,9 mmol) en acetonitrilo (10 ml) se calentó a 120°C durante 50 minutos bajo microondas. Luego se enfrió hasta temperatura ambiente y se diluyó con DCM (60 ml). La fase orgánica se lavó con agua (10 ml), se secó sobre $MgSO_4$, se filtró y se concentró. El residuo se purificó sobre gel de sílice eluyendo con 1/1 EtOAc/Hexano para dar el producto deseado (0,42 g, 79%). MS (ESMS, M+H 486)

La reducción del compuesto 5—nitro se logró por hidrogenación como se indicó con anterioridad.

Preparación 63



Paso 1: Preparación de 3,6—dihidro—2H—piran—4—il éster del ácido trifluoro—metansulfónico

A una solución de 4—tetrahidropiranona (2g, 0,02 mol) en THF (10 ml) a -78°C, LiHMDS (1 M, 11 ml) se agregó gota a gota a través de una jeringa. La solución formada luego se agitó a -78°C durante aproximadamente 1 hora. La reacción se entibió hasta la temperatura ambiente brevemente y se enfrió nuevamente hasta -78°C. Luego se agregó 2—[N, N—bis(trifluorometilsulfonil)amino]—5—cloropirina (7,85 g, 0,02 mol) en cuatro porciones. La mezcla resultante de reacción se entibió en forma gradual hasta la temperatura ambiente y se agitó durante hasta la mañana siguiente. Luego de la

eliminación del solvente, el residuo se purificó usando cromatografía (se eluyó con DCM/Hexano = 80/20) para dar producto un aceite incoloro (3 g).

Paso 2: Preparación de 4—(4,4,5,5—Tetrametil—[1.3,2]dioxaborolan—2—il)—3,6—dihidro—2H—piran

Un balón de 250 ml que contiene 3, 6—dihidro—2H—piran—4—ilo éster del ácido trifluoro—metanosulfónico (2.7 g, 11,6 mmol), $PdCl_2$(dppf) (440 mg, 0,6 mmol) y acetato de potasio (3g, 36 mmol) en dioxano (20 ml) se enjuagó con Ar tres veces. La mezcla de reacción se calentó a 80°C durante hasta la mañana siguiente. Luego de la reacción se enfrió hasta temperatura ambiente, la mezcla de reacción se filtró a través de una columna empacada con celite y el filtrado se concentró. El residuo se purificó usando cromatografía en columna (10 % hexano en diclorometano) y el producto se obtuvo como un sólido blanco (2g, 81% de Rendimiento).

Paso 3: Preparación de 3—(3,6—Dihidro—2H—piran—4—il)—5—nitro—1—tritil—1H—indazol

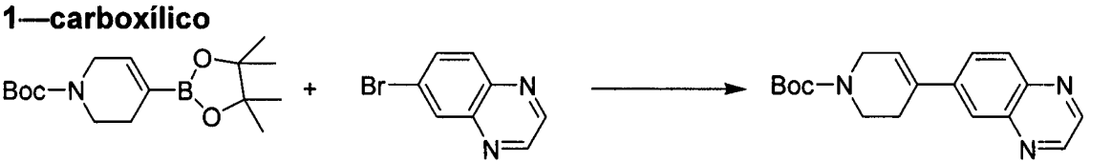
A mezcla que contenía 4—(4,4,5,5—Tetrametil—[1.3,2]dioxaborolan—2—il)—3,6—dihidro—2H—piran (0,8 g, 3,8 mmol), 3—Bromo—5—nitro—1—tritil—1H—indazol (2g, 4,0 mmol), $PdCl_2$(dppf) (150 mg, 0,2 mmol) y fosfato de potasio (2.6 g, 12 mmol) en dioxano (10 ml) se enjuagó con Ar y se calentó a 80 °C durante hasta la mañana siguiente bajo Ar. La LC—MS indició la finalización de la reacción y la mezcla se filtró a través de celite. El filtrado se concentró y se purificó en una columna (10 hexano en diclorometano) para dar 1.2 g de producto (64 % de Rendimiento).

Paso 4: Preparación de 3—(3,6—Dihidro—2H—piran—4—il)—1—tritil—1H—indazol—5—ilamina y 3—(Tetrahidro—piran—4—il)—1—tritil—1H—indazol—5—ilamina

A una solución de 3—(3,6—Dihidro—2H—piran—4—il)—5—nitro—1—tritil—1H—indazol (100 mg, 0,2 mmol) en Metanol se agregó y Pd/C (10%, 20 mg). La mezcla de reacción se evacuó bajo vacío y se llenó hidrógeno gaseoso. Luego de repetir tres veces la reacción se mantuvo bajo atmósfera de hidrógeno hasta la mañana siguiente a temperatura ambiente. La LCMS mostro que este material de partida se había consumido completamente y se obtuvieron ambos 3—(3,6—dihidro—2H—piran—4—il)—1—tritil—1H—indazol—5—ilamina y 3—(tetrahidro—piran—4—il)—1—tritil—1H—indazol—5—ilamina. Los dos productos se separaron usando HPLC prep. para dar ambos productos en 60 % y 40 % de Rendimiento respectivamente.

Preparación 87

ter—butil éster del ácido 4—Quinoxalin—6—il—3,6—dihidro—2H—piridin—1—carboxílico

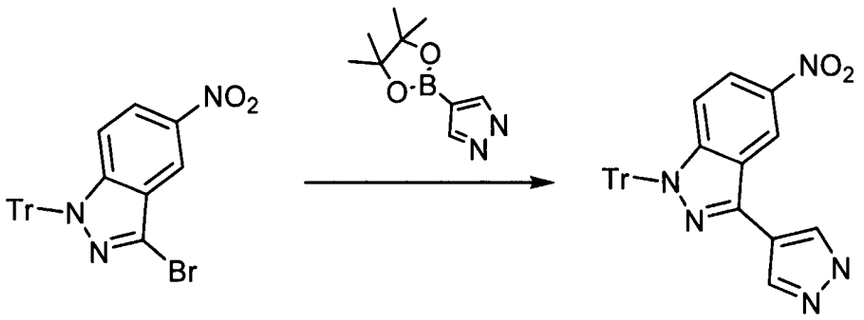


Una solución que contenía ter—butil éster del ácido 6—bromo—quinoxalina (417 mg, 2.0 mmol), 4—(4,4,5,5—tetrametil—[1.3,2]dioxaborolan—2—il)—3,6—dihidro—2H—piridin—1—carboxílico (600 mg, 1,94 mmol), tetrakis [trifenilfosfin] paladio (108 mg, 0,1 mmol) y carbonato de sodio (solución 2 M, 3 ml) en 5 ml de dioxano/etanol/agua (7:3:1) se calentó a 160°C usando reactor de microondas durante 15 minutos. Luego de la reacción, acetato de etilo se agregó y la mezcla se filtró, se lavó con agua. Luego de la concentración al vacío, el producto se purificó usando cromatografía en columna (5% metanol en diclorometano)

Preparación 88

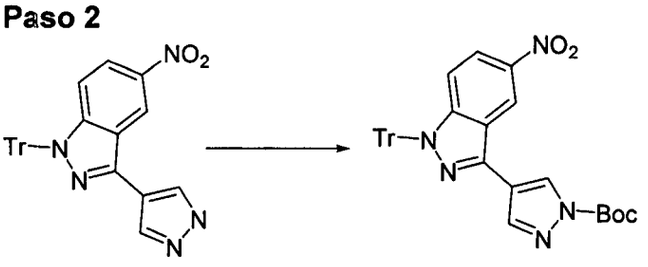
1—N ter—butil éster del ácido Tritil—4—(5—Amino—1—metil—1H—indazol—3—il)—pirazol—1—carboxílico

Paso 1



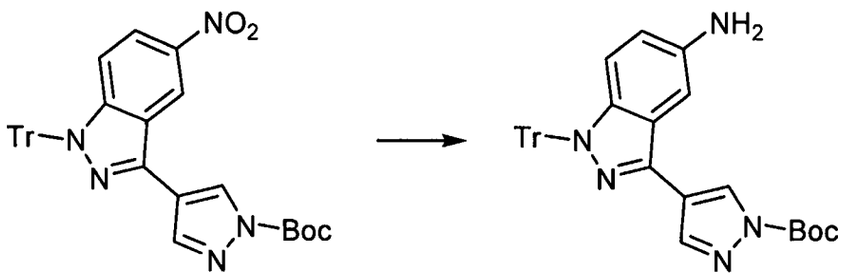
A un vial que contiene 3—bromo—5—nitro—1—tritil—1H—indazol (1,45 g, 3,00 mmol), 4—(4,4,5,5—TETRAMETIL—1.3,2—DIOXABOROLAN—2—IL)—1H—PIRAZOL (0,873 g, 4,50 mmol) [1.1'—Bis(difenilfosfin)ferroceno]dicloropaladio(II), complejo con diclorometano (1:1) (0,245 g, 0,300 mmol) y Fosfato de potasio (1,59 g, 7,50 mmol) en una mezcla de 1,4—Dioxano (25 ml, 320 mmol) Agua (12 ml, 670 mmol) se desgasificó bajo una atmósfera de Nitrógeno. Esta mezcla de reacción se calentó a 80 °C hasta la mañana siguiente bajo una atmósfera de Nitrógeno. La TLC (20%EtOAc/hexano) mostró material de partida. La MS mostró (M+H) en 472. La reacción se diluyó con EtOAc y Agua (50/50 ml) y se filtró a través de celite. La fase orgánica se lavó con agua, se secó sobre sulfato de magnesio (2 g, 20 mmol) y rotavap para dar un producto en bruto, 2,2 g. El producto en bruto se cromatografió (30%EtOAc/Hexano) en Biotage (40L) para obtener el producto (fracción 2), M+H at 472. 5—nitro—3—(1H—pirazol—4—il)—1—tritil—1H—indazol (0,54 g; Rendimiento = 38%)

Paso 2



En un a Balón se agregó 5—nitro—3—(1H—pirazol—4—il)—1—tritil—1H—indazol (0,390 g, 0,827 mmol, material de partida sin reaccionar, cloruro de metileno (5,00 ml, 78,0 mmol), Di—ter—Butildicarbonato (0,228 g, 1.04 mmol) 4—Dimetilaminopiridina (0,127 g, 1.04 mmol) La reacción se agitó durante 2 días bajo atmósfera de Nitrógeno. La TLC (20%EtOAc/Hexano) mostró la reacción completa. La reacción se cargó en Biotage 40S y se eluyó con 20%EtOAc/hexano para dar ter—butilo 4—(5—nitro—1—tritil—1H—indazol—3—il)—1H—pirazol—1—carboxilate (0,44 g; Rendimiento = 93%)

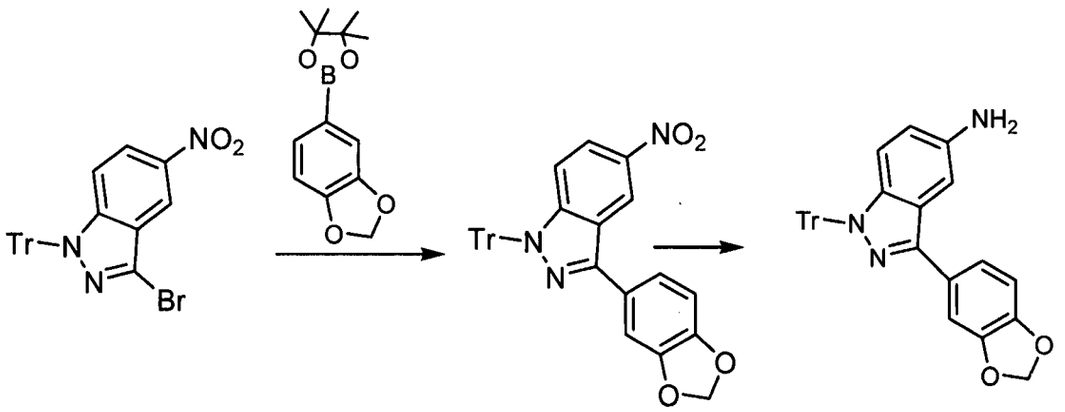
Paso 3



En un Balón se agregó 4—(5—nitro—1—tritil—1H—indazol—3—il)—1H—pirazol—1—carboxilato de ter—butilo (0,440 g, 0,770 mmol) y 10 ml de MeOH y 5 ml de EtOAc seguido de Paladio (0,100 g, 0,000470 mmol). La reacción se desgasificó bajo Hidrógeno (2000 ml, 90 mmol) en el globo, se agitó hasta la mañana siguiente. La TLC (20%EtOAc/Hexano) y MS mostraron la reacción completa. La reacción se filtró a través de Celite y se pasó por rotovap hasta la sequedad para dar ter—butilo 4—(5—amino—1—tritil—1H—indazol—3—il)—1H—pirazol—1—carboxilate (0,400 g; Rendimiento = 95,9%)

Preparación 89

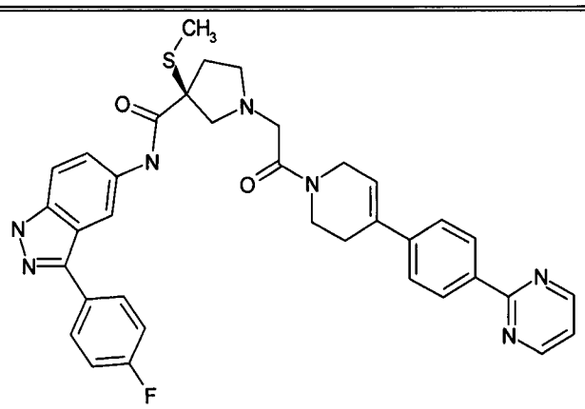
Preparación de 1—N—Tritil—3—Benzo[1.3]dioxol—5—il—1—metil—1H—indazol—5—ilamina

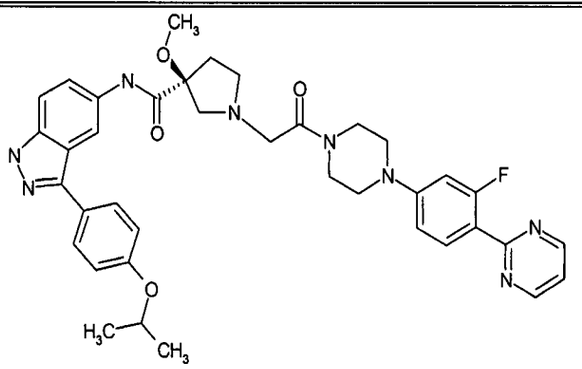
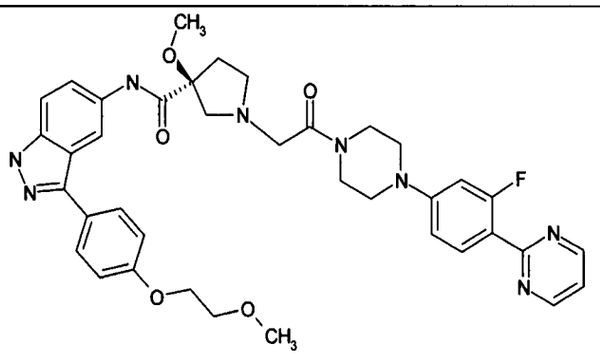
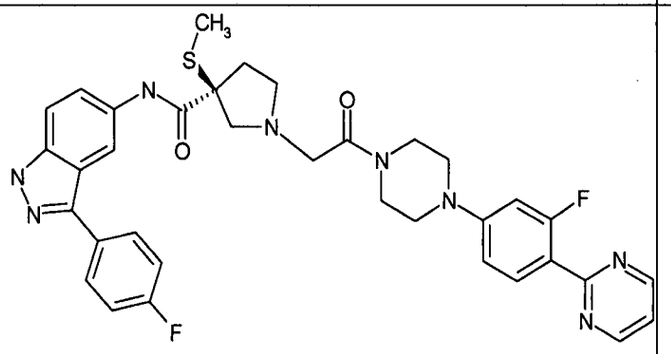


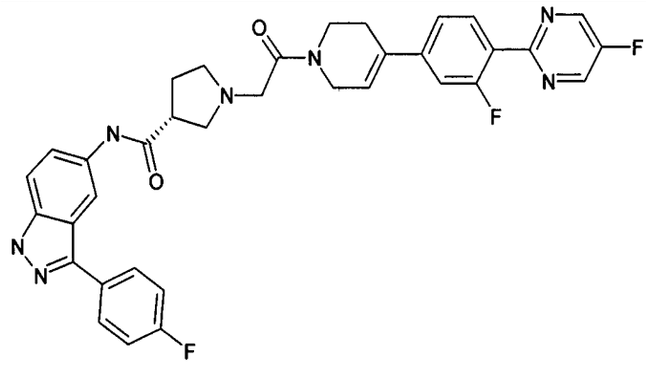
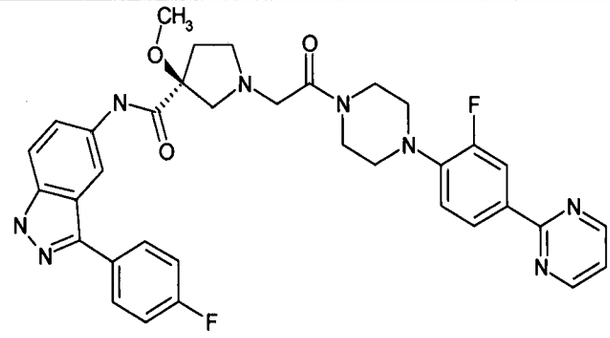
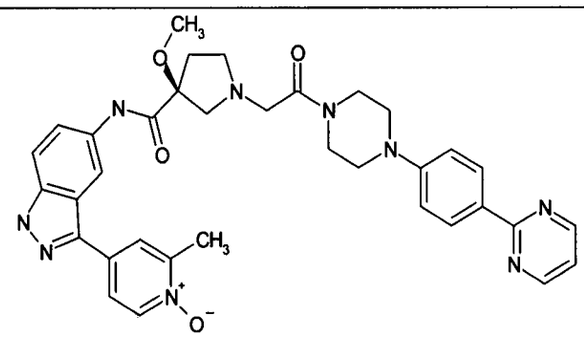
1—N—Tritil—3—Benzo[1.3]dioxol—5—il—1—metil—1H—indazol—5—ilamina se preparó por la sustitución de 5—(4,4,5,5—Tetrametil—[1.3,2]dioxaborolan—2—il)—benzo[1.3]dioxol en lugar de 4—(4,4,5,5—Tetrametil—[1.3,2]dioxaborolan—2—il)—1H—pirazol en la Preparación 88 in Pasos 1 y 3.

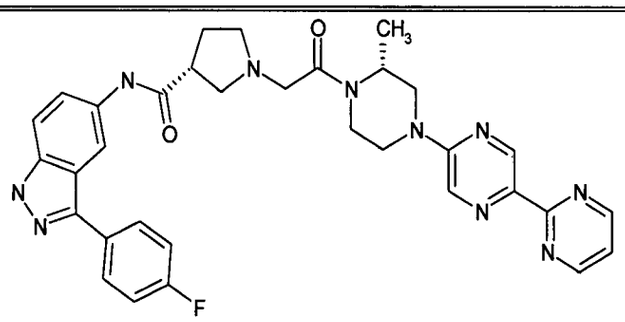
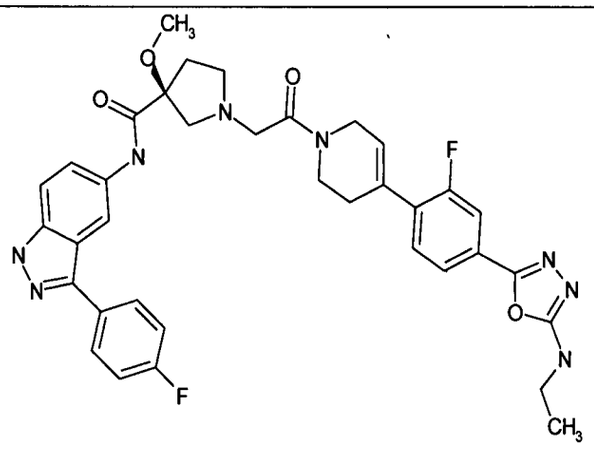
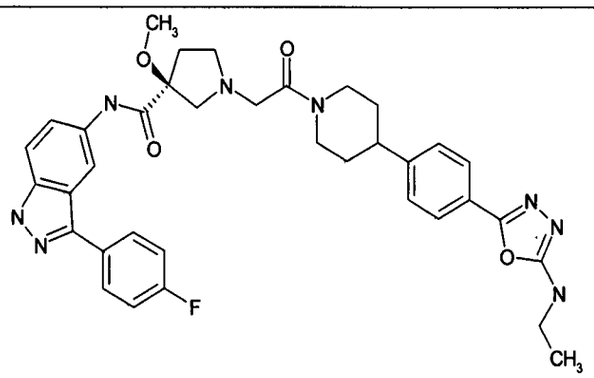
La Tabla 27 provee data para los compuestos de los Ejemplos 613 a 623.

Tabla 27

Ej No.	COMPUESTO	M+1	Tiempo de Retención (min)
613 (16AA)		648,4	2,8

Ej No.	COMPUESTO	M+1	Tiempo de Retención (min)
614 (9AB)		693,4	2,84
615 11AB		709,4	2,54
616 (13AB)		669,4	2,75

Ej No.	COMPUESTO	M+1	Tiempo de Retención (min)
617 (25AB)		638,4	3,33
619 (33AB)		653,4	2,89
620		648,4	2,12

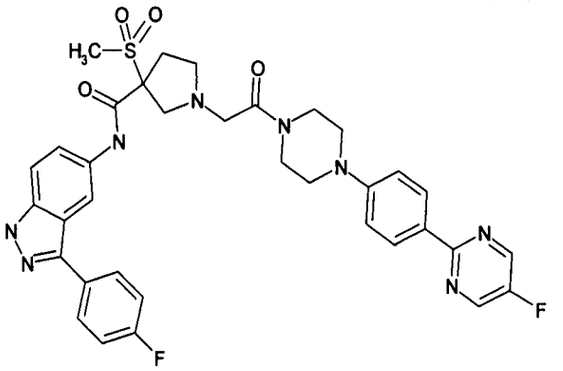
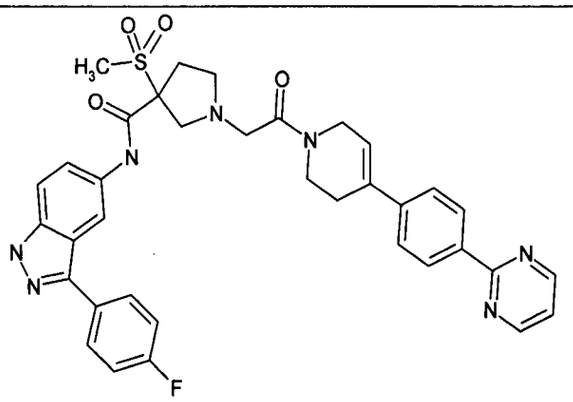
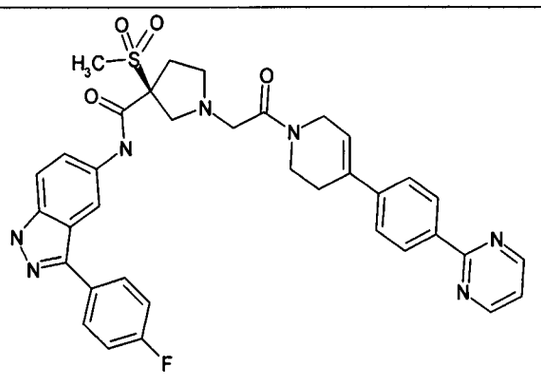
Ej No.	COMPUESTO	M+1	Tiempo de Retención (min)
621		623	2,42
622		683,4	2,98
623		667,4	2,69

Ejemplos 625 hasta 825

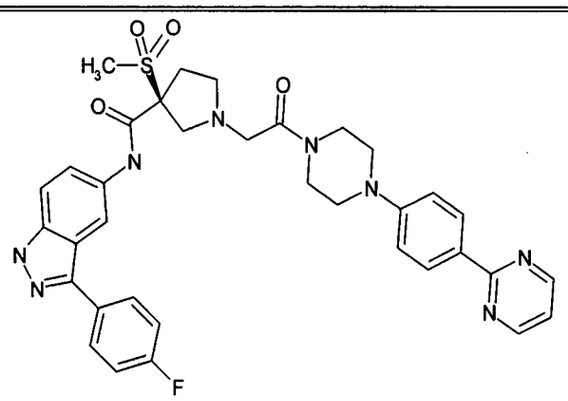
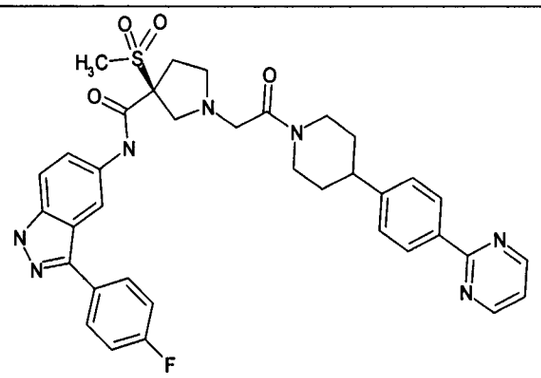
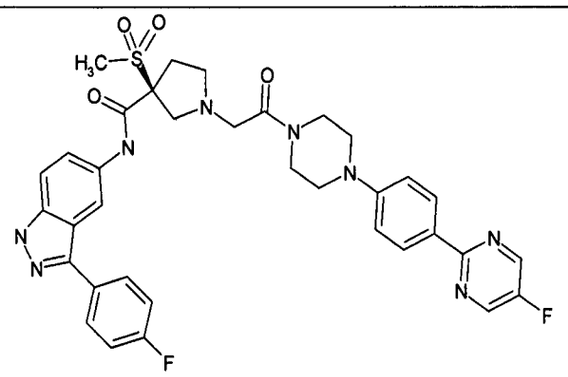
Siguiendo el procedimiento descrito con anterioridad, como también aquellos indicados en la Tabla 28, se prepararon los compuestos en la Tabla 28.

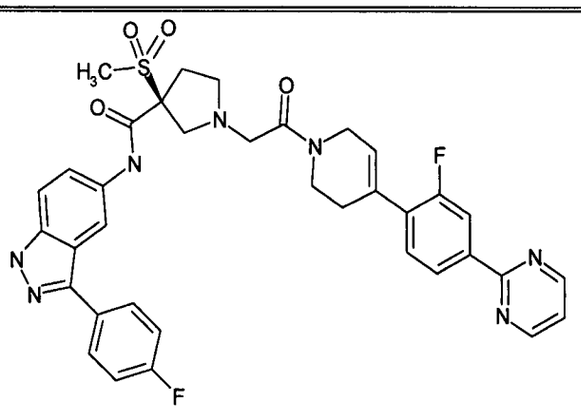
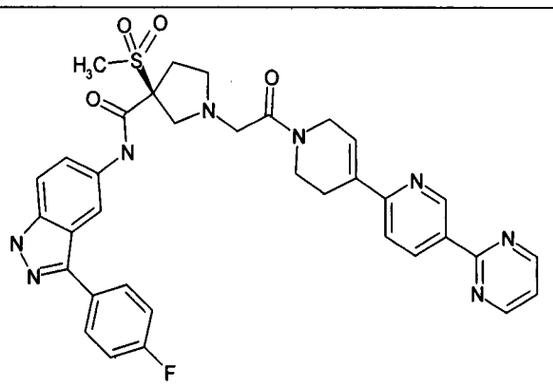
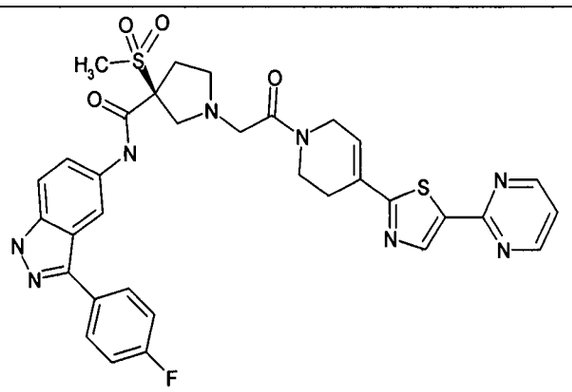
401

Tabla 28

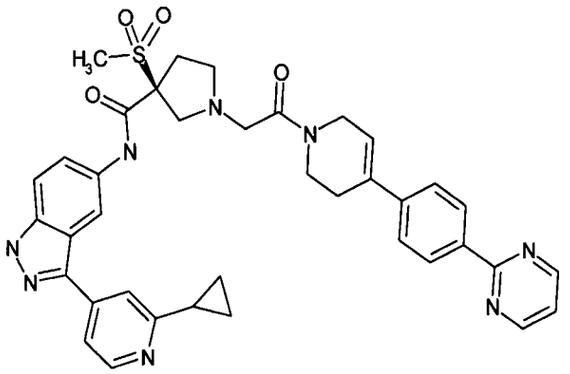
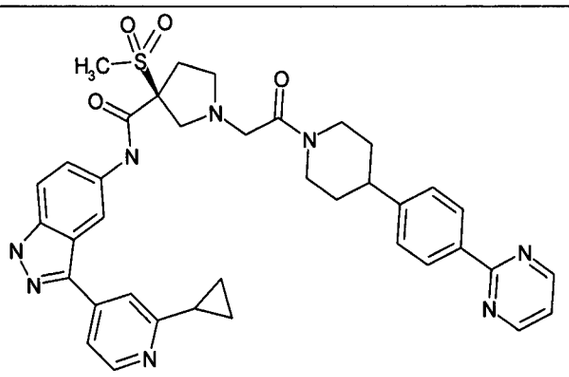
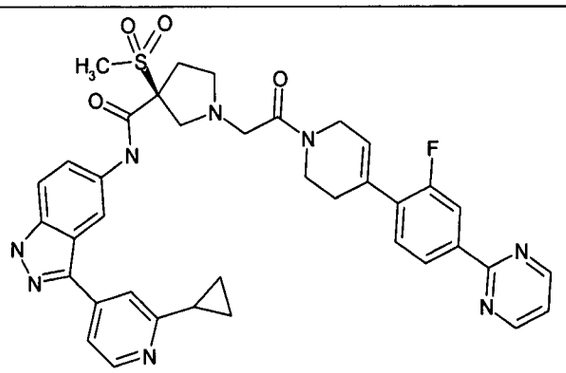
Ej No.	COMPUESTO	M+1	Tiempo de Retención (min)
625		701,4	3,05
626		680,4	2,99
627	 (ver también Ejemplo 619)	680,4	2,8

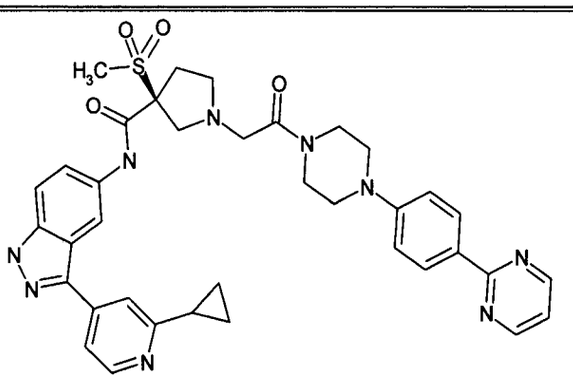
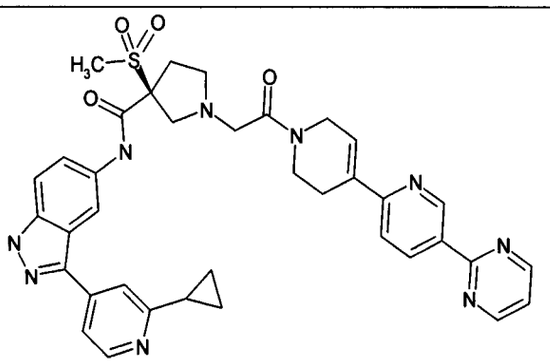
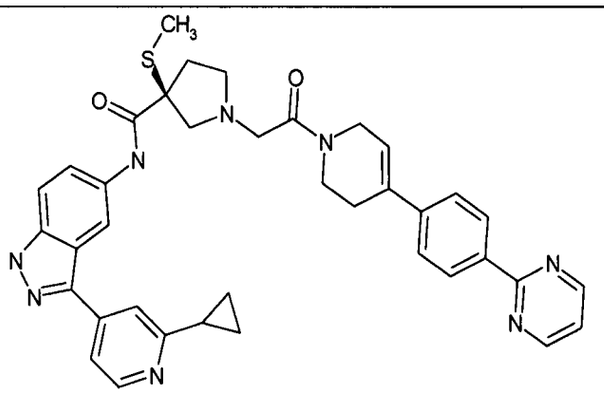
612

Ej No.	COMPUESTO	M+1	Tiempo de Retención (min)
628		683,4	2,93
629		682.4	2,83
630		701,4	3,04

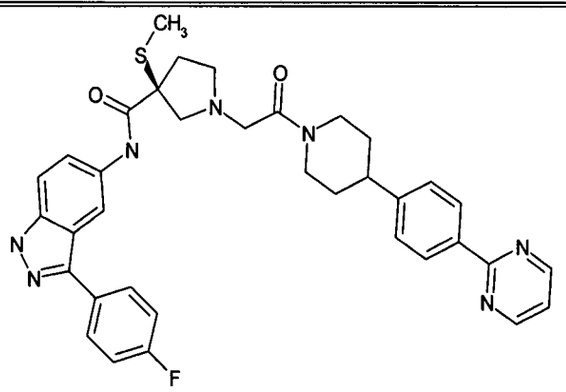
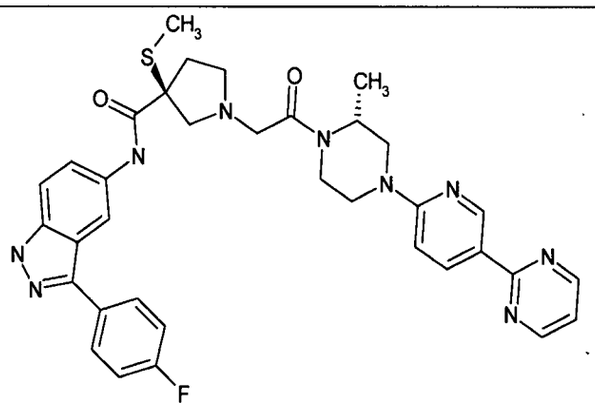
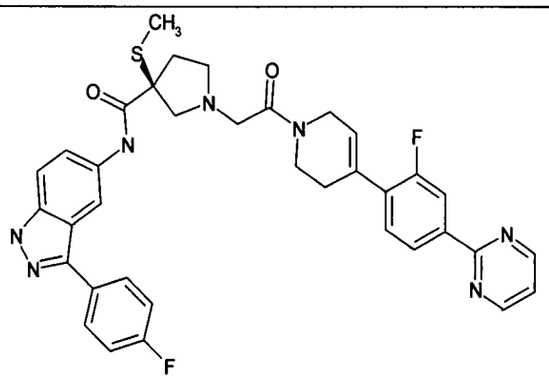
Ej No.	COMPUESTO	M+1	Tiempo de Retención (min)
631		698,4	3,1
632		681,4	2,5
633		687,4	2,54

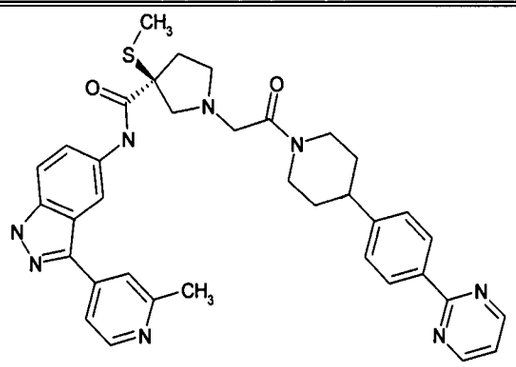
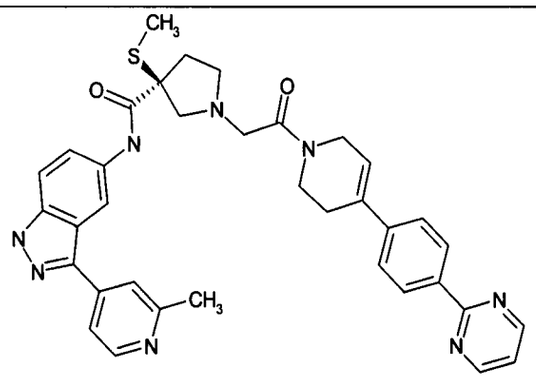
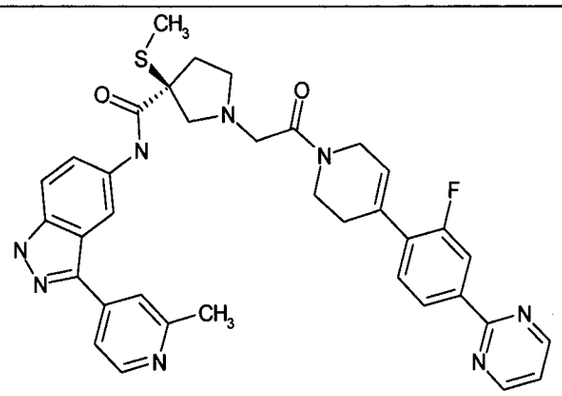
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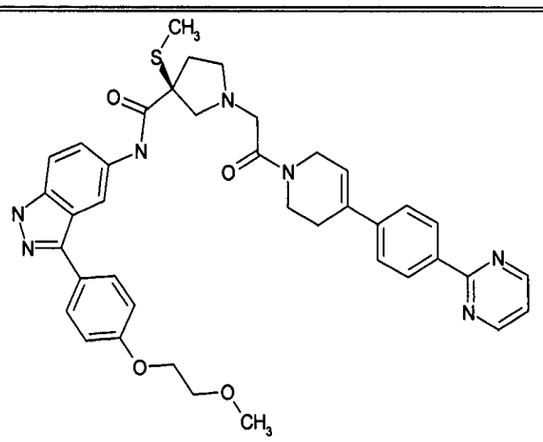
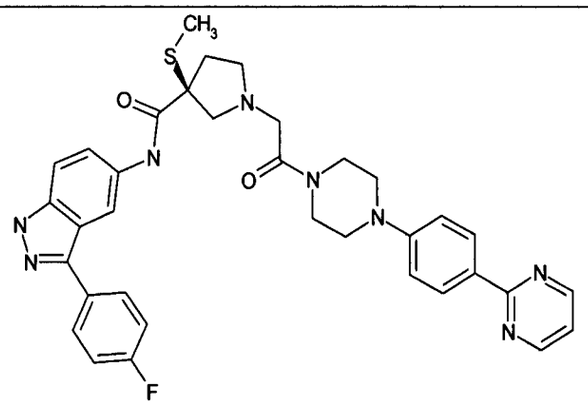
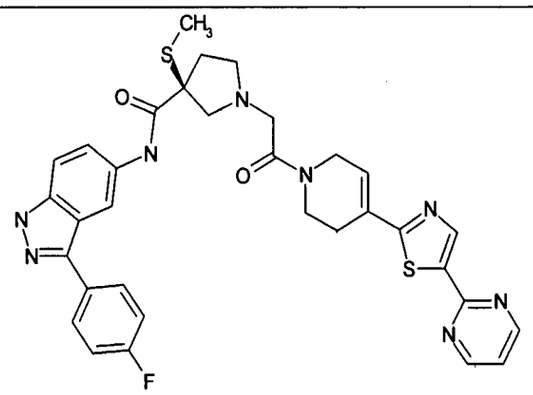
Ej No.	COMPUESTO	M+1	Tiempo de Retención (min)
634		703,4	2,33
635		705,4	2,25
636		721,4	2,38

Ej No.	COMPUESTO	M+1	Tiempo de Retención (min)
637		706,4	2,14
638		704,4	1,93
639		671,4	2,31

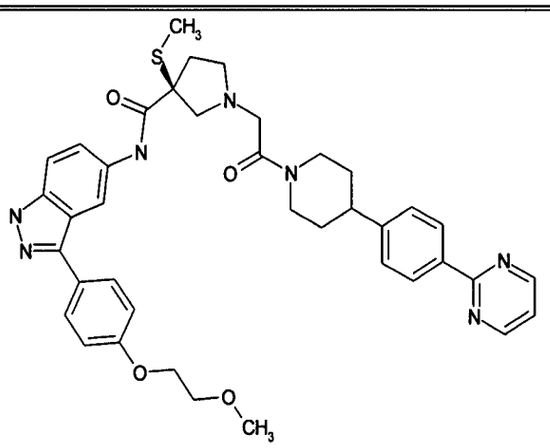
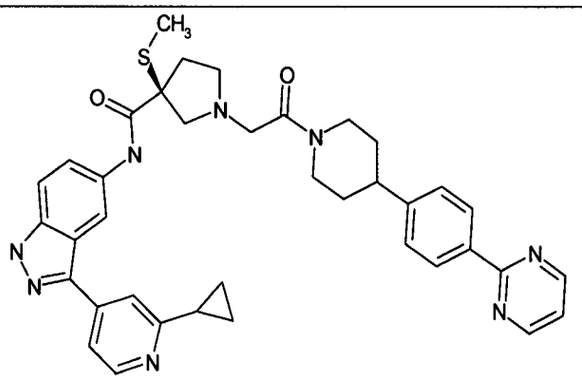
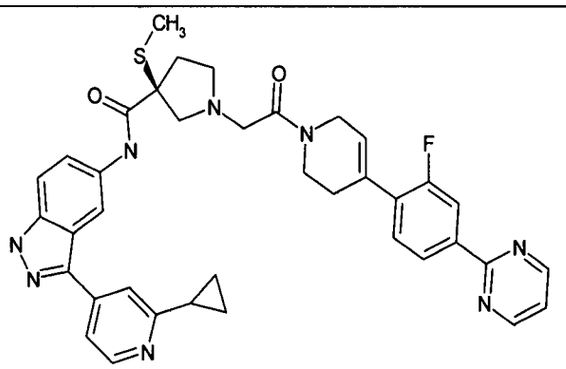
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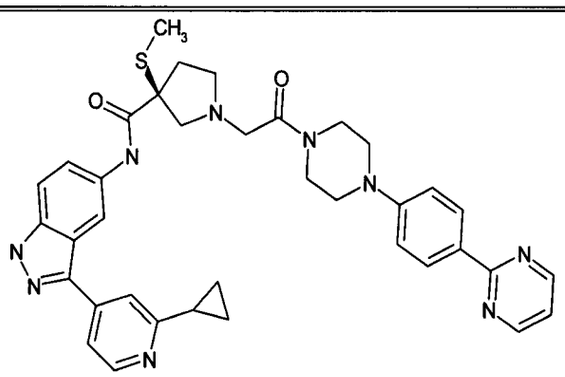
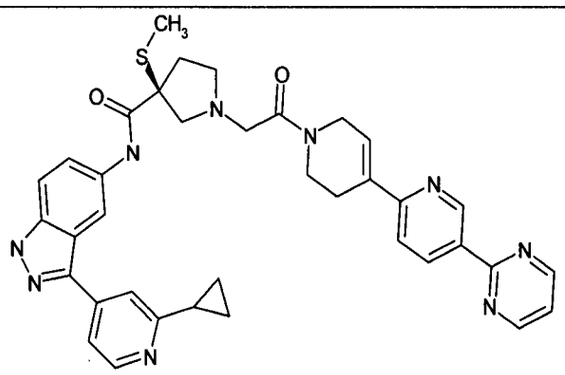
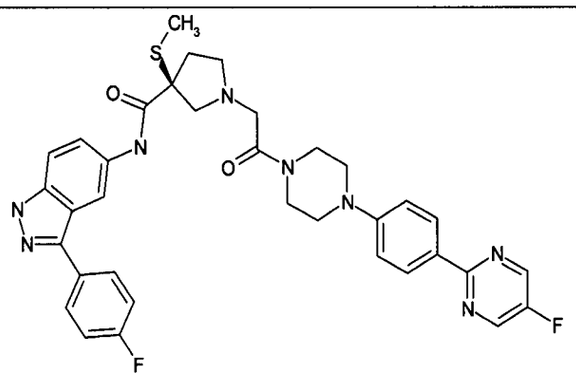
Ej No.	COMPUESTO	M+1	Tiempo de Retención (min)
640		650,4	2,8
641		666,4	2,37
642		666,4	3,14

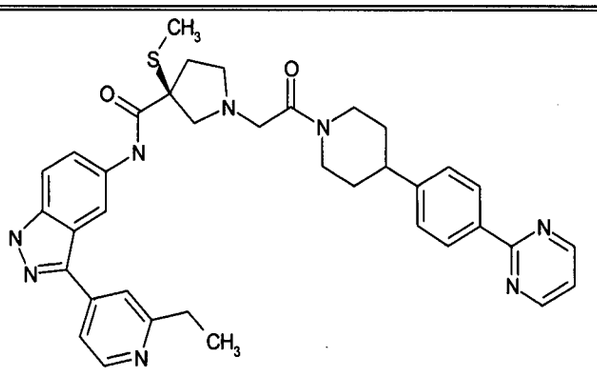
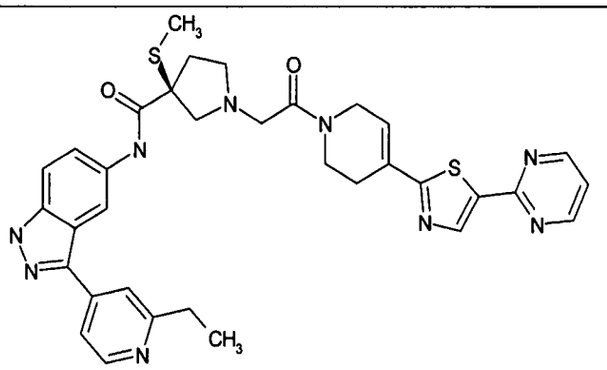
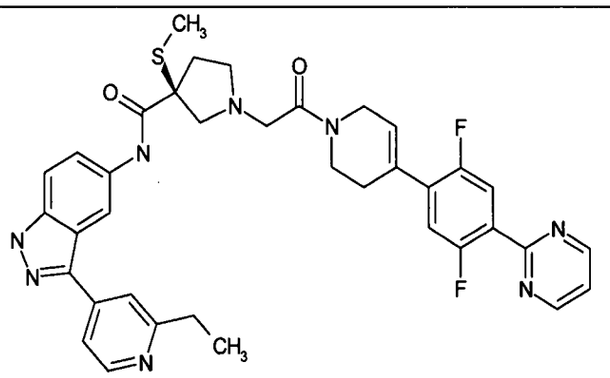
Ej No.	COMPUESTO	M+1	Tiempo de Retención (min)
643		647,4	2,16
644		645,4	2,03
645		663,4	2,14

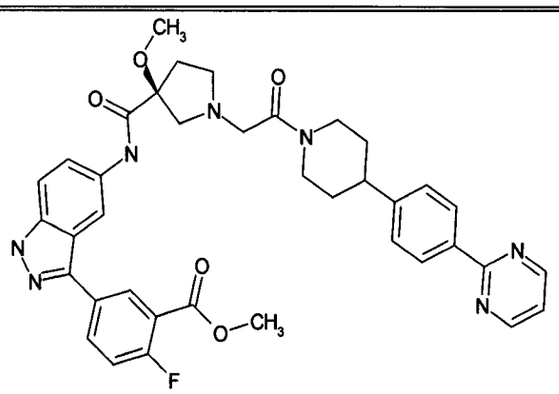
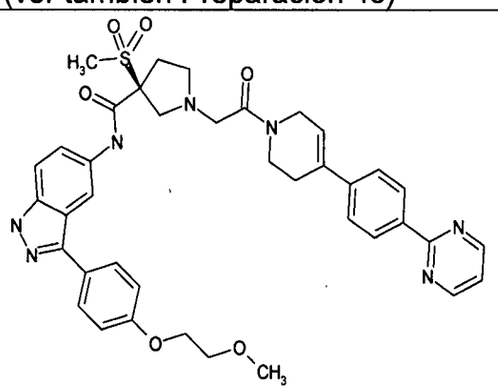
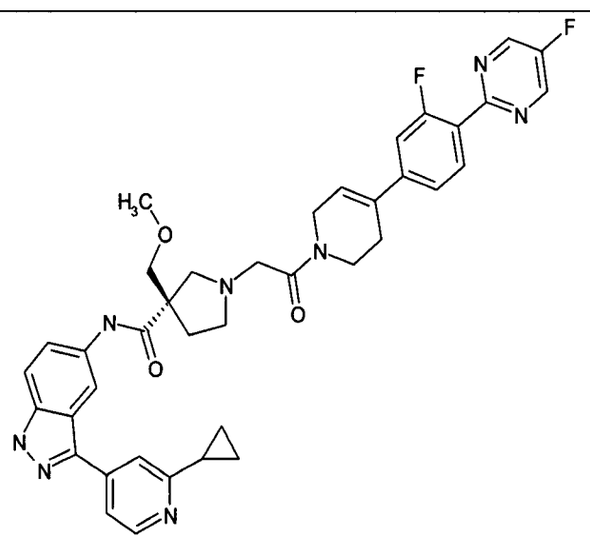
Ej No.	COMPUESTO	M+1	Tiempo de Retención (min)
646		704,4	2,72
647		651,4	2.74
648		655,4	2.72

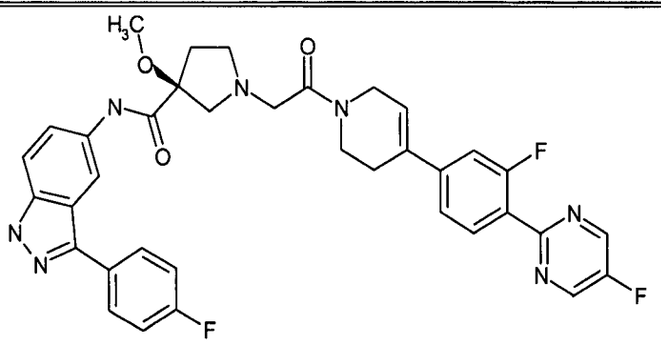
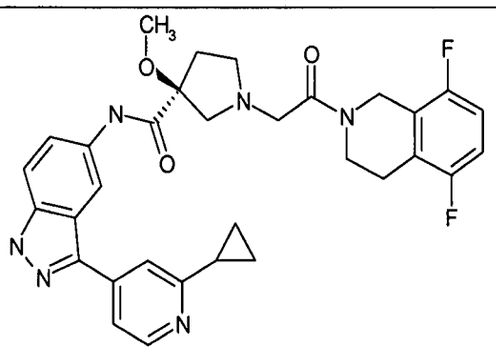
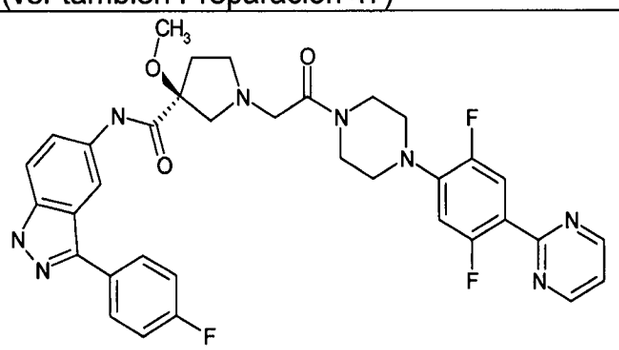
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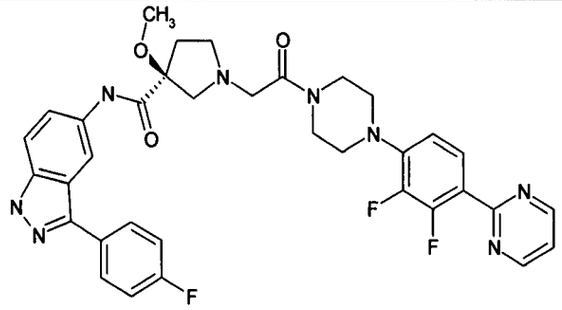
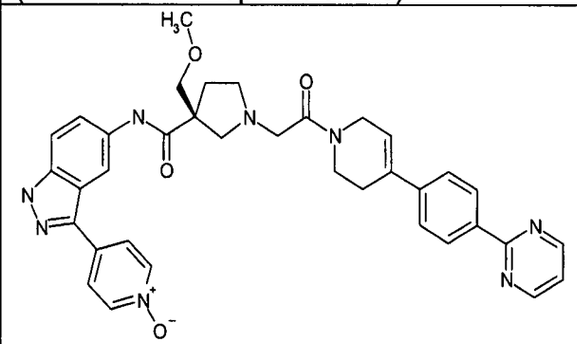
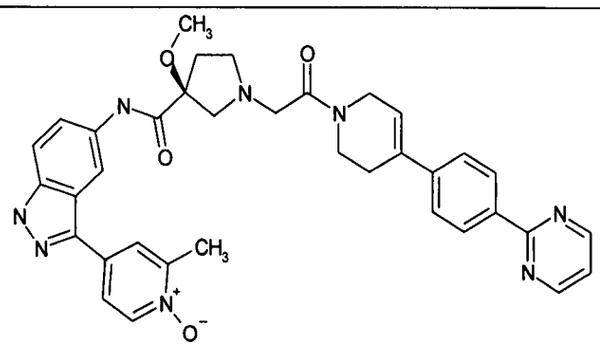
Ej No.	COMPUESTO	M+1	Tiempo de Retención (min)
649		706,4	2.8
650		673,4	2.29
651		689,4	2.4

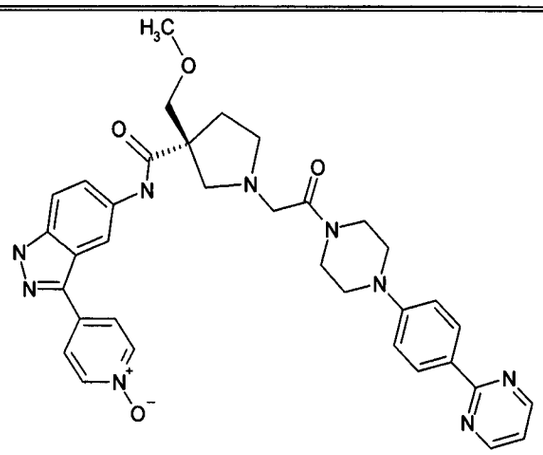
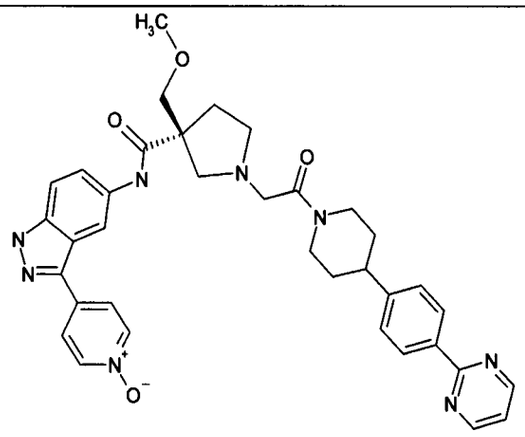
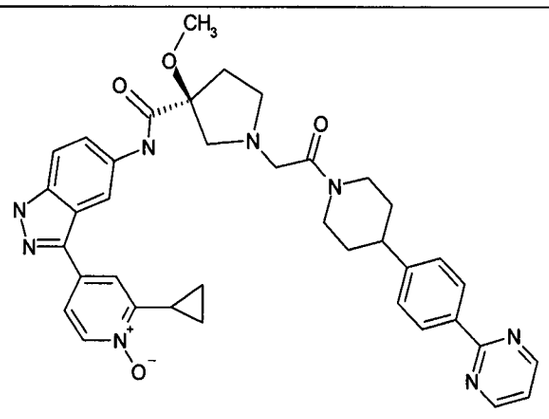
Ej No.	COMPUESTO	M+1	Tiempo de Retención (min)
652		674,4	2.17
653		672.4	2.01
654		669,4	3,16

Ej No.	COMPUESTO	M+1	Tiempo de Retención (min)
655		661,4	2.82
656		666,3	2.66
657		695,3	2.83

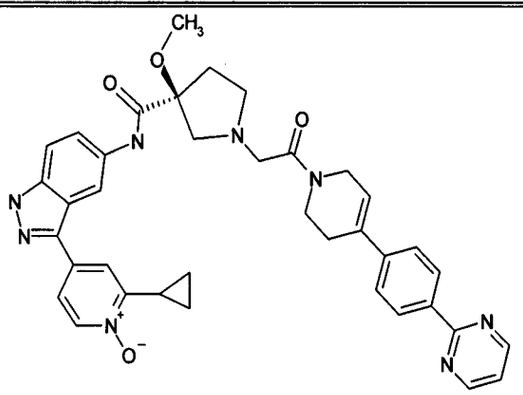
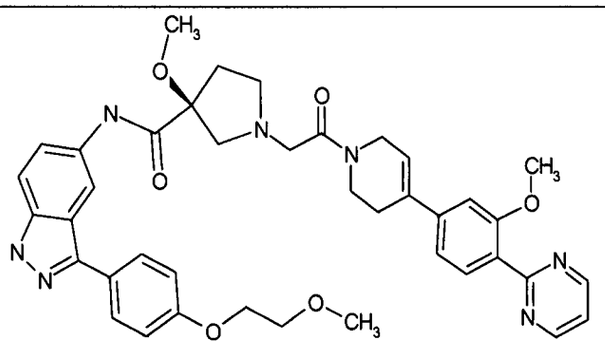
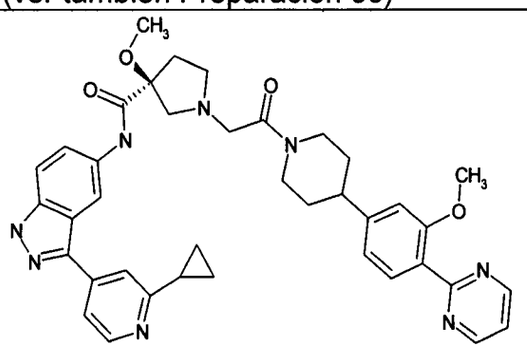
Ej No.	COMPUESTO	M+1	Tiempo de Retención (min)
658	 (ver también Preparación 46)	692.4	2.92
659		736,4	2.8
660	 (ver también Ejemplo 618)	705,4	2,51

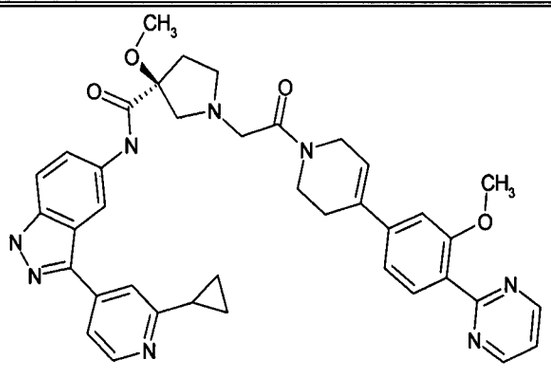
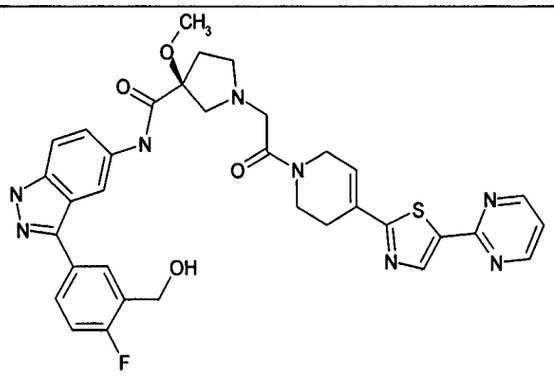
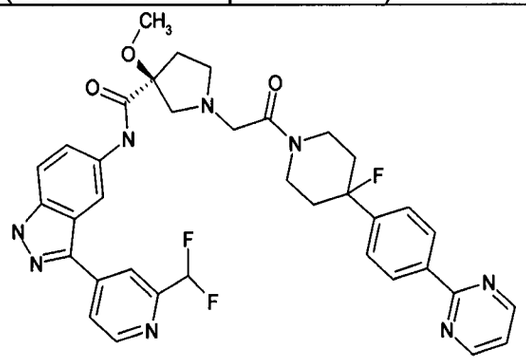
Ej No.	COMPUESTO	M+1	Tiempo de Retención (min)
661		668,4	3,06
662	 (ver también Preparación 47)	587,3	2.46
663	 (ver también Preparación 49)	671,4	2.8

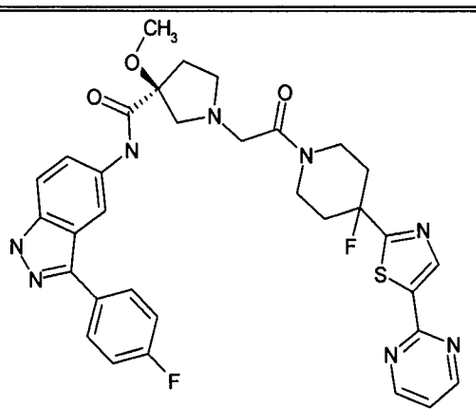
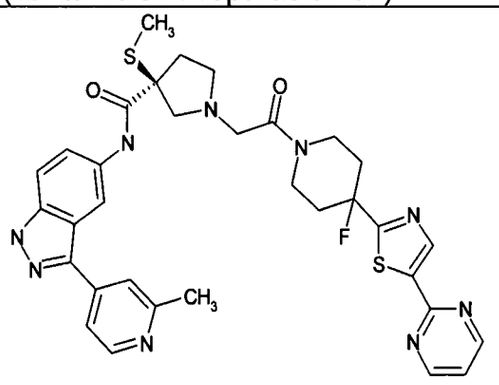
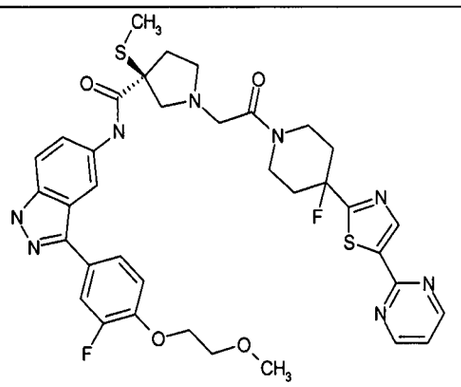
Ej No.	COMPUESTO	M+1	Tiempo de Retención (min)
664	 (ver también Preparación 48)	671,4	2.78
665		645,4	2.48
666	 (ver también Ejemplo 620)	645,4	2.31

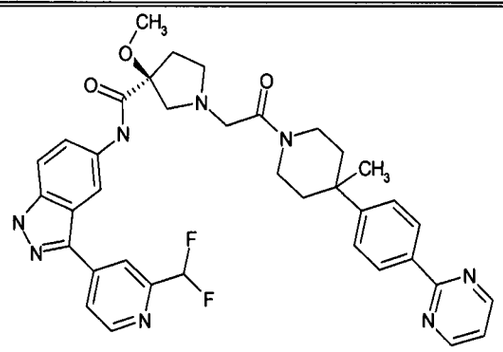
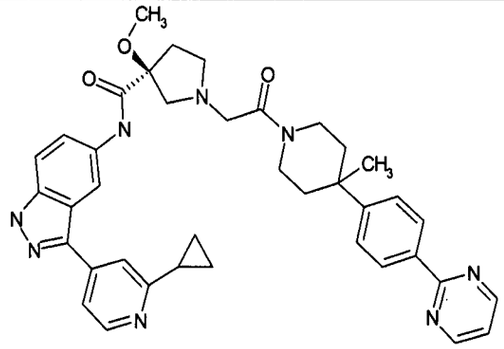
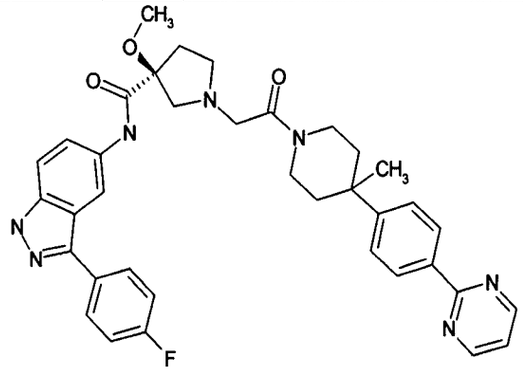
Ej No.	COMPUESTO	M+1	Tiempo de Retención (min)
667		648,4	2.15
668		647,4	2.28
669		673,4	2,56

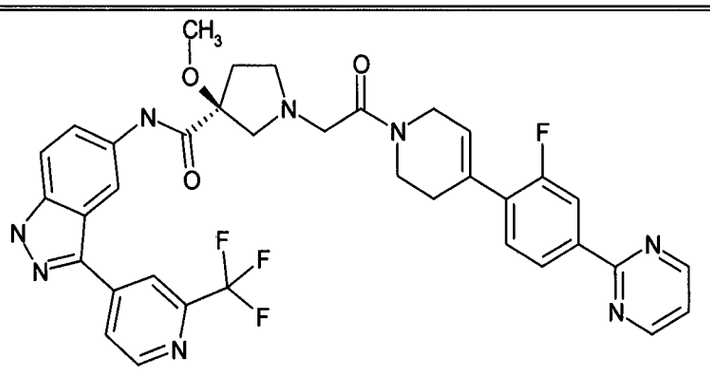
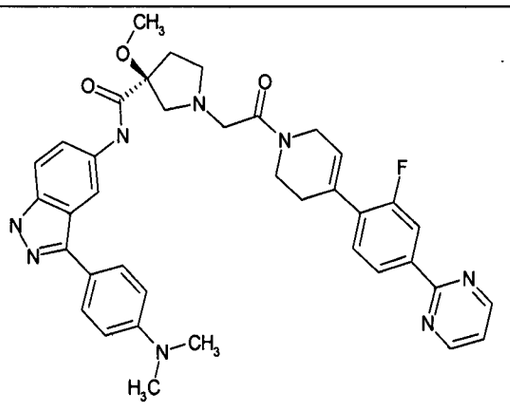
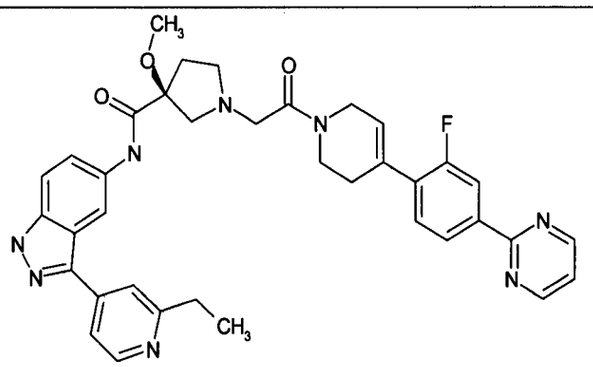
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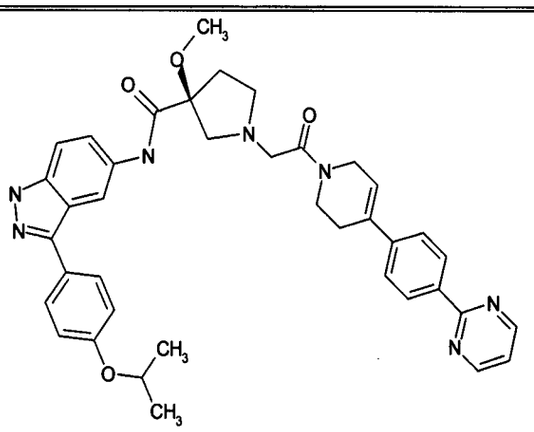
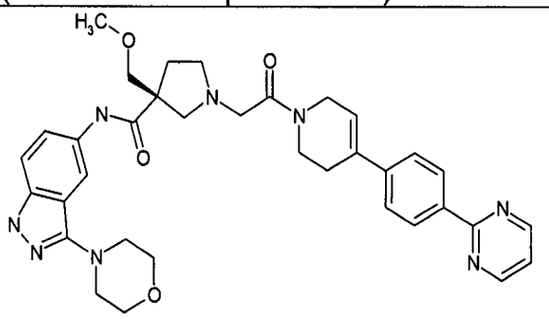
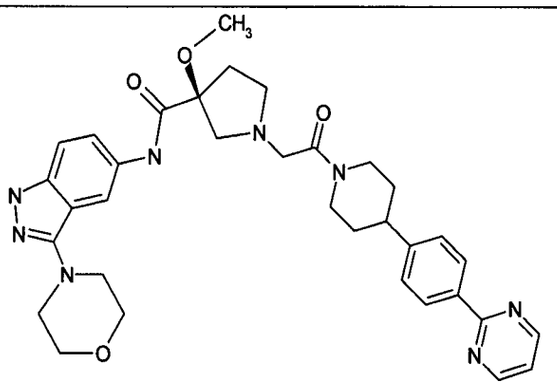
Ej No.	COMPUESTO	M+1	Tiempo de Retención (min)
670		671,4	2,58
671	 (ver también Preparación 50)	718,4	2.67
672		687,4	2.18

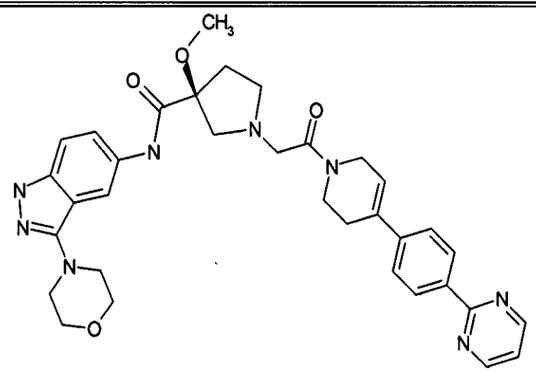
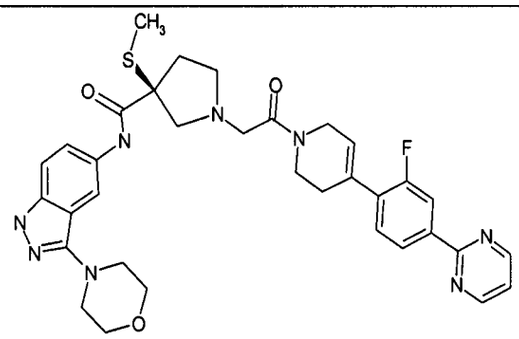
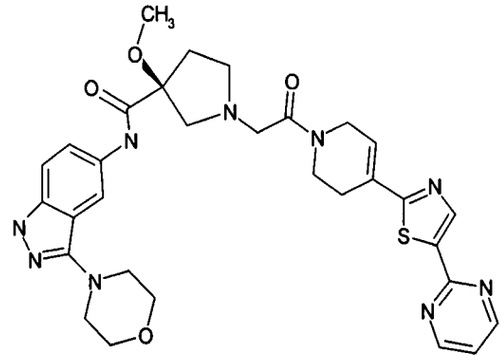
Ej No.	COMPUESTO	M+1	Tiempo de Retención (min)
673		685,4	2.13
674	 (ver también Preparación 51)	669,4	2.45
675	 (ver también Preparación 52)	685,4	2.98

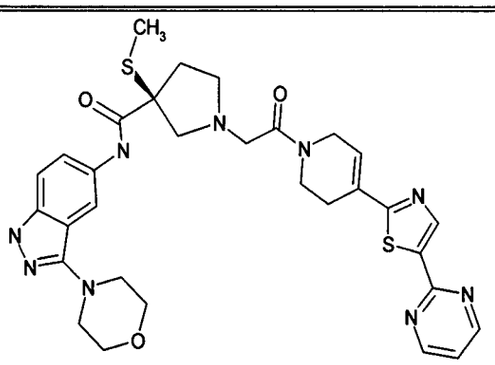
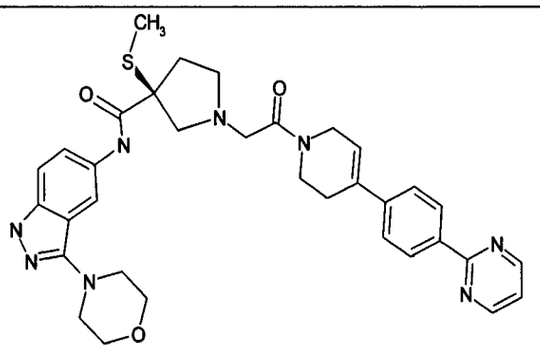
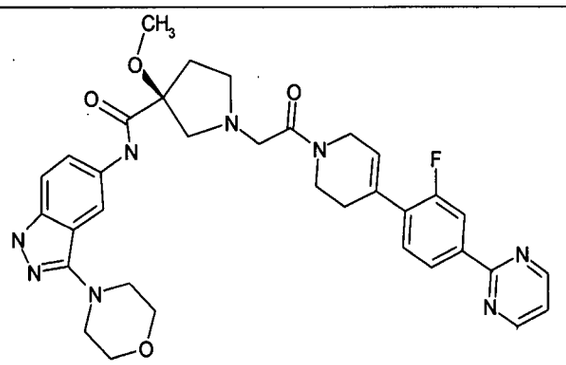
Ej No.	COMPUESTO	M+1	Tiempo de Retención (min)
676	 (ver también Preparación 54)	659,4	2.86
677		672.4	2.01
678		749,4	2.9

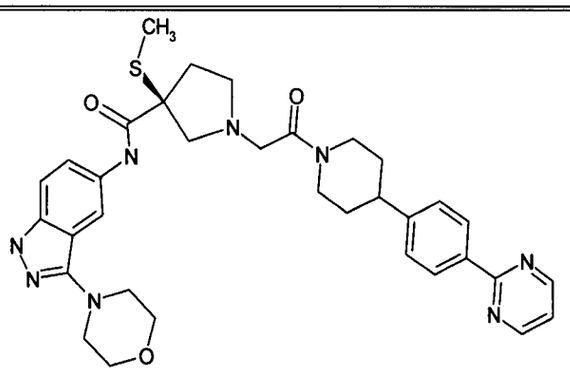
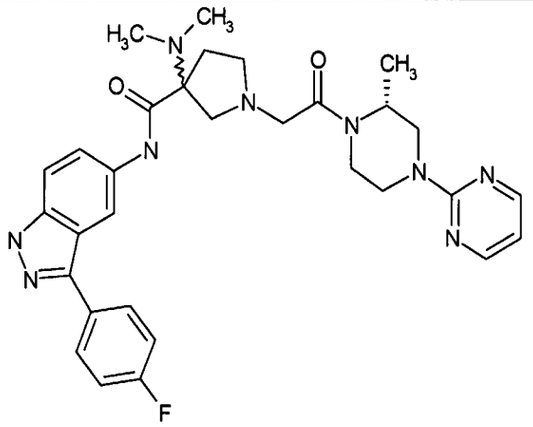
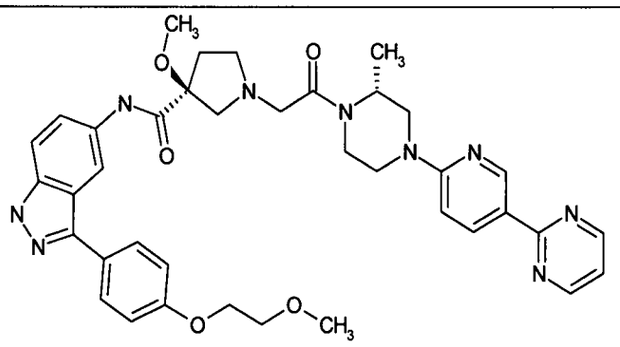
Ej No.	COMPUESTO	M+1	Tiempo de Retención (min)
679		681,4	2.85
680	 (ver también Preparación 55)	671,4	2.47
681		648,4	2.87

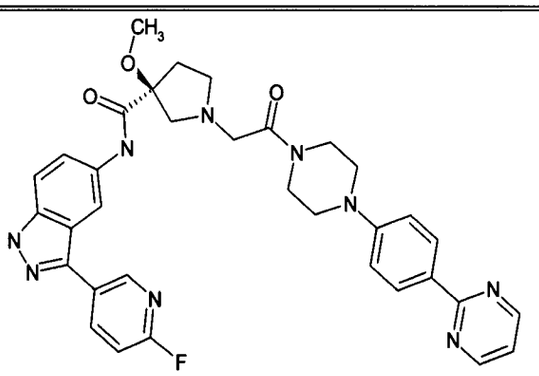
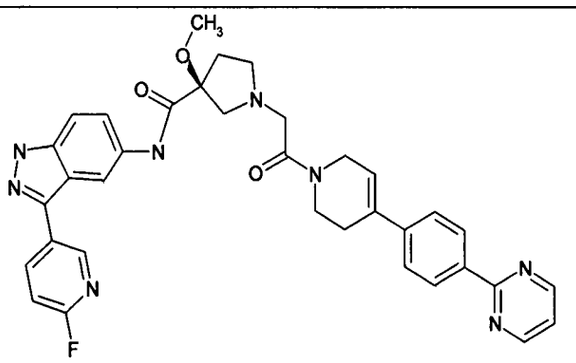
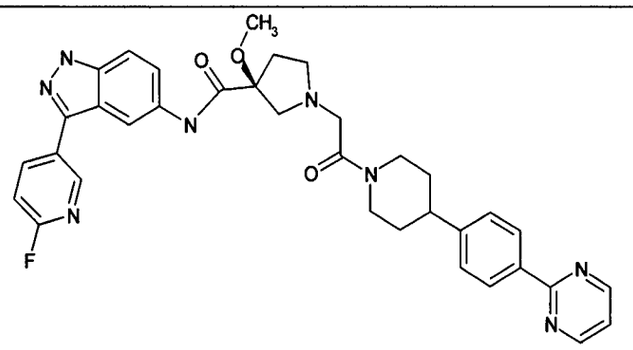
Ej No.	COMPUESTO	M+1	Tiempo de Retención (min)
682		701,4	3,36
683		675,4	2.33
684		661,7	3,21

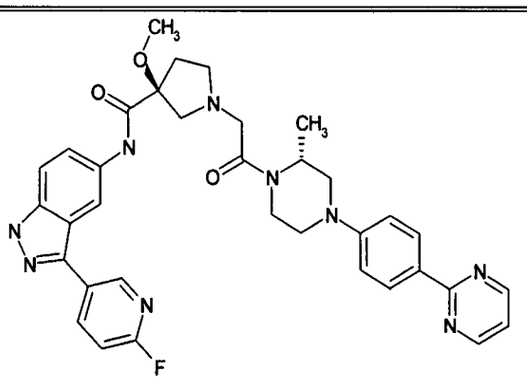
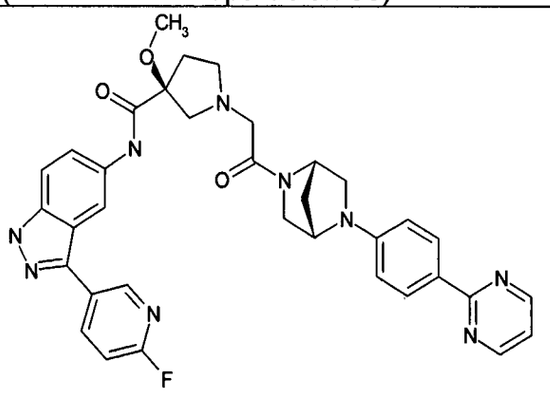
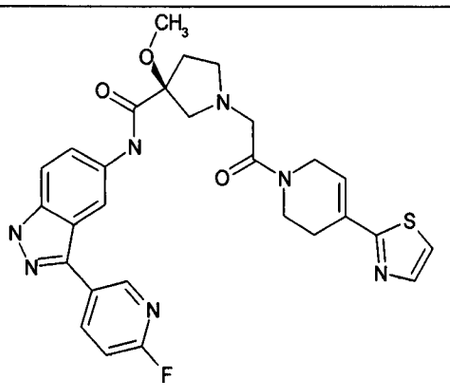
Ej No.	COMPUESTO	M+1	Tiempo de Retención (min)
685	 (ver también Preparación 56)	623	2.41
686		637	2.65
687		625	2.47

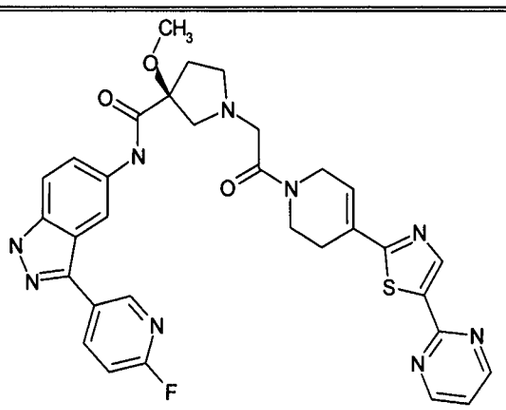
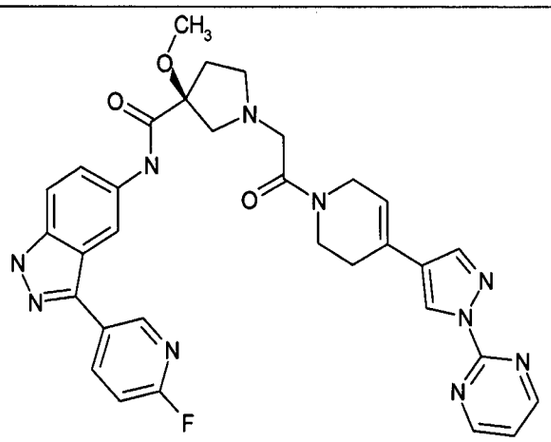
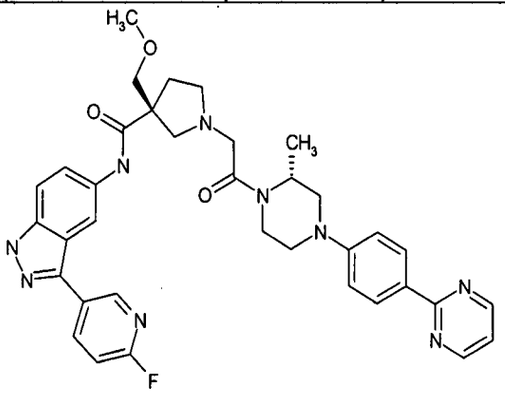
Ej No.	COMPUESTO	M+1	Tiempo de Retención (min)
688		672	3,08
689		657	2.63
690		630	2.18

Ej No.	COMPUESTO	M+1	Tiempo de Retención (min)
691		646	2.29
692		639	2.46
693		641	2,51

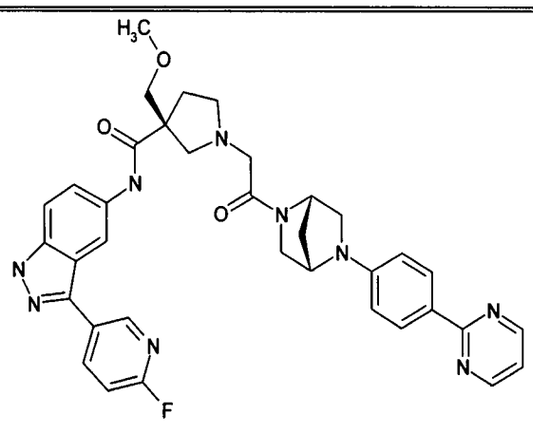
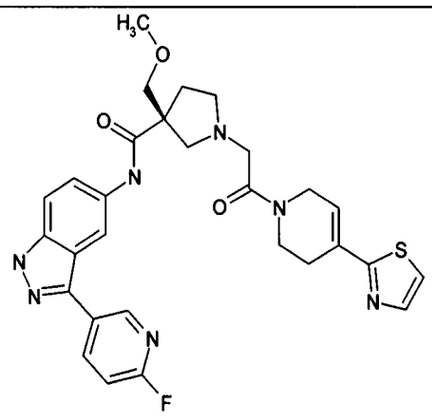
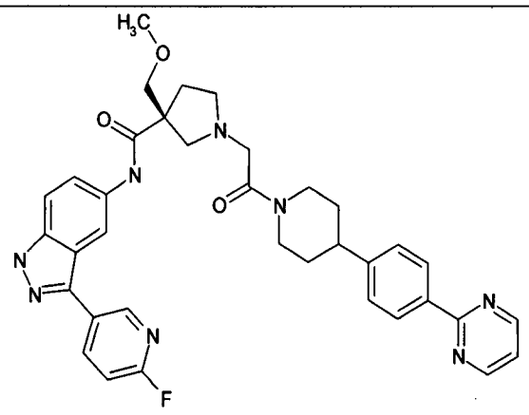
Ej No.	COMPUESTO	M+1	Tiempo de Retención (min)
694		641	2.49
695		586	2.62
696	 (ver también Preparación 57)	706	2.46

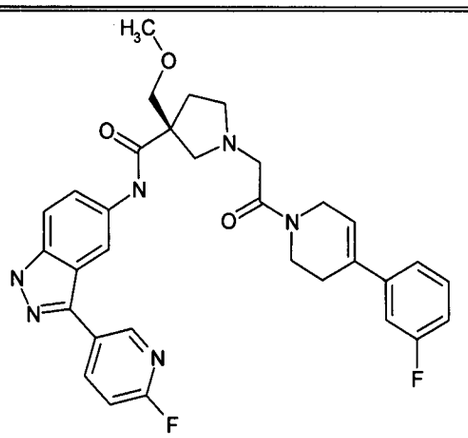
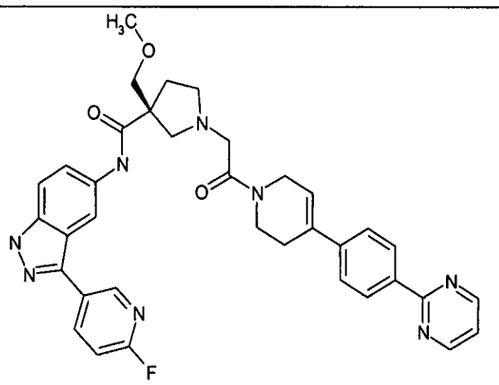
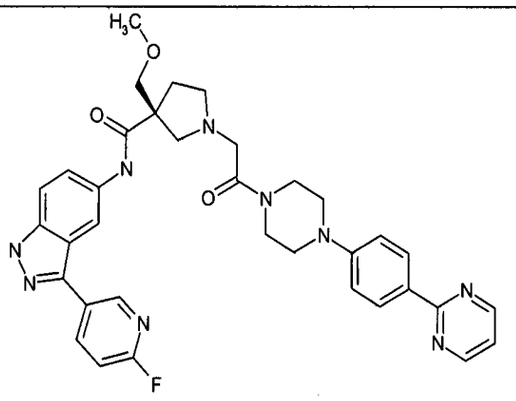
Ej No.	COMPUESTO	M+1	Tiempo de Retención (min)
697		636,7	3,12
698		633,7	3,46
699		635,7	3,33

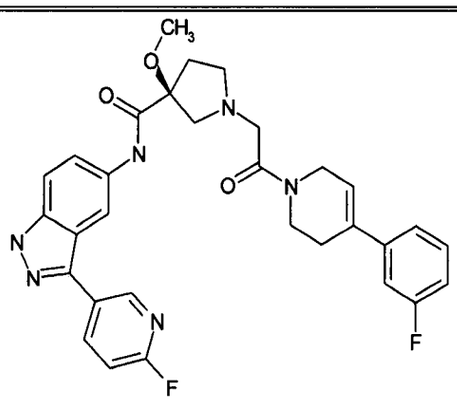
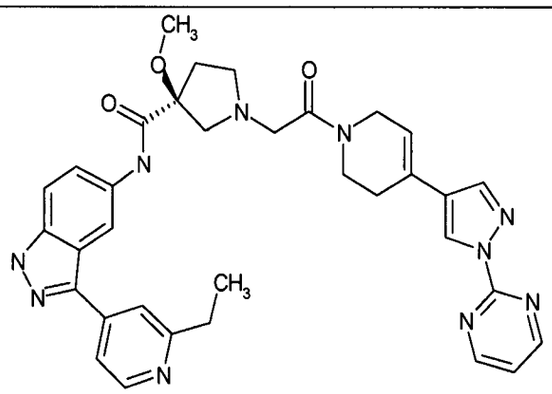
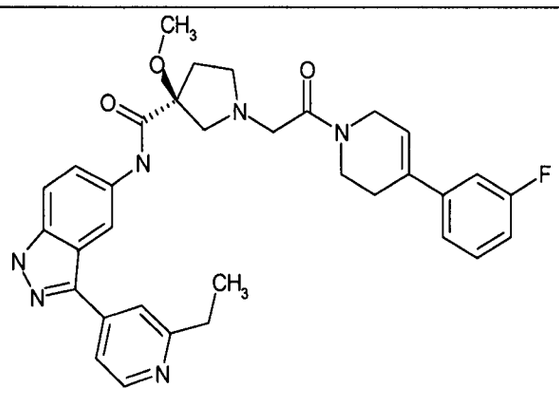
Ej No.	COMPUESTO	M+1	Tiempo de Retención (min)
700	 (ver también Preparación 58)	650,7	3,24
701		648,7	3,05
702		562.6	2.83

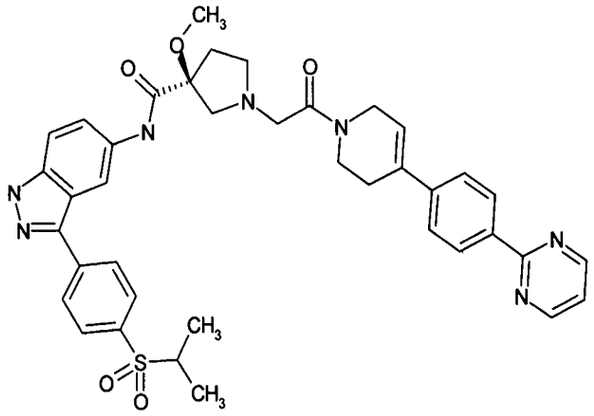
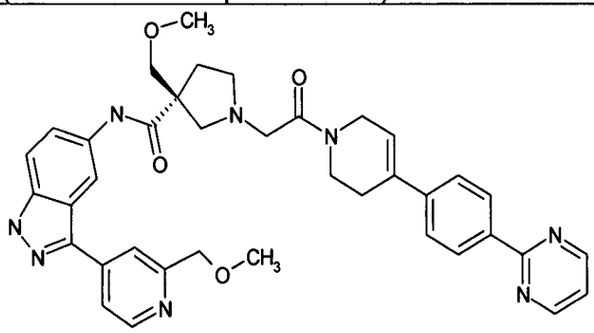
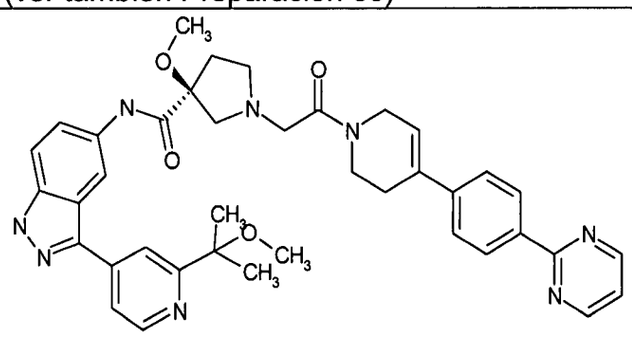
Ej No.	COMPUESTO	M+1	Tiempo de Retención (min)
703		640,7	3,12
704	 (ver también Preparación 59)	623,7	2.88
705		664,7	3,4

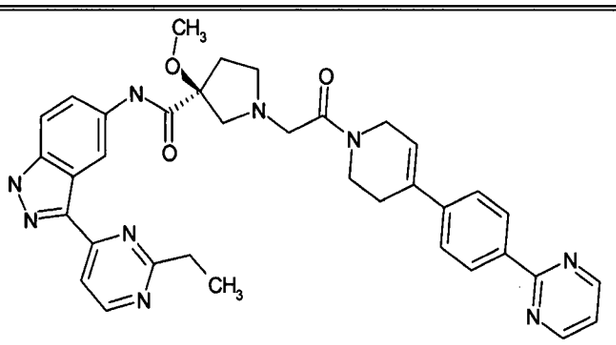
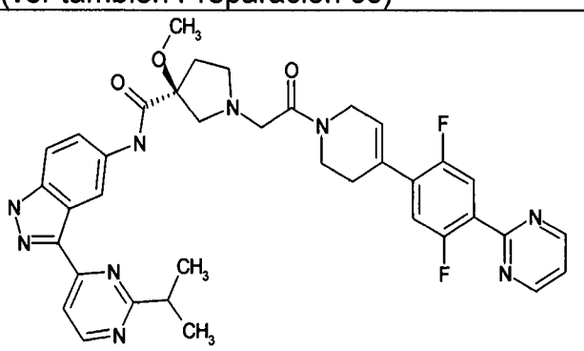
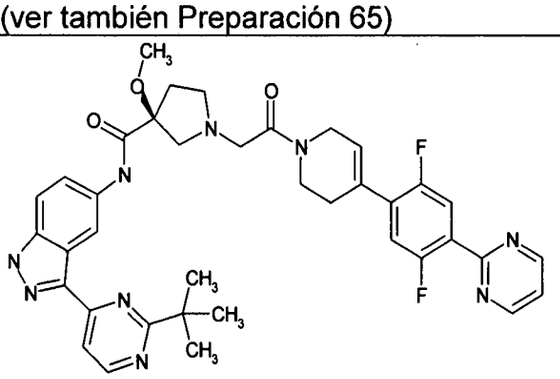
838

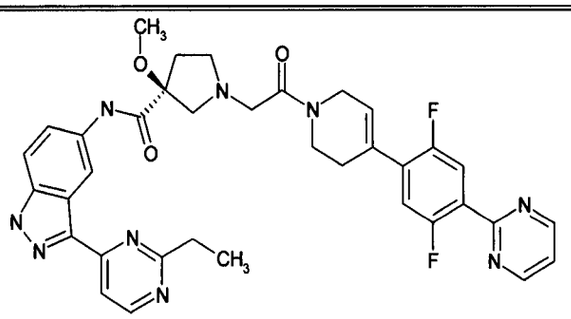
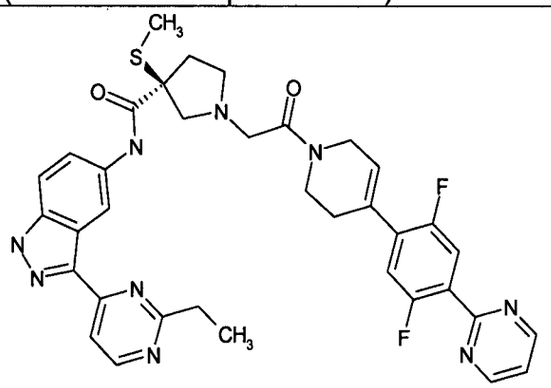
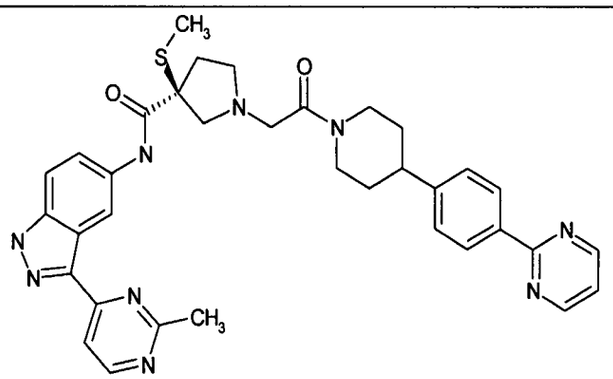
Ej No.	COMPUESTO	M+1	Tiempo de Retención (min)
706		662.7	3,16
707		576,7	2.97
708		649,7	3,45

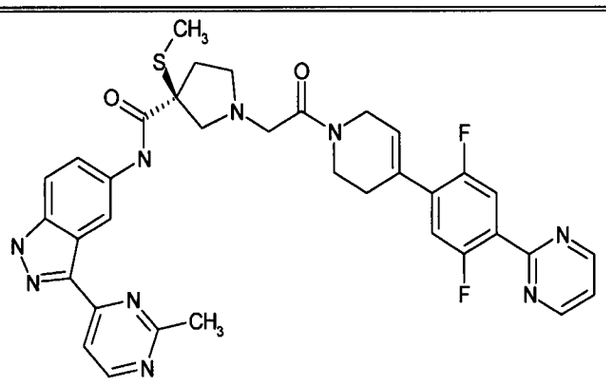
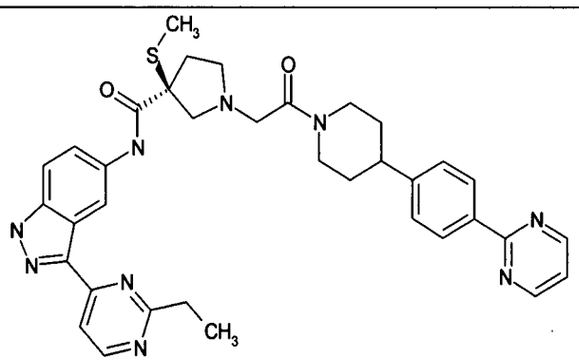
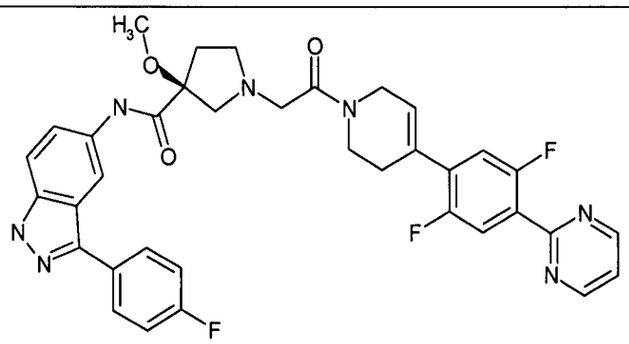
Ej No.	COMPUESTO	M+1	Tiempo de Retención (min)
709		587,6	3,58
710		647,7	3,49
711		650,7	3,23

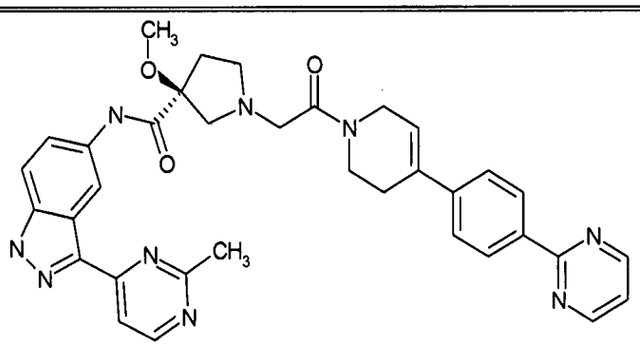
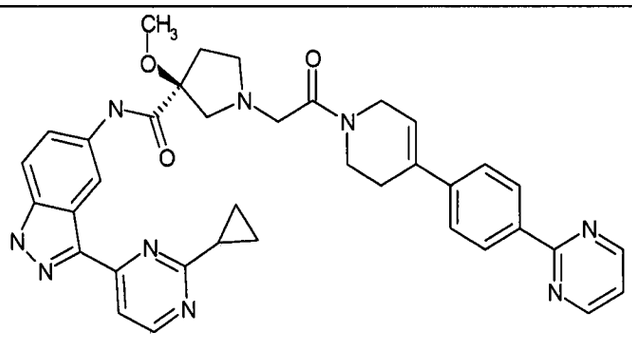
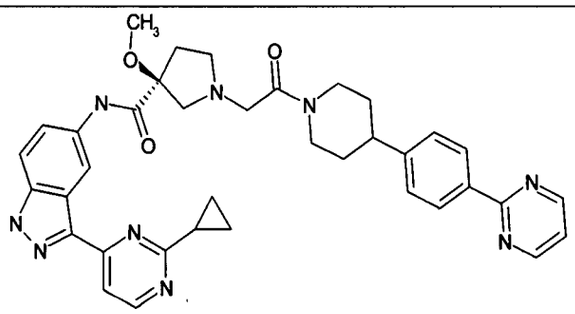
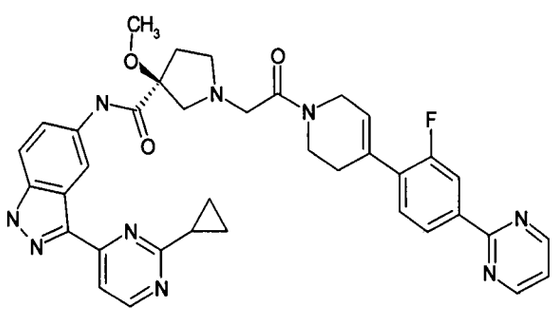
Ej No.	COMPUESTO	M+1	Tiempo de Retención (min)
712		573,6	3,45
713		633,7	2.34
714	 (ver también Preparación 60)	583,7	2.81

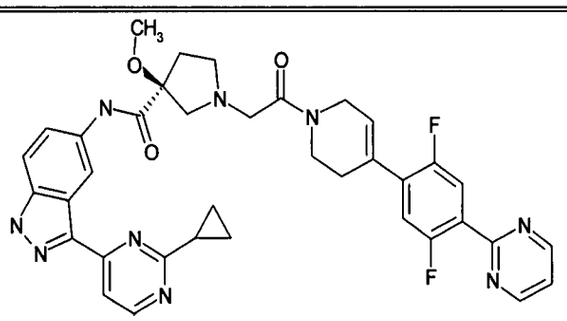
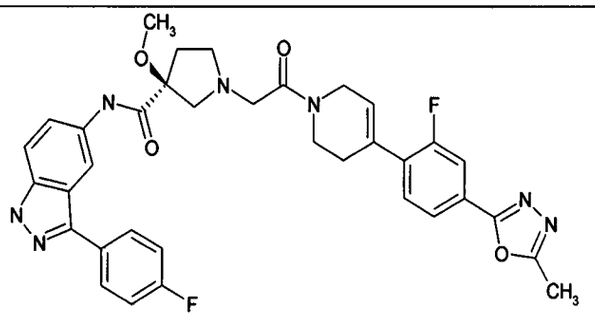
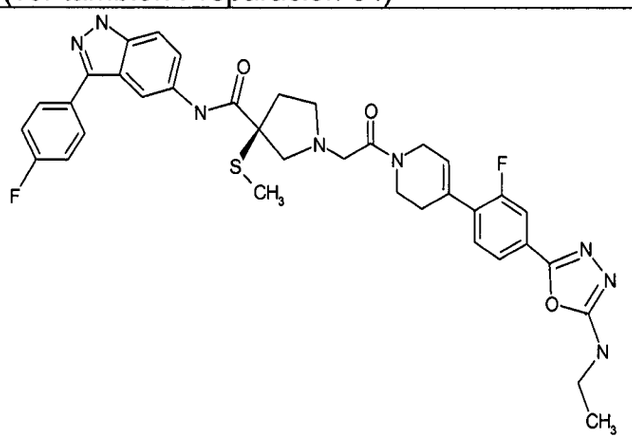
Ej No.	COMPUESTO	M+1	Tiempo de Retención (min)
715	 (ver también Preparación 62)	602.8	3,65
716	 (ver también Preparación 63)	709,8	2.62
717	 (ver también Preparación 64)	683,9	3

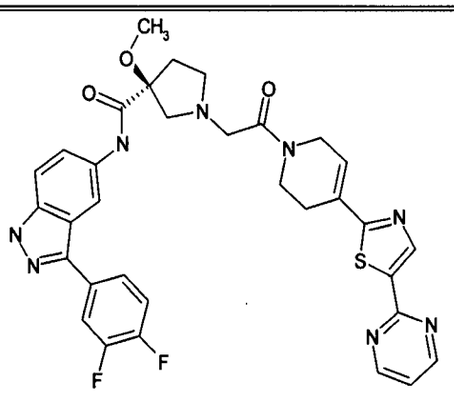
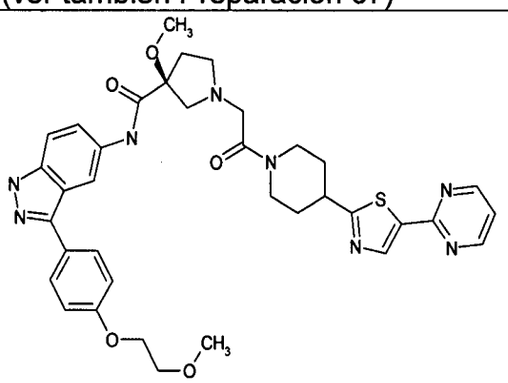
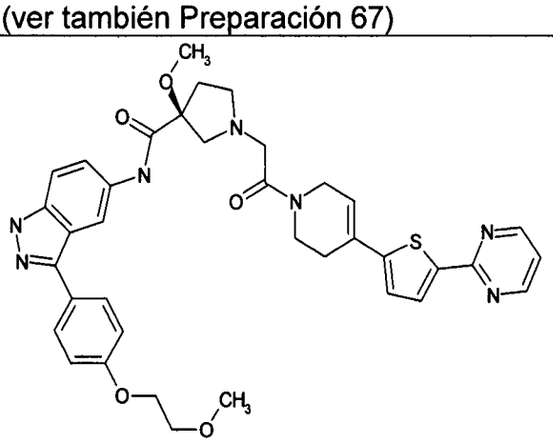
Ej No.	COMPUESTO	M+1	Tiempo de Retención (min)
718	 (ver también Preparación 65)	676,8	3,09
719	 (ver también Preparación 65)	694,3	3,71
720	 (ver también Preparación 65)	708,4	4,08

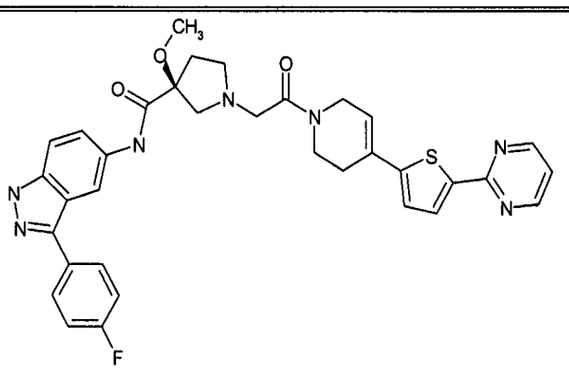
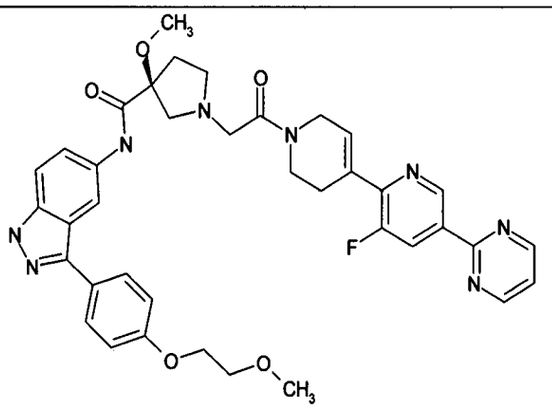
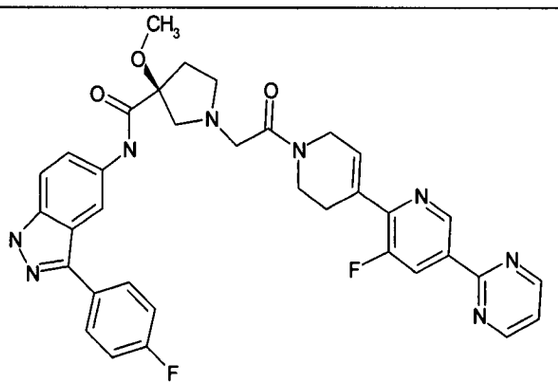
Ej No.	COMPUESTO	M+1	Tiempo de Retención (min)
721	 (ver también Preparación 65)	680,3	3,09
722		696,2	3,52
723		648,3	2.98

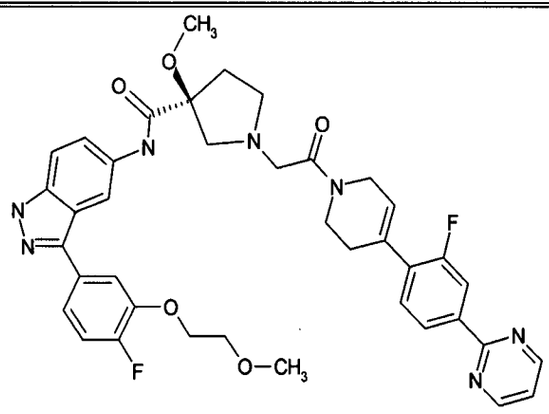
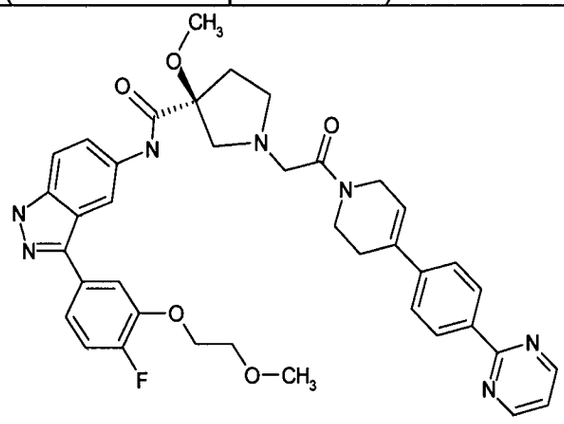
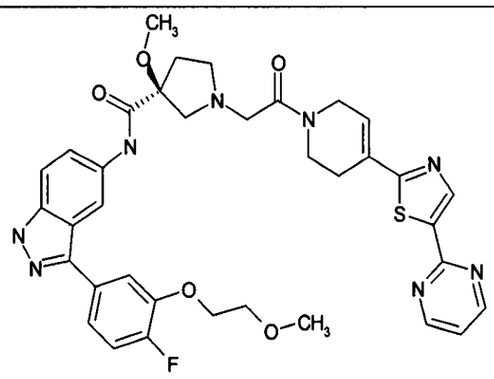
Ej No.	COMPUESTO	M+1	Tiempo de Retención (min)
724		682.2	3,01
725		667,3	3,12
726	 (ver también Preparación 66)	668,4	3,21

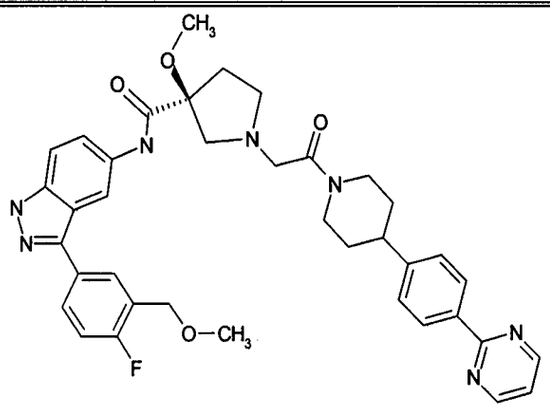
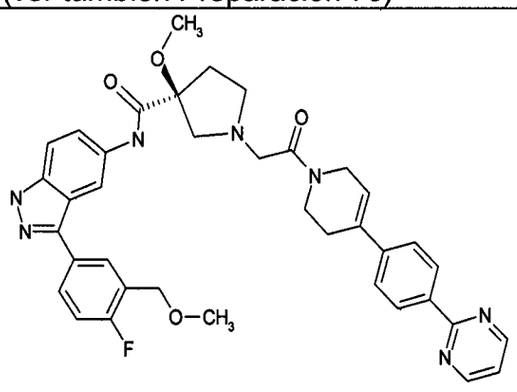
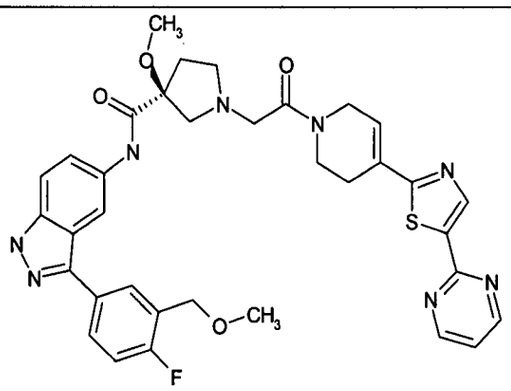
Ej No.	COMPUESTO	M+1	Tiempo de Retención (min)
727		630,3	3,29
728		656	3,22
729		658,3	3,38
730		674	3,84

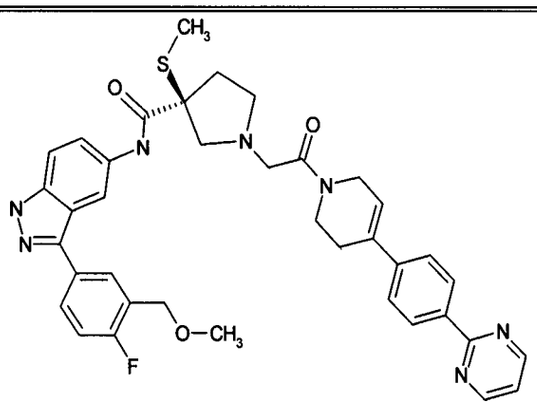
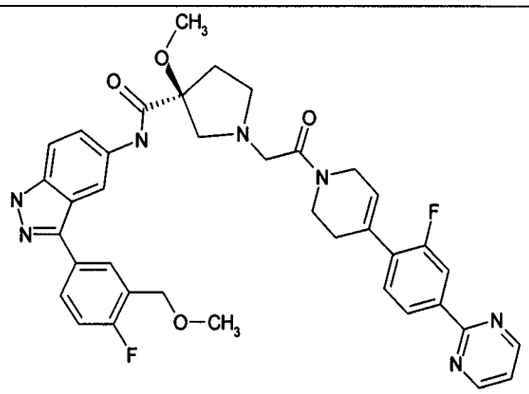
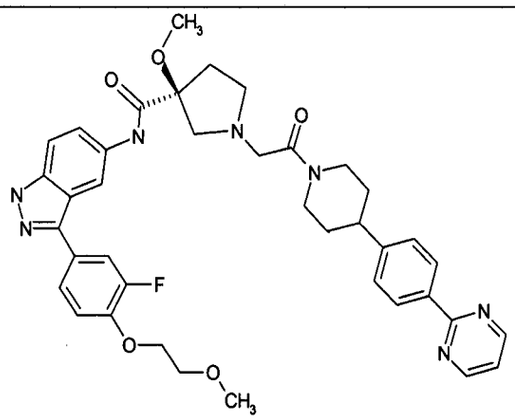
Ej No.	COMPUESTO	M+1	Tiempo de Retención (min)
731		692	3,41
732	 (ver también Preparación 84)	654,4	3,02
733		699,4	2.9

Ej No.	COMPUESTO	M+1	Tiempo de Retención (min)
734	 (ver también Preparación 67)	657,4	2.73
735	 (ver también Preparación 67)	697,3	3,31
736	 (ver también Preparación 68)	694,2	4,07

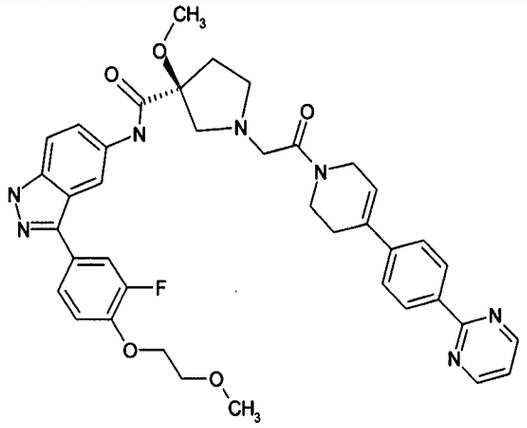
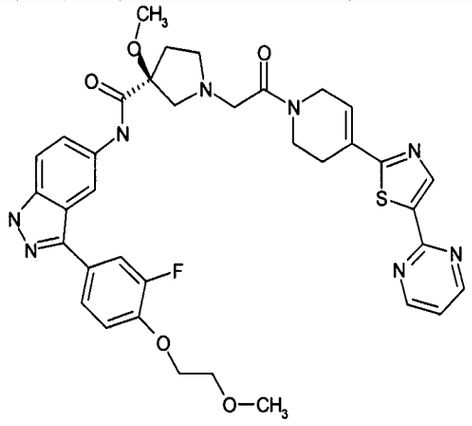
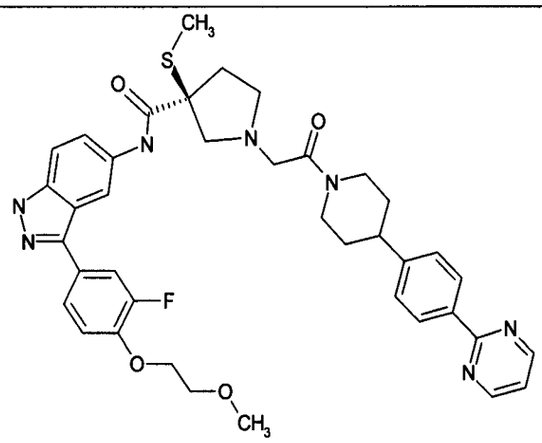
Ej No.	COMPUESTO	M+1	Tiempo de Retención (min)
737		638,3	3,56
738		707,3	3,57
739		651.3	3,69

Ej No.	COMPUESTO	M+1	Tiempo de Retención (min)
740	 (ver también Preparación 69)	724,4	3,16
741		706,4	3,24
742		713,4	2.7

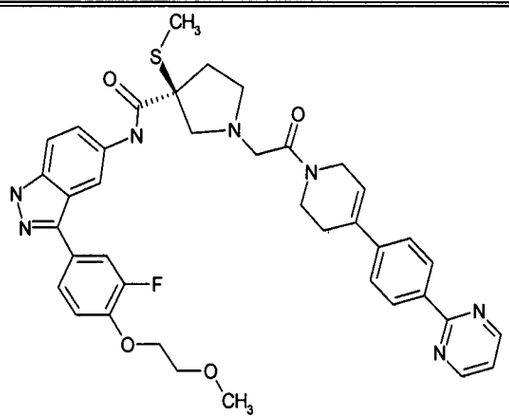
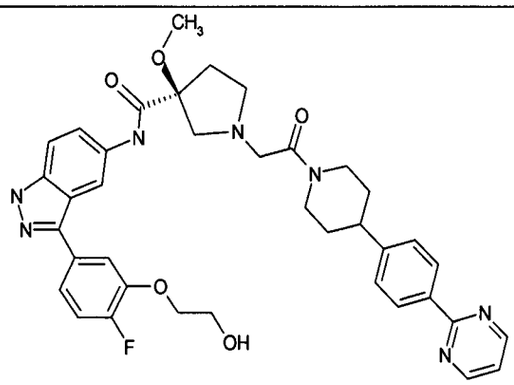
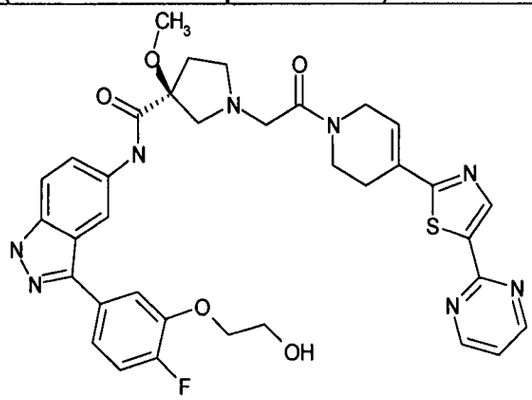
Ej No.	COMPUESTO	M+1	Tiempo de Retención (min)
743	 (ver también Preparación 70)	678,4	3,2
744		676,4	3,18
745		683,4	2.71

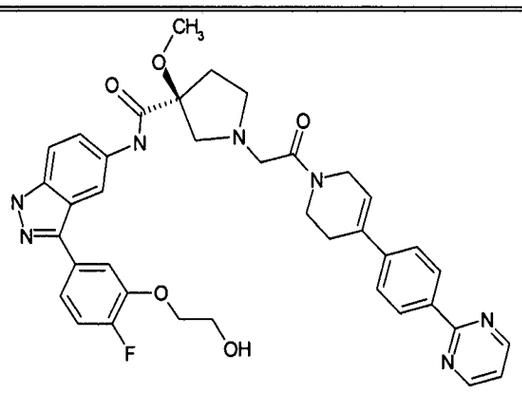
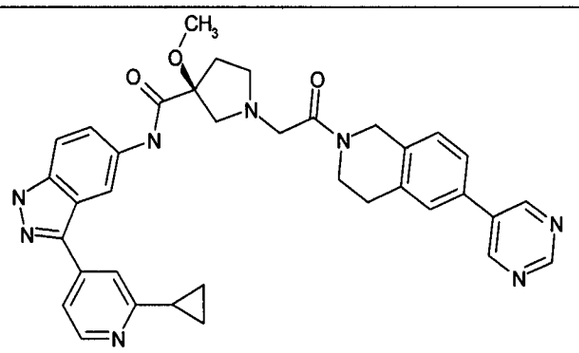
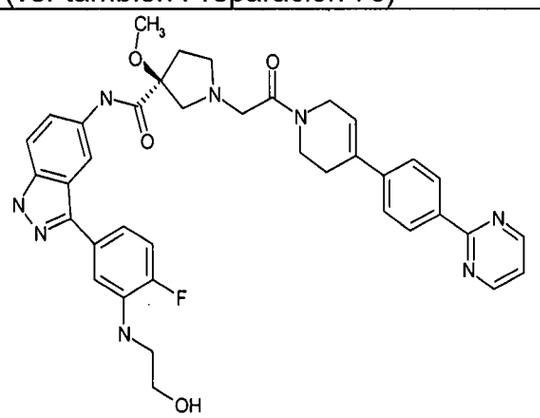
Ej No.	COMPUESTO	M+1	Tiempo de Retención (min)
746		692.4	2.91
747		694,4	2.91
748		708,4	2.81

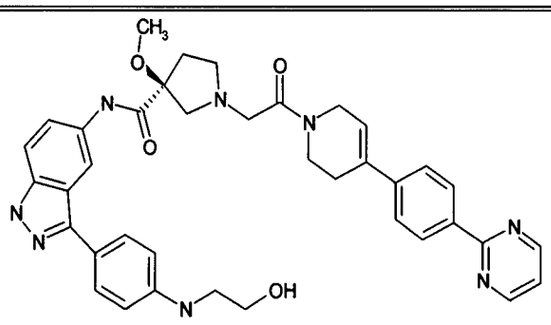
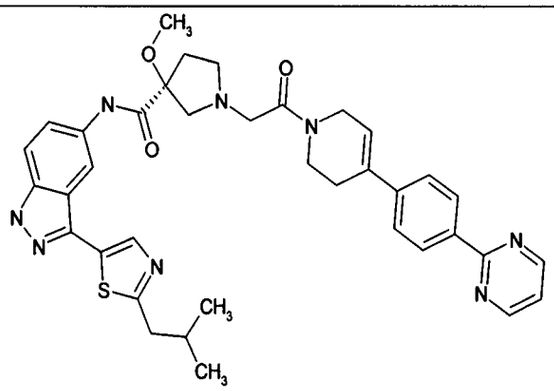
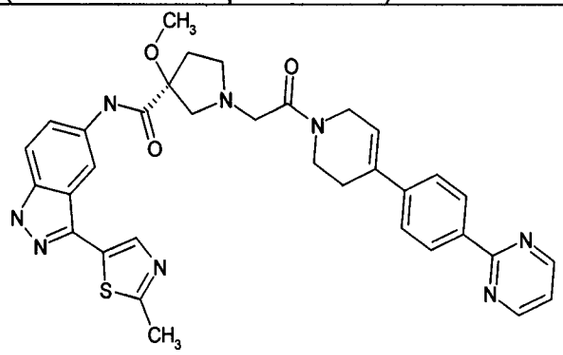
852

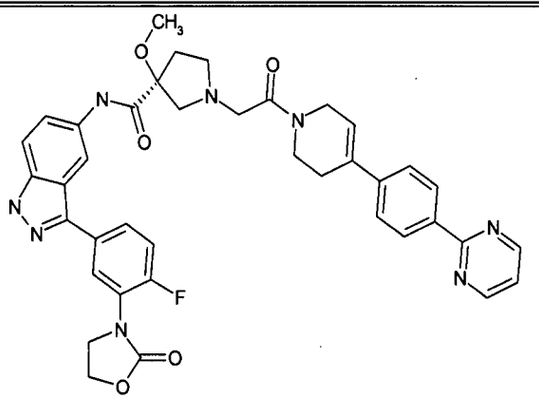
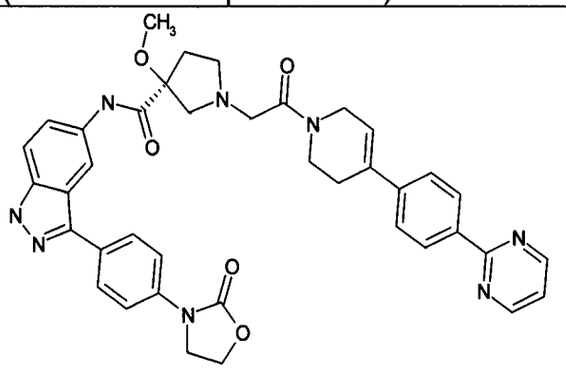
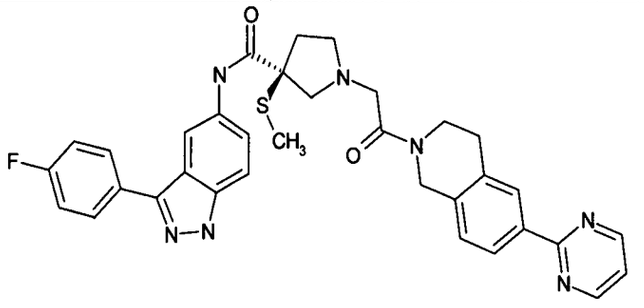
Ej No.	COMPUESTO	M+1	Tiempo de Retención (min)
749	 (ver también Preparación 71)	706,4	2.85
750		713,4	2.68
751		724,4	2.94

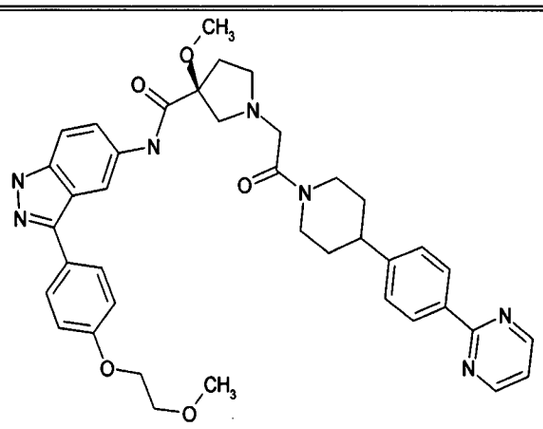
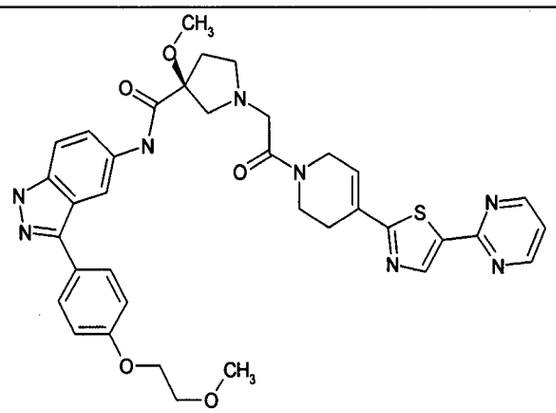
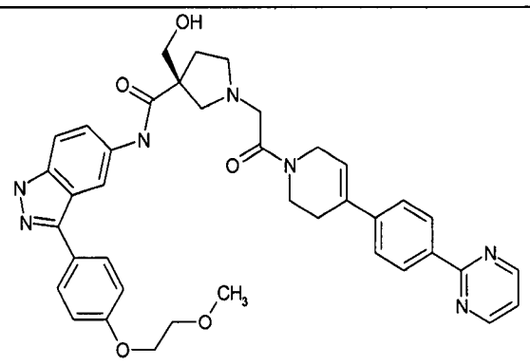
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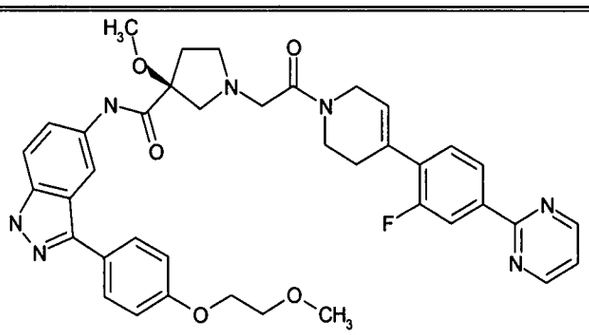
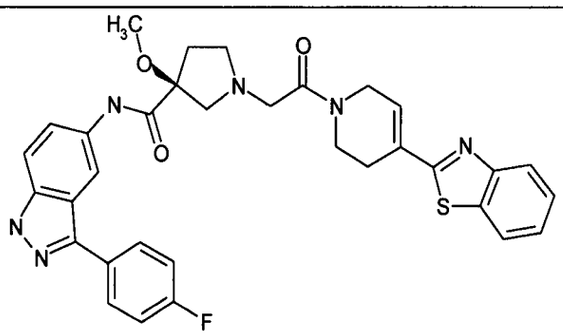
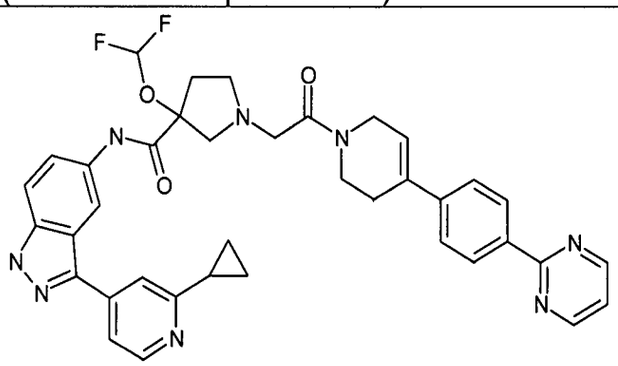
Ej No.	COMPUESTO	M+1	Tiempo de Retención (min)
752		722.4	2.97
753	 (ver también Preparación 72)	694,4	2.62
754		699,4	2.44

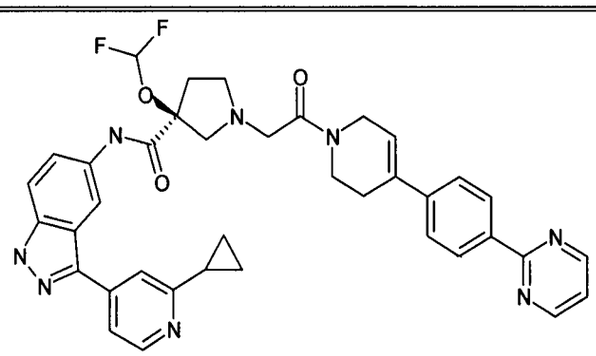
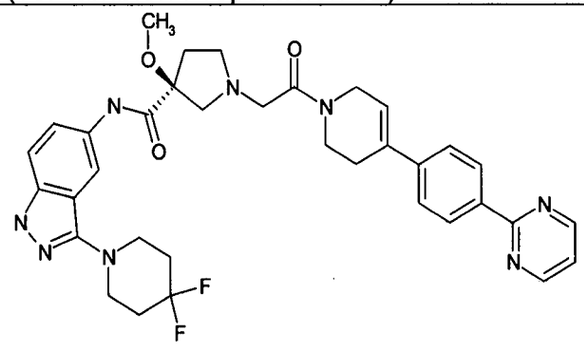
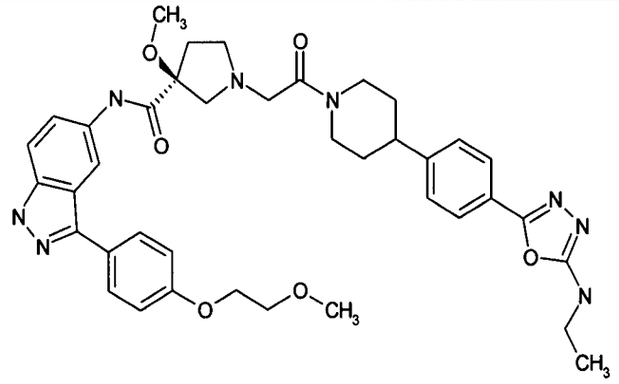
Ej No.	COMPUESTO	M+1	Tiempo de Retención (min)
755		692.4	2.65
756	 (ver también Preparación 73)	629,7	2,57
757	 (ver también Preparación 74)	691.2	3,54

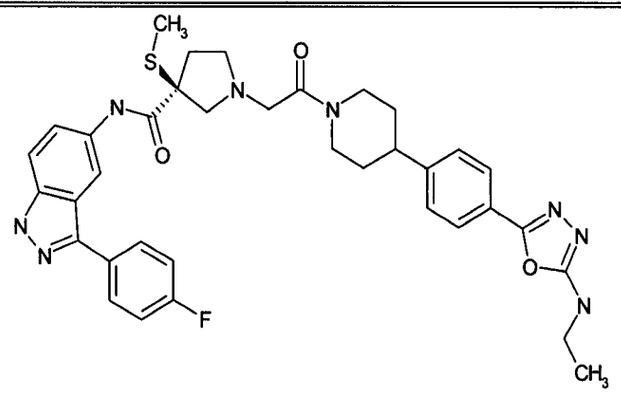
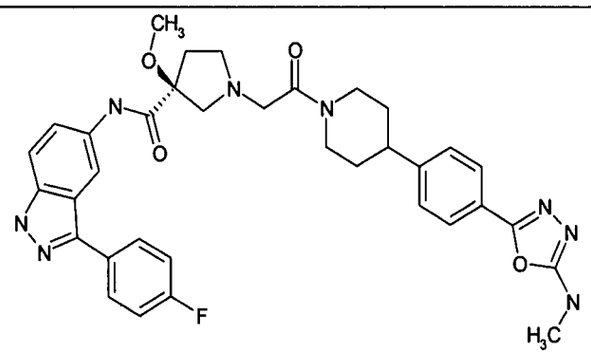
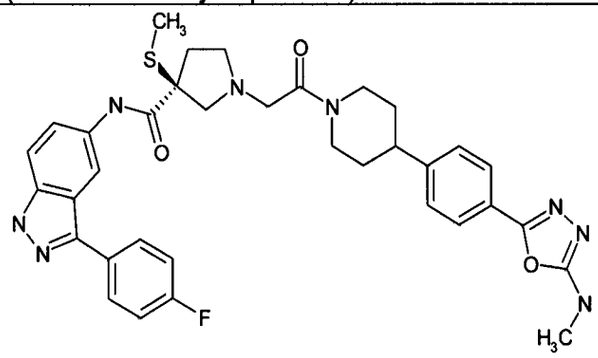
Ej No.	COMPUESTO	M+1	Tiempo de Retención (min)
758		673,2	2.92
759	 (ver también Preparación 76)	677,2	3,93
760	 (ver también Preparación 77)	635,2	3,33

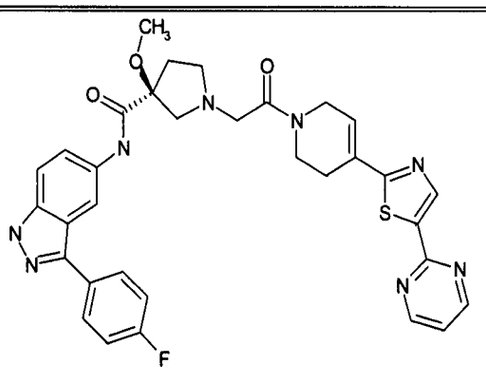
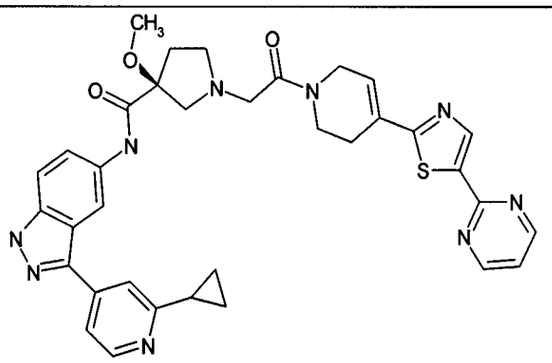
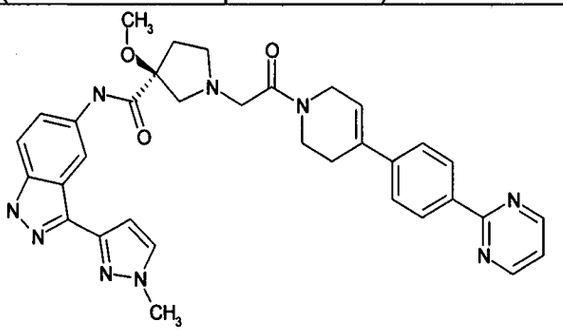
Ej No.	COMPUESTO	M+1	Tiempo de Retención (min)
761	 (ver también Preparación 78)	717,2	3,8
762	 (ver también Preparación 79)	699,7	3,31
763	 (ver también Preparación 80)	622.3	3,52

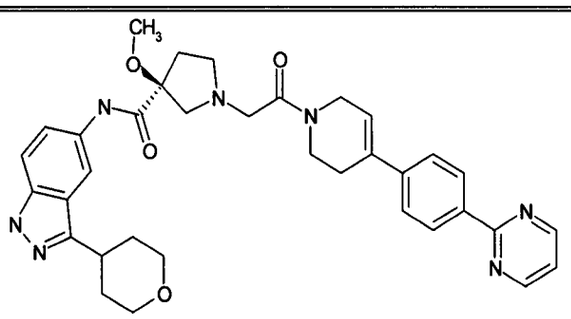
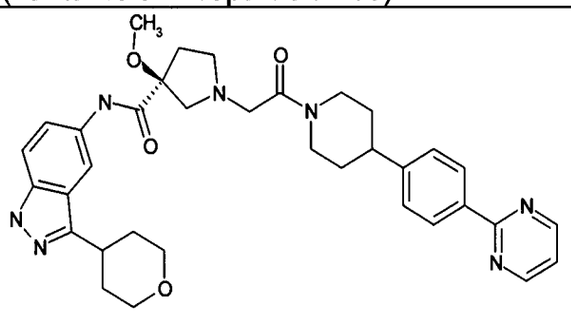
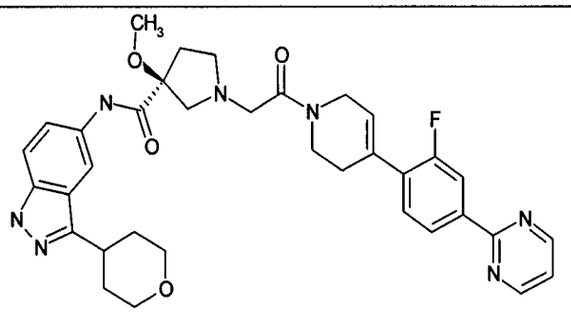
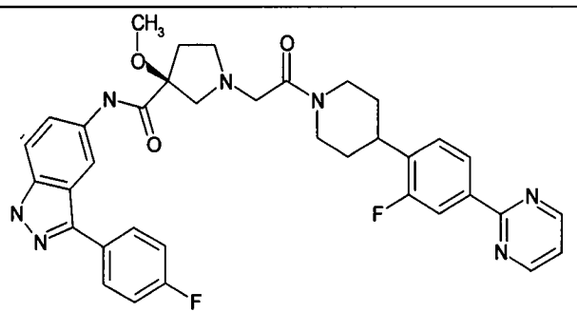
Ej No.	COMPUESTO	M+1	Tiempo de Retención (min)
764		690,3	3,8
765		695,3	3,56
766		688,4	3,43

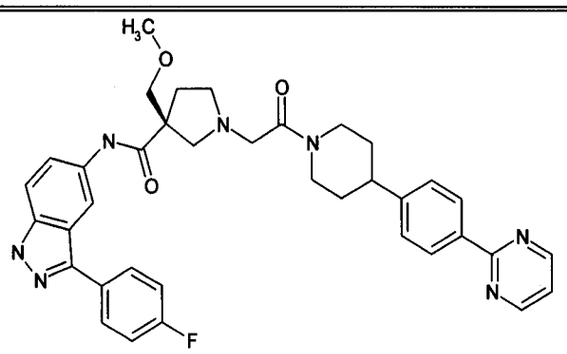
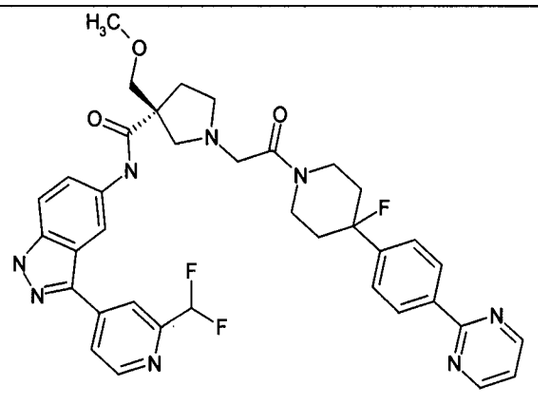
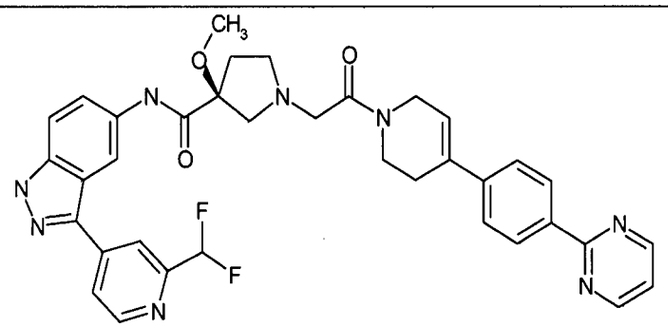
Ej No.	COMPUESTO	M+1	Tiempo de Retención (min)
767		706,4	3,05
768	 (ver también Preparación 81)	611.3	3,17
769		691,4	2.44

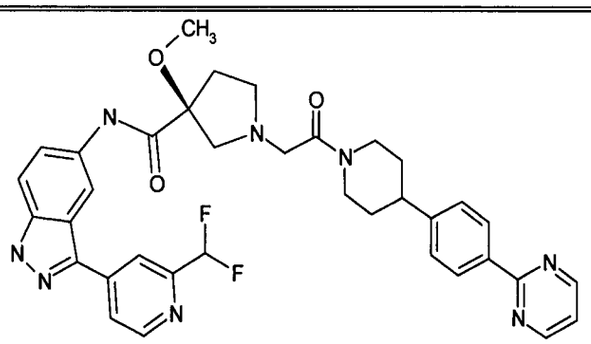
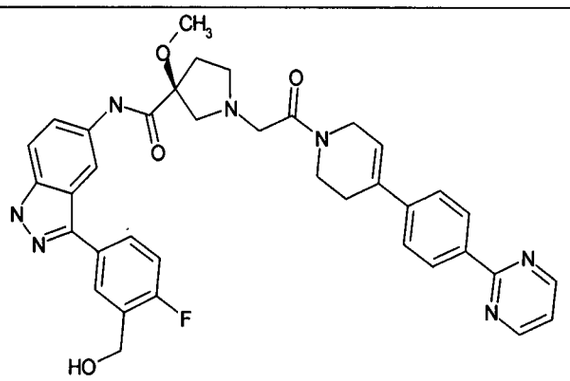
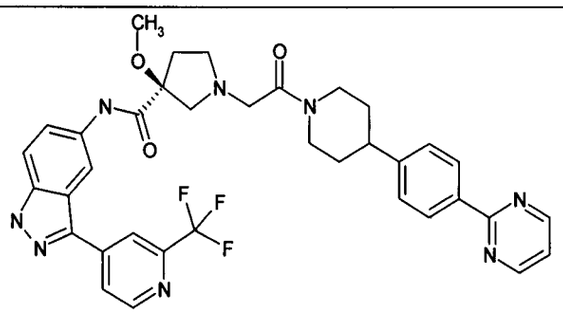
Ej No.	COMPUESTO	M+1	Tiempo de Retención (min)
770	 (ver también Preparación 82)	691,4	2.31
771	 (ver también Preparación 83)	657,4	2.78
772		723,4	2.64

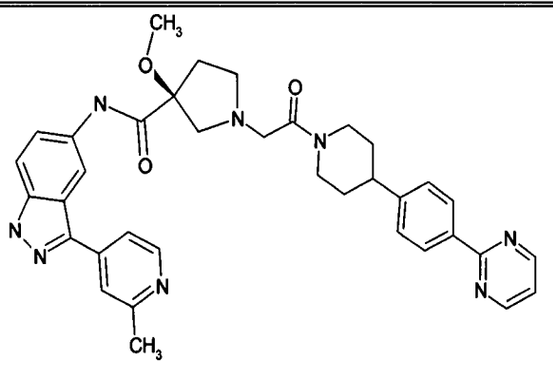
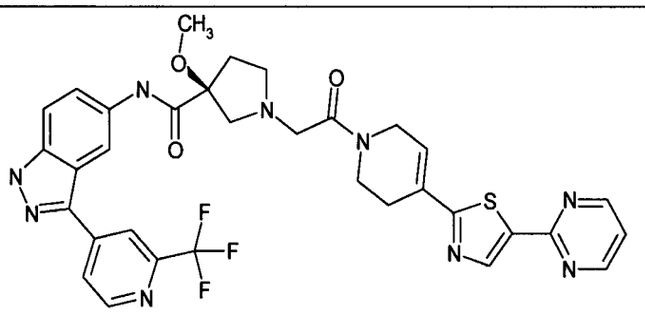
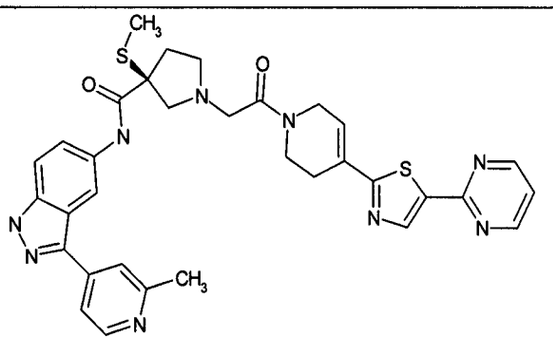
Ej No.	COMPUESTO	M+1	Tiempo de Retención (min)
773		683,4	2.67
774	 (ver también Ejemplo 624)	653,4	2,54
775		669,4	2,58

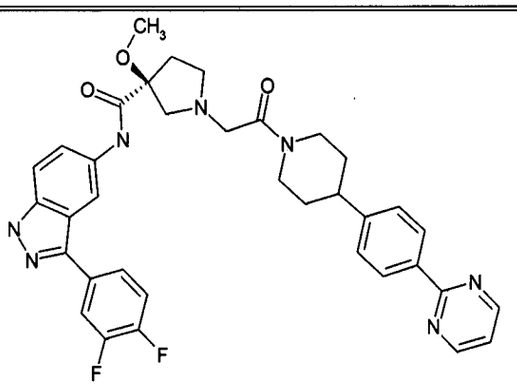
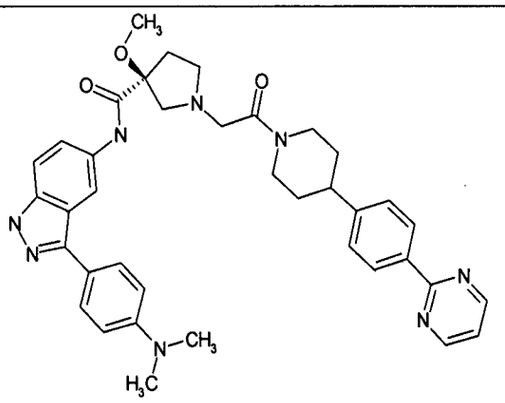
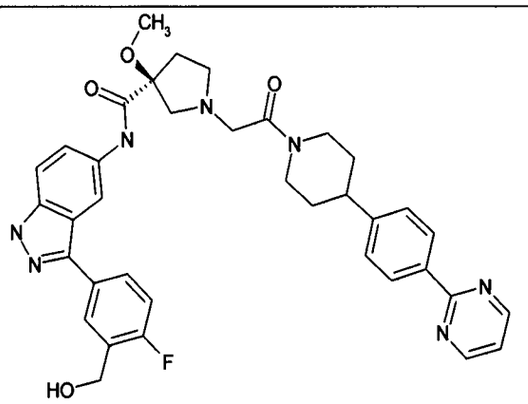
Ej No.	COMPUESTO	M+1	Tiempo de Retención (min)
776		639,7	3,41
777	 (ver también Preparación 67)	662	2.72
778	 (ver también Preparación 85)	618	3,19

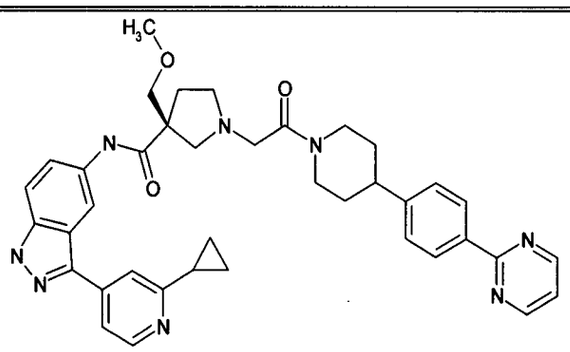
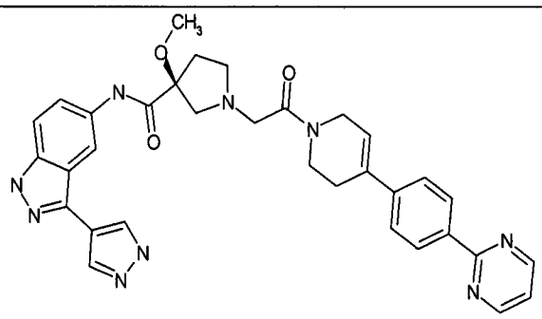
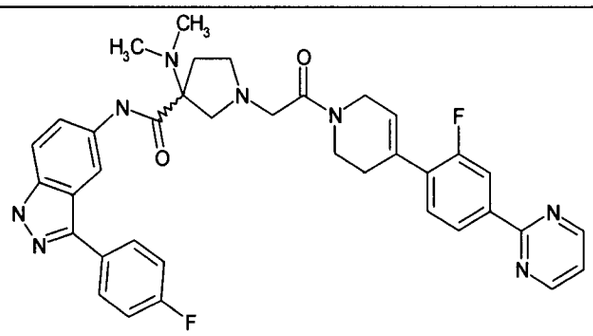
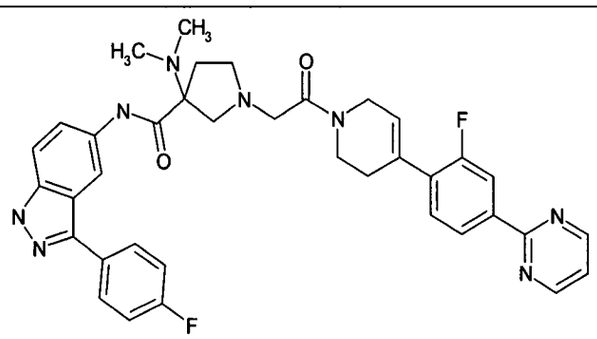
Ej No.	COMPUESTO	M+1	Tiempo de Retención (min)
779	 (ver también Preparación 86)	622	3,16
780		624	3,13
781		640	3,37
782		652.4	3,35

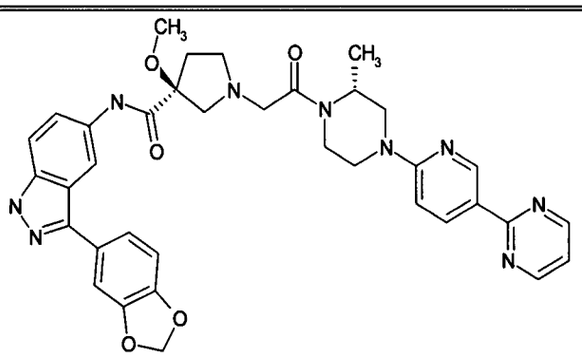
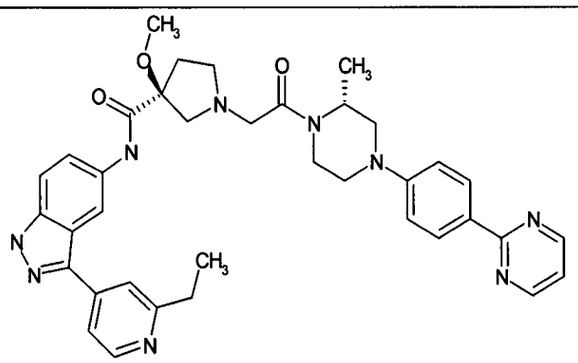
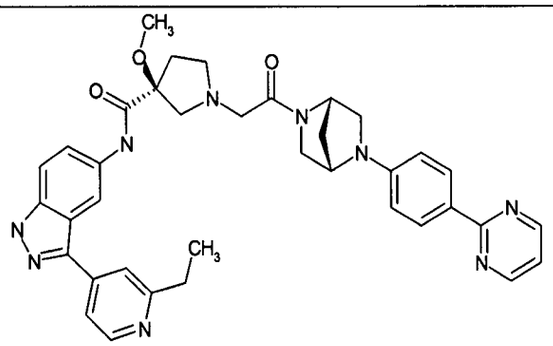
Ej No.	COMPUESTO	M+1	Tiempo de Retención (min)
783		648,4	3,11
784		699,4	3
785		665,4	2.97

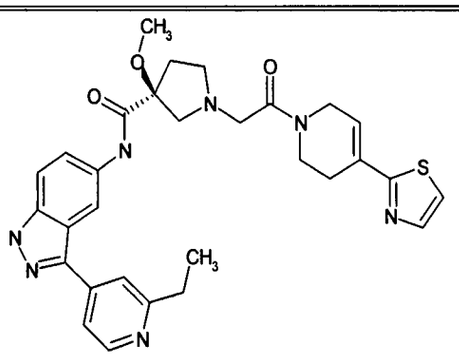
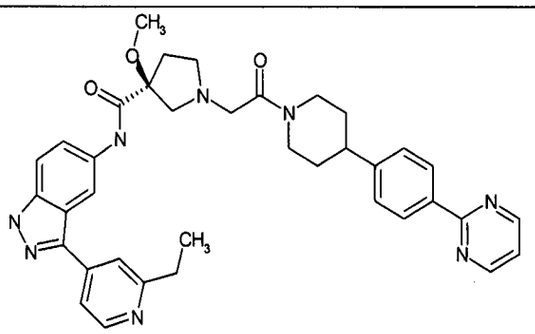
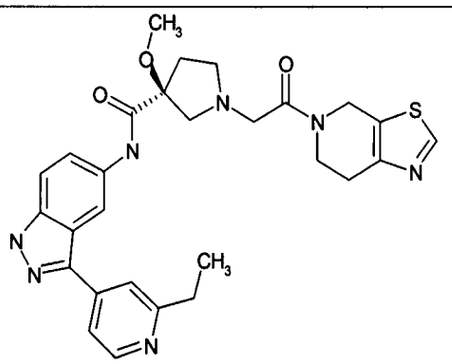
Ej No.	COMPUESTO	M+1	Tiempo de Retención (min)
786		667,4	2.89
787		662.4	2.84
788		685,4	2.92

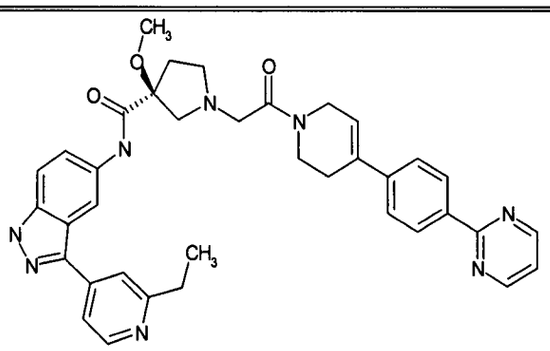
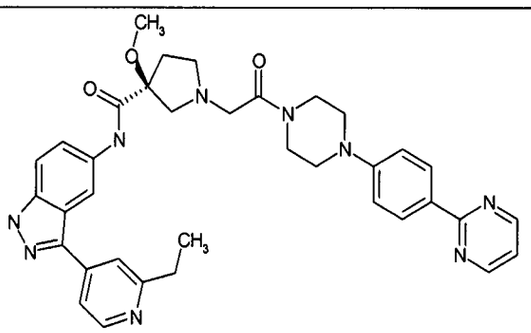
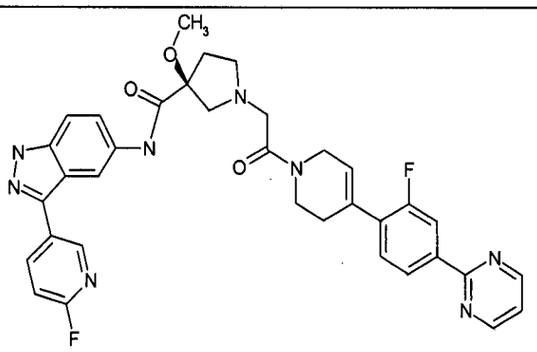
Ej No.	COMPUESTO	M+1	Tiempo de Retención (min)
789		631.3	2.07
790		690,4	2.75
791		652.4	1,83

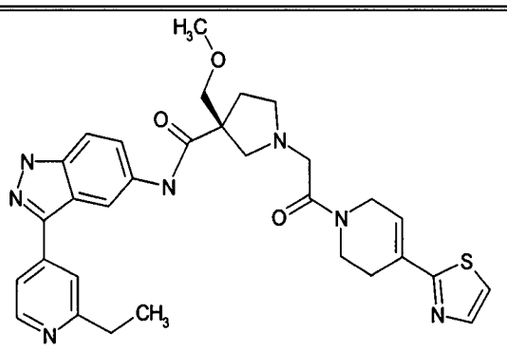
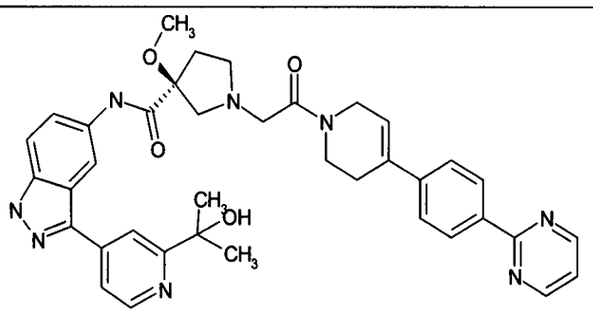
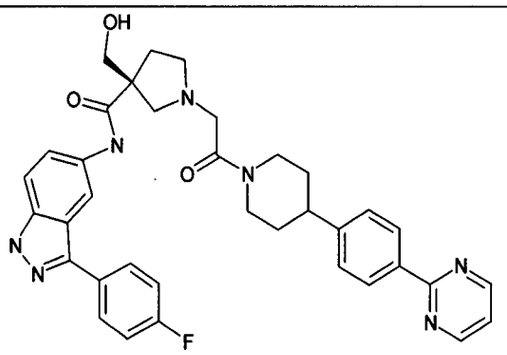
Ej No.	COMPUESTO	M+1	Tiempo de Retención (min)
792		652.4	2.94
793		659,4	2.41
794		664,4	2.76

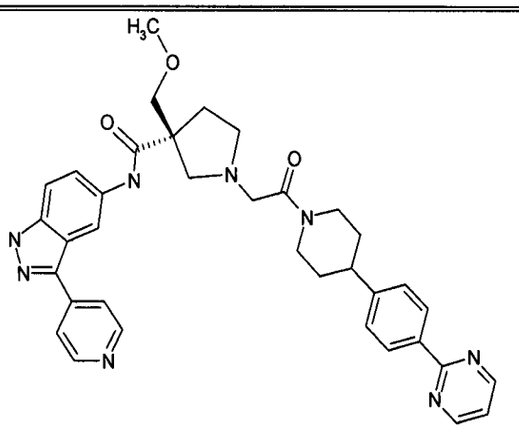
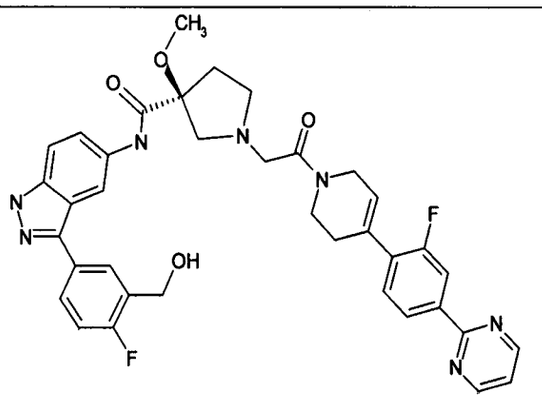
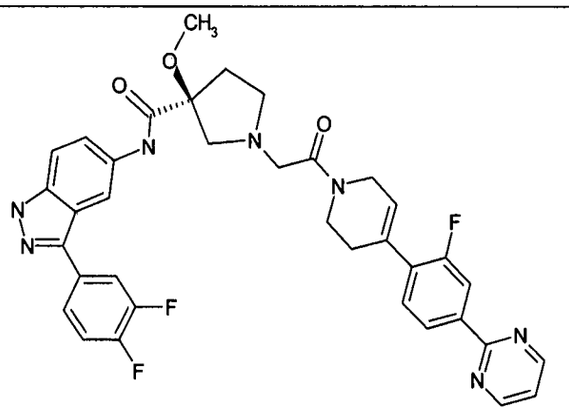
Ej No.	COMPUESTO	M+1	Tiempo de Retención (min)
795		671	2,59
796		604	2.33
797		663	3,26
798		663	3,26

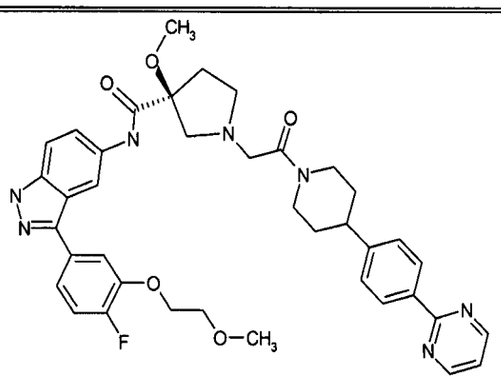
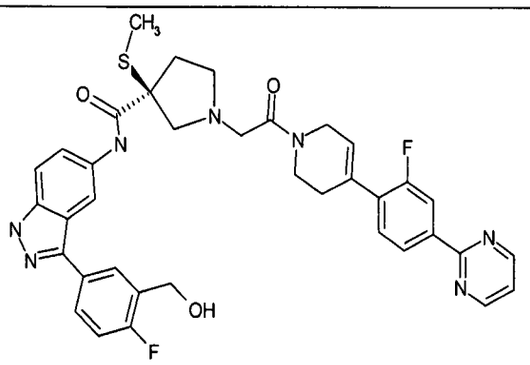
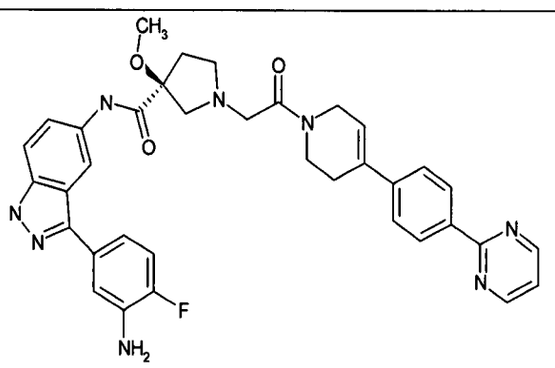
Ej No.	COMPUESTO	M+1	Tiempo de Retención (min)
799		676	2.49
800		660,8	2.71
801		658,8	2,5

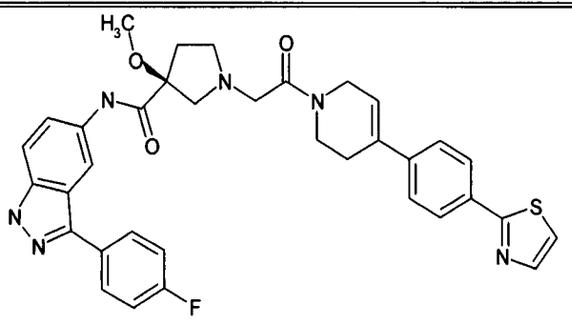
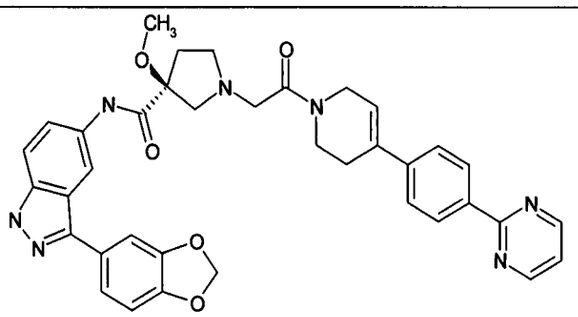
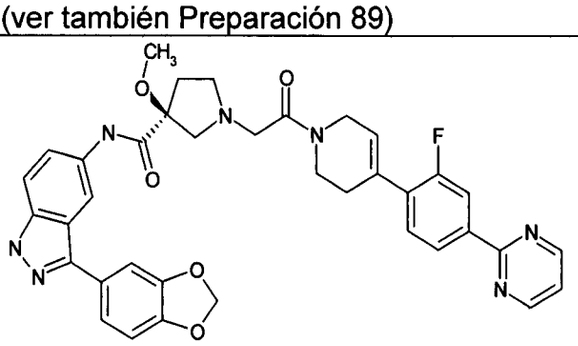
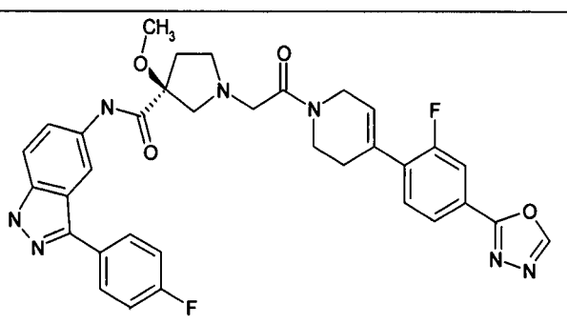
Ej No.	COMPUESTO	M+1	Tiempo de Retención (min)
802		572.7	2.27
803		645,8	2.73
804		546,7	2.02

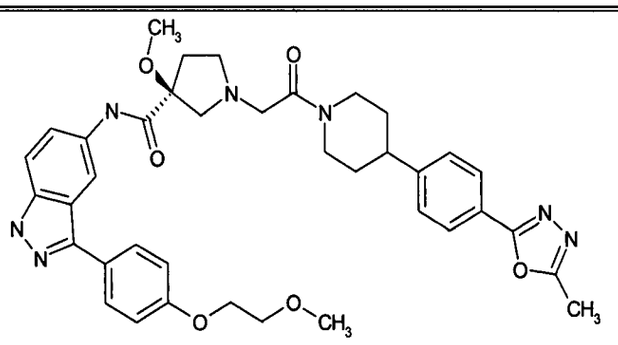
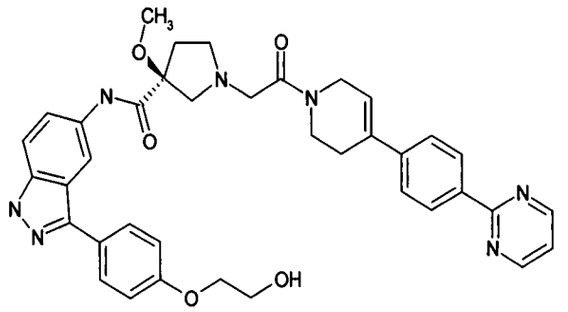
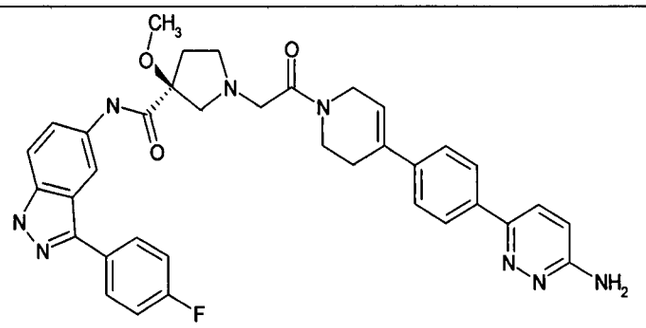
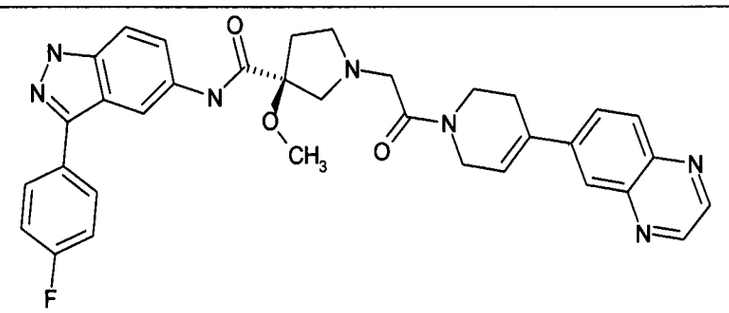
Ej No.	COMPUESTO	M+1	Tiempo de Retención (min)
805		643,7	2.76
806		646,8	2,55
807		651,7	3,99

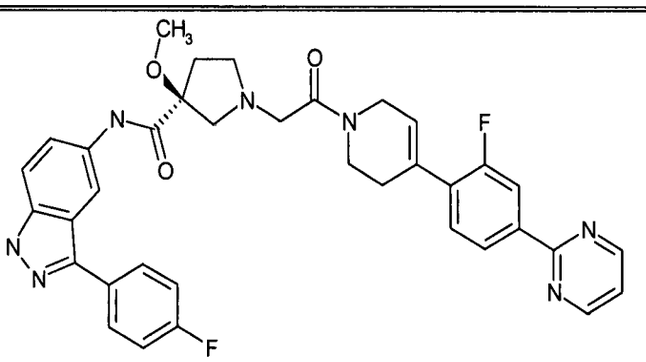
Ej No.	COMPUESTO	M+1	Tiempo de Retención (min)
808		586,7	2.28
809		576,7	2.75
810		634,3	3,52

Ej No.	COMPUESTO	M+1	Tiempo de Retención (min)
811		631.3	2.25
812		680,4	2.91
813		668,4	3,31

Ej No.	COMPUESTO	M+1	Tiempo de Retención (min)
814		708,4	3,07
815		696,4	2.84
816		647,2	3,34

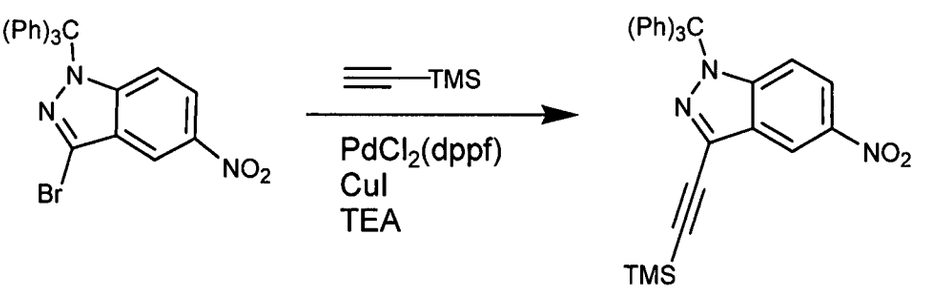
Ej No.	COMPUESTO	M+1	Tiempo de Retención (min)
817		637,4	3,34
818	 (ver también Preparación 89)	658,4	3,13
819		676,4	3,11
820		640,4	2.78

Ej No.	COMPUESTO	M+1	Tiempo de Retención (min)
821		694,4	2.64
822		674,4	2,53
823		647,4	2.38
824	 (ver también Preparación 87)	606	3,32

Ej No.	COMPUESTO	M+1	Tiempo de Retención (min)
825		650,4	3,28

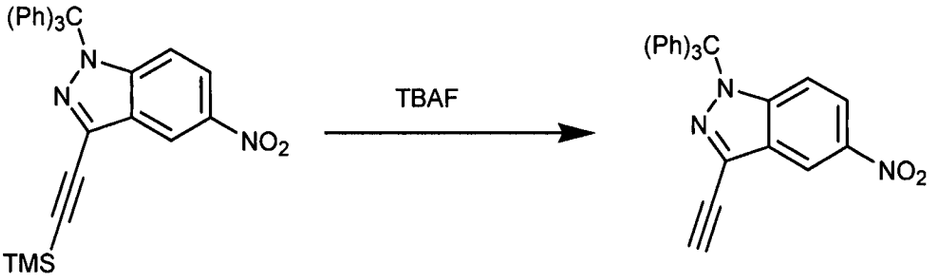
Ejemplos 826 y 827

Síntesis de 5-Nitro-3-trimetilsilaniletinil-1-tritil-1H-indazol:



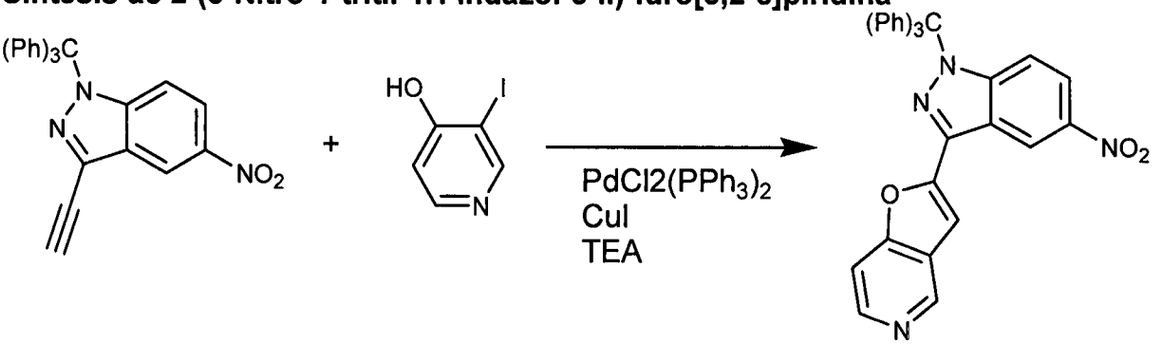
A mezcla de 3-bromo-5-nitro-1-tritil-1H-indazol (4,83 g, 10 mmol), etinil-trimetil-silano (1g, 10 mmol), yoduro de cobre (I) (91 mg, 0,5 mmol), $PdCl_2$(dppf) (337 mg, 0,5 mmol) y trietilamina (1.2 g, 12 mmol) en DMF (50 ml) se agitó hasta la mañana siguiente at 80 °C bajo argón. Luego se agregó acetato de etilo (100 ml), seguido de agua. La fase orgánica se recolectó y la fase acuosa se extrajo tres veces con acetato de etilo. La fracción orgánica combinada se lavó con agua y luego salmuera. El solvente se eliminó bajo vacío y el producto se purificó usando cromatografía (20% hexano en diclorometano) para dar el producto deseado (3,4 g) en un 67% de Rendimiento.

Síntesis de 3-ethinil-5-nitro-1-tritil-1H-indazol:



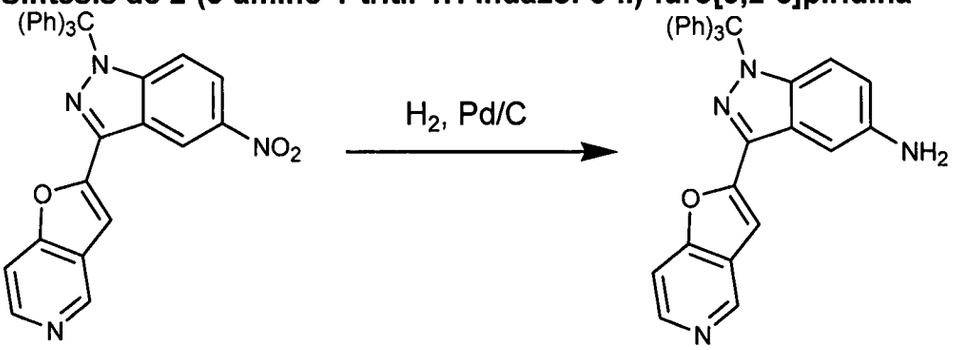
A una solución de 5-nitro-3-trimetilsilaniletinil-1-tritil-1H-indazol (700 mg, 1,4 mmol) en THF (5 ml) se agregó fluoruro de tributilamonio (1M, 2.8 ml, 2.8 mmol). La solución resultante se agitó a temperatura ambiente durante 2 horas. La TLC mostró la compleción de la reacción. Luego de la eliminación del Solvente al vacío, el producto se purificó usando sílice (20 hexano en diclorometano) para dar 560 mg del producto del título (93% de Rendimiento).

Síntesis de 2-(5-Nitro-1-tritil-1H-indazol-3-il)-furo[3,2-c]piridina



Una mezcla de reacción que contiene 3-etinil-5-nitro-1-tritil-1H-indazol (215 mg, 0,5 mmol), 3-yodo-piridin-4-ol (132 mg, 0,6 mmol), yoduro de cobre (I) (4,5 mg, 0,025 mmol), $PdCl_2(PPh_3)_2$ y trietilamina (120 mg, 1.2 mmol) en DMF (3 ml) se calentó a 100 °C hasta la mañana siguiente bajo argón. Luego de completar la reacción (mostrado por TLC), acetato de etilo (50 ml)se agregó y la mezcla de reacción se agregó a agua. La fase orgánica se recolectó, se lavó con agua, salmuera y se concentró bajo vacío. Luego de purificación usando sílice (7% metanol en diclorometano), se obtuvo el producto deseado (210 mg, 0,4 mmol) en 80% de Rendimiento.

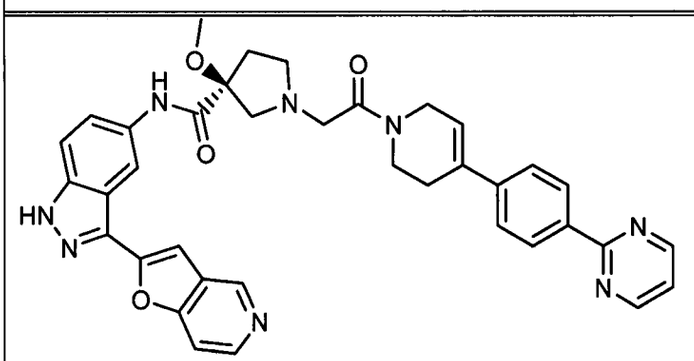
Síntesis de 2-(5-amino-1-tritil-1H-indazol-3-il)-furo[3,2-c]piridina

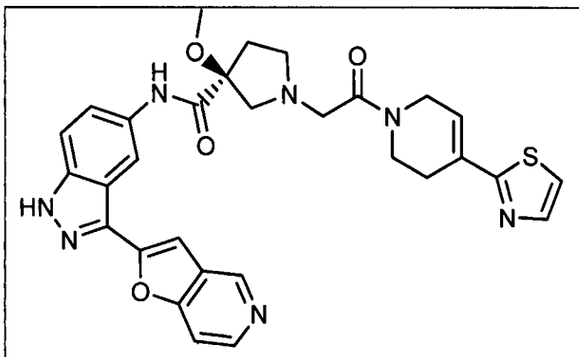


En un balón equipado con un globo, a mezcla 2-(5-Nitro-1-tritil-1H-indazol-3-il)-furo[3,2-c]piridina (210 mg, 0,4 mmol) y 5% Pd sobre carbón (21 mg) en acetato de etilo y metanol (10 ml, 1:1) se hidrogenó hasta la mañana siguiente a temperatura ambiente para dar 157 mg del producto deseado (80% de Rendimiento).

Siguiendo procedimientos descritos anteriormente se prepararon los compuestos en la Tabla 29.

Tabla 29

Compuesto	Tiempo de retención (min)	M+1
 (Ejemplo 826)	2.67	655

 (Ejemplo 827)	2.18	584

ENSAYOS

Ensayo de ERK2 Acoplado:

La actividad de los compuestos contra ERK2 inactivo se evaluó se evaluó en un ensayo de MEK1/ERK2 IMAP acoplado de la siguiente manera: Se diluyeron compuestos hasta 25x concentración final de prueba en 100% DMSO. Se agregó 14µl de buffer de quinasa (Tris.HCl 10mM pH 7,2. $MgCl_2$ 10mM, 0,01% Tween-20, 1mM DTT) que contiene 0,4ng proteína de ratón ERK2 no fosforilada a cada pocillo de una placa de ensayo de 384 pocillos. 1µl de 25x compuesto se agregó a cada pocillo y se incubó a temperatura ambiente durante 30 minutos para permitir una oportunidad de que el compuesto se una la enzima inactiva. La concentración de DMSO durante la incubación inicial es de 6,7%. Se determinó que la actividad de ERK2 es insensible a concentraciones de DMSO de hasta un 20%. ERK2 se activó luego y su actividad de quinasa se midió con la incorporación de 10µl de buffer de quinasa con los siguientes componentes (concentración final por reacción): 2ng de proteína MEK1 humana activa (fosforilada) y 4 µM (total) de péptidos de sustrato ERK2 IMAP (3,9µM IPTTPITTTYFFFK-$CONH_2$ no rotulado y 100nM IPTTPITTTYFFFK(5-carboxifluoresceína)-$CONH_2$) y 30 µM ATP. La concentración de DMSO durante la activación de ERK fue del 4%. Luego de una hora, las reacciones se terminaron con la incorporación de 60µl de detecciones de IMAP en buffer de unión

(Molecular Devices). Se dejó equilibrar la unión durante 30 minutos antes de leer la placa en un lector de placas LJL Analyst Fluorescence Polarization. Se calculó la inhibición del compuesto relativa a DMSO y estándares completamente inhibidos. Los compuestos activos se confirmaron nuevamente en un ensayo independiente.

Ensayo de ERK2 Activo:

La actividad de ERK2 activado también se determinó en el formato del ensayo IMAP usando el procedimiento como se indicó con anterioridad. 1µl de 25x compuesto se agregó a 14µl de buffer de quinasa que contiene 0,25ng de proteína totalmente fosforilada activa de Ratón ERK2. Luego de una incubación de 30 minutos, las reacciones se iniciaron por la incorporación de 10µl de buffer de quinasa que contenía 1µM de péptido de sustrato de ERK2 para IMAP (0,9µM IPTTPITTTYFFFK-$CONH_2$ no rotulado y 100nM IPTTPITTTYFFFK(5-carboxifluoresceína)-$CONH_2$) y 30µM ATP. Las reacciones procedieron durante 30 minutos antes de la terminación por la incorporación de 60µl de perlas de detección para IMAP en buffer de unión. Se leyeron las placas como anteriormente luego de 30 minutos de equilibrio de la unión. Los compuestos activos se re-confirmaron en un ensayo independiente.

Ensayo en Agar Blando:

El crecimiento independiente del anclaje es una característica de las líneas celulares tumorigénicas. Las células tumorales humanas pueden suspenderse en medio de cultivo que contiene 0,3% agarosa y una concentración indicada de un inhibidor de la farnesil transferasa. La solución puede superponerse sobre medio de crecimiento solidificado con 0,6% agarosa que contiene la misma concentración de inhibidor de ERK1 y ERK2 como capa superior. Luego de solidificar la fase superior, las placas pueden incubarse durante 10-16 días a 37°C

bajo 5% CO_2 para permitir el crecimiento de colonias. Luego de la incubación, las colonias pueden realizarse por superposición del agar con una solución de MTT (bromuro de 3—[4,5—dimetil—tiazol—2—il]—2,5—difeniltetrazolio, azul de Tiazolilo) (1 mg/m en PBS). Se realiza el recuento de las colonias y puede determinarse el valor de IC_{50}.

El ABC (área bajo la curva de concentración - tiempo durante las primeras 6 horas (ABC_{6hr}) en la Tabla 30 que sigue se determinó usando el Protocolo de la selección de Casete de Aceleración Rápida de Rata (CARRS)

Dosificación a los animales y recolección de la muestra

Se pre-canularon ratas macho de Sprague-Dawley (Charles River, Co.) (arteria femoral) para facilitar tiempos de extracción de sangre precisos, y para reducir el estrés de los animales provocado por los sangrados seriales. Luego del ayuno durante la noche, se administró a dos ratas por vía oral un compuesto a una dosis de 10 mg/kg en un volumen de dosis de 5- ml/kg. Se extrajo sangre en tubos que contienen heparina serialmente de cada animal a 0,5, 1, 2, 3, 4 y 6 h luego de la administración y se centrifugaron para generar plasma. Aproximadamente 100 µl de plasma se recolectaron en momentos individuales. Las muestras de plasma se analizaron a -20°C hasta el análisis.

Muestra de Plasma y preparación de la curva estándar

Se generó un conjunto de 12 muestras de plasma de rata para cada NCE (es decir 6 momentos y n = 2 ratas). Estas 12 muestras se agruparon en dos ratas en cada momento para suministrar 6 muestras en pool (una muestra por punto en el tiempo) para cada NCE. Las muestras en pool se evaluaron como casetes de seis (36 muestras en total) para proveer datos en los seis compuestos. Las alícuotas de 50 µl de las 36 muestras de plasma se colocaron en pocillos individuales de una placa de 96 pocillos. Un compuesto adicional (con frecuencia un análogo estructural de los compuestos de prueba) se seleccionó como

estándar interno. Se preparó una curva de mini calibración (tres puntos más un cero) para cada compuesto evaluado. Se midió el plasma de rata sin medicamento en alícuotas de 1 ml y cada alícuota se marcó con concentraciones conocidas de los compuestos para generar estándares de las concentraciones deseadas. Las concentraciones de los estándares se eligieron para separar la concentración esperada de las muestras en pool en base a los datos históricos de estudios anteriores en otros compuestos. Para este trabajo, se determinaron estándares que contienen concentraciones de 25, 250 y 2500 ng NCE/ ml de plasma. Los estándares de plasma se precipitaron por duplicado junto con las muestras. La precipitación de las proteínas ocurrió luego de la incorporación de 150 µl de acetonitrilo que contenía el estándar interno a una concentración de 1 ng/ ml en cada pocillo de muestra usando el sistema Tomtec Quadra 96. Las muestras precipitadas y estándares se pasaron por vórtex y se centrifugaron en una placa de 96 pocillos. Aproximadamente 50-100 µ del sobrenadante se retiraron y se colocaron en una placa fresca de 96 pocillos usando el sistema Tomtec Quadra 96. Un volumen de 5-10 µl del sobrenadante se usó para análisis por HPLC-MS/MS. La curva mini-estándar se corrió por duplicado, una vez antes y una vez después de las muestras. De este modo, un total de 14 muestras del estudio más estándares se analizaron por compuesto. Además, se inyectaron blancos de solvente antes y después de cada conjunto de 14 y luego de la mayor calibración estándar para cada compuesto; por lo tanto, un total de 103 inyecciones se realizó en cada sistema de HPLC para cada conjunto de seis compuestos. Se pudieron realizar múltiples inyecciones de blanco con solvente a partir de un pocillo único. Se diseñaron doce pocillos blanco de solvente en cada placa de 96 pocillos. De este modo, un lote (casete) de seis NCEs se preparó y se evaluó usando un formato de placa de 96 pocillos.

Análisis por HPLC-MS/MS

Todos los compuestos se analizaron usando métodos de monitoreo de reacción seleccionados (SRM) con instrumentos para LC/MS/MS. Una vez que el desarrollo del método se había completado, el ensayo se fijó rápidamente usando un patrón de secuencias de inyección estándar para el ensayo CARRS.

Los compuestos finales de los Ejemplos 1, 2. 4-61, 65-73, 77-84, 86, 88-98, 100, 102-114, 116-118, 120, 121, 124, 125, 151-155, 159-179, 183, 184, 186, 188-193, 196-199, 202-205, 250, 253-259, 260-299, 301-318, 320-323, 332-347, 356 (Isómero Z), 356 (Isómero E), 357-360, 362. 362 (compuesto 9P), 364, 368-436, 440-509, 511-602, 606, 607, 609-623, y 625 hasta 824 tenían un IC50 de AERK2 en el rango de 0,16 hasta 20.000 nM. Los compuestos finales de los Ejemplos 1 hasta 611 se describen en la WO2007/070398 (publicada el 21 de junio de 2007).

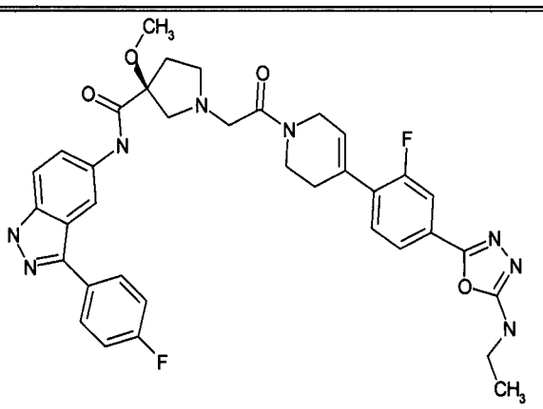
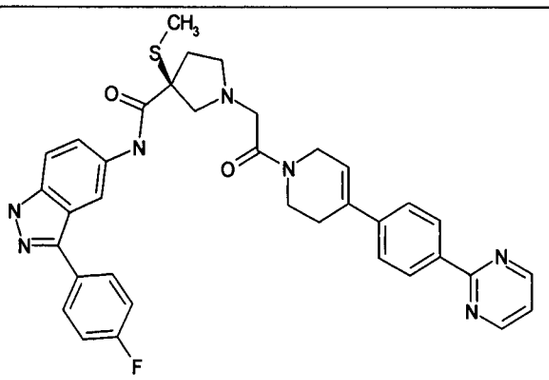
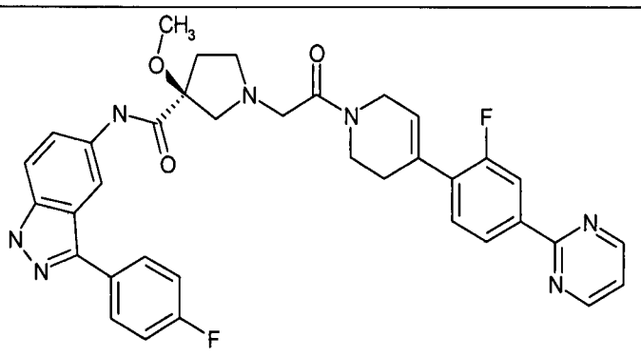
Los compuestos finales de los Ejemplos 1, 2. 4-28, 61, 86, 88, 89, 92, 95, 98, 100, 120, 125, 132. 142. 152. 154, 168, 176, 183, 184, 186, 188-193, 196-199, 202-205, 250, 251, 253-259, 261, 264, 269, 271, 274-276, 282. 286, 289, 290, 292, 294, 302. 303, 304, 306, 314-316, 332. 333, 335, 338, 343, 358, 362. 368-370, 384-390, 440-493, 510-558, 606, 611, 613-617, 620, 622, 623, 627-630, 634, 635, 639, 641, 643-645, 647, 651, 654-658, 661, 663, 666, 669, 670, 672, 673, 675-677, 679, 680, 682, 685, 688-694, 696-703, 705-707, 710-735, 737, 738, 740, 741, 743-745, 747, 749, 751-753, 755, 757, 758, 760-762. 764, 765, 767, 770-772, 776, 777, 779, 785, 786, 788, 789, 792. 793, 794, 796, 799, 802. 803-805, 807-809, 811-812. 814-816, 818-820, 822, y 823 tenían un IC_{50} de AERK2 en el rango de 0,16 hasta 18 nM. Los compuestos finales de los Ejemplos 1 hasta 611 se describen en la WO2007/070398 (publicada el 21 de junio de 2007).

Los compuestos finales de los Ejemplos 6, 100, 183, 184, 186, 188-192. 261, 440-450, 510-517 y 787 tenían un IC_{50} de AERK2en el rango de 0,16 hasta

1,5 nM. Los compuestos finales de 6, 100, 183, 184, 186, 188-192. 261, 440-450, 510-517 se describen en la WO2007/070398 (publicada el 21 de junio de 2007).

La Tabla 30 provee datos de IC_{50} de AERK2 y datos de ABC de Rata para los compuestos de esta invención.

Tabla 30

Ej.	Compuesto	IC50 AERK2 (nM)	ABC de Rata PO (nM.h)
622		5	1128
613		10	25914
825		20	1101

Para preparar las composiciones farmacéuticas a partir de los compuestos descritos por esta invención, los vehículos aceptables desde el punto de vista farmacéutico pueden ser tanto sólidos como líquidos. Las preparaciones de forma sólida incluyen polvos, comprimidos, gránulos dispersables, cápsulas, cachés, y supositorios. Los polvos y comprimidos pueden estar comprendidos por aproximadamente 5 hasta aproximadamente 95 por ciento de principio activo. Los vehículos sólidos apropiados se conocen en el arte, por ej., carbonato de magnesio, estearato de magnesio, talco, azúcar o lactosa. Los comprimidos, polvos, cachés y cápsulas pueden usarse como formas de dosificación sólidas apropiadas para administración oral. Los ejemplos de vehículos aceptables desde el punto de vista farmacéutico y métodos para la fabricación de varias composiciones pueden encontrarse en A. Gennaro (ed.), Remington: The Science and Practice de Pharmacy, 20th Edition, (2000), Lippincott Williams & Wilkins, Baltimore, MD.

Las preparaciones de forma líquida incluyen soluciones, suspensiones y emulsiones. Como ejemplo pueden mencionarse soluciones en agua o agua-propilenglicol para inyección parenteral, o la incorporación de edulcorantes y opacantes para soluciones orales, suspensiones y emulsiones. Las preparaciones de forma líquida también pueden incluir soluciones para administración intranasal.

Las preparaciones en aerosol apropiadas para inhalación pueden incluir soluciones y sólidos en forma de polvo, que pueden combinarse con un vehículo aceptable desde el punto de vista farmacéutico, tales como un gas comprimido inerte, por ej., nitrógeno.

También se incluyen las preparaciones de forma sólida que pretenden convertirse, inmediatamente antes de usar, en preparaciones de forma sólida para

administración ya sea oral o parenteral. Dichas formas incluyen soluciones, suspensiones y emulsiones.

Los compuestos de la invención también pueden administrarse por vía transdérmica. Las composiciones transdérmicas pueden tomar la forma de cremas, lociones, aerosoles y/o emulsiones y pueden incluirse en un parche transdérmico del tipo de matriz o depósito como los que son convencionales en el arte para este fin.

Con preferencia el compuesto se administra por vía oral.

Con preferencia, la preparación farmacéutica está en forma de dosificación unitaria. En dicha forma, las preparaciones subdivididas en dosis unitarias de tamaños apropiados que contienen las cantidades apropiadas de principio activo, por ej., una cantidad efectiva para lograr la finalidad deseada.

La cantidad del Compuesto activo en una dosis unitaria de preparación puede variarse o ajustarse desde aproximadamente 0,01 mg hasta aproximadamente 1000 mg, con preferencia desde aproximadamente 0,01 mg hasta aproximadamente 750 mg, con mayor preferencia desde aproximadamente 0,01 mg hasta aproximadamente 500 mg, y con la mayor preferencia desde aproximadamente 0,01 mg hasta aproximadamente 250 mg de acuerdo con la aplicación particular.

La dosificación real empleada puede variarse dependiendo de los requerimientos del paciente y la severidad de la afección tratada. La determinación del régimen de dosificación apropiado para una situación particular se encuentra dentro de la experiencia en el arte. Para conveniencia, la dosificación diaria total puede dividirse y administrarse en porciones durante el día según se requiera.

La cantidad y la frecuencia de administración de los compuestos de la invención y/o sus sales aceptables desde el punto de vista farmacéutico se

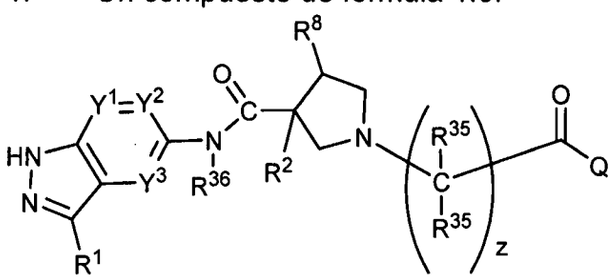
regularán de acuerdo con el criterio del médico tratante considerando factores tales como la edad, la condición y el tamaño del paciente como también la severidad de los síntomas tratados. Un régimen de dosificación diaria recomendada para administración oral puede variar desde aproximadamente 0,04 mg/día hasta aproximadamente 4000 mg/día, en dos a cuatro dosis divididas.

Mientras que la presente invención has se ha descrito en conjunción con las realizaciones específicas establecidas con anterioridad, muchas alternativas, modificaciones y variaciones a la misma resultarán obvias para aquellos con experiencia normal en el arte. Todas dichas alternativas, modificaciones y variaciones pretenden caer dentro del espíritu y el alcance de la presente invención.

REIVINDICACIONES

Habiendo así especialmente descrito y determinado la naturaleza de la presente invención y la forma como la misma ha de ser llevada a la práctica, se declara reivindicar como de propiedad y derecho exclusivo.

1. Un compuesto de fórmula 1.0:



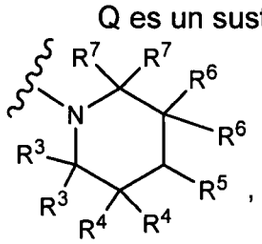
(1.0)

o sus sales, ésteres, y solvatos aceptables desde el punto de vista farmacéutico, en los cuales:

Y^1, Y^2 y Y^3 se seleccionan, cada uno en forma independiente, del grupo que consiste en: -CH=, -N= y $-CR^9=$;

z es de 1 hasta 3;

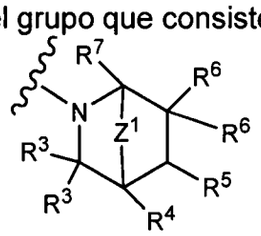
Q es un sustituyente seleccionado del grupo que consiste en:



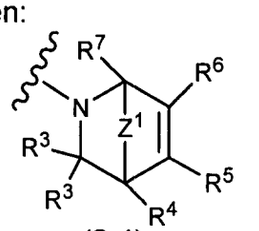
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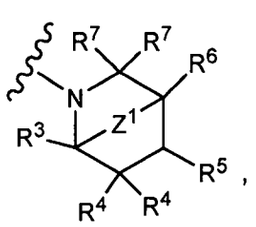
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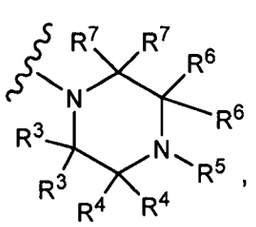
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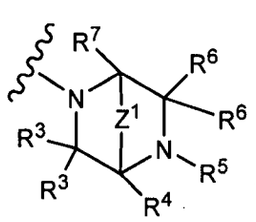
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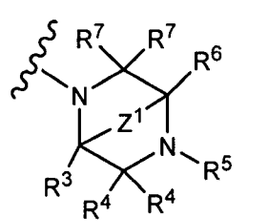
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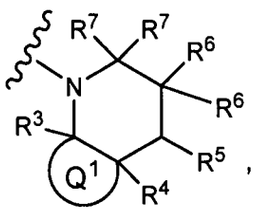
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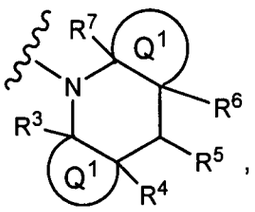


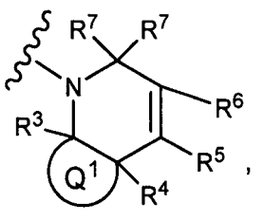
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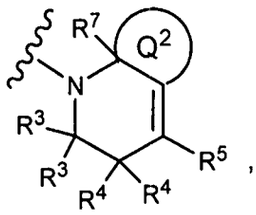


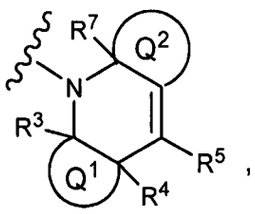
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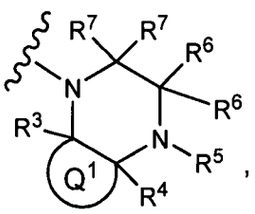

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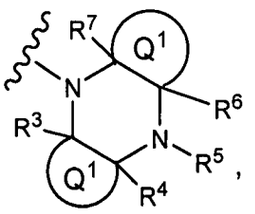

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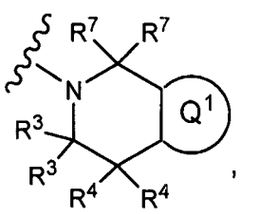

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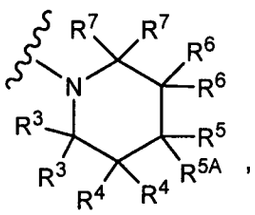

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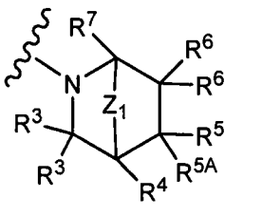

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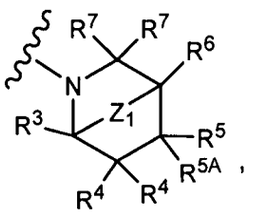

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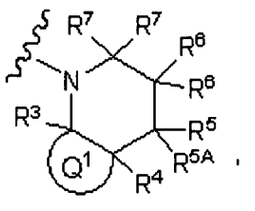

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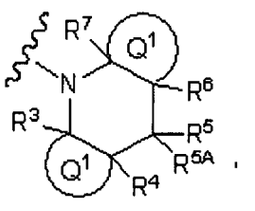

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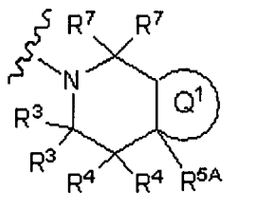

(2.17),


(2.18),


(2.19),


(2.20),


(2.21), y


(2.22);

Cada Q^1 representa un anillo seleccionado en forma independiente del grupo que consiste en: cicloalquilo, cicloalquilo sustituido, heterocicloalquilo,

heterocicloalquilo sustituido, arilo, arilo sustituido, heteroarilo, y heteroarilo sustituido, donde dichos anillos sustituidos están sustituidos con 1 hasta 3 sustituyentes seleccionados en forma independiente del grupo que consiste en: halo y los restos R^{10}; siempre que cuando Q^1 es arilo, heteroarilo, arilo sustituido o heteroarilo sustituido entonces los átomos de carbono en la unión del anillo no están sustituidos;

Q^2 representa un anillo seleccionado del grupo que consiste en: cicloalquilo, cicloalquilo sustituido, heterocicloalquilo, y heterocicloalquilo sustituido, donde dichos anillos sustituidos están sustituidos con 1 hasta 3 sustituyentes seleccionados en forma independiente del grupo que consiste en: los restos R^{10};

Z^1 representa $-(C(R^{24})_2)_w-$ donde cada R^{24} se selecciona en forma independiente del grupo que consiste en: H, alquilo y F, y donde w es 1, 2 o 3;

Z^2 se selecciona del grupo que consiste en: $-N(R^{44})-$, -O- y $-C(R^{46})_2-$;

m es 1 hasta 6;

n es 1 hasta 6;

p es 0 hasta 6;

t es 0, 1, o 2;

R^1 se selecciona del grupo que consiste en:

(1) –CN,

(2) $-NO_2$.

(3) $-OR^{10}$,

(4) $-SR^{10}$,

(5) $-N(R^{10})_2$.

(6) R^{10},

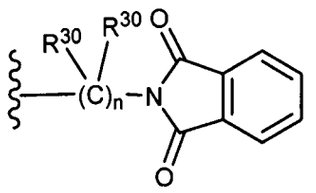
(7) $-C(O)R^{10}$,

(8) $-(C(R^{30})_2)_n-NR^{32}-C(O)-R^{10}$,

(9) $-(C(R^{30})_2)_n-NR^{32}-S(O)_t-R^{10}$,

(10) $-(C(R^{30})_2)_n-NR^{32}-C(O)-N(R^{32})-R^{10}$,

(11)



,

(12) $-CF_3$,

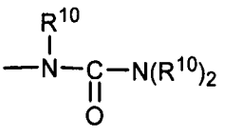
(13) $-C(O)OR^{10}$,

(14) $-(C(R^{30})_2)_nR^{13}$ (por ej., $-(CH_2)_nR^{13}$),

(15) alquenilo,

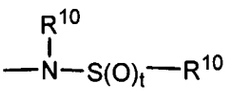
(16) $-NR^{32}-C(O)-R^{14}$,

(17)



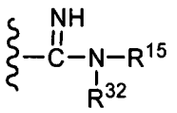
donde cada R^{10} se selecciona en forma independiente,

(18)



donde cada R^{10} se selecciona en forma independiente,

(19)



,

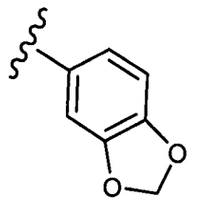
(20) $-C(O)-NR^{32}-(C(R^{30})_2)_p-OR^{10}$,

(21) $-C(O)N(R^{10})_2$ donde cada R^{10} se selecciona en forma independiente,

(22) $-C(O)-NR^{32}-C(R^{18})_3$,

(23) $-C(O)-NR^{32}-(C(R^{30})_2)_n-C(O)-N(R^{10})_2$.

(24) heterocicloalquenilo,

(25)  , y

(26) arilalquenilo-;

R^2 se selecciona del grupo que consiste en:

(1) H,

(2) -CN,

(3) halo,

(4) alquilo,

(5) alquilo sustituido en el cual dicho alquilo sustituido está sustituido con 1 hasta 3 sustituyentes seleccionados del grupo que consiste en: (a) -OH, (b) -O-alquilo (por ej., -O-(alquilo C_1-C_3), (c) -O-alquilo sustituido con 1 hasta 3 átomos F, y (d) $-N(R^{40})_2$ donde cada R^{40} se selecciona en forma independiente del grupo que consiste en: (i) H, (ii) alquilo C_1-C_3, (iii) $-CF_3$, y (e) halo,

(6) alquinilo,

(7) alquenilo,

(8) $-(CH_2)_mR^{11}$,

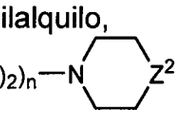
(9) $-N(R^{26})_2$.

(10) $-OR^{23}$,

(11) $-N(R^{26})C(O)R^{42}$.

(12) cicloalquilo,

(13) cicloalquilalquilo,

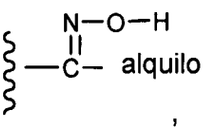
(14)  ,

(15) –O-(alquilo sustituido) en el cual dicho alquilo sustituido está sustituido con 1 hasta 3 átomos F,

(16) -$S(O)_t$-alquilo,

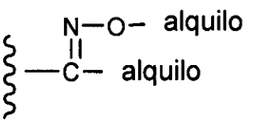
(17) –C(O)-alquilo,

(18)



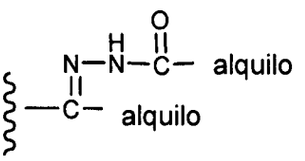
,

(19)



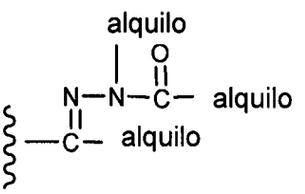
donde cada alquilo se selecciona en forma independiente,

(20)



con cada alquilo seleccionado en forma independiente,

(21)



donde cada alquilo se selecciona en forma independiente,

(22) –$N(R^{48})$-C(O)-R^{48} donde cada R^{48} se selecciona en forma independiente del grupo que consiste en: H y alquilo, y

(23) –C(O)-alquilo, tales como, por ejemplo, -C(O)-alquilo (C_1-C_6), tales como, por ejemplo, -$C(O)CH_3$;

cada R^3, R^4, R^5, R^6 y R^7 se selecciona en forma independiente del grupo que consiste en:

(1) H,

(2) alquenilo,

(3) alquenilo sustituido,

(4) alquilo,

(5) alquilo sustituido,

(6) cicloalquilo,

(7) cicloalquilo sustituido,

(8) cicloalquilalquilo-,

(9) cicloalquilalquilo sustituido-,

(10) heterocicloalquilo,

(11) heterocicloalquilo sustituido,

(12) heterocicloalquilalquilo-,

(13) heterocicloalquilalquilo sustituido-,

(14) $-C(O)R^{10}$,

(15) arilheteroarilo-,

(16) sustituido arilheteroarilo-,

(17) heteroarilarilo-,

(18) heteroarilarilo- sustituido,

(19) arilo,

(20) arilo sustituido,

(21) heteroarilo,

(22) heteroarilo sustituido,

(23) heteroarilheteroarilo-,

(24) heteroarilheteroarilo- sustituido,

(25) arilaminoheteroarilo-,

(26) arilaminoheteroarilo- sustituido,

(27) arilalquinilo-,

(28) arilalquinilo- sustituido,

(29) heteroarilalquinilo-,

(30) heteroarilalquinilo- sustituido, y

(31) benzoheteroarilo,

donde dichos grupos (7), (9), (11), (13), (16), (18), (20), (22), (24), (26), (28) y (30), R^3, R^4, R^5, R^6 y R^7 sustituidos, están sustituidos con 1 hasta 3 sustituyentes seleccionados en forma independiente del grupo que consiste en: $-NH_2$, $-NHR^{20}$, $-N(R^{20})_2$ donde cada R^{20} se selecciona en forma independiente, alquilo, alquenilo, halo, $-C(O)-NH-R^{28}$, $-C(O)OR^{28}$, $-C(O)R^{28}$, y $-OR^{20}$, y

donde dichos grupos R^3, R^4, R^5, R^6 y R^7 sustituidos (3) y (5) están sustituidos con 1 hasta 3 sustituyentes seleccionados en forma independiente del grupo que consiste en: $-NH_2$, halo (por ej., F, Cl y Br, y en otro ejemplo F), $-C(O)-NH-R^{28}$ (por ej., $-C(O)-NH-CH_3$), $-C(O)OR^{28}$ (por ej., $-C(O)OC_2H_5$), y $-C(O)R^{28}$ (por ej., $-C(O)CH_3$);

R^{5A} se selecciona del grupo que consiste en: halo, -OH, alquilo, y –O-alquilo;

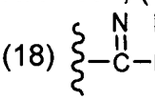
R^8 se selecciona del grupo que consiste en: H, -OH, $-N(R^{10})_2$, $-NR^{10}C(O)R^{12}$, y alquilo;

cada R^9 se selecciona en forma independiente del grupo que consiste en: halógeno, -CN, $-NO_2$, $-OR^{10}$, $-SR^{10}$, $-N(R^{10})_2$, y R^{10};

cada R^{10} se selecciona en forma independiente del grupo que consiste en: H, alquilo, arilo, arilalquilo, heteroarilo, heteroarilalquilo, cicloalquilo, cicloalquilalquilo, heterocicloalquilo, heterocicloalquilalquilo, alquilheteroarilo-, alquilarilo-, alquilo sustituido, arilo sustituido, arilalquilo sustituido, heteroarilo sustituido, sustituido heteroarilalquilo, cicloalquilo sustituido, cicloalquilalquilo sustituido, heterocicloalquilo sustituido, heterocicloalquilalquilo sustituido, alquilheteroarilo- sustituido, alquilarilo- sustituido, heterocicloalquenilo, y heterocicloalquenilo sustituido, y donde:

dicho alquilo sustituido con R^{10} está sustituido con 1 hasta 3 sustituyentes seleccionados en forma independiente del grupo que consiste en: $-NH_2$, $-NHR^{20}$, $-NO_2$, -CN, $-OR^{26}$, halo, $-C(O)-NH-R^{26}$, $-C(O)OR^{26}$, y $-C(O)R^{26}$, y

dicho arilo sustituido con R^{10}, arilalquilo sustituido, heteroarilo sustituido, heteroarilalquilo sustituido, cicloalquilo sustituido, cicloalquilalquilo sustituido, heterocicloalquilo sustituido, heterocicloalquilalquilo sustituido, alquilheteroaril-sustituido y alquilaril- sustituido están sustituidos con 1 hasta 3 sustituyentes seleccionados en forma independiente del grupo que consiste en: (1) $-NH_2$, (2) $-NO_2$, (3) -CN, (4) -OH, (5) $-OR^{20}$, (6) $-OCF_3$, (7) alquilo sustituido con 1 hasta 3 átomos halo, (8) $-C(O)R^{38}$, (9) alquilo, (10) alquenilo, (11) halo, (12) $-C(O)-NH-R^{26}$, (13) $-C(O)OR^{38}$, (14) $-C(O)-NR^{32}-(C(R^{30})_2)_n-N(R^{38})_2$, (15) $-S(O)_tR^{38}$, (16) $-C(O)-NR^{32}-R^{38}$, (17) $-NR^{32}-C(O)-R^{38}$,

(18) 

(19) $-NHR^{20}$, (20) cicloalquilo, (21) –O-alquil-O-R^{20}, (22) hidroxialquilo, (23) $-N(R^{20})_2$ donde cada R^{20} se selecciona en forma independiente, (24) –alquil-OR^{20}, (25) –O-alquil-OH, (26) –NH(hidroxialquilo), y (27) oxazolidinona seleccionados en forma independiente;

R^{11} se selecciona del grupo que consiste en: F, -OH, -CN, $-OR^{10}$, $-NHNR^1R^{10}$, $-SR^{10}$ y heteroarilo;

R^{12} se selecciona del grupo que consiste en: alquilo, arilo, heteroarilo, cicloalquilo, cicloalquilalquilo, heterocicloalquilo y heterocicloalquilalquilo;

R^{14} se selecciona del grupo que consiste en: alquilo, arilo, heteroarilo, cicloalquilo, cicloalquilalquilo-, heterocicloalquilo, alquilheterocicloalquilo, heterocicloalquilalquilo-, alquilheteroaril- y alquilarilo-;

R^{15} se selecciona del grupo que consiste en: H, -OH, alquilo, arilo, heteroarilo, cicloalquilo, cicloalquilalquilo-, heterocicloalquilo y heterocicloalquilalquilo-, alquilheteroaril- y alquilarilo-;

R^{20} representa alquilo;

R^{23} se selecciona del grupo que consiste en: H, alquilo, arilo, cicloalquilo, y cicloalquilalquilo-;

cada R^{26} se selecciona en forma independiente del grupo que consiste en: H y alquilo;

R^{28} es alquilo;

cada R^{30} se selecciona en forma independiente del grupo que consiste en: H, alquilo, y F;

cada R^{32} se selecciona en forma independiente del grupo que consiste en: H y alquilo, y donde cada R^{32} es en general H;

cada R^{35} se selecciona en forma independiente del grupo que consiste en: H y alquilo C_1 hasta C_6;

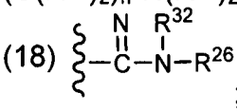
R^{36} se selecciona del grupo que consiste en: H, alquilo, y –O-alquilo;

cada R^{38} se selecciona en forma independiente del grupo que consiste en: H, alquilo, arilo, arilalquilo, heteroarilo, heteroarilalquilo, cicloalquilo, cicloalquilalquilo, heterocicloalquilo, heterocicloalquilalquilo, alquilheteroarilo-, alquilarilo-, alquilo sustituido, arilo sustituido, arilalquilo sustituido, heteroarilo sustituido, sustituido heteroarilalquilo, cicloalquilo sustituido, cicloalquilalquilo sustituido, heterocicloalquilo sustituido, heterocicloalquilalquilo sustituido, alquilheteroaril- sustituido y alquilarilo- sustituido, y donde:

dicho alquilo sustituido R^{38} está sustituido con 1 hasta 3 sustituyentes seleccionados en forma independiente del grupo que consiste en: $-NH_2$., $-NO_2$, -CN, $-OR^{26}$, halo, $-C(O)-NH-R^{28}$, $-C(O)OR^{28}$, y $-C(O)R^{28}$, y

dicho arilo sustituido R^{38}, arilalquilo sustituido, heteroarilo sustituido, sustituido heteroarilalquilo, cicloalquilo sustituido, cicloalquilalquilo sustituido, heterocicloalquilo sustituido, heterocicloalquilalquilo sustituido, alquilheteroaril-sustituido y alquilaril- sustituido están sustituidos con 1 hasta 3 sustituyentes

seleccionados en forma independiente del grupo que consiste en: (1) $-NH_2$, (2) $-NO_2$, (3) -CN, (4) -OH, (5) $-OR^{20}$, (6) $-OCF_3$, (7) $-CF_3$, (8) $-C(O)R^{26}$, (9) alquilo, (10) alquenilo, (11) halo, (12) $-C(O)-NH-R^{26}$, (13) $-C(O)OR^{26}$, (14) $-C(O)-NR^{32}-(C(R^{30})_2)_n-N(R^{26})_2$, (15) $-S(O)_tR^{26}$, (16) $-C(O)N(R^{32})(R^{26})$, (17) $-NR^{32}C(O)R^{26}$,

(18)  ; y

(19) $-NHR^{20}$;

R^{42} se selecciona del grupo que consiste en: alquilo, arilo, heteroarilo, y cicloalquilo;

R^{44} se selecciona del grupo que consiste en: H, alquilo, cicloalquilo, y cicloalquilalquilo;

cada R^{46} se selecciona en forma independiente del grupo que consiste en: H, alquilo, cicloalquilo, y cicloalquilalquilo; y

siempre que:

(1) Q^1 es un anillo sustituido en el cual por lo menos un sustituyente es halo; y/o

(2) R^2 está alquilo sustituido en el cual dicho sustituyente es $-OCH_3$, o R^2 se selecciona del grupo que consiste en: $-CH_2OH$ y $-CH_2OCH_3$; y/o

(3) por lo menos uno de R^3, R^4, R^5, R^6, y R^7 es:

(i) seleccionado del grupo que consiste en: oxadiazolilfenilo-, piridazinilfenilo-, pirimidinilpirazinilo-, oxadiazolilfenilo- sustituido, piridazinilfenilo-sustituido, pirimidinilpirazinilo- sustituido, y benzoheteroarilo; o

(ii) seleccionado del grupo que consiste en:

(a) cicloalquilo sustituido,

(b) cicloalquilalquilo sustituido-,

(c) heterocicloalquilo sustituido,

(d) heterocicloalquilalquilo sustituido-,

(e) sustituido arilheteroarilo-,

(f) heteroarilarilo- sustituido,

(g) arilo sustituido,

(h) heteroarilo sustituido,

(i) heteroarilheteroarilo- sustituido,

(j) arilaminoheteroarilo- sustituido,

(k) arilalquinilo- sustituido, y

(l) heteroarilalquinilo- sustituido, y

donde por lo menos un sustituyente en por lo menos uno por lo menos uno de dicho grupo (ii)(a) hasta (ii)(l) R^3, R^4, R^5, R^6, o R^7 se selecciona del grupo que consiste en: $-NHR^{20}$, $-N(R^{20})_2$ (donde cada R^{20} se selecciona en forma independiente), y $-OR^{20}$; y/o

(4) R^{5A} es alquilo; y/o

(5) R^{10} es un arilo sustituido, y por lo menos uno sustituyente se selecciona del grupo que consiste en:

(a) $-S(O)_tR^{38}$ donde R^{38} es isopropilo,

(b) –O-alquil-O-R^{20},

(c) hidroxialquilo,

(d) $-N(R^{20})_2$.

(e) –alquil-OR^{20},

(f) –O-alquil-OH,

(g) –NH(hidroxialquilo), y

(h) oxazolidinona; y/o

(6) R^{20} es isopropilo.

2. El compuesto de la Reivindicación 1 en el cual la salvedad es que:

(1) Q^1 es un anillo sustituido en el cual por lo menos uno sustituyente es halo; y/o

(2) R^2 está alquilo sustituido en el cual dicho sustituyente es $-OCH_3$, o R^2 se selecciona del grupo que consiste en: $-CH_2OH$ y $-CH_2OCH_3$; y/o

(3) R^5 es:

(i) seleccionado del grupo que consiste en: oxadiazolilfenilo-, piridazinilfenilo-, pirimidinilpirazinilo-, oxadiazolilfenilo- sustituido, piridazinilfenilo- sustituido, pirimidinilpirazinilo- sustituido, y benzoheteroarilo; o

(ii) seleccionado del grupo que consiste en:

(a) cicloalquilo sustituido,

(b) cicloalquilalquilo sustituido-,

(c) heterocicloalquilo sustituido,

(d) heterocicloalquilalquilo sustituido-,

(e) arilheteroarilo- sustituido,

(f) heteroarilarilo- sustituido,

(g) arilo sustituido,

(h) heteroarilo sustituido,

(i) heteroarilheteroarilo- sustituido,

(j) arilaminoheteroarilo- sustituido,

(k) arilalquinilo- sustituido, y

(l) heteroarilalquinilo- sustituido, y

donde por lo menos un sustituyente en por lo menos uno por lo menos uno de dicho grupo (ii)(a) hasta (ii)(l) R^3, R^4, R^5, R^6, o R^7 se selecciona del grupo que consiste en: $-NHR^{20}$ (por ej., $-NHCH_2CH_3$ y $-NHCH_3$), $-N(R^{20})_2$ (donde cada R^{20} se selecciona en forma independiente), y $-OR^{20}$ (por ej., $-OCH_3$); y/o

(4) R^{5A} es alquilo (por ej., alquilo C_1 hasta C_6, tales como, por ejemplo, $-CH_3$); y/o

(5) R^{10} es un arilo sustituido, y por lo menos un sustituyente se selecciona del grupo que consiste en:

(a) –O-alquil-O-R^{20},

(b) hidroxialquilo,

(c) –$N(R^{20})_2$,

(d) –alquil-OR^{20},

(e) –O-alquil-OH,

(f) –NH(hidroxialquilo), y

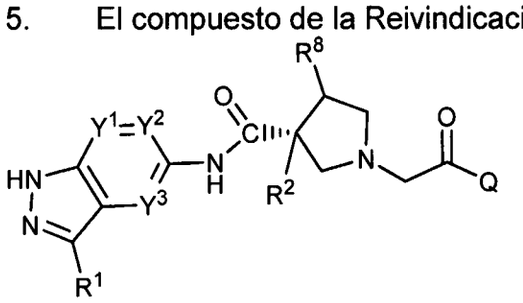
(g) oxazolidinona; y/o

(6) R^{20} es isopropilo.

3. El compuesto de la Reivindicación 1 donde R^2 es alquilo sustituido en el cual dicho sustituyente es $-OCH_3$.

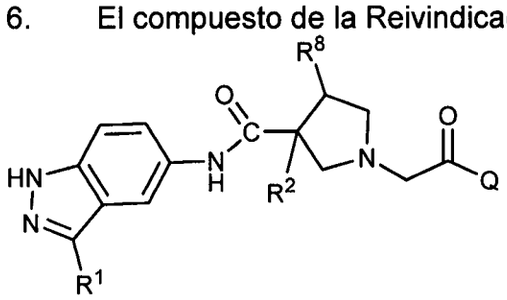
4. El compuesto de la Reivindicación 1 donde R^2 se selecciona del grupo que consiste en: $-CH_2OH$ y $-CH_2OCH_3$.

5. El compuesto de la Reivindicación 1 que tiene la fórmula:



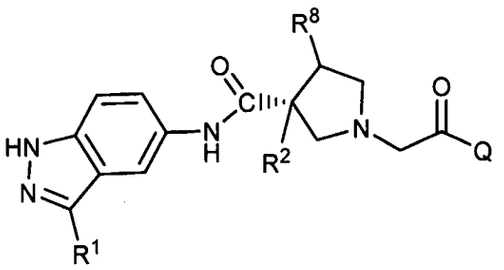
(1.1)

6. El compuesto de la Reivindicación 1 que tiene la fórmula:



(1.2)

; o

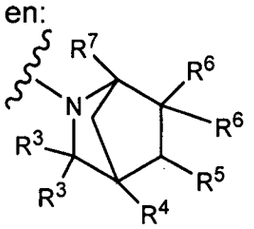


(1.3)

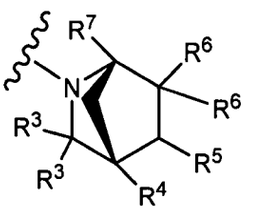
7. El compuesto de la Reivindicación 3 en el cual Q se selecciona del grupo que consiste en: 2.1, 2.2. 2.3, 2.4, 2,5, 2.6, 2.7, 2.8, 2.17, 2.18, 2.19, 2.20, 2.21, y 2.22.

8. El compuesto de la Reivindicación 1 en el cual Z^1 es $-CH_2-$, y cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y metilo.

9. El compuesto de la Reivindicación 7 en el cual Q se selecciona del grupo que consiste en: restos 2.1, 2.2. y 2.3, y 2.3 se selecciona del grupo que consiste en:

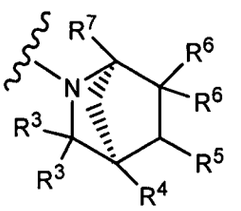


(2.3A)



(2.3B)

y

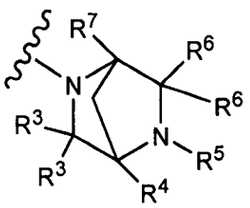
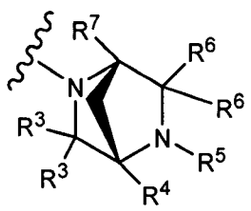
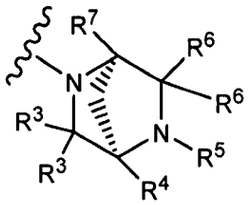


(2.3C) , y

cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y metilo.

10. El compuesto de la Reivindicación 9 donde cada R^3, R^4, R^6, y R^7 es H, y Q se selecciona del grupo que consiste en: 2.1 y 2.3B.

11. El compuesto de la Reivindicación 7 en el cual Q se selecciona del grupo que consiste en: restos 2.6 y 2.7, y 2.7 se selecciona del grupo que consiste en:


(2.7A) ,

(2.7B) y

(2.7C) , y

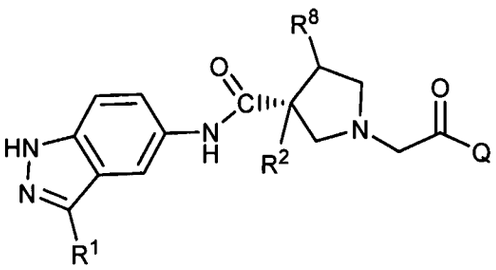
cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y metilo.

12. El compuesto de la Reivindicación 11 donde cada R^3, R^4, R^6, y R^7 es H, y Q se selecciona del grupo que consiste en: 2.6, 2.7A, y 2.7B.

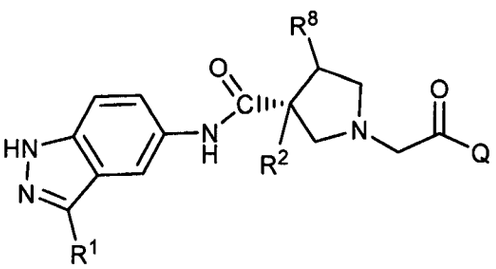
13. El compuesto de la Reivindicación 1 en el cual Q es 2.17, y cada R^3, R^4, R^6, y R^7 se selecciona en forma independiente del grupo que consiste en: H y metilo.

14. El compuesto de la Reivindicación 13 donde cada R^3, R^4, R^6, y R^7 es H.

15. El compuesto de la Reivindicación 10 donde el compuesto de fórmula 1.0 es:


(1.3)

16. El compuesto de la Reivindicación 12 donde el compuesto de fórmula 1.0 es:


(1.3)

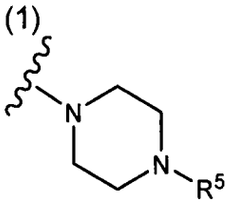
17. El compuesto de la Reivindicación 10 en el cual Q es 2.1, y R^3, R^4, R^6, y R^7 son cada uno H.

18. El compuesto de la Reivindicación 12 en el cual Q es 2.6.

19. El compuesto de la Reivindicación 12 en el cual Q se selecciona del grupo que consiste en: 2.7A y 2.7B.

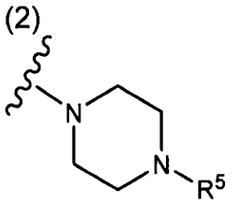
20. El compuesto de la Reivindicación 1 en el cual Q se selecciona del grupo que consiste en:

(1)



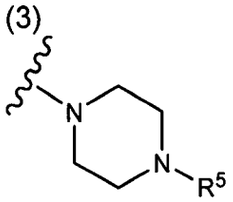
(2.6A) ;

(2)



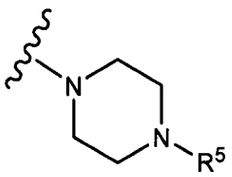
sustituido con uno o dos sustituyentes seleccionados en forma independiente del grupo que consiste en grupos R^3, siempre que dicho uno o dos sustituyentes no son H;

(3)



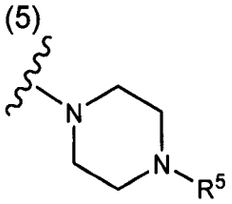
sustituido con uno o dos grupos alquilo;

(4)



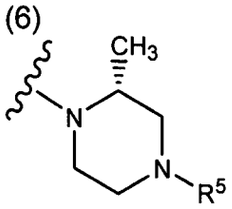
sustituido con uno o dos grupos metilo;

(5)



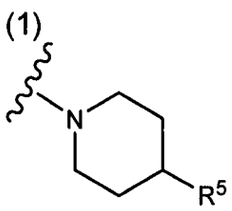
sustituido con un grupo metilo; y

(6)



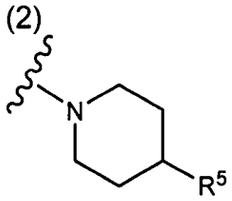
21. El compuesto de la Reivindicación 1 en el cual Q se selecciona del grupo que consiste en:

(1)



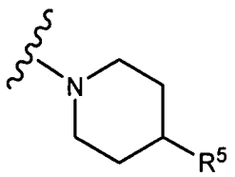
sustituido con uno o dos sustituyentes seleccionados en forma independiente del grupo que consiste en grupos R^3, siempre que dicho uno o dos sustituyentes no son H;

(2)



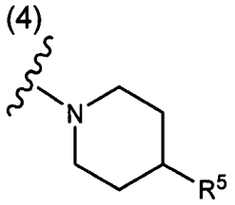
sustituido con uno o dos grupos alquilo;

(3)



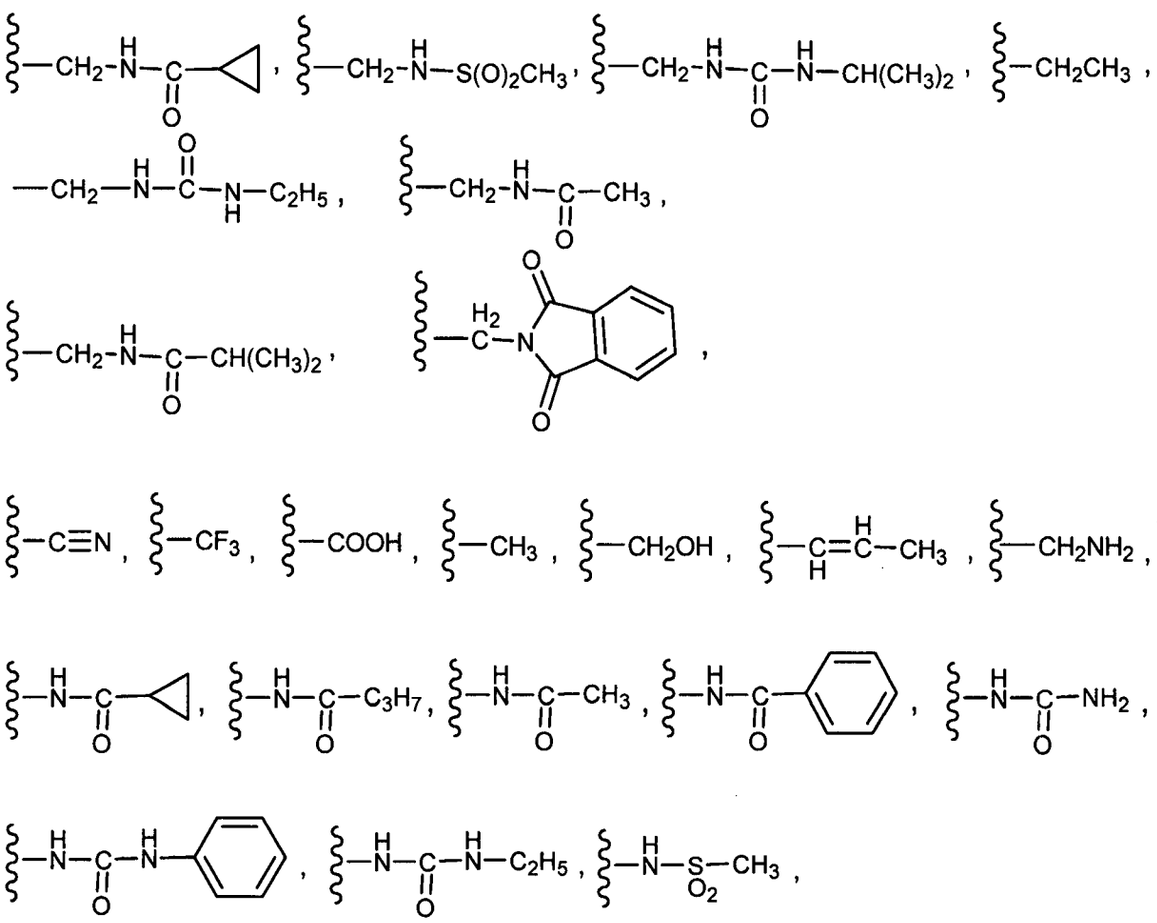
sustituido con uno o dos grupos metilo; y

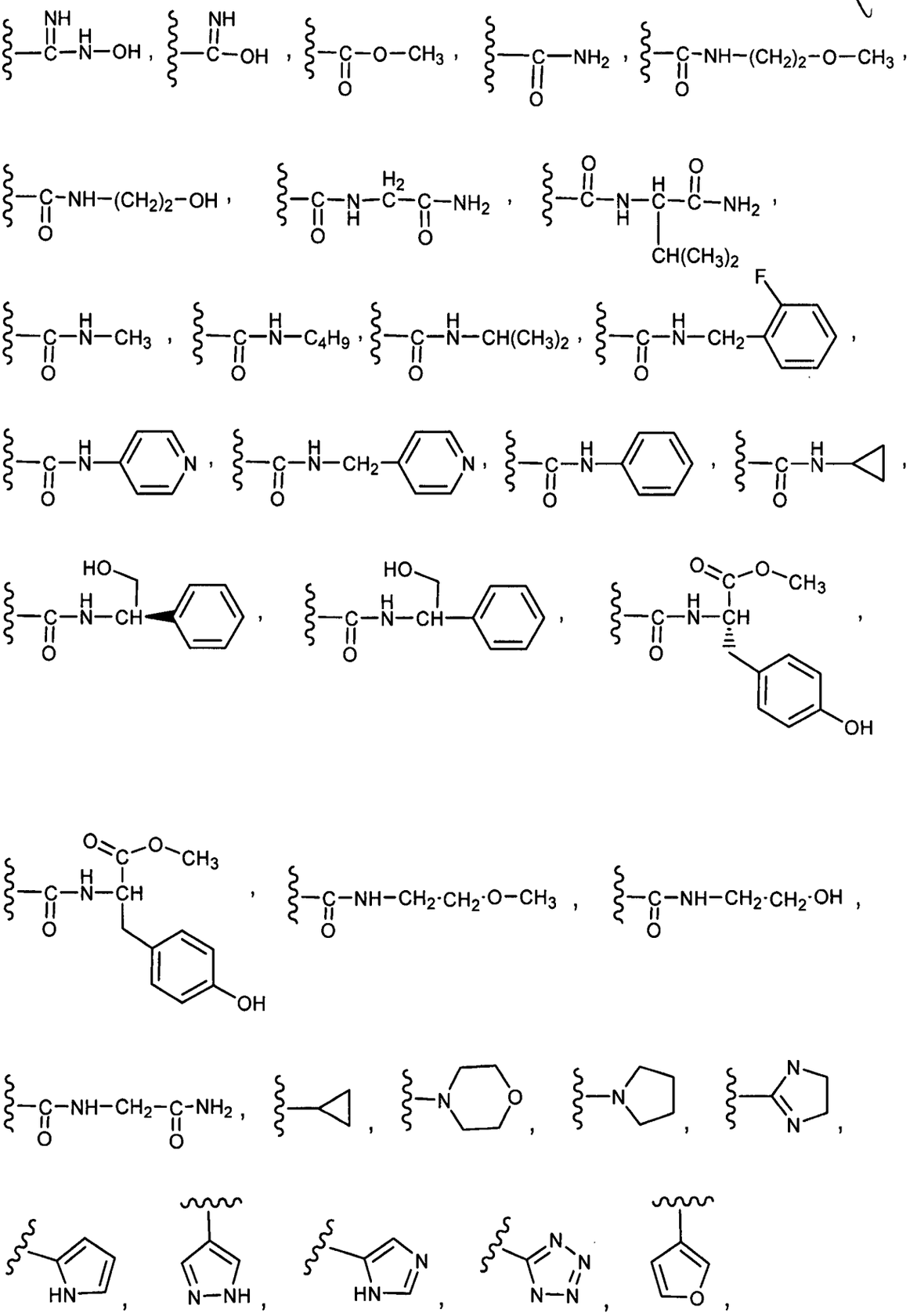
(4)

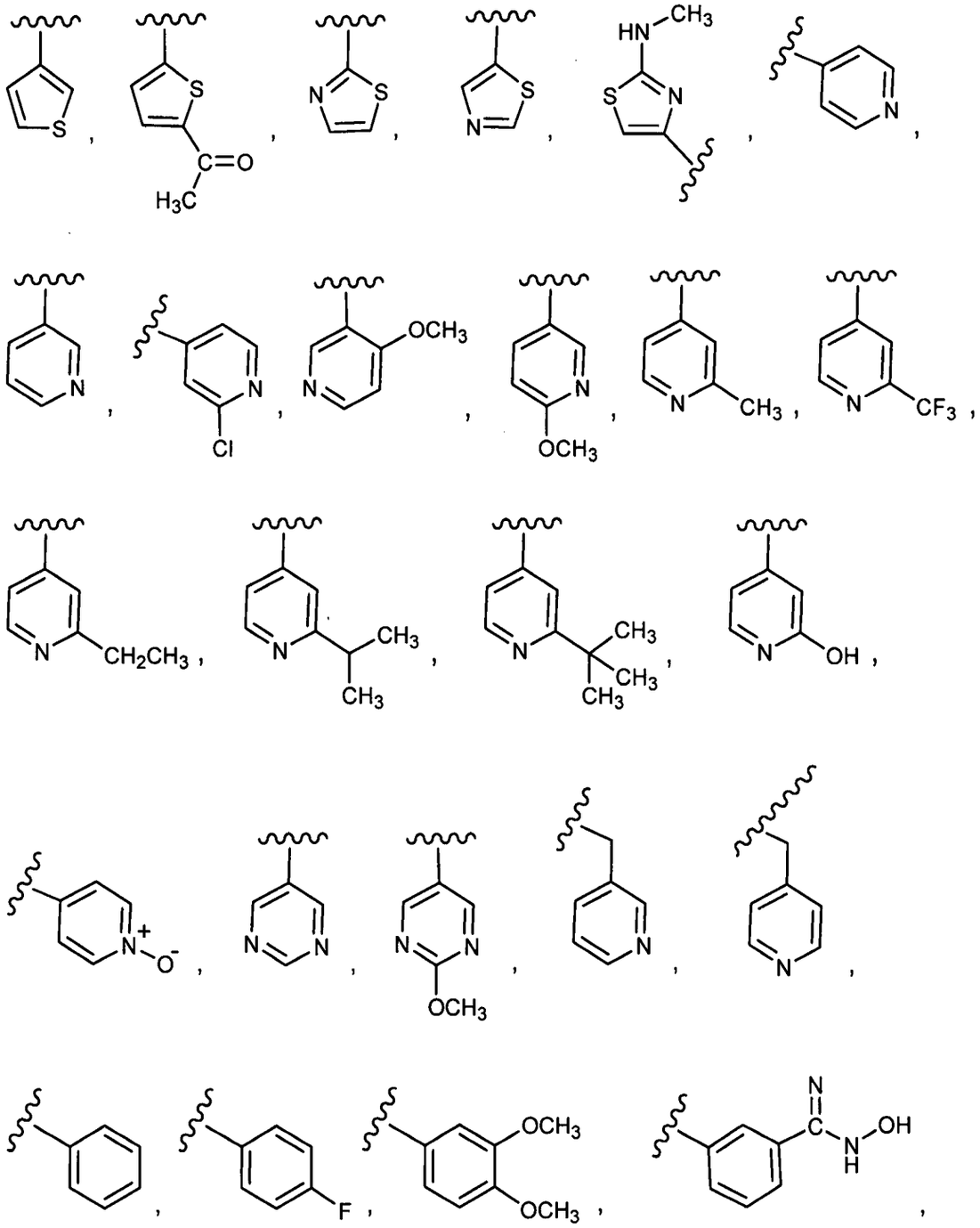


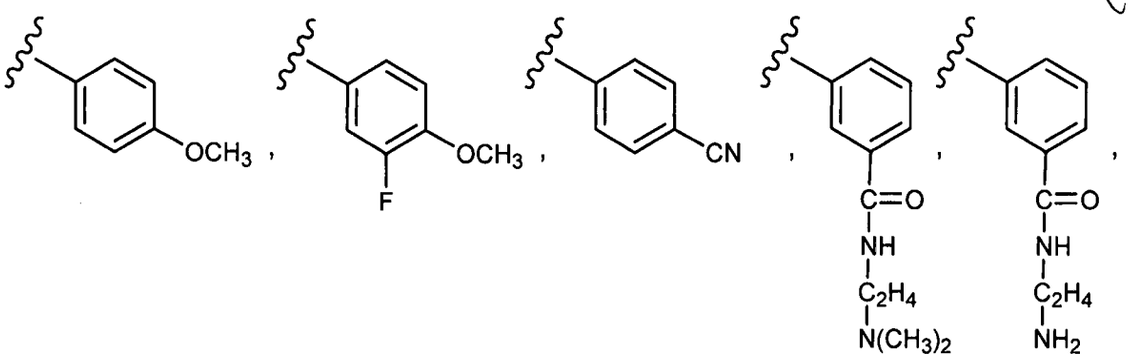
sustituido con un grupo metilo.

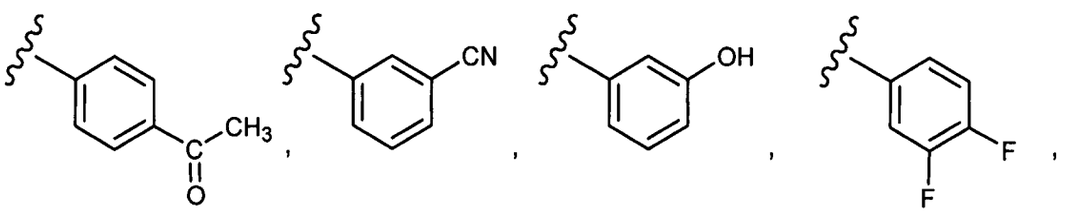
22. El compuesto de la Reivindicación 1 donde R^1 se selecciona del grupo que consiste en:

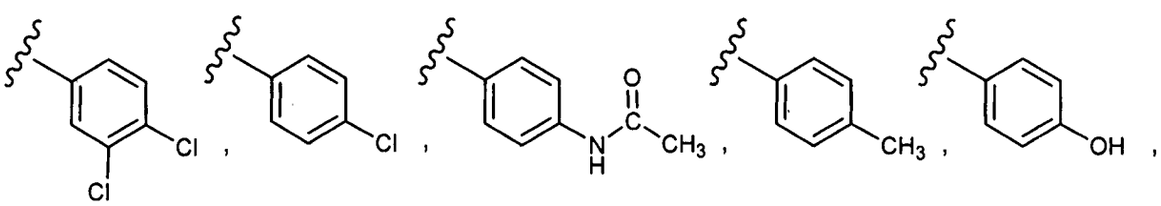


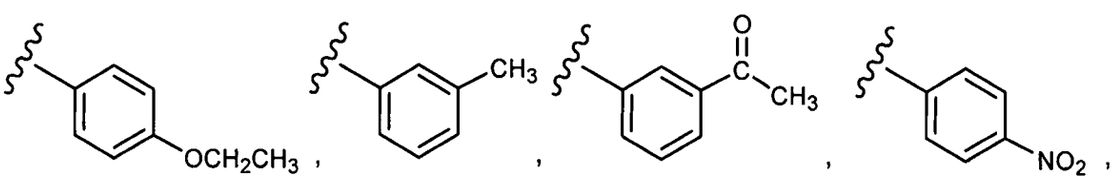


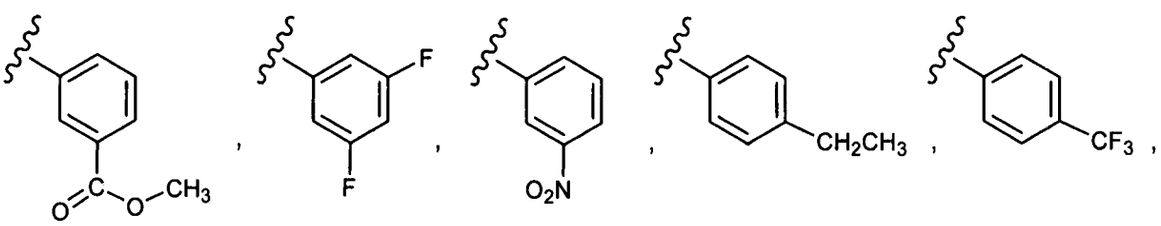


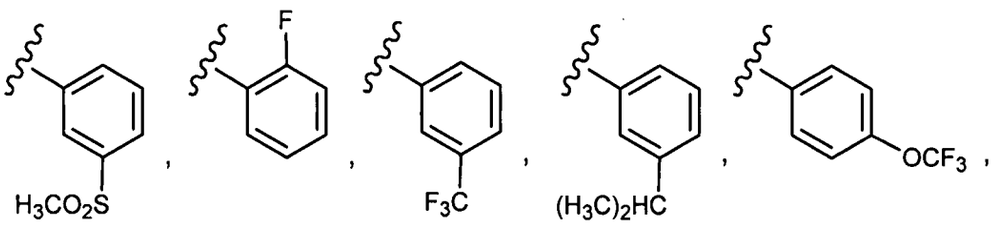

OCH3
OCH3
F
CN
C=O
NH
C2H4
N(CH3)2
C=O
NH
C2H4
NH2

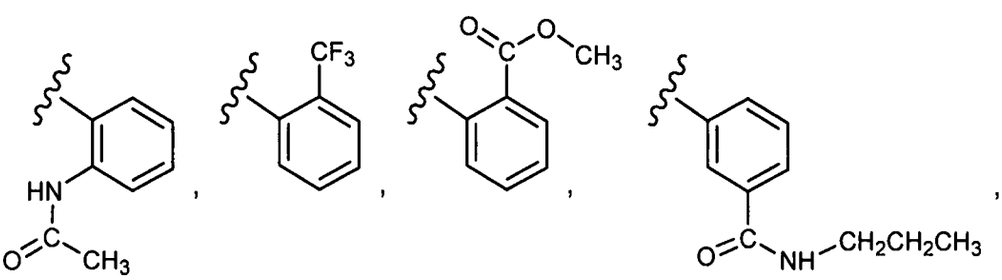

CH3
C
O
CN
OH
F
F

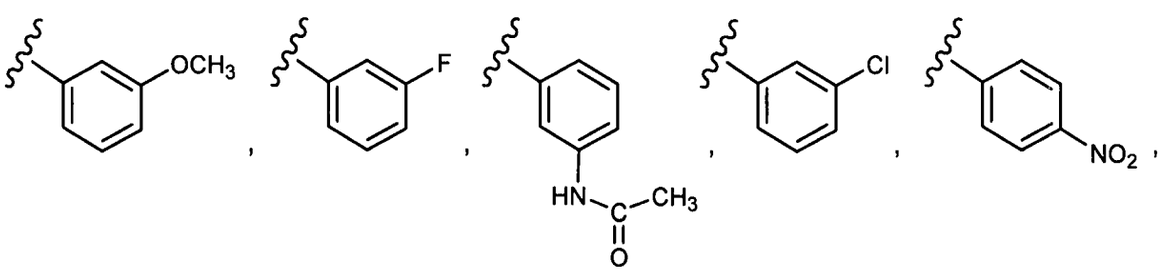

Cl
Cl
Cl
N
H
O
C
CH3
CH3
OH

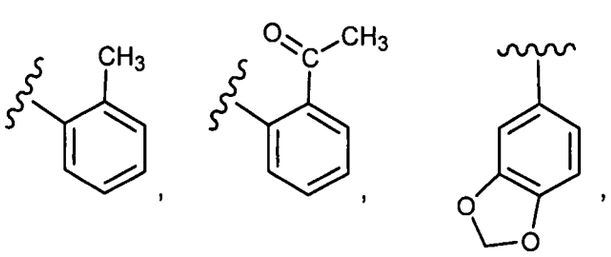

OCH2CH3
CH3
O
C
CH3
NO2

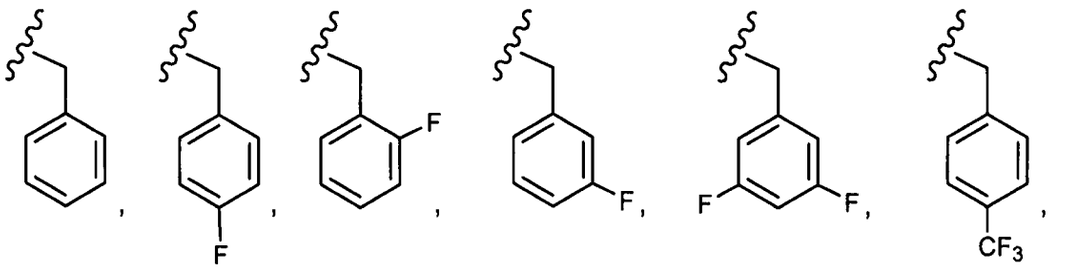

O
C
O
CH3
F
F
O2N
CH2CH3
CF3

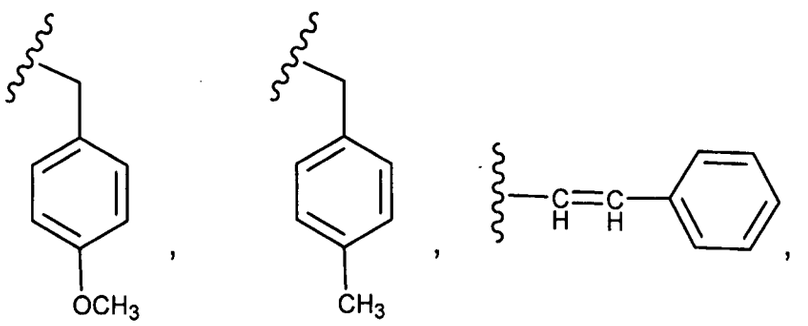

F
H_3CO_2S
F_3C
$(H_3C)_2HC$
OCF_3
$CH(CH_3)_2$
OCH_3
OCH_3
Cl
F
F

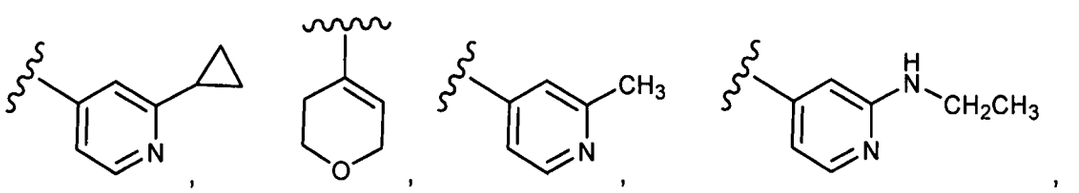

HN
O
C
CH_3
CF_3
O
C
O
CH_3
O
C
NH
$CH_2CH_2CH_3$

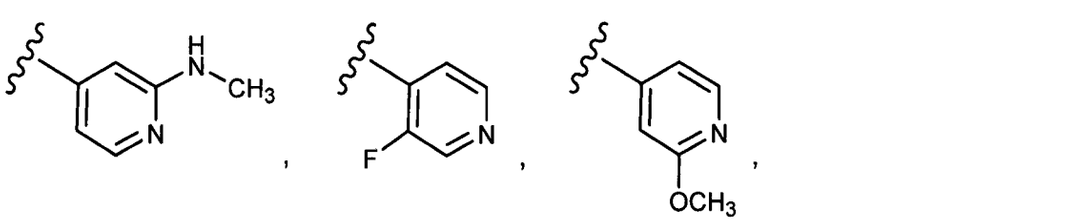

OCH_3
F
HN
C
CH_3
O
Cl
NO_2

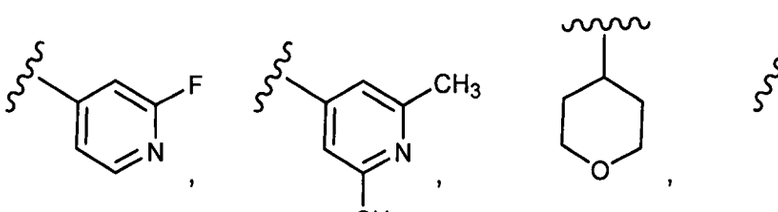

CH_3
O
C
CH_3
O
O

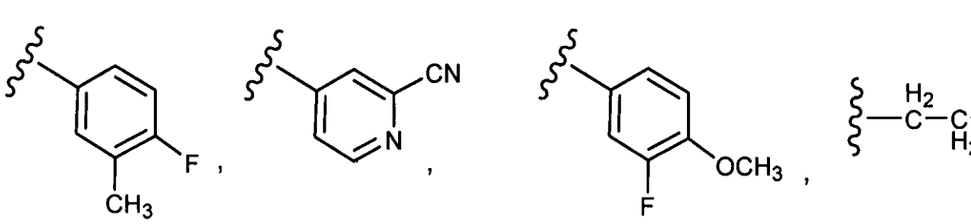




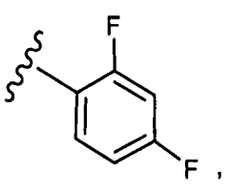
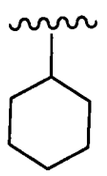
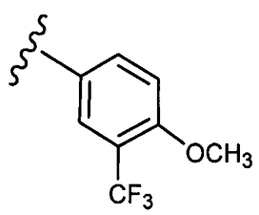
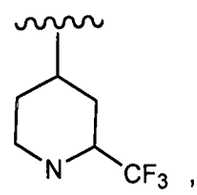
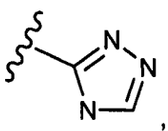
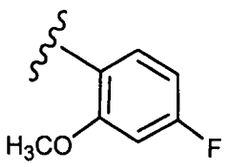
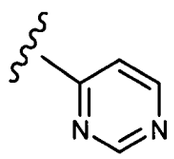
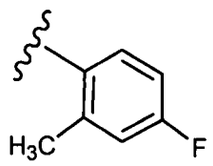


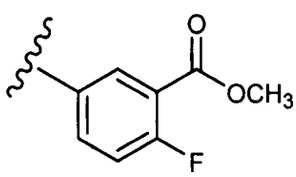
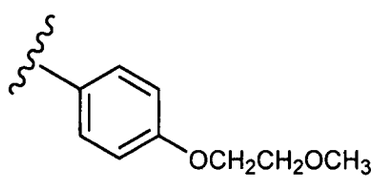
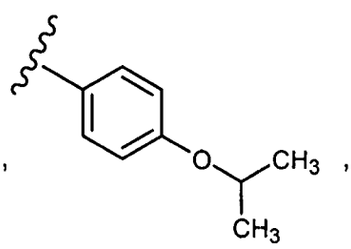


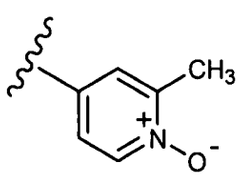
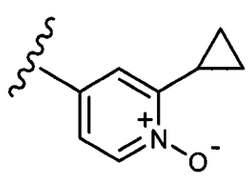
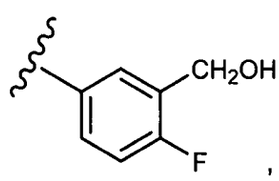


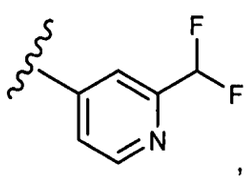
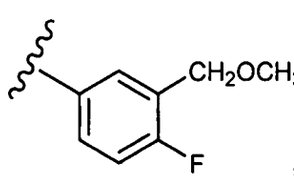


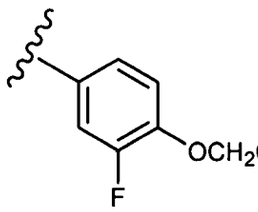
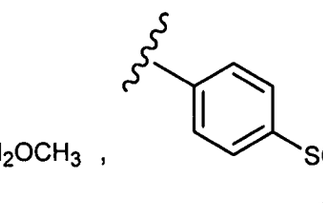



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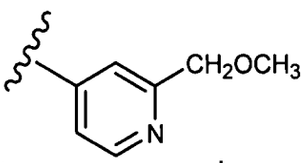
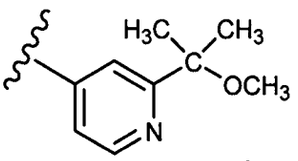
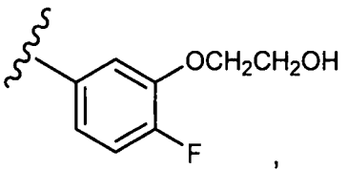
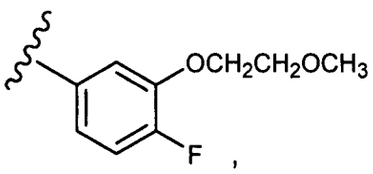
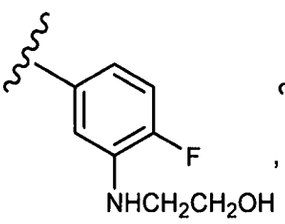
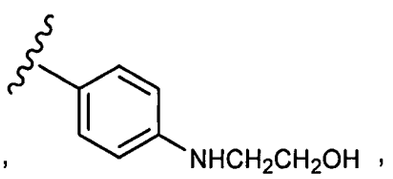
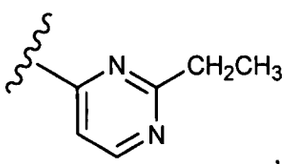
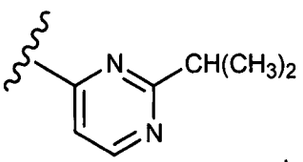
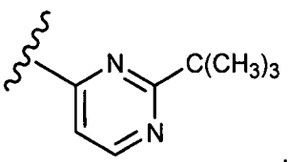
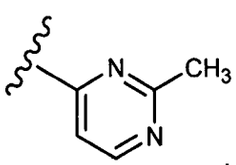
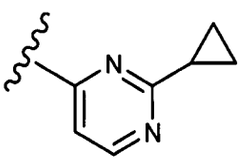
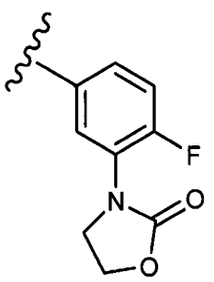
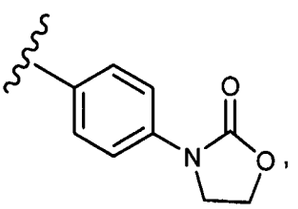
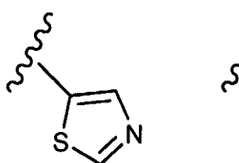
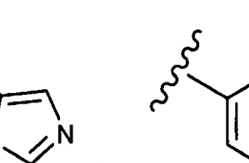
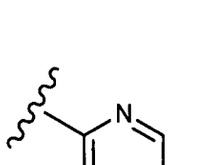

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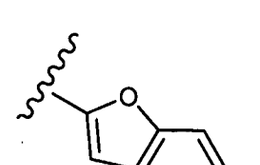

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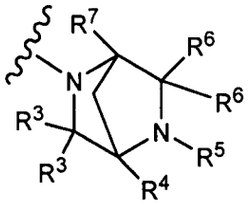
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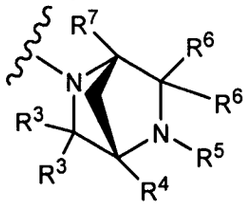



















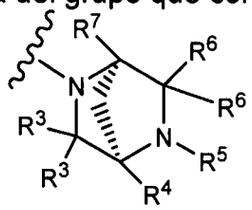
y

30. El compuesto de la Reivindicación 22 en el cual Q se selecciona del grupo que consiste en: 2.6 y 2.7, y 2.7 se selecciona del grupo que consiste en:


(2.7A)


(2.7B)

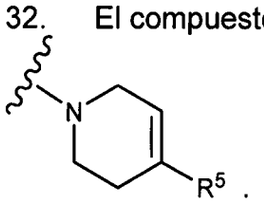
y


(2.7C)

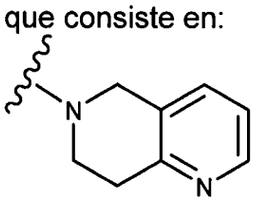
y R^3, R^4, R^6, y R^7 se seleccionan, cada uno en forma independiente, del grupo que consiste en: H y alquilo.

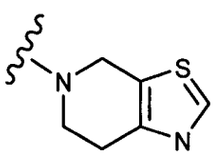
31. El compuesto de la Reivindicación 30 donde R^3, R^4, R^6, y R^7 son cada uno H, y Q se selecciona del grupo que consiste en; 2.6 y 2.7B.

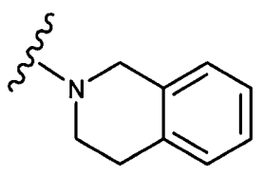
32. El compuesto de la Reivindicación 1 en el cual Q es

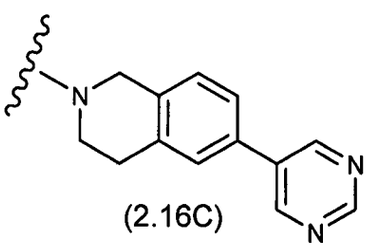


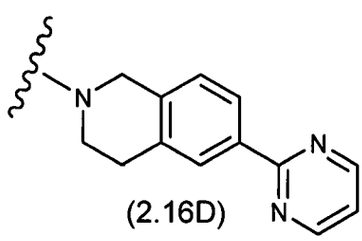
33. El compuesto de la Reivindicación 1 en el cual Q se selecciona del grupo que consiste en:


(2.16A)

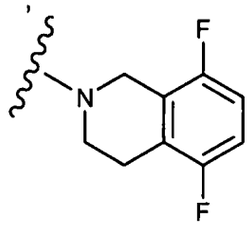

(2.16A1)


(2.16B)

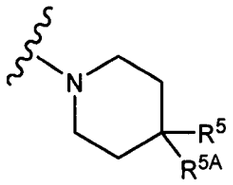

(2.16C)


(2.16D)

y


(2.16E)

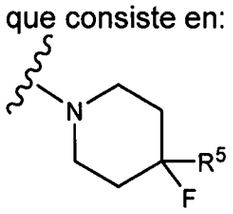
34. El compuesto de la Reivindicación 1 en el cual Q es:



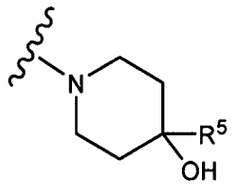
(2.17A)

y R^{5A} se selecciona del grupo que consiste en: halo, -OH, alcoxi, y alquilo.

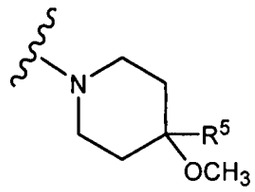
35. El compuesto de la Reivindicación 1 en el cual Q se selecciona del grupo que consiste en:



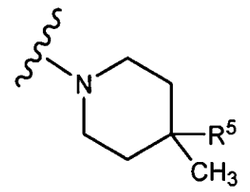
(2.17B)



(2.17C)

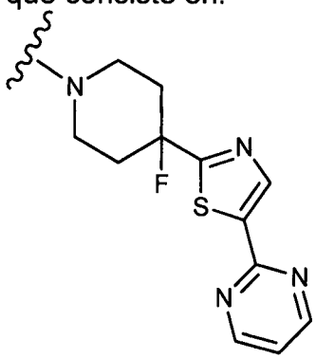


(2.17E) y

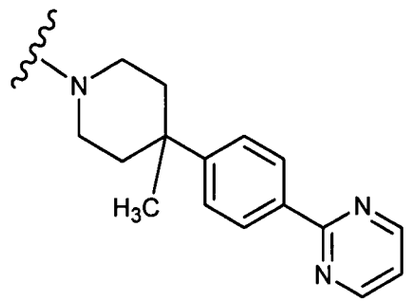


(2.17G).

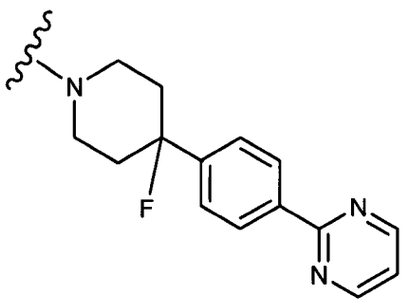
36. El compuesto de la Reivindicación 1 en el cual Q se selecciona del grupo que consiste en:

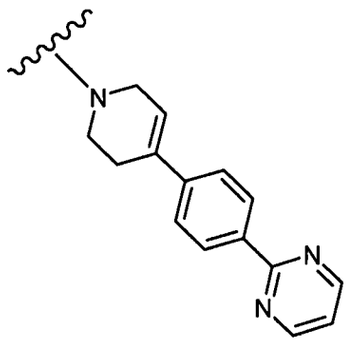


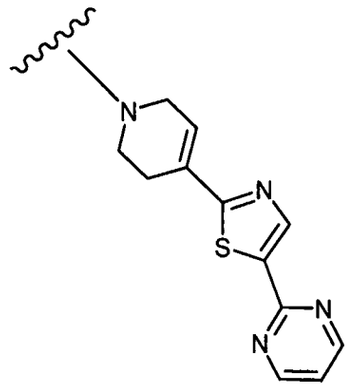
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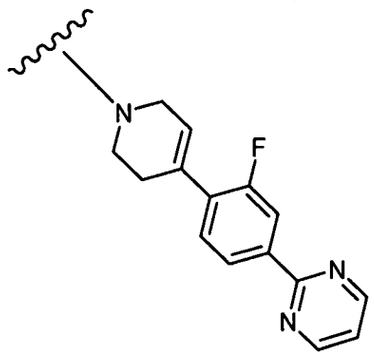


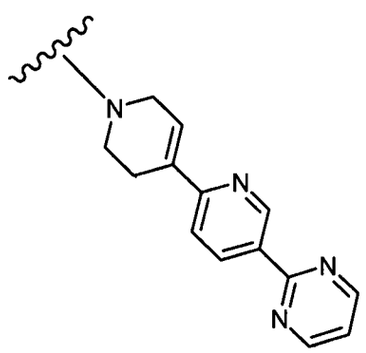
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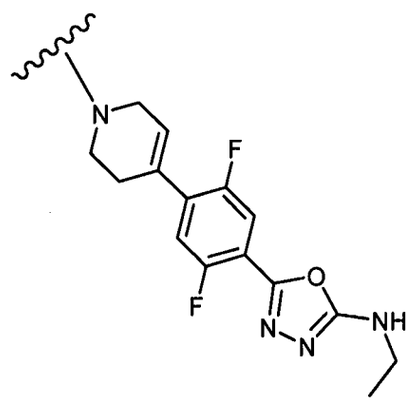


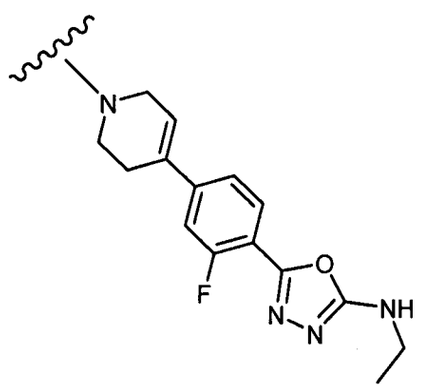


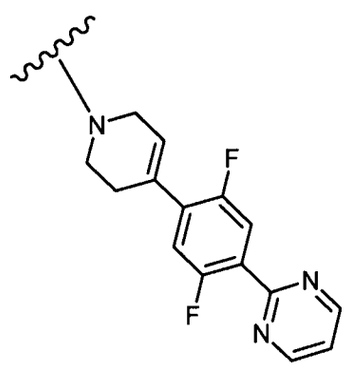


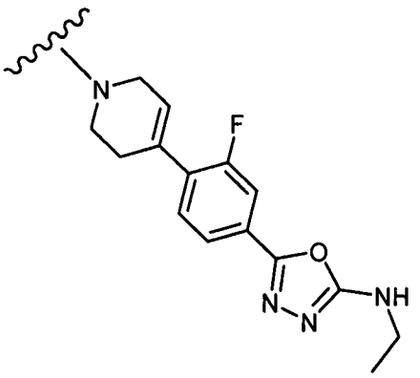




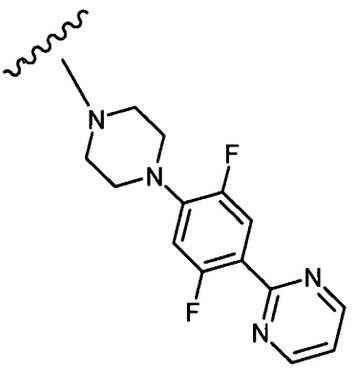








y



37. El compuesto de la Reivindicación 1 donde dicho compuesto es un compuesto de fórmula 1.0.

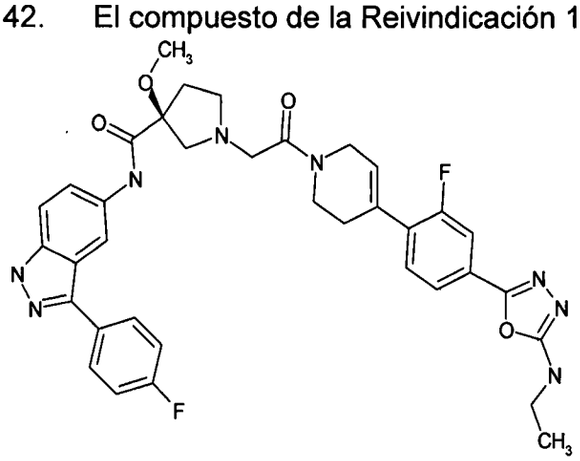
38. El compuesto de la Reivindicación 1 donde dicho compuesto es una sal del compuesto de fórmula 1.0.

39. El compuesto de la Reivindicación 1 donde dicho compuesto es un éster del compuesto de fórmula 1.0.

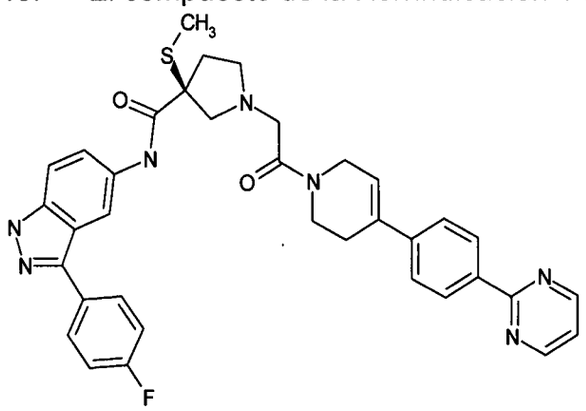
40. El compuesto de la Reivindicación 1 donde dicho compuesto es un solvato del compuesto de fórmula 1.0.

41. Un compuesto seleccionado del grupo que consiste en los compuestos finales de los Ejemplos 612 hasta 827.

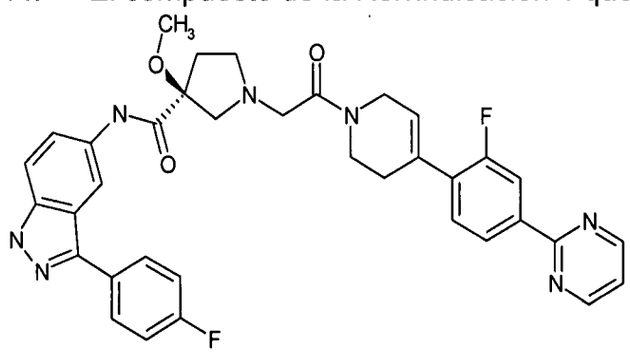
42. El compuesto de la Reivindicación 1 que tiene la fórmula;



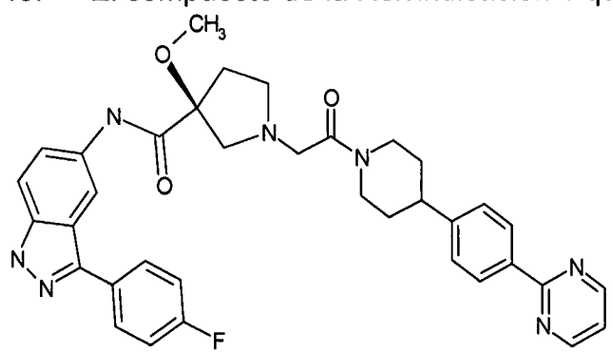
43. El compuesto de la Reivindicación 1 que tiene la fórmula



44. El compuesto de la Reivindicación 1 que tiene la fórmula



45. El compuesto de la Reivindicación 1 que tiene la fórmula



46. Una composición farmacéutica que comprende por lo menos un compuesto de cualquiera de las Reivindicaciones 1 hasta 45 y un vehículo aceptable desde el punto de vista farmacéutico.

47. Un uso de por lo menos uno compuesto de cualquiera de las Reivindicaciones 1 hasta 45:

(1) para la fabricación de un medicamento para tratar el cáncer; o

(2) para la fabricación de un medicamento para tratar el cáncer, dicho medicamento se usa en combinación con por lo menos un agente quimioterapéutico; o

(3) para la fabricación de un medicamento para tratamiento del cáncer, dicho medicamento se usa en combinación con por lo menos un agente quimioterapéutico, y terapia de rayos; o

(4) para la fabricación de un medicamento para tratar el cáncer, dicho medicamento se usa en combinación con por lo menos un agente quimioterapéutico seleccionado del grupo que consiste en: (1) taxanos, (2) compuestos coordinadores de platino, (3) inhibidores del factor de crecimiento epidérmico (FCE) que son anticuerpos, (4) inhibidores del FCE que son moléculas pequeñas, (5) inhibidores del factor de crecimiento endolitial vascular (VEGF) que son anticuerpos, (6) inhibidores de quinasa de VEGF que son moléculas pequeñas, (7) antagonistas del receptor de estrógenos o moduladores selectivos del receptor de estrógenos (SERMs), (8) derivados de nucleósidos anti-tumorales, (9) epotilonas, (10) inhibidores de topoisomerasa, (11) alcaloides vinca, (12) anticuerpos que son inhibidores de αVβ3 integrinas, (13) antagonistas de folato, (14) inhibidores de la ribonucleótido reductasa, (15) antraciclinas, (16) agentes biológicos; (17) inhibidores de la angiogénesis y/o supresores del factor de necrosis tumoral alfa (TNF-alfa) tales como talidomida (o imida relacionada), (18) inhibidores de la quinasa Bcr/abl, (19) inhibidores de MEK1 y/o MEK 2 que son moléculas pequeñas, (20) inhibidores de IGF-1 y IGF-2 que son moléculas pequeñas, (21) inhibidores de moléculas pequeñas de quinasas RAF y BRAF, (22) inhibidores de moléculas pequeñas de quinasas dependientes del ciclo

celular tales como CDK1, CDK2. CDK4 y CDK6, (23) agentes alquilantes, y (24) inhibidores de la farnesil transferasa de la proteína; o

(5) para la fabricación de un medicamento para tratamiento del cáncer, dicho medicamento se administra con por lo menos uno inhibidor de transducción de señal; o

(6) para la fabricación de un medicamento para tratamiento del cáncer, dicho cáncer se selecciona del grupo que consiste en: cáncer de pulmón, cáncer de páncreas, cáncer de colon, leucemias mieloides, cáncer de tiroides, síndrome mielodisplásico, carcinoma de vejiga, carcinoma epidérmico, melanoma, cáncer de mama, cáncer de próstata, cánceres de cuello y cabeza, cáncer de ovario, cánceres de cerebro, cánceres de origen mesenquimal, sarcomas, tetracarcinomas, nuroblastomas, carcinomas de riñón, hepatomas, linfoma de no Hodgkin, mieloma múltiple, y carcinoma de tiroides anaplásico; o

(7) para la fabricación de un medicamento para tratar el cáncer en las cuales dicho cáncer se selecciona del grupo que consiste en: melanoma, cáncer de páncreas, cáncer de tiroides, cáncer colo-rectal, cáncer de pulmón, cáncer de mama, y cáncer de ovario; o

(8) para la fabricación de un medicamento para tratar el cáncer, dicho medicamento se usa en combinación con una cantidad efectiva de por lo menos un agente quimioterapéutico, en las cuales dicho cáncer se selecciona del grupo que consiste en: melanoma, cáncer de páncreas, cáncer de tiroides, cáncer colorectal, cáncer de pulmón, cáncer de mama, y cáncer de ovario; o

(9) para la fabricación de un medicamento para tratamiento del melanoma; o

(10) para la fabricación de un medicamento para tratamiento de un melanoma, dicho medicamento se usa en combinación con por lo menos un agente quimioterapéutico; o

(11) para la fabricación de un medicamento para tratamiento del cáncer de páncreas; o

(12) para la fabricación de un medicamento para tratamiento del cáncer de páncreas, dicho medicamento se usa en combinación con por lo menos un agente quimioterapéutico; o

(13) para la fabricación de un medicamento para tratamiento del cáncer de tiroides; o

(14) para la fabricación de un medicamento para tratamiento del cáncer de tiroides, dicho medicamento se usa, en combinación con por lo menos un agente quimioterapéutico; o

(15) para la fabricación de un medicamento para tratamiento del cáncer colo-rectal; o

(16) para la fabricación de un medicamento para tratamiento del cáncer colo-rectal, dicho medicamento se usa en combinación con por lo menos un agente quimioterapéutico; o

(17) para la fabricación de un medicamento para tratamiento del cáncer de pulmón; o

(18) para la fabricación de un medicamento para tratamiento del cáncer de pulmón, dicho medicamento se usa en combinación con por lo menos un agente quimioterapéutico; o

(19) para la fabricación de un medicamento para tratamiento del cáncer de mama; o

(20) para la fabricación de un medicamento para tratamiento del cáncer de mama, dicho medicamento se usa en combinación con por lo menos un agente quimioterapéutico; o

(21) para la fabricación de un medicamento para tratamiento del cáncer de ovario; o

(22) para la fabricación de un medicamento para tratamiento del cáncer de ovario, dicho medicamento se usa en combinación con por lo menos un agente quimioterapéutico; o

(23) para la fabricación de un medicamento para tratamiento del cáncer de mama dependiente de hormonas, dicho medicamento se usa en combinación con agentes anti-hormonales; o

(24) para la fabricación de un medicamento para tratamiento del cáncer de mama dependiente de hormonas, dicho medicamento se usa en combinación con agentes anti-hormonales, y por lo menos un agente quimioterapéutico; o

(25) para la fabricación de un medicamento para prevenir el cáncer de mama dependiente de hormonas, dicho medicamento se usa en combinación con agentes anti-hormonales; o

(26) para la fabricación de un medicamento para prevenir el cáncer de mama dependiente de hormonas, dicho medicamento se usa en combinación con agentes anti-hormonales, y por lo menos un agente quimioterapéutico; o

(27) para la fabricación de un medicamento para el tratamiento del cáncer de cerebro; o

(28) para la fabricación de un medicamento para el tratamiento del cáncer de cerebro, dicho medicamento se usa en combinación con por lo menos un agente quimioterapéutico; o

(29) para la fabricación de un medicamento para el tratamiento del cáncer de cerebro, dicho medicamento se usa en combinación con un agente quimioterapéutico en el cual dicho agente quimioterapéutico es temozolomida; o

(30) para la fabricación de un medicamento para tratamiento del cáncer de próstata; o

(31) para la fabricación de un medicamento para tratamiento del cáncer de próstata, dicho medicamento se usa en combinación con por lo menos un agente quimioterapéutico; o

(32) para la fabricación de un medicamento para tratamiento del síndrome mielodisplásico; o

(33) para la fabricación de un medicamento para tratamiento del síndrome mielodisplásico, dicho medicamento se usa en combinación con por lo menos un agente quimioterapéutico; o

(34) para la fabricación de un medicamento para tratamiento de las leucemias mieloides; o

(35) para la fabricación de un medicamento para tratamiento de las leucemias mieloides, dicho medicamento se usa en combinación con por lo menos un agente quimioterapéutico; o

(36) para la fabricación de un medicamento para tratamiento de la leucemia mielógena aguda; o

(37) para la fabricación de un medicamento para tratamiento de la leucemia mielógena aguda, dicho medicamento se usa en combinación con por lo menos un agente quimioterapéutico; o

(38) para la fabricación de un medicamento para tratamiento del leucemia mielomonocítica crónica; o

(39) para la fabricación de un medicamento para tratamiento del leucemia mielomonocítica crónica, dicho medicamento se usa en combinación con por lo menos un agente quimioterapéutico; o

(40) para la fabricación de un medicamento para tratamiento de la leucemia mielógena crónica; o

(41) para la fabricación de un medicamento para tratamiento de la leucemia mielógena crónica, dicho medicamento se usa en combinación con por lo menos un agente quimioterapéutico; o

(42) para la fabricación de un medicamento para tratamiento del cáncer de vejiga; o

(43) para la fabricación de un medicamento para tratamiento del cáncer de vejiga, dicho medicamento se usa en combinación con por lo menos un agente quimioterapéutico; o

(44) para la fabricación de un medicamento para tratamiento del linfoma de no Hodgkin; o

(45) para la fabricación de un medicamento para tratamiento del linfoma de no Hodgkin, dicho medicamento se usa en combinación con por lo menos un agente quimioterapéutico; o

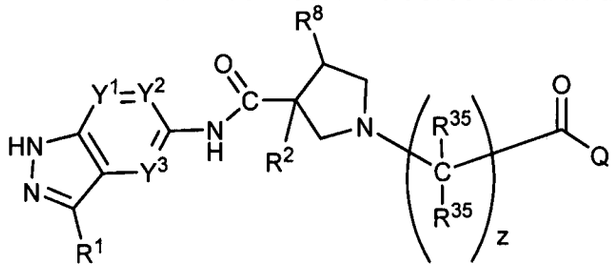
(46) para la fabricación de un medicamento para tratamiento del mieloma múltiple; o

(47) para la fabricación de un medicamento para tratamiento del mieloma múltiple, dicho medicamento se usa en combinación con por lo menos un agente quimioterapéutico.

p. p. de: SCHERING CORPORATION

RESUMEN

Se describen los inhibidores de ERK de fórmula 1.0:



(1.0)

y sus sales, ésteres y solvatos aceptables desde el punto de vista farmacéutico. Q es un anillo de piperidina o piperazina que pueden tener un puente o anillo fusionado. El anillo de piperidina puede tener un enlace doble en el anillo. Todos los demás sustituyentes son como se los define aquí. También se describen métodos de tratamiento para el cáncer usando los compuestos de fórmula 1.0.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/006979

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/14 C07D403/14 C07D407/14 C07D409/14 C07D413/14
C07D417/14 C07D491/056 A61K31/4245 A61K31/444 A61K31/506
A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2005/113541 A (VERTEX PHARMA [US]; MARTINEZ-BOTELLA GABRIEL [US]; HALE MICHAEL R [US]) 1 December 2005 (2005-12-01) paragraph [0011] paragraph [0014] example 6 example 7	1-47
A	WO 02/064586 A (VERTEX PHARMA [US]; CAO JINGRONG [US]; GREEN JEREMY [US]; HALE MICHAEL) 22 August 2002 (2002-08-22) page 6, line 12 - page 7, line 31 page 16, line 18 - page 17, line 11	1-47

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 September 2008	08/10/2008

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Koch, Kristian

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/006979

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 02/088090 A (VERTEX PHARMA [US]; HALE MICHAEL ROBIN [US]) 7 November 2002 (2002-11-07) page 3, line 12 - page 5, line 15	1-47
P,X	WO 2007/070398 A (SCHERING CORP [US]; COOPER ALAN [US]; DENG YONGQI [US]; SHIPPS GERALD) 21 June 2007 (2007-06-21) cited in the application claim 1 examples 422,424,427-429,431,432,465,563	1-40,46, 47

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2008/006979

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005113541 A	01-12-2005	AR 051735 A1	07-02-2007
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		JP 2004520402 T	08-07-2004
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		EP 1461334 A2	29-09-2004
		JP 2004538266 T	24-12-2004
		MX PA03009847 A	12-02-2004
WO 2007070398 A	21-06-2007	AR 056891 A1	31-10-2007
		AU 2006326616 A1	21-06-2007
		EP 1966151 A1	10-09-2008
		US 2007191604 A1	16-08-2007

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 09-139231- -00000-0000

Fecha: 2009-12-04 16:59:34 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 928

Industria y Comercio SUPERINTENDENCIA	LISTA DE CHEQUEO ADMISIÓN A TRÁMITE – NUEVAS CREACIONES

PATENTE DE INVENCIÓN ☐ MODELO DE UTILIDAD ☐ **Art 33 Decisión 486/00**

- ☐ Indicación que se solicita una patente.
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Descripción de la invención
- ☐ Dibujos de ser estos pertinentes
- ☐ Comprobante de pago de las tasas establecidas (De ser el caso formato de descuento)

Completa ☐ Incompleta ☐

PATENTE DE INVENCIÓN PCT ☐ MODELO DE UTILIDAD PCT ☐ **Art.33 Decisión 486/00, Circular Única**

- ☑ Indicación que se solicita una PCT
- ☑ Copia de la solicitud en español, tal como fue presentada inicialmente (capítulo descriptivo, reivindicatorio, resumen)
- ☑ Dibujos de ser estos pertinentes
- ☑ Comprobante de pago de las tasas establecidas (de ser el caso formato de descuento)

Completa ☑ Incompleta ☐

DISEÑO INDUSTRIAL ☐ **(Art. 119 Decisión 486/00)**

- ☐ Indicación que se solicita Diseño industrial
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Representación gráfica y fotográfica del Diseño industrial o muestra del material que incorpora el diseño
- ☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐

ESQUEMA DE TRAZADO ☐ **(Art. 92 Decisión 486/00)**

- ☐ Indicación que se solicita un esquema de trazado
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Representación gráfica de un esquema de trazado
- ☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐

Industria y Comercio
SUPERINTENDENCIA

Bogotá,
2020

Doctor(a)
OLARTE GARCIA CARLOS REYNALDO
Apoderado(a) y/o Representante de
SCHERING CORPORATION

REFERENCIA	Radicación No.	9 139231
	Solicitud internacional	PCT/US2008/006979
	Fecha inicio fase nacional	05/01/2010
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	1304

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. El solicitante debe presentar un nuevo titulo que permita identificar la materia de la cual trata la solicitud, ya que el titulo relacionado no se encuentra con la precisión necesaria para identificar claramente el objeto de la solicitud de patente. (Regla 4.3 PCT, Art 26-27 D-486, Circular única 5.2.9)

2. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante, conforme a lo establecido por el artículo 26 literal k) de la Decisión 486 de la Comisión de la Comunidad Andina. Cuando se trate de documentos otorgados en el extranjero, estos deberán legalizarse de conformidad con lo dispuesto por los artículos 259 y 260 del Código de Procedimiento Civil. Cuando se trate de las declaraciones a que hace referencia la Regla 4.17 ii) del Tratado de Cooperación en Materia de Patentes PCT., el alcance de las tales declaraciones se determinará según indiquen claramente una cesión de derechos del inventor al solicitante o su causante, de conformidad con lo dispuesto en el numeral 5.2.15 del Capítulo Quinto, Título X de la Circular Única de Superintendencia de Industria y Comercio.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

Continua en la página siguiente...

Industria y Comercio
SUPERINTENDENCIA

Bogotá,
2020

Doctor(a)
OLARTE GARCIA CARLOS REYNALDO
Apoderado(a) y/o Representante de
SCHERING CORPORATION

REFERENCIA	Radicación No.	9 139231
	Solicitud internacional	PCT/US2008/006979
	Fecha inicio fase nacional	05/01/2010
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	[illegible] 1305

Teniendo en cuenta que el capítulo reivindicatorio presentado excede de quince reivindicaciones, es necesario que cancele la tasa establecida por cada reivindicación adicional presentada, de conformidad con lo dispuesto en la resolución de tasas vigente para la fecha de presentación de la solicitud, so pena de que no sean tenidas en cuenta dentro del presente trámite administrativo.

En consecuencia, con fundamento en lo previsto por el artículo 12 del Código Contencioso Administrativo, se le requiere para que dentro del término de dos (2) meses siguientes a la fecha de notificación del presente oficio atienda el requerimiento aquí señalado. Lo anterior, con el alcance que para tal efecto establece el artículo 13 de la misma codificación, respecto de las reivindicaciones adicionales.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del titulo primero de la Circular Única Nº 10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Directora de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista de fecha 05 FEB. 2010
adpa11

Radicación No.:9 139231

ALIX CARMENZA CESPEDES DE VERGEL
Directora de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista de fecha 05 FEB. 2010
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