Organizacion y
Digitalizacion CSA Ltda
CSA126903

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-116702- -00000-0000
Fecha: 2010-09-21 15:26:51 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION - Folios: 392

Industria y Comercio
SUPERINTENDENCIA

PCT

INVENTARIO

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIRECCIÓN DE NUEVAS CREACIONES

10-116702

SOLICITUD DE PATENTE DE INVENCIÓN

1/2

TITULO: COMPUESTOS NOVEDOSOS QUE SON INHIBIDORES DE ERK REFERENCIA A UNA SOLICITUD RELACIONADA

SOLICITANTE: SCHERING CORPORATION

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

APODERADO: CARLOS R. OLARTE

BOGOTÁ 21 de Septiembre de 2010

P2010/000123

21-09-2010
No Ex

OLARTERAISBECK
OLARTE RAISBECK MC

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-116702- -00000-0000
Fecha: 2010-09-21 15:26:51 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 392

PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2010/000123**

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, New Jersey 07033 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: Diagonal 34 No. 5-28 Bogotá
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 DJUNTA
Dirección: VER PAGINA ADJUNTA
Nacionalidad o Domicilio: VER PAGINA ADJUNTA

(5) **PCT (86)**

Solicitud Internacional No. PCT/US2009/034447 Fecha Febrero 19, 2009

Publicación Internacional No. WO 2009/105500 Fecha Agosto 27, 2009

(6) Título (54) COMPUESTOS NOVEDOSOS QUE SON INHIBIDORES DE ERK
REFERENCIA A UNA SOLICITUD RELACIONADA

Clasificación Internacional (51) C07D 403/14, A61K 31/435

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

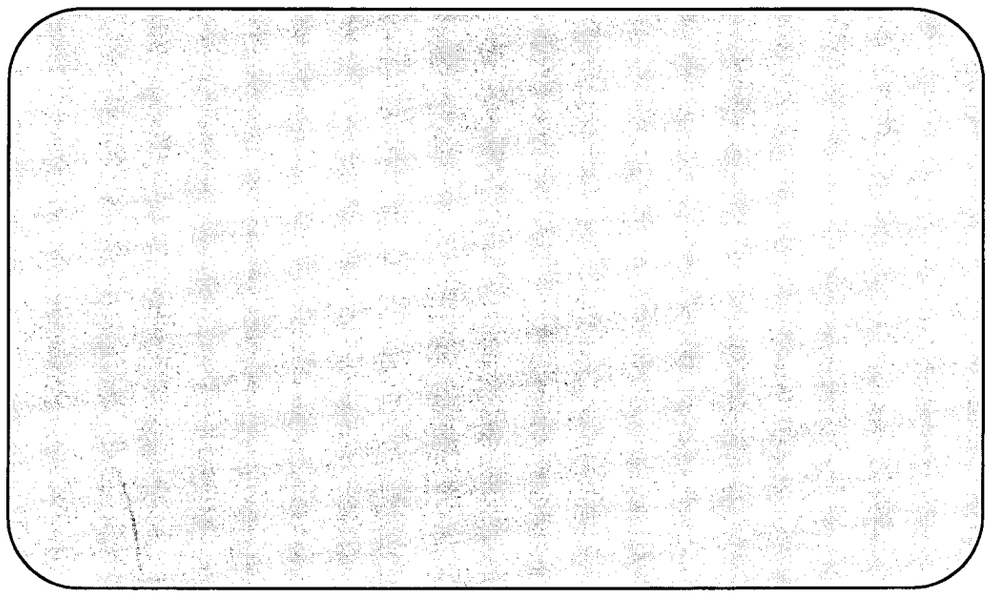
(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Febrero 21, 2008	61/030.407

(9) **Comprobante de pago No.** 10- **Fecha** Septiembre 21, 2010

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

ALAN B. COOPER
23 Natalie Drive, West Caldwell,
New Jersey 07006
Estados Unidos de America
Nacionalidad: Estadounidense

YANG NAN
163 Linden Avenue, Malden,
Massachusetts 02148
Estados Unidos de America
Nacionalidad: Estadounidense

YONGQI DENG
55 Ellison Road, Newton,
Massachusetts 02459
Estados Unidos de America
Nacionalidad: Estadounidense

GERALD W. SHIPPS. Jr.
5 Daniel Drive, Stoneham,
Massachusetts 02180
Estados Unidos de America
Nacionalidad: Estadounidense

NENG-YANG SHIH
2 Tyler Road, Lexington,
Massachusetts 02420
Estados Unidos de America
Nacionalidad: Estadounidense

HUGH Y. ZHU
29 Deerwood Trail W.,
Warren New Jersey 07059
Estados Unidos de America
Nacionalidad: China

JOSEPH M. KELLY
112 Princeton Road, Parlin,
New Jersey 08859
Estados Unidos de America
Nacionalidad: Irlanda

SUBRAHMANYAM GUDIPATI
15 Hyacinth Drive, Apt. #2L,
Fords, New Jersey 08863
Estados Unidos de America
Nacionalidad: India

RONALD J. DOLL
8 Concord Lane,
Convent Station NJ 07960
Estados Unidos de America
Nacionalidad: Estadounidense

MEHUL F PATEL
4 Chester Avenue, Apt. #4, Waltham,
Massachusetts 02453

Estados Unidos de America
Nacionalidad: Estadounidense

JAGDISH A DESAI
3 Forest Park Terrace, Monroe Township,
New Jersey 08831
Estados Unidos de America
Nacionalidad: Estadounidense

JAMES J-S WANG
47 Unami Terrace, Westfield,
New Jersey 07090
Estados Unidos de America
Nacionalidad: Estadounidense

SUNIL PALIWAL
5 Golf View Court, Monroe Township,
New Jersey 08831
Estados Unidos de America
Nacionalidad: Estadounidense

HON-CHUNG TSUI
41 Cortland Drive, East Brunswick,
New Jersey 08816
Estados Unidos de America
Nacionalidad: China

SOBHANA BABU BOGA
79 Country Club Lane, Scotch Plains,
New Jersey 07076
Estados Unidos de America
Nacionalidad: India

ABDUL-BASIT ALHASSAN
1 Country Club Lane, Scotch Plains,
New Jersey 07076
Estados Unidos de America
Nacionalidad: Ghana

XIAOLEI GAO
111 Timothy Place, Bridgewater,
New Jersey 08807
Estados Unidos de America
Nacionalidad: China

LIANG ZHU
17 Charlesbank Way – Apt. B, Waltham,
Massachusetts 02453
Estados Unidos de America
Nacionalidad: China

XIN YAO
181 Spruce Mill Lane, Scotch Plains,
New Jersey 07076
Estados Unidos de America
Nacionalidad: China

5

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 10 - 78,703
FECHA : SEPTIEMBRE 21 DE 2010

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-116702- -00000-0000
Fecha: 2010-09-21 15:26:51 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 392

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	378377226	21/09/2010	554,000.00

***** 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	554,000.00
		TOTAL : $	554,000.00

SON: QUINIENTOS CINCUENTA Y CUATRO 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

6

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.

Neira C

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

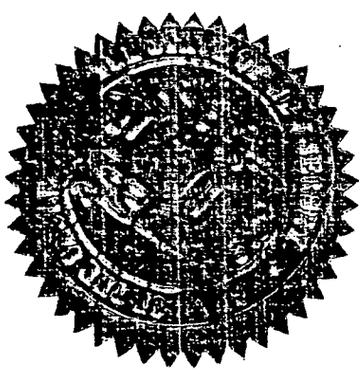
5. AT TRENTON, NEW JERSEY

6. THE 29TH DAY OF AUGUST 2003

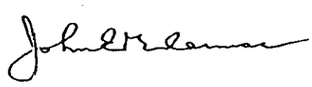
7. BY: John E McCormac, CPA, NEW JERSEY TREASURER

8. NO. A180345

9. SEAL/STAMP:



10. SIGNATURE



OLARTERAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

WORLD TRADE CENTER – TORRE C
CALLE 100 NO. 8A-55 PISO 10
BOGOTA, COLOMBIA
TELEPHONE: +57-1 638-6200
FAX: +57-1 638-6201

www.olarteraisbeck.com

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

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

WORLD TRADE CENTER – TORRE C
CALLE 100 NO. 8A-55 PISO 10
BOGOTA, COLOMBIA
TELEPHONE: +57-1 638-6200
FAX: +57-1 638-6201

www.olarteraisbeck.com

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 y 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):

NOTARY PUBLIC OF NEW JERSEY

BLIC (Signature): Marguerite LaCorte

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

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
27 August 2009 (27.08.2009)

PCT

(10) International Publication Number
WO 2009/105500 A1

(51) International Patent Classification:
C07D 403/14 (2006.01) *A61K 31/435* (2006.01)

(21) International Application Number:
PCT/US2009/034447

(22) International Filing Date:
19 February 2009 (19.02.2009)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/030,407 21 February 2008 (21.02.2008) US

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

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **COOPER, Alan, B.** [US/US]; 23 Natalie Drive, West Caldwell, New Jersey 07006 (US). **NAN, Yang** [US/US]; 163 Linden Avenue, Malden, Massachusetts 02148 (US). **DENG, Yongqi** [US/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, Y.** [CN/US]; 29 Deerwood Trail W., Warren, New Jersey 07059 (US). **KELLY, Joseph, M.** [IE/US]; 112 Princeton Road, Parlin, New Jersey 08859 (US). **GUDIPATI, Subrahmanyam** [IN/US]; 15 Hyacinth Drive, Apt. #2L, Fords, New Jersey 08863 (US). **DOLL, Ronald J.** [US/US]; 8 Concord Lane, Convent Station, NJ 07960 (US). **PATEL, Mehul, F.** [US/US]; 4 Chester Avenue, Apt. #4, Waltham, Massachusetts 02453 (US). **DESAI, Jagdish, A.** [US/US]; 3 Forest Park Terrace, Monroe Township, New Jersey 08831 (US). **WANG, James, J-S** [US/US]; 47 Unami Terrace, Westfield, New Jersey 07090 (US). **PALIWAL, Sunil** [US/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 - Apt. B, Waltham, Massachusetts 02453 (US). **YAO, Xin** [CN/US]; 181 Spruce Mill Lane, Scotch Plains, New Jersey 07076 (US).

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

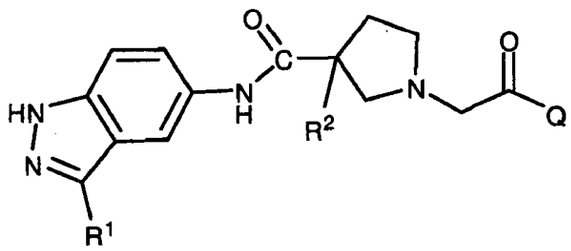
Declarations under Rule 4.17:

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

— *with international search report (Art. 21(3))*

(54) **Title**: COMPOUNDS THAT ARE ERK INHIBITORS



(1.0)

(57) **Abstract**: Disclosed are the ERK inhibitors of formula 1.0: and the pharmaceutically acceptable salts, and solvates thereof. Q is a tetrahydopyridinyl ring. All other substitutents are as defined herein. Also disclosed are methods of treating cancer using the compounds of formula 1.0.

WO 2009/105500 A1

COMPOUNDS THAT ARE ERK INHIBITORS

REFERENCE TO RELATED APPLICATION

This Application claims the benefit of U.S. Provisional Application Serial No. 61/030407 filed February 21, 2008.

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.

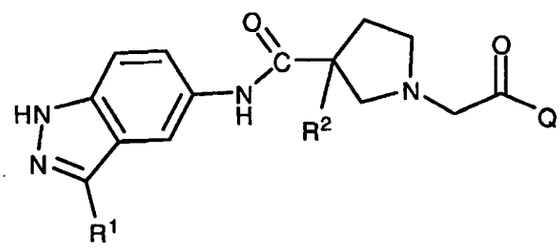
Therefore, a welcome contribution to the art would be small-molecules (i.e., compounds) that inhibit ERK activity (i.e., ERK1 and ERK2 activity), which small-molecules would be useful for treating a broad spectrum of cancers, such as, for example, melanoma, pancreatic cancer, thryroid cancer, colorectal 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, and solvates thereof, wherein: Q is a tetrahydropyridinyl (e.g., 1,2,3,6-tetrahydopyridinyl), or a substituted tetrahydropyridinyl (e.g., a substituted 1,2,3,6-tetrahydo-pyridinyl); and R^1 and R^2 are as defined below.

This invention provides compounds of formula 1.0.

This invention provides compounds of formula 1.0 in pure or isolated form.

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

This invention provides solvates of the compounds of formula 1.0.

This invention provides compounds of formula 1.0 wherein from one up to the total number of hydrogens are deuterium.

This invention provides compounds of formula 1.0 wherein at least one H is deuterium.

This invention provides compounds of formula 1.0 wherein 1 to 5 H are deuterium.

This invention provides compounds of formula 1.0 wherein one H is deuterium.

This invention provides compounds A1 to A16 and A18 to A48.

This invention provides compounds A1 to A16 and A18 to A30.

This invention provides compounds A1 to A16 and A18 to A26.

This invention provides compounds A31 to A48.

This invention also provides a pharmaceutical composition comprising an effective amount of at least one compound of formula 1.0 and a pharmaceutically acceptable carrier.

This invention also provides a pharmaceutical composition comprising an effective amount of at least one compound of formula 1.0 and an effective amount of at least one other 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 compound of formula 1.0.

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 compound of formula 1.0.

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 compound of formula 1.0.

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 compound of formula 1.0.

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 compound of formula 1.0.

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 compound of formula 1.0.

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 compound of formula 1.0, in combination with an effective amount of at least one 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 compound of formula 1.0, in combination with an effective amount of at least one 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 compound of formula 1.0 in combination with at least one 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 compound of formula 1.0 in combination with at least one signal transduction inhibitor.

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
Anhy	Anhydrous

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
Et	Ethyl
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
Py	Pyridine
Pyr	Pyridine
Rb	Round bottom flask
Rbt	Round bottom flask
RT (r.t.)	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; thus, in one example "at least one" means one, in another example "at least one" means two, and in another example "at least one" means three;

"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; thus, in one example "at least one" means one, in another example "at least one" means two, and in another example "at least one" means three;

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

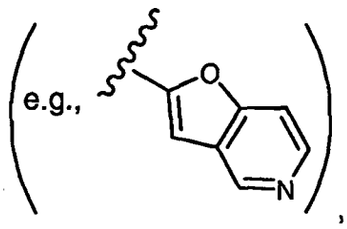
"heteroaralkenyl" means a heteroaryl-alkenyl- group (i.e., the bond to the parent moiety is through the alkenyl group) wherein the heteroaryl group is unsubstituted or substituted as defined below, and the alkenyl group is unsubstituted or substituted as defined above;

"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;

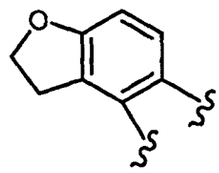
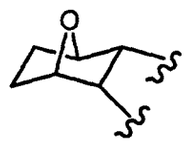
"heterocycloalkylalkyl" (or heterocyclylalkyl) means a heterocycloalkyl-alkyl- group (i.e., the bond to the parent moiety is through the alkyl group) wherein the heterocycloalkyl group (i.e., the heterocyclyl group) is unsubstituted or substituted as defined below, and the alkyl group is unsubstituted 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. And any one or more of these hydrogen atoms can be deuterium.

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-C_{10})alkyl, (C_3-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-C_6)alkyl or benzyl, —C(OY^{82})Y^{84} wherein Y^{82} is (C_1-C_4) alkyl and Y^{84} is (C_1-C_6)alkyl, carboxy (C_1-C_6)alkyl, amino(C_1-C_4)alkyl or mono-N—or di-N,N-(C_1-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-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.

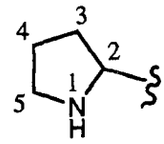
Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, aluminum salts, zinc salts, salts with organic bases (for example, organic amines) such as benzathines, diethylamine, dicyclohexylamines,

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.

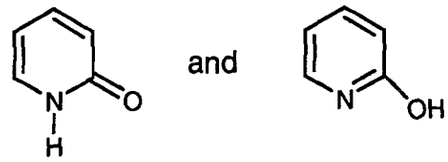
In hetero-atom containing ring systems of this invention, there are no hydroxyl groups on carbon atoms adjacent to a N, O or S, and there are no N or S groups on carbon adjacent to another heteroatom. Thus, for example, in the ring:



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.

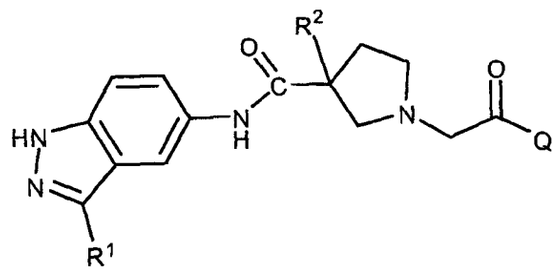
As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

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, chlorine, and iodine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, ^{36}Cl, and ^{123}I, respectively.

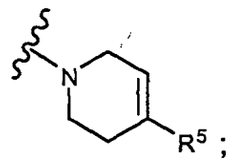
Certain isotopically-labelled compounds of formula 1.0 (e.g., those labeled with ^{3}H and ^{14}C) are useful in compound and/or substrate tissue distribution assays. Tritiated (i.e., ^{3}H) and carbon-14 (i.e., ^{14}C) isotopes are particularly preferred for their ease of preparation and detectability. Certain isotopically-labelled compounds of Formula (I) can be useful for medical imaging purposes. E.g., those labeled with positron-emitting isotopes like ^{11}C or ^{18}F can be useful for application in Positron Emission Tomography (PET) and those labeled with gamma ray emitting isotopes like ^{123}I can be useful for application in Single photon emission computed tomography (SPECT). 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 labeled compounds of Formula (I), in particular those containing isotopes with longer half lives (T1/2 >1 day), can generally be prepared by following procedures analogous to those disclosed in the Schemes and/or in the Examples herein below, by substituting an appropriate isotopically labeled reagent for a non-isotopically labeled reagent.

This invention provides compounds of formula 1.0:



(1.0)

or the pharmaceutically acceptable salts, or solvates thereof, wherein R^1, R^2 and Q are independently selected, and wherein:

Q is: 

R^1 is selected from the group consisting of: heteroaryl and substituted heteroaryl, wherein said substituted heteroaryl is substituted with 1 to 3 (preferably 1) substituents independently selected from the group consisting of: -OH, alkoxy, and –O-alkylene-O-alkyl;

R^2 is selected from the group consisting of: -O-alkyl and -S-alkyl; and

R^5 is selected from the group consisting of:

(a) triazolyl-phenyl-,

(b) triazolyl-phenyl- wherein said phenyl is optionally substituted with 1 to 3 substituents independently selected from the group consisting of: halo (e.g., Br, Cl, F, and in one example F) and alkoxy (e.g., C_1-C_6alkoxy, and in one example, C_1-C_2alkoxy, and in another example $-OCH_3$),

(c) substituted triazolyl-phenyl- wherein said phenyl is optionally substituted with 1 to 3 substituents independently selected from the group consisting of: halo (e.g., Br, Cl, F, and in one example F) and alkoxy (e.g., C_1-C_6alkoxy, and in one example, C_1-C_2alkoxy, and in another example $-OCH_3$), and said triazolyl group is substituted with one or two substitutents independently selected from the group consisting of: alkyl, hydroxy substituted alkyl, -alkylene-O-alkyl, and amino (i.e., $-NH_2$),

(d) triazolyl-thienyl-,

(e) triazolyl-thienyl- wherein said thienyl is optionally substituted with 1 to 2 substituents independently selected from the group consisting of: halo (e.g., Br, Cl, F, and in one example F) and alkoxy (e.g., C_1-C_6alkoxy, and in one example, C_1-C_2alkoxy, and in another example $-OCH_3$),

(f) substituted triazolyl-thienyl- wherein said thienyl is optionally substituted with 1 to 2 substituents independently selected from the group consisting of: halo (e.g., Br, Cl, F, and in one example F) and alkoxy (e.g., C_1-C_6alkoxy, and in one example, C_1-C_2alkoxy, and in another example $-OCH_3$), and said triazolyl group is substituted with one or two substitutents independently selected from the group consisting of: alkyl, hydroxy substituted alkyl, -alkylene-O-alkyl, and amino (i.e., $-NH_2$),

(g) triazolyl-pyridyl-,

(h) triazolyl-pyridyl- wherein said pyridyl is optionally substituted with 1 to 3 substituents independently selected from the group consisting of: halo (e.g., Br, Cl, F, and in one example F), alkyl, and alkoxy (e.g., C_1-C_6alkoxy, and in one example, C_1-C_2alkoxy, and in another example $-OCH_3$), provided that the carbon atoms adjacent to the nitrogen atom in said pyridyl are not substituted with halo, and

(i) substituted triazolyl-pyridyl- wherein: (1) said pyridyl is optionally substituted with 1 to 3 substituents independently selected from the group consisting of: halo (e.g., Br, Cl, F, and in one example F), alkyl, and alkoxy (e.g., C_1-C_6alkoxy, and in one example, C_1-C_2alkoxy, and in another example $-OCH_3$), provided that the

carbon atoms adjacent to the nitrogen atom in said pyridyl are not substituted with halo, and (2) said triazolyl group is substituted with one or two substitutents independently selected from the group consisting of: alkyl, hydroxy substituted alkyl, -alkylene-O-alkyl, and amino (i.e., $-NH_2$),

(j) triazolyl-thiazolyl-,

(k) triazolyl-thiazolyl- wherein said thiazolyl is optionally substituted with 1 substituent independently selected from the group consisting of: halo (e.g., Br, Cl, F, and in one example F), alkyl, and alkoxy (e.g., C_1-C_6alkoxy, and in one example, C_1-C_2alkoxy, and in another example $-OCH_3$), amino (i.e., NH_2), alkylamino, and dialkylamino wherein each alkyl is independently selected, and

(l) substituted triazolyl-thiazolyl- wherein (1) said thiazolyl is optionally substituted with 1 substituent independently selected from the group consisting of: halo (e.g., Br, Cl, F, and in one example F), alkyl, and alkoxy (e.g., C_1-C_6alkoxy, and in one example, C_1-C_2alkoxy, and in another example $-OCH_3$), amino (i.e., NH_2), alkylamino, and dialkylamino wherein each alkyl is independently selected, and (2) said triazolyl group is substituted with one or two substitutents independently selected from the group consisting of: alkyl, hydroxy substituted alkyl, -alkylene-O-alkyl, and amino (i.e., $-NH_2$),

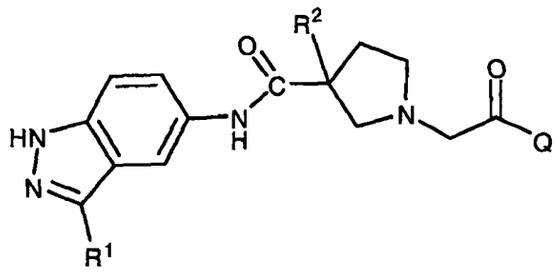
(m) pyridazinyl-thienyl-,

(n) pyridazinyl-thienyl- wherein said thienyl is optionally substituted with 1 to 2 substituents independently selected from the group consisting of: halo (e.g., Br, Cl, F, and in one example F) and alkoxy (e.g., C_1-C_6alkoxy, and in one example, C_1-C_2alkoxy, and in another example $-OCH_3$), and

(o) substituted pyridazinyl-thienyl- wherein (1) said thienyl is optionally substituted with 1 to 2 substituents independently selected from the group consisting of: halo (e.g., Br, Cl, F, and in one example F) and alkoxy (e.g., C_1-C_6alkoxy, and in one example, C_1-C_2alkoxy, and in another example $-OCH_3$), and (2) said pyridazinyl group is substituted with 1 to 3 substitutents independently selected from the group consisting of: =O, alkyl, amino (i.e., $-NH_2$), alkylamino, dialkylamino wherein each alkyl is independently selected, and halo (e.g., Br, Cl, F, and in one example F), provided that the carbon atoms adjacent to the nitrogen atoms in said pyridazinyl are not substituted with halo, and

provided that when said -alkylene-O-alkyl group is bound to the nitrogen of said triazolyl in (c), (f), (i) and (l) of R^5 the alkylene moiety of said -alkylene-O-alkyl group is not $-CH_2-$ (i.e., the alkylene moiety is 2 or more carbons in length).

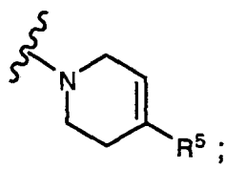
This invention provides compounds of formula 1.0:



(1.0)

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

Q is:



R^1 is selected from the group consisting of: heteroaryl and substituted heteroaryl, wherein said substituted heteroaryl is substituted with 1 to 3 (preferably 1) substituents independently selected from the group consisting of: -OH, alkoxy, and –O-alkylene-O-alkyl;

R^2 is selected from the group consisting of: -O-alkyl and -S-alkyl; and

R^5 is selected from the group consisting of:

(a) triazolyl-phenyl-,

(b) triazolyl-phenyl- wherein said phenyl is optionally substituted with 1 to 3 substituents independently selected from the group consisting of: halo (e.g., Br, Cl, F, and in one example F) and alkoxy (e.g., C_1-C_6alkoxy, and in one example, C_1-C_2alkoxy, and in another example $-OCH_3$),

(c) substituted triazolyl-phenyl- wherein said phenyl is optionally substituted with 1 to 3 substituents independently selected from the group consisting of: halo (e.g., Br, Cl, F, and in one example F) and alkoxy (e.g., C_1-C_6alkoxy, and in one example, C_1-C_2alkoxy, and in another example $-OCH_3$), and said triazolyl group is substituted with one or two substitutents independently selected from the group consisting of: alkyl, hydroxy substituted alkyl, -alkylene-O-alkyl, and amino (i.e., $-NH_2$);

(d) triazolyl-thienyl-,

(e) triazolyl-thienyl- wherein said thienyl is optionally substituted with 1 to 2 substituents independently selected from the group consisting of: halo (e.g., Br, Cl, F, and in one example F) and alkoxy (e.g., C_1-C_6alkoxy, and in one example, C_1-C_2alkoxy, and in another example $-OCH_3$), and

(f) substituted triazolyl-thienyl- wherein said thienyl is optionally substituted with 1 to 2 substituents independently selected from the group consisting of: halo (e.g., Br, Cl, F, and in one example F) and alkoxy (e.g., C_1-C_6alkoxy, and in one example, C_1-C_2alkoxy, and in another example $-OCH_3$), and said triazolyl group is substituted with one or two substitutents independently selected from the group consisting of: alkyl, hydroxy substituted alkyl, -alkylene-O-alkyl, and amino (i.e., $-NH_2$), and

provided that when said -alkylene-O-alkyl group is bound to the nitrogen of said triazolyl in (c) and (f) of R^5 the alkylene moiety of said -alkylene-O-alkyl group is not $-CH_2-$ (i.e., the alkylene moiety is 2 or more carbons in length).

Those skilled in the art will appreciate that the term "alkylene", as used in the substituents -O-alkylene-O-alkyl and -alkylene-O-alkyl, means a divalent saturated hydrocarbon group. Thus, an example of an alkylene moiety is $-CH_2-CH_2-$, and an example of an -O-alkylene-O-alkyl moiety is $-O-(CH_2)_2-O-CH_3$, and an example of an -alkylene-O-alkyl moiety is $-(CH_2)_2-O-CH_3$.

Those skilled in the art will also appreciate that the term alkylene also includes the moiety $-CH_2-$.

Examples of the R^1 heteroaryl group include, but are not limited to, pyridyl, pyrrolyl, pyrazolyl, imidazolyl, furanyl, thienyl, thiazolyl, pyridyl N-O, and pyrimidinyl.

Examples of the R^1 substitued heteroaryl group include, but are not limited to, substituted pyridyl, substituted pyrrolyl, substituted pyrazolyl, substituted imidazolyl, substituted furanyl, substituted thienyl, substituted thiazolyl, substituted pyridyl N-O, and substituted pyrimidinyl.

In one embodiment of this invention R^1 is pyridyl.

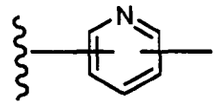
In another embodiment of this invention R^1 is substituted pyridyl.

In another embodiment of this invention R^1 is pyridyl substituted with one substitutent.

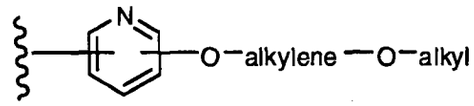
The substitutents on the substituted R^1 groups (e.g., the substituted pyridyl) are independently selected from the group consisting of: -OH, alkoxy, and –O-alkylene-O-alkyl. Examples of the alkoxy group include, for example,

C_1 to C_6alkoxy (such as, for example, -O-CH_3, -O-C_2H_5, and –O-$CH(CH_3)_2$). Examples of the –O-alkylene-O-alkyl group include, for example, –O-(C_1-C_4)alkylene-O-(C_1-C_6)alkyl, –O-(C_1-C_2)alkylene-O-(C_1-C_3alkyl), and –O-$(CH_2)_2$-O-CH_3).

Examples of R^1 include, for example,



and

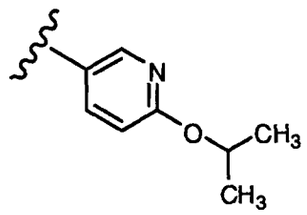


In one embodiment of this invention R^1 is pyridyl substituted with alkoxy.

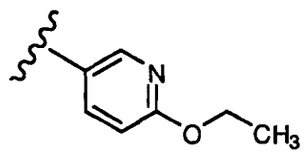
In another embodiement of this invention R^1 is substituted with –$OCH(CH_3)_2$.

In another embodiement of this invention R^1 is substituted with –OC_2H_5.

In another embodiment of this invention R^1 is:



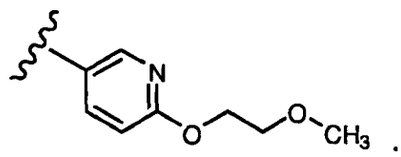
In another embodiment of this invention R^1 is:



In another embodiment of this invention R^1 is substituted with –O-alkylene-O-alkyl.

In another embodiment of this invention R^1 is substituted with –$OCH_2CH_2OCH_3$.

In another embodiment of this invention R^1 is:



Examples of the R^2 -O-alkyl group include, for example, –O-(C_1-C_6)alkyl, –O-(C_1-C_2)alkyl, and –OCH_3.

Examples of the R^2 -S-alkyl group include, for example, –S-(C_1-C_6)alkyl, –S-(C_1-C_2)alkyl, and –SCH_3.

In one embodiment of this invention R^2 is a –O-(C_1-C_2)alkyl group.

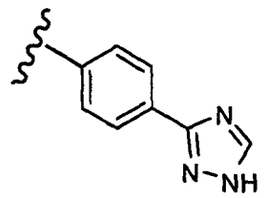
In another embodiment of this invention R^2 is $-OCH_3$.

In another embodiment of this invention R^2 is a $-S-(C_1-C_2)$alkyl group.

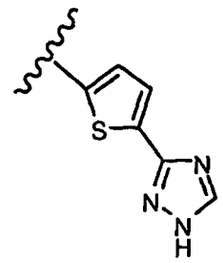
In another embodiment of this invention R^2 is $-SCH_3$.

In one embodiment of this invention R^5 is a triazolyl-phenyl moiety wherein the triazolyl moiety is bonded to the phenyl moiety by a ring carbon of the triazolyl moiety

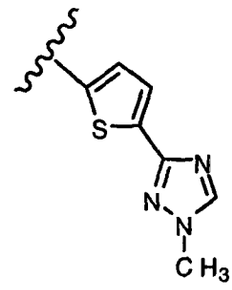
In one embodiment of this invention R^5 is a triazolyl-phenyl- moiety, such as, for example,



In another embodiment of this invention R^5 is a triazolyl-thienyl- moiety, such as, for example,



In another embodiment of this invention R^5 is a triazolyl-thienyl- moiety, such as, for example,



In another embodiment of this invention the substituted triazolyl moiety of said R^5 group is substituted on the ring nitrogen.

When the triazolyl moiety of R^5 is substituted with alkyl, examples of the alkyl groups include, for example, $-C_1-C_6$alkyl, $-C_1-C_4$alkyl, $-C_1-C_2$alkyl, and $-CH_3$. And in one embodiment, there is alkyl substitution on the triazolyl moiety of R^5 and said alkyl is $-CH_3$.

When the triazolyl moiety of R^5 is substituted with -alkylene-O-alkyl groups, examples of the -alkylene-O-alkyl groups include, for example, -C_1-C_4alkylene-O-C_1-C_6alkyl, -C_1-C_2alkylene-O-C_1-C_2alkyl, -C_1-C_4alkylene-O-CH_3, and –$CH_2CH_2OCH_3$. And in one embodiment, there is -alkylene-O-alkyl substitution on the triazolyl moiety of R^5 and said -alkylene-O-alkyl is –$CH_2CH_2OCH_3$. When the nitrogen of the triazolyl moiety of R^5 is substituted with -alkylene-O-alkyl group, examples of the -alkylene-O-alkyl group includes, for example, -C_2-C_4alkylene-O-C_1-C_6alkyl, -C_2alkylene-O-C_1-C_2alkyl, -C_2-C_4alkylene-O-CH_3, and –$CH_2CH_2OCH_3$. And in one embodiment, there is -alkylene-O-alkyl substitution on the nitrogen of the triazolyl moiety of R^5 and said -alkylene-O-alkyl is –$CH_2CH_2OCH_3$.

When the triazolyl moiety of R^5 is substituted with hydroxy substituted alkyl groups, examples of the hydroxy substituted alkyl groups include, for example, hydroxy substituted -C_1-C_4alkyl, hydroxy substituted -C_1-C_2alkyl, and hydroxy substituted -CH_3. Examples also include, for example, –$CH_2COH(CH_3)_2$, and -CH_2CH_2OH.

When the phenyl moiety of R^5 is substituted with halo atoms, examples of the halo atoms include, for example, Cl, F and Br. In one embodiment of this invention the halo on the phenyl is F. In another embodiment of this invention the phenyl is substituted with one F.

In one embodiment of this invention R^5 is a substituted triazolyl-phenyl- wherein said triazolyl is substituted and said phenyl is unsubstituted.

In another embodiment of this invention R^5 is a substituted triazolyl-phenyl- wherein said triazolyl is substituted on the nitrogen and said phenyl is unsubstituted.

In another embodiment of this invention R^5 is a substituted triazolyl-phenyl- wherein said triazolyl is substituted on the carbon and said phenyl is unsubstituted.

In another embodiment of this invention R^5 is a substituted triazolyl-phenyl- wherein said triazolyl is substituted on the nitrogen and on the carbon, and said phenyl is unsubstituted.

In another embodiment of this invention R^5 is a substituted triazolyl-phenyl- wherein said triazolyl is substituted and said phenyl is substituted.

In another embodiment of this invention R^5 is a substituted triazolyl-phenyl- wherein said triazolyl is substituted on the nitrogen and said phenyl is substituted.

In another embodiment of this invention R^5 is a substituted triazolyl-phenyl- wherein said triazolyl is substituted on the carbon and said phenyl is substituted.

In another embodiment of this invention R^5 is a substituted triazolyl-phenyl- wherein said triazolyl is substituted on the nitrogen and on the carbon, and said phenyl is substituted.

In another embodiment of this invention R^5 is a substituted triazolyl-phenyl- wherein said triazolyl is unsubstituted and said phenyl is substituted.

In another embodiment of this invention R^5 is an unsubstituted triazolyl-phenyl-.

In another embodiment of this invention R^5 is a substituted triazolyl-phenyl- wherein the triazolyl is substituted on the nitrogen with $-CH_2COH(CH_3)_2$.

In another embodiment of this invention R^5 is a substituted triazolyl-phenyl- wherein the triazolyl is substituted on the nitrogen with $-CH_2CH_2OH$.

In another embodiment of this invention R^5 is a substituted triazolyl-phenyl- wherein the triazolyl is substituted on the nitrogen with an alkyl group.

In another embodiment of this invention R^5 is a substituted triazolyl-phenyl- wherein the triazolyl is substituted on the nitrogen with an alkyl group and substituted on the carbon with an alkyl group, wherein each alkyl group is independently selected.

In another embodiment of this invention R^5 is a substituted triazolyl-phenyl- wherein the triazolyl is substituted on the nitrogen with a $-CH_3$ group.

In another embodiment of this invention R^5 is a substituted triazolyl-phenyl- wherein the triazolyl is substituted on the nitrogen with a $-CH_3$ group and on the carbon with a $-CH_3$ group.

In another embodiment of this invention R^5 moiety is a substituted triazolyl-phenyl- wherein the triazolyl is substituted on the carbon with a $-NH_2$ group.

In another embodiment of this invention R^5 is a substituted triazolyl-phenyl- wherein the triazolyl is substituted on the nitrogen with an -alkylene-O-alkyl group.

In another embodiment of this invention R^5 is a substituted triazolyl-phenyl- wherein the triazolyl is substituted on the nitrogen with a $-CH_2CH_2OCH_3$ group.

In another embodiment of this invention R^5 moiety is a substituted triazolyl-phenyl- wherein said phenyl moiety is substituted with halo, and said triazolyl moiety is substituted as described in any of the above embodiments.

In another embodiment of this invention R^5 is a substituted triazolyl-phenyl- wherein said phenyl moiety is substituted with one halo, and said triazolyl moiety is substituted as described in any one of the above embodiments.

In another embodiment of this invention R^5 is a substituted triazolyl-phenyl- wherein said phenyl moiety is substituted with F, and said triazolyl moiety is substituted as described in any one of the above embodiments.

In another embodiment of this invention R^5 is a substituted triazolyl-phenyl- wherein said phenyl moiety is substituted with one F, and said triazolyl moiety is substituted as described in any one of the above embodiments.

In another embodiment of this invention R^5 is a substituted triazolyl-phenyl- group wherein said phenyl moiety is substituted with one F, and said triazolyl moiety is substituted on the nitrogen with a hydroxyl substituted alkyl group.

In another embodiment of this invention R^5 is a substituted triazolyl-phenyl- wherein said phenyl moiety is substituted with one F, and said triazolyl moiety is substituted on the nitrogen with a $-CH_2CH_2OH$ group.

In another embodiment of this invention R^5 is a substituted triazolyl-phenyl- wherein said phenyl moiety is substituted with one F, and said triazolyl moiety is substituted on the nitrogen with a -alkylene-O-alkyl group.

In another embodiment of this invention R^5 is a substituted triazolyl-phenyl- wherein said phenyl moiety is substituted with one F, and said triazolyl moiety is substituted on the nitrogen with a $-CH_2CH_2OCH_3$ group.

In another embodiment of this invention R^5 is a substituted triazolyl-phenyl- wherein said phenyl moiety is substituted with halo, and said triazolyl moiety is unsubstituted.

In another embodiment of this invention R^5 is a substituted triazolyl-phenyl- wherein said phenyl moiety is substituted with one halo, and said triazolyl moiety is unsubstituted.

In another embodiment of this invention R^5 is a substituted triazolyl-phenyl- wherein said phenyl moiety is substituted with F, and said triazolyl moiety is unsubstituted.

In another embodiment of this invention R^5 is a substituted triazolyl-phenyl- wherein said phenyl moiety is substituted with one F, and said triazolyl moiety is unsubstituted.

In another embodiment of this invention R^5 moiety is a substituted triazolyl-phenyl- wherein said phenyl moiety is substituted with alkoxy, and said triazolyl moiety is substituted as described in any of the above embodiments.

In another embodiment of this invention R^5 is a substituted triazolyl-phenyl- wherein said phenyl moiety is substituted with one alkoxy, and said triazolyl moiety is substituted as described in any one of the above embodiments.

In another embodiment of this invention R^5 is a substituted triazolyl-phenyl- wherein said phenyl moiety is substituted with $-OCH_3$, and said triazolyl moiety is substituted as described in any one of the above embodiments.

In another embodiment of this invention R^5 is a substituted triazolyl-phenyl- wherein said phenyl moiety is substituted with one $-OCH_3$, and said triazolyl moiety is substituted as described in any one of the above embodiments.

In another embodiment of this invention R^5 is a substituted triazolyl-phenyl- group wherein said phenyl moiety is substituted with one $-OCH_3$, and said triazolyl moiety is substituted on the nitrogen with a hydroxyl substituted alkyl group.

In another embodiment of this invention R^5 is a substituted triazolyl-phenyl- wherein said phenyl moiety is substituted with one $-OCH_3$, and said triazolyl moiety is substituted on the nitrogen with a $-CH_2CH_2OH$ group.

In another embodiment of this invention R^5 is a substituted triazolyl-phenyl- wherein said phenyl moiety is substituted with one $-OCH_3$, and said triazolyl moiety is substituted on the nitrogen with a -alkylene-O-alkyl group.

In another embodiment of this invention R^5 is a substituted triazolyl-phenyl- wherein said phenyl moiety is substituted with one $-OCH_3$, and said triazolyl moiety is substituted on the nitrogen with a $-CH_2CH_2OCH_3$ group.

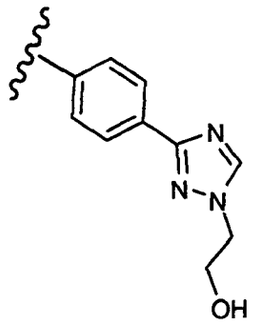
In another embodiment of this invention R^5 is a substituted triazolyl-phenyl- wherein said phenyl moiety is substituted with alkoxy, and said triazolyl moiety is unsubstituted.

In another embodiment of this invention R^5 is a substituted triazolyl-phenyl- wherein said phenyl moiety is substituted with one alkoxy, and said triazolyl moiety is unsubstituted.

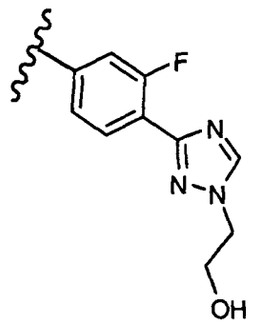
In another embodiment of this invention R^5 is a substituted triazolyl-phenyl- wherein said phenyl moiety is substituted with with $-OCH_3$, and said triazolyl moiety is unsubstituted.

In another embodiment of this invention R^5 is a substituted triazolyl-phenyl- wherein said phenyl moiety is substituted with one $-OCH_3$, and said triazolyl moiety is unsubstituted.

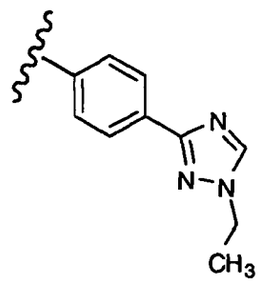
In another embodiment of this invention R^5 is:



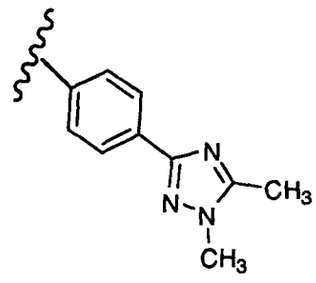
In another embodiment of this invention R^5 is:



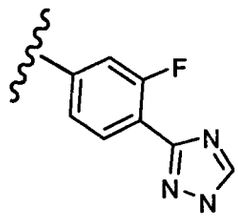
In another embodiment of this invention R^5 is:



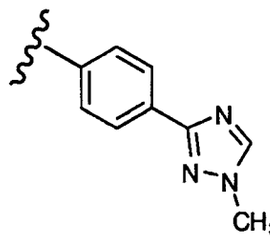
In another embodiment of this invention R^5 is:



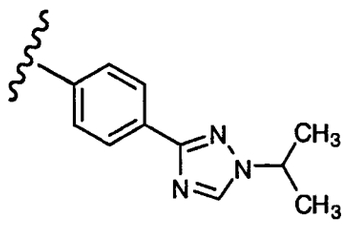
In another embodiment of this invention R^5 is:



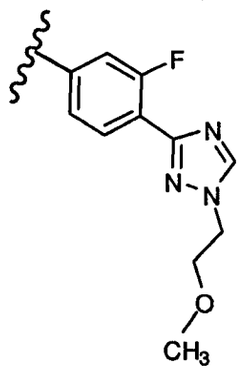
In another embodiment of this invention R^5 is:



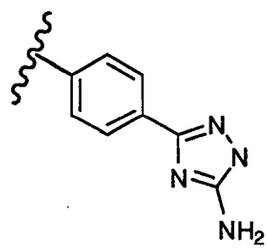
In another embodiment of this invention R^5 is:



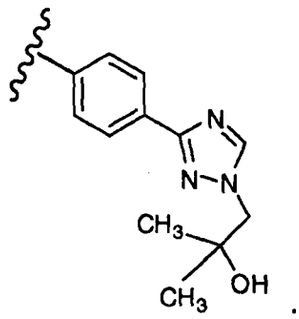
In another embodiment of this invention R^5 is:



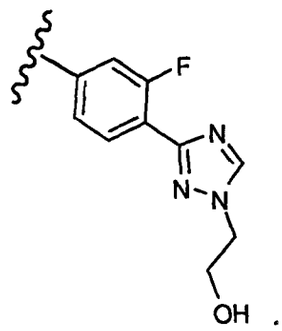
In another embodiment of this invention R^5 is:



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 a substituted triazolyl-thienyl- wherein said triazolyl is substituted and said thienyl is unsubstituted.

In another embodiment of this invention R^5 is a substituted triazolyl-thienyl- wherein said triazolyl is substituted on the nitrogen and said thienyl is unsubstituted.

In another embodiment of this invention R^5 is a substituted triazolyl-thienyl- wherein said triazolyl is substituted on the carbon and said thienyl is unsubstituted.

In another embodiment of this invention R^5 is a substituted triazolyl-thienyl- wherein said triazolyl is substituted on the nitrogen and on the carbon, and said thienyl is unsubstituted.

In another embodiment of this invention R^5 is a substituted triazolyl-thienyl- wherein said triazolyl is substituted and said thienyl is substituted.

In another embodiment of this invention R^5 is a substituted triazolyl-thienyl- wherein said triazolyl is substituted on the nitrogen and said thienyl is substituted.

In another embodiment of this invention R^5 is a substituted triazolyl-thienyl- wherein said triazolyl is substituted on the carbon and said thienyl is substituted.

In another embodiment of this invention R^5 is a substituted triazolyl-thienyl- wherein said triazolyl is substituted on the nitrogen and on the carbon, and said thienyl is substituted.

In another embodiment of this invention R^5 is a substituted triazolyl-thienyl- wherein said triazolyl is unsubstituted and said thienyl is substituted.

In another embodiment of this invention R^5 is an unsubstituted triazolyl-thienyl-.

In another embodiment of this invention R^5 is a substituted triazolyl-thienyl- wherein the triazolyl is substituted on the nitrogen with $-CH_2COH(CH_3)_2$.

In another embodiment of this invention R^5 is a substituted triazolyl-thienyl- wherein the triazolyl is substituted on the nitrogen with $-CH_2CH_2OH$.

In another embodiment of this invention R^5 is a substituted triazolyl-thienyl- wherein the triazolyl is substituted on the nitrogen with an alkyl group.

In another embodiment of this invention R^5 is a substituted triazolyl-thienyl- wherein the triazolyl is substituted on the nitrogen with an alkyl group and substituted on the carbon with an alkyl group, wherein each alkyl group is independently selected.

In another embodiment of this invention R^5 is a substituted triazolyl-thienyl- wherein the triazolyl is substituted on the nitrogen with a $-CH_3$ group.

In another embodiment of this invention R^5 is a substituted triazolyl-thienyl- wherein the triazolyl is substituted on the nitrogen with a $-CH_3$ group and on the carbon with a $-CH_3$ group.

In another embodiment of this invention R^5 moiety is a substituted triazolyl-thienyl- wherein the triazolyl is substituted on the carbon with a $-NH_2$ group.

In another embodiment of this invention R^5 is a substituted triazolyl-thienyl- wherein the triazolyl is substituted on the nitrogen with an -alkylene-O-alkyl group.

In another embodiment of this invention R^5 is a substituted triazolyl-thienyl- wherein the triazolyl is substituted on the nitrogen with a $-CH_2CH_2OCH_3$ group.

In another embodiment of this invention R^5 moiety is a substituted triazolyl-thienyl- wherein said thienyl moiety is substituted with halo, and said triazolyl moiety is substituted as described in any of the above embodiments.

In another embodiment of this invention R^5 is a substituted triazolyl-thienyl- wherein said thienyl moiety is substituted with one halo, and said triazolyl moiety is substituted as described in any one of the above embodiments.

In another embodiment of this invention R^5 is a substituted triazolyl-thienyl- wherein said thienyl moiety is substituted with F, and said triazolyl moiety is substituted as described in any one of the above embodiments.

In another embodiment of this invention R^5 is a substituted triazolyl-thienyl- wherein said thienyl moiety is substituted with one F, and said triazolyl moiety is substituted as described in any one of the above embodiments.

In another embodiment of this invention R^5 is a substituted triazolyl-thienyl- group wherein said thienyl moiety is substituted with one F, and said triazolyl moiety is substituted on the nitrogen with a hydroxyl substituted alkyl group.

In another embodiment of this invention R^5 is a substituted triazolyl-thienyl- wherein said thienyl moiety is substituted with one F, and said triazolyl moiety is substituted on the nitrogen with a $-CH_2CH_2OH$ group.

In another embodiment of this invention R^5 is a substituted triazolyl-thienyl- wherein said thienyl moiety is substituted with one F, and said triazolyl moiety is substituted on the nitrogen with a -alkylene-O-alkyl group.

In another embodiment of this invention R^5 is a substituted triazolyl-thienyl- wherein said thienyl moiety is substituted with one F, and said triazolyl moiety is substituted on the nitrogen with a $-CH_2CH_2OCH_3$ group.

In another embodiment of this invention R^5 is a substituted triazolyl-thienyl- wherein said thienyl moiety is substituted with halo, and said triazolyl moiety is unsubstituted.

In another embodiment of this invention R^5 is a substituted triazolyl-thienyl- wherein said thienyl moiety is substituted with one halo, and said triazolyl moiety is unsubstituted.

In another embodiment of this invention R^5 is a substituted triazolyl-thienyl- wherein said thienyl moiety is substituted with F, and said triazolyl moiety is unsubstituted.

In another embodiment of this invention R^5 is a substituted triazolyl-thienyl- wherein said thienyl moiety is substituted with one F, and said triazolyl moiety is unsubstituted.

In another embodiment of this invention R^5 moiety is a substituted triazolyl-thienyl- wherein said thienyl moiety is substituted with alkoxy, and said triazolyl moiety is substituted as described in any of the above embodiments.

In another embodiment of this invention R^5 is a substituted triazolyl-thienyl- wherein said thienyl moiety is substituted with one alkoxy, and said triazolyl moiety is substituted as described in any one of the above embodiments.

In another embodiment of this invention R^5 is a substituted triazolyl-thienyl- wherein said thienyl moiety is substituted with $-OCH_3$, and said triazolyl moiety is substituted as described in any one of the above embodiments.

In another embodiment of this invention R^5 is a substituted triazolyl-thienyl- wherein said thienyl moiety is substituted with one $-OCH_3$, and said triazolyl moiety is substituted as described in any one of the above embodiments.

In another embodiment of this invention R^5 is a substituted triazolyl-thienyl- group wherein said thienyl moiety is substituted with one $-OCH_3$, and said triazolyl moiety is substituted on the nitrogen with a hydroxyl substituted alkyl group.

In another embodiment of this invention R^5 is a substituted triazolyl-thienyl- wherein said thienyl moiety is substituted with one $-OCH_3$, and said triazolyl moiety is substituted on the nitrogen with a $-CH_2CH_2OH$ group.

In another embodiment of this invention R^5 is a substituted triazolyl-thienyl- wherein said thienyl moiety is substituted with one $-OCH_3$, and said triazolyl moiety is substituted on the nitrogen with a -alkylene-O-alkyl group.

In another embodiment of this invention R^5 is a substituted triazolyl-thienyl- wherein said thienyl moiety is substituted with one $-OCH_3$, and said triazolyl moiety is substituted on the nitrogen with a $-CH_2CH_2OCH_3$ group.

In another embodiment of this invention R^5 is a substituted triazolyl-thienyl- wherein said thienyl moiety is substituted with alkoxy, and said triazolyl moiety is unsubstituted.

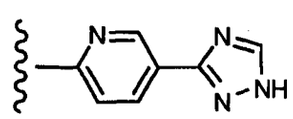
In another embodiment of this invention R^5 is a substituted triazolyl-thienyl- wherein said thienyl moiety is substituted with one alkoxy, and said triazolyl moiety is unsubstituted.

In another embodiment of this invention R^5 is a substituted triazolyl-thienyl- wherein said thienyl moiety is substituted with $-OCH_3$, and said triazolyl moiety is unsubstituted.

In another embodiment of this invention R^5 is a substituted triazolyl-thienyl- wherein said thienyl moiety is substituted with one $-OCH_3$, and said triazolyl moiety is unsubstituted.

In another embodiment of this invention R^5 is triazolyl-pyridyl-.

In another embodiment of this invention R^5 is



.

In another embodiment of this invention R^5 is a substituted triazolyl-pyridyl- wherein said triazolyl is substituted and said pyridyl is unsubstituted.

In another embodiment of this invention R^5 is a substituted triazolyl-pyridyl- wherein said triazolyl is substituted on the nitrogen and said pyridyl is unsubstituted.

In another embodiment of this invention R^5 is a substituted triazolyl-pyridyl- wherein said triazolyl is substituted on the carbon and said pyridyl is unsubstituted.

In another embodiment of this invention R^5 is a substituted triazolyl-pyridyl- wherein said triazolyl is substituted on the nitrogen and on the carbon, and said pyridyl is unsubstituted.

In another embodiment of this invention R^5 is a substituted triazolyl-pyridyl- wherein said triazolyl is substituted and said pyridyl is substituted.

In another embodiment of this invention R^5 is a substituted triazolyl-pyridyl- wherein said triazolyl is substituted on the nitrogen and said pyridyl is substituted.

In another embodiment of this invention R^5 is a substituted triazolyl-pyridyl- wherein said triazolyl is substituted on the carbon and said pyridyl is substituted.

In another embodiment of this invention R^5 is a substituted triazolyl-pyridyl- wherein said triazolyl is substituted on the nitrogen and on the carbon, and said pyridyl is substituted.

In another embodiment of this invention R^5 is a substituted triazolyl-pyridyl- wherein said triazolyl is unsubstituted and said pyridyl is substituted.

In another embodiment of this invention R^5 is a substituted triazolyl-pyridyl- wherein the triazolyl is substituted on the nitrogen with alkyl.

When the pyridyl moiety of R^5 is substituted with alkyl, examples of the alkyl groups include, for example, -C_1-C_6alkyl, -C_1-C_4alkyl, -C_1-C_2alkyl, and -CH_3.

When the pyridyl moiety of R^5 is substituted with halo atoms, examples of the halo atoms include, for example, Cl, F and Br, provided that the carbon atoms adjacent to the nitrogen atom in said pyridyl are not substituted with halo. In one embodiment of this invention the halo on the pyridyl is F. In another embodiment of this invention the pyridyl is substituted with one F.

In another embodiment of this invention R^5 is a substituted triazolyl-pyridyl- wherein the triazolyl is substituted on the nitrogen with $-CH_2COH(CH_3)_2$, and the pyridyl is unsubstituted.

In another embodiment of this invention R^5 is a substituted triazolyl-pyridyl- wherein the triazolyl is substituted on the nitrogen with $-CH_2CH_2OH$, and the pyridyl is unsubstituted.

In another embodiment of this invention R^5 is a substituted triazolyl-pyridyl- wherein the triazolyl is substituted on the nitrogen with an alkyl group, and the pyridyl is unsubstituted.

In another embodiment of this invention R^5 is a substituted triazolyl-pyridyl- wherein the triazolyl is substituted on the nitrogen with an alkyl group and substituted on the carbon with an alkyl group, wherein each alkyl group is independently selected, and the pyridyl is unsubstituted.

In another embodiment of this invention R^5 is a substituted triazolyl-pyridyl- wherein the triazolyl is substituted on the nitrogen with a $-CH_3$ group, and the pyridyl is unsubstituted.

In another embodiment of this invention R^5 is a substituted triazolyl-pyridyl- wherein the triazolyl is substituted on the nitrogen with a $-CH_3$ group and on the carbon with a $-CH_3$ group, and the pyridyl is unsubstituted.

In another embodiment of this invention R^5 moiety is a substituted triazolyl-pyridyl- wherein the triazolyl is substituted on the carbon with a $-NH_2$ group, and the pyridyl is unsubstituted.

In another embodiment of this invention R^5 is a substituted triazolyl-pyridyl- wherein the triazolyl is substituted on the nitrogen with an -alkylene-O-alkyl group, and the pyridyl is unsubstituted, and provided that the alkylene moiety of said -alkylene-O-alkyl group is not $-CH_2-$ (i.e., the alkylene moiety is 2 or more carbons in length).

In another embodiment of this invention R^5 is a substituted triazolyl-pyridyl- wherein the triazolyl is substituted on the nitrogen with a $-CH_2CH_2OCH_3$ group, and the pyridyl is unsubstituted.

In another embodiment of this invention R^5 moiety is a substituted triazolyl-pyridyl- wherein said pyridyl moiety is substituted with halo, provided that the carbon atoms adjacent to the nitrogen atom in said pyridyl are not substituted with halo, and said triazolyl moiety is substituted as described in any of the above embodiments describing substituted triazolyl groups.

In another embodiment of this invention R^5 is a substituted triazolyl-pyridyl- wherein said pyridyl moiety is substituted with one halo, provided that a carbon atom adjacent to the nitrogen atom in said pyridyl is not substituted with said halo, and said triazolyl moiety is substituted as described in any one of the above embodiments, describing triazolyl groups.

In another embodiment of this invention R^5 is a substituted triazolyl-pyridyl- wherein said pyridyl moiety is substituted with F, provided that a carbon atom adjacent to the nitrogen atom in said pyridyl is not substituted with said F, and said triazolyl moiety is substituted as described in any one of the above embodiments, describing triazolyl groups.

In another embodiment of this invention R^5 is a substituted triazolyl-pyridyl- wherein said pyridyl moiety is substituted with one F, provided that a carbon atom adjacent to the nitrogen atom in said pyridyl is not substituted with said F, and said triazolyl moiety is substituted as described in any one of the above embodiments describing triazolyl groups.

In another embodiment of this invention R^5 is a substituted triazolyl-pyridyl- group wherein said pyridyl moiety is substituted with one F, provided that a carbon atom adjacent to the nitrogen atom in said pyridyl is not substituted with said F, and said triazolyl moiety is substituted on the nitrogen with a hydroxyl substituted alkyl group.

In another embodiment of this invention R^5 is a substituted triazolyl-pyridyl- wherein said pyridyl moiety is substituted with one F, provided that a carbon atom adjacent to the nitrogen atom in said pyridyl is not substituted with said F, and said triazolyl moiety is substituted on the nitrogen with a $-CH_2CH_2OH$ group.

In another embodiment of this invention R^5 is a substituted triazolyl-pyridyl- wherein said pyridyl moiety is substituted with one F, provided that a carbon atom adjacent to the nitrogen atom in said pyridyl is not substituted with said F, and said triazolyl moiety is substituted on the nitrogen with an -alkylene-O-alkyl group, and the alkylene moiety of said -alkylene-O-alkyl group is not $-CH_2-$ (i.e., the alkylene moiety is 2 or more carbons in length).

In another embodiment of this invention R^5 is a substituted triazolyl-pyridyl- wherein said pyridyl moiety is substituted with one F, provided that a carbon atom adjacent to the nitrogen atom in said pyridyl is not substituted with said F, and said triazolyl moiety is substituted on the nitrogen with a $-CH_2CH_2OCH_3$ group.

In another embodiment of this invention R^5 is a substituted triazolyl-pyridyl- wherein said pyridyl moiety is substituted with halo, provided that the carbon atoms adjacent to the nitrogen atom in said pyridyl are not substituted with halo, and said triazolyl moiety is unsubstituted.

In another embodiment of this invention R^5 is a substituted triazolyl-pyridyl- wherein said pyridyl moiety is substituted with one halo, provided that a carbon atom adjacent to the nitrogen atom in said pyridyl is not substituted with said halo, and said triazolyl moiety is unsubstituted.

In another embodiment of this invention R^5 is a substituted triazolyl-pyridyl- wherein said pyridyl moiety is substituted with F, provided that a carbon atom adjacent to the nitrogen atom in said pyridyl is not substituted with said F, and said triazolyl moiety is unsubstituted.

In another embodiment of this invention R^5 is a substituted triazolyl-pyridyl- wherein said pyridyl moiety is substituted with one F, provided that a carbon atom adjacent to the nitrogen atom in said pyridyl is not substituted with said F, and said triazolyl moiety is unsubstituted.

In another embodiment of this invention R^5 moiety is a substituted triazolyl-pyridyl- wherein said pyridyl moiety is substituted with alkoxy, and said triazolyl moiety is substituted as described in any of the above embodiments describing substituted triazolyl groups.

In another embodiment of this invention R^5 is a substituted triazolyl-pyridyl- wherein said pyridyl moiety is substituted with one alkoxy, and said triazolyl moiety is substituted as described in any one of the above embodiments describing substituted triazolyl groups.

In another embodiment of this invention R^5 is a substituted triazolyl-pyridyl- wherein said pyridyl moiety is substituted with $-OCH_3$, and said triazolyl moiety is substituted as described in any one of the above embodiments describing substituted triazolyl groups.

In another embodiment of this invention R^5 is a substituted triazolyl-pyridyl- wherein said pyridyl moiety is substituted with one $-OCH_3$, and said triazolyl moiety is substituted as described in any one of the above embodiments describing substituted triazoly groups.

In another embodiment of this invention R^5 is a substituted triazolyl-pyridyl- group wherein said pyridyl moiety is substituted with one $-OCH_3$, and said triazolyl moiety is substituted on the nitrogen with a hydroxyl substituted alkyl group.

In another embodiment of this invention R^5 is a substituted triazolyl-pyridyl- wherein said pyridyl moiety is substituted with one $-OCH_3$, and said triazolyl moiety is substituted on the nitrogen with a $-CH_2CH_2OH$ group.

In another embodiment of this invention R^5 is a substituted triazolyl-pyridyl- wherein said pyridyl moiety is substituted with one $-OCH_3$, and said triazolyl moiety is substituted on the nitrogen with a -alkylene-O-alkyl group, and the alkylene moiety of said -alkylene-O-alkyl group is not $-CH_2-$ (i.e., the alkylene moiety is 2 or more carbons in length).

In another embodiment of this invention R^5 is a substituted triazolyl-pyridyl- wherein said pyridyl moiety is substituted with one $-OCH_3$, and said triazolyl moiety is substituted on the nitrogen with a $-CH_2CH_2OCH_3$ group.

In another embodiment of this invention R^5 is a substituted triazolyl-pyridyl- wherein said pyridyl moiety is substituted with alkoxy, and said triazolyl moiety is unsubstituted.

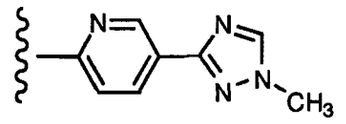
In another embodiment of this invention R^5 is a substituted triazolyl-pyridyl- wherein said pyridyl moiety is substituted with one alkoxy, and said triazolyl moiety is unsubstituted.

In another embodiment of this invention R^5 is a substituted triazolyl-pyridyl- wherein said pyridyl moiety is substituted with $-OCH_3$, and said triazolyl moiety is unsubstituted.

In another embodiment of this invention R^5 is a substituted triazolyl-pyridyl- wherein said pyridyl moiety is substituted with one $-OCH_3$, and said triazolyl moiety is unsubstituted.

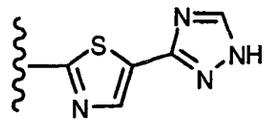
In another embodiment of this invention R^5 is a substituted triazolyl-pyridyl- wherein said triazolyl is substituted with 1 or 2 groups indepenendently selected from the group consisting of: (a) hydroxyl substituted alkyl group (e.g., $-CH_2COH(CH_3)_2$, and $-CH_2CH_2OH$), (b) alkyl (e.g., $-C_1-C_6$alkyl, $-C_1-C_4$alkyl, $-C_1-C_2$alkyl, and $-CH_3$), (c) $-NH_2$, and (d) -alkylene-O-alkyl (e.g., $-CH_2CH_2OCH_3$), provided that the alkylene moiety of said -alkylene-O-alkyl group is not $-CH_2-$ (i.e., the alkylene moiety is 2 or more carbons in length) when said -alkylene-O-alkyl group is bound to the nitrogen of said triazolyl; and said pyridyl is substituted with 1 to 3 groups independently selected from the group consisting of: (a) alkyl (e.g., $-C_1-C_6$alkyl, $-C_1-C_4$alkyl, $-C_1-C_2$alkyl, and $-CH_3$), (b) halo (e.g., Cl, F and Br) and provided that carbon atoms adjacent to the nitrogen atom in said pyridyl are not substituted with halo, and (c) alkoxy (e.g., $-OCH_3$).

In another embodiment of this invention R^5 is



In another embodiment of this invention R^5 is triazolyl-thiazolyl-.

In another embodiment of this invention R^5 is



In another embodiment of this invention R^5 is a substituted triazolyl-thiazolyl- wherein said triazolyl is substituted and said thiazolyl is unsubstituted.

In another embodiment of this invention R^5 is a substituted triazolyl-thiazolyl- wherein said triazolyl is substituted on the nitrogen and said thiazolyl is unsubstituted.

In another embodiment of this invention R^5 is a substituted triazolyl-thiazolyl- wherein said triazolyl is substituted on the carbon and said thiazolyl is unsubstituted.

In another embodiment of this invention R^5 is a substituted triazolyl-thiazolyl- wherein said triazolyl is substituted on the nitrogen and on the carbon, and said thiazolyl is unsubstituted.

When the thiazolyl moiety of R^5 is substituted with alkyl, examples of the alkyl groups include, for example, -C_1-C_6alkyl, -C_1-C_4alkyl, -C_1-C_2alkyl, and -CH_3.

When the thiazolyl moiety of R^5 is substituted with halo atoms, examples of the halo atoms include, for example, Cl, F and Br. In one embodiment of this invention the halo on the thiazolyl is F. In another embodiment of this invention the thiazolyl is substituted with one F.

When the thiazolyl moiety of R^5 is substituted with an alkylamino group, examples of the alkylamino group include, for example, C_1-C_6alkyl-NH-, C_1-C_2alkyl-NH-, CH_3-NH-, and CH_3CH_2-NH-.

When the thiazolyl moiety of R^5 is substituted with a dialkylamino group, examples of the dialkylamino group include, for example, (C_1-C_6alkyl)$_2$-N- wherein each alkyl is independently selected, (C_1-C_2alkyl)$_2$-N- wherein each alkyl is independently selected, $(CH_3)_2N$-, $(CH_3CH_2)_2$-N-, and $(CH_3)(CH_3CH_2)$N-.

In another embodiment of this invention R^5 is a substituted triazolyl-thiazolyl- wherein said triazolyl is substituted and said thiazolyl is substituted.

In another embodiment of this invention R^5 is a substituted triazolyl-thiazolyl- wherein said triazolyl is substituted on the nitrogen and said thiazolyl is substituted.

In another embodiment of this invention R^5 is a substituted triazolyl-thiazolyl- wherein said triazolyl is substituted on the carbon and said thiazolyl is substituted.

In another embodiment of this invention R^5 is a substituted triazolyl-thiazolyl- wherein said triazolyl is substituted on the nitrogen and on the carbon, and said thiazolyl is substituted.

In another embodiment of this invention R^5 is a substituted triazolyl-thiazolyl- wherein said triazolyl is unsubstituted and said thiazolyl is substituted.

In another embodiment of this invention R^5 is a substituted triazolyl-thiazolyl- wherein the triazolyl is substituted on the nitrogen with alkyl, and said thiazolyl is unsubstituted.

In another embodiment of this invention R^5 is a substituted triazolyl-thiazoly- wherein the triazolyl is substituted on the nitrogen with $-CH_2COH(CH_3)_2$, and said thiazolyl is unsubstituted.

In another embodiment of this invention R^5 is a substituted triazolyl-thiazolyl- wherein the triazolyl is substituted on the nitrogen with $-CH_2CH_2OH$, and said thiazolyl is unsubstituted.

In another embodiment of this invention R^5 is a substituted triazolyl-thiazolyl- wherein the triazolyl is substituted on the nitrogen with an alkyl group and substituted on the carbon with an alkyl group, wherein each alkyl group is independently selected, and said thiazolyl is unsubstituted.

In another embodiment of this invention R^5 is a substituted triazolyl-thiazolyl- wherein the triazolyl is substituted on the nitrogen with a $-CH_3$ group, and said thiazolyl is unsubstituted.

In another embodiment of this invention R^5 is a substituted triazolyl-thiazolyl- wherein the triazolyl is substituted on the nitrogen with a $-CH_3$ group and on the carbon with a $-CH_3$ group, and said thiazolyl is unsubstituted.

In another embodiment of this invention R^5 moiety is a substituted triazolyl-thiazolyl- wherein the triazolyl is substituted on the carbon with a $-NH_2$ group, and said thiazolyl is unsubstituted.

In another embodiment of this invention R^5 is a substituted triazolyl-thiazolyl- wherein the triazolyl is substituted on the nitrogen with an -alkylene-O-alkyl group, provided that the alkylene moiety of said -alkylene-O-alkyl group is not $-CH_2-$ (i.e., the alkylene moiety is 2 or more carbons in length), and said thiazolyl is unsubstituted.

In another embodiment of this invention R^5 is a substituted triazolyl-thiazolyl- wherein the triazolyl is substituted on the nitrogen with a $-CH_2CH_2OCH_3$ group, and said thiazolyl is unsubstituted.

In another embodiment of this invention R^5 moiety is a substituted triazolyl-thiazolyl- wherein said thiazolyl moiety is substituted with halo, and said triazolyl moiety is substituted as described in any of the above embodiments describing substituted triazolyl groups.

In another embodiment of this invention R^5 is a substituted triazolyl-thiazolyl- wherein said thiazolyl moiety is substituted with F, and said triazolyl moiety is substituted as described in any one of the above embodiments describing substituted triazolyl groups.

In another embodiment of this invention R^5 is a substituted triazolyl-thiazolyl- group wherein said thiazolyl moiety is substituted with one F, and said triazolyl moiety is substituted on the nitrogen with a hydroxyl substituted alkyl group.

In another embodiment of this invention R^5 is a substituted triazolyl-thiazolyl- wherein said thiazolyl moiety is substituted with one F, and said triazolyl moiety is substituted on the nitrogen with a $-CH_2CH_2OH$ group.

In another embodiment of this invention R^5 is a substituted triazolyl-thiazolyl- wherein said thiazolyl moiety is substituted with one F, and said triazolyl moiety is substituted on the nitrogen with an -alkylene-O-alkyl group.

In another embodiment of this invention R^5 is a substituted triazolyl-thiazolyl- wherein said thiazolyl moiety is substituted with one F, and said triazolyl moiety is substituted on the nitrogen with a $-CH_2CH_2OCH_3$ group.

In another embodiment of this invention R^5 is a substituted triazolyl-thiazolyl- wherein said thiazolyl moiety is substituted with halo, and said triazolyl moiety is unsubstituted.

In another embodiment of this invention R^5 is a substituted triazolyl-thiazolyl- wherein said thiazolyl moiety is substituted with F, and said triazolyl moiety is unsubstituted.

In another embodiment of this invention R^5 moiety is a substituted triazolyl-thiazolyl- wherein said thiazolyl moiety is substituted with alkoxy, and said triazolyl moiety is substituted as described in any of the above embodiments describing substituted triazolyl groups.

In another embodiment of this invention R^5 is a substituted triazolyl-thiazolyl- wherein said thiazolyl moiety is substituted with $-OCH_3$, and said triazolyl moiety is substituted as described in any one of the above embodiments describing substituted triazolyl groups.

In another embodiment of this invention R^5 is a substituted triazolyl-thiazolyl- group wherein said thiazolyl moiety is substituted with one $-OCH_3$, and said triazolyl moiety is substituted on the nitrogen with a hydroxyl substituted alkyl group.

In another embodiment of this invention R^5 is a substituted triazolyl-thiazolyl- wherein said thiazolyl moiety is substituted with one $-OCH_3$, and said triazolyl moiety is substituted on the nitrogen with a $-CH_2CH_2OH$ group.

In another embodiment of this invention R^5 is a substituted triazolyl-thiazolyl- wherein said thiazolyl moiety is substituted with one $-OCH_3$, and said triazolyl moiety is substituted on the nitrogen with an -alkylene-O-alkyl group, and the alkylene moiety of said -alkylene-O-alkyl group is not $-CH_2-$ (i.e., the alkylene moiety is 2 or more carbons in length).

In another embodiment of this invention R^5 is a substituted triazolyl-thiazolyl- wherein said thiazolyl moiety is substituted with one $-OCH_3$, and said triazolyl moiety is substituted on the nitrogen with a $-CH_2CH_2OCH_3$ group.

In another embodiment of this invention R^5 is a substituted triazolyl-thiazolyl- wherein said thiazolyl moiety is substituted with alkoxy, and said triazolyl moiety is unsubstituted.

In another embodiment of this invention R^5 is a substituted triazolyl-thiazolyl- wherein said thiazolyl moiety is substituted with $-OCH_3$, and said triazolyl moiety is unsubstituted.

In another embodiment of this invention R^5 is a substituted triazolyl-thiazolyl- wherein said thiazolyl moiety is substituted with an alkylamino, and said triazolyl moiety is substituted as described in any of the above embodiments describing triazolyl groups.

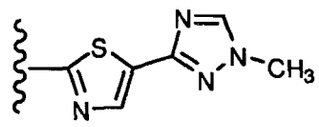
In another embodiment of this invention R^5 is a substituted triazolyl-thiazolyl- wherein said thiazolyl moiety is substituted with a dialkylamino, and said triazolyl moiety is substituted as described in any of the above embodiments describing substituted triazolyl groups.

In another embodiment of this invention R^5 is a substituted triazolyl-thiazolyl- wherein said thiazolyl moiety is substituted with an alkylamino, and said triazolyl moiety is unsubstituted.

In another embodiment of this invention R^5 is a substituted triazolyl-thiazolyl- wherein said thiazolyl moiety is substituted with a dialkylamino, and said triazolyl moiety is unsubstituted.

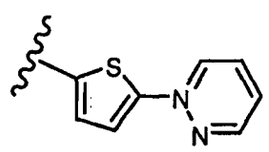
In another embodiment of this invention R^5 is a substituted triazolyl-thiazolyl- wherein said triazolyl is substituted with 1 or 2 groups indepenendently selected from the group consisting of: (a) hydroxyl substituted alkyl group (e.g., $-CH_2COH(CH_3)_2$, and $-CH_2CH_2OH$), (b) alkyl (e.g., $-C_1$-C_6alkyl, $-C_1$-C_4alkyl, $-C_1$-C_2alkyl, and $-CH_3$), $-NH_2$, and (c) -alkylene-O-alkyl (e.g., $-CH_2CH_2OCH_3$), provided that the alkylene moiety of said -alkylene-O-alkyl group is not $-CH_2-$ (i.e., the alkylene moiety is 2 or more carbons in length) when said -alkylene-O-alkyl group is bound to the nitrogen of said triazolyl; and said thiazolyl is substituted with 1 group selected from the group consisting of: (a) alkyl (e.g., $-C_1$-C_6alkyl, or $-C_1$-C_4alkyl, or $-C_1$-C_2alkyl, or $-CH_3$), (b) halo (e.g., Cl, F, or Br), (c) alkylamino (e.g., C_1-C_6alkyl-NH-, or C_1-C_2alkyl-NH-, or CH_3-NH-, or CH_3CH_2-NH-), and (d) dialkylamino (e.g., $(C_1$-C_6alkyl$)_2$-N- wherein each alkyl is independently selected, or $(C_1$-C_2alkyl$)_2$-N- wherein each alkyl is independently selected, or $(CH_3)_2$N-, or $(CH_3CH_2)_2$-N-, or $(CH_3)(CH_3CH_2)$N-).

In another embodiment of this invention R^5 is



In another embodiment of this invention R^5 is pyridazinyl-thienyl-.

In another embodiment of this invention R^5 is



When the pyridazinyl moiety of R^5 is substituted with alkyl, examples of the alkyl groups include, for example, $-C_1$-C_6alkyl, $-C_1$-C_4alkyl, $-C_1$-C_2alkyl, and $-CH_3$.

When the pyridazinyl moiety of R^5 is substituted with halo atoms, examples of the halo atoms include, for example, Cl, F and Br. In one embodiment of this invention the halo on the pyridazinyl is F. In another embodiment of this invention the

pyridazinyl is substituted with one F. When the pyridazinyl moiety is substituted with halos, the carbons adjacent to the nitrogens are not substituted with halos.

When the pyridazinyl moiety of R^5 is substituted with an alkylamino group, examples of the alkylamino group include, for example, C_1-C_6alkyl-NH-, C_1-C_2alkyl-NH-, CH_3-NH-, and CH_3CH_2-NH-.

When the pyridazinyl moiety of R^5 is substituted with a dialkylamino group, examples of the dialkylamino group include, for example, $(C_1$-C_6alkyl$)_2$-N- wherein each alkyl is independently selected, $(C_1$-C_2alkyl$)_2$-N- wherein each alkyl is independently selected, $(CH_3)_2N$-, $(CH_3CH_2)_2$-N-, and $(CH_3)(CH_3CH_2)$N-.

In another embodiment of this invention R^5 is a substituted pyridazinyl-thienyl- wherein said pyridazinyl is substituted and said thienyl is unsubstituted.

In another embodiment of this invention R^5 is a substituted pyridazinyl-thienyl- wherein said pyridazinyl is substituted with a =O group, and said thienyl is unsubstituted.

In another embodiment of this invention R^5 is a substituted pyridazinyl-thienyl- wherein said pyridazinyl is substituted with an alkyl group, and said thienyl is unsubstituted.

In another embodiment of this invention R^5 is a substituted pyridazinyl-thienyl- wherein said pyridazinyl is substituted with a methyl group, and said thienyl is unsubstituted.

In another embodiment of this invention R^5 is a substituted pyridazinyl-thienyl- wherein said pyridazinyl is substituted with a =O group, and with an alkyl group, and said thienyl is unsubstituted.

In another embodiment of this invention R^5 is a substituted pyridazinyl-thienyl- wherein said pyridazinyl is substituted with a =O group, and with a methyl group, and said thienyl is unsubstituted.

In another embodiment of this invention R^5 is a substituted pyridazinyl-thienyl- wherein said pyridazinyl is substituted with an amino group, and said thienyl is unsubstituted.

In another embodiment of this invention R^5 is a substituted pyridazinyl-thienyl- wherein said pyridazinyl is substituted with an alkylamino group, and said thienyl is unsubstituted.

In another embodiment of this invention R^5 is a substituted pyridazinyl-thienyl- wherein said pyridazinyl is substituted with a dialkylamino group, and said thienyl is unsubstituted.

In another embodiment of this invention R^5 is a substituted pyridazinyl-thienyl- wherein said pyridazinyl is substituted and said thienyl is substituted.

In another embodiment of this invention R^5 is a substituted pyridazinyl-thienyl- wherein said pyridazinyl is unsubstituted and said thienyl is substituted.

In another embodiment of this invention R^5 is a substituted pyridazinyl-thienyl- wherein said pyridazinyl is unsubstituted and said thienyl is substituted with 1 to 2 independently selected halos.

In another embodiment of this invention R^5 is a substituted pyridazinyl-thienyl- wherein said pyridazinyl is unsubstituted and said thienyl is substituted with 1 to 2 halos independently selected from the group consisting of: Br, Cl and F.

In another embodiment of this invention R^5 is a substituted pyridazinyl-thienyl- wherein said pyridazinyl is unsubstituted and said thienyl is substituted with 1 to 2 independently selected alkoxy groups.

In another embodiment of this invention R^5 is a substituted pyridazinyl-thienyl- wherein said pyridazinyl is unsubstituted and said thienyl is substituted with 1 to 2 $-OCH_3$ groups.

In another embodiment of this invention R^5 is a substituted pyridazinyl-thienyl- wherein said pyridazinyl is substituted as described in any one of the embodiments above describing substituted pyridazinyl groups, and said thienyl is substituted.

In another embodiment of this invention R^5 is a substituted pyridazinyl-thienyl- wherein said pyridazinyl is substituted as described in any one of the embodiments above describing substituted pyridazinyl groups, and said thienyl is substituted with 1 to 2 independently selected halos.

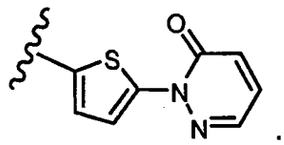
In another embodiment of this invention R^5 is a substituted pyridazinyl-thienyl- wherein said pyridazinyl is substituted as described in any one of the embodiments above describing substituted pyridazinyl groups, and said thienyl is substituted with 1 to 2 halos independently selected from the group consisting of: Br, Cl and F.

In another embodiment of this invention R^5 is a substituted pyridazinyl-thienyl- wherein said pyridazinyl is substituted as described in any one of the embodiments above describing substituted pyridazinyl groups, and said thienyl is substituted with 1 to 2 independently selected alkoxy groups.

In another embodiment of this invention R^5 is a substituted pyridazinyl-thienyl- wherein said pyridazinyl is substituted as described in any one of the embodiments above describing substituted pyridazinyl groups, and said thienyl is substituted with 1 to 2 $-OCH_3$ groups.

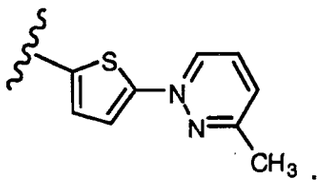
In another embodiment of this invention R^5 is a substituted pyridazinyl-thienyl- wherein said pyridazinyl is substituted with 1 or 2 groups indepenendently selected from the group consisting of alkyl (e.g., methyl) and =O, and said thienyl is substituted with 1 to 2 groups independently selected from the group consisting of: alkoxy (e.g., $-OCH_3$), halo (e.g., Br, Cl and F).

In another embodiment of this invention R^5 is



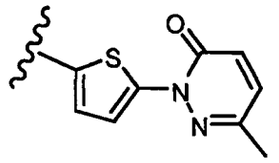
.

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 a substituted triazolyl-phenyl- group wherein (a) said triazolyl moiety is optionally substituted on the nitrogen with a substituent selected from the group consisting of: $-CH_2COH(CH_3)_2$ and $-CH_2CH_2OH$, (b) said triazolyl moiety is optionally substituted on the nitrogen with an alkyl group, (c) said triazolyl moiety is optionally substituted on the nitrogen with an alkyl group, and on the carbon with an alkyl group, (d) said triazolyl moiety is optionally substituted on the nitrogen with a $-CH_3$ group, (e) said triazolyl moiety is optionally substituted on the nitrogen with one $-CH_3$ group, and on the carbon with one $-CH_3$ group, (f) said triazolyl moiety is optionally substituted on the carbon with a $-NH_2$ group, or (g) said triazolyl moiety is optionally substituted on the nitrogen with a $-CH_2CH_2OCH_3$ group; and wherein said phenyl moiety is optionally substituted with halo.

In another embodiment of this invention R^5 is a substituted triazolyl-phenyl-group wherein (a) said triazolyl moiety is optionally substituted on the nitrogen with a substituent selected from the group consisting of: $-CH_2COH(CH_3)_2$ and $-CH_2CH_2OH$, (b) said triazolyl moiety is optionally substituted on the nitrogen with an alkyl group, (c) said triazolyl moiety is optionally substituted on the nitrogen with an alkyl group, and on the carbon with an alkyl group, (d) said triazolyl moiety is optionally substituted on the nitrogen with a $-CH_3$ group, (e) said triazolyl moiety is optionally substituted on the nitrogen with one $-CH_3$ group, and on the carbon with one $-CH_3$ group, (f) said triazolyl moiety is optionally substituted on the carbon with a $-NH_2$ group, or (g) said triazolyl moiety is optionally substituted on the nitrogen with a $-CH_2CH_2OCH_3$ group; and wherein said phenyl moiety is substituted with halo.

In another embodiment of this invention R^5 is a substituted triazolyl-phenyl-group wherein (a) said triazolyl moiety is substituted on the nitrogen with a substituent selected from the group consisting of: $-CH_2COH(CH_3)_2$ and $-CH_2CH_2OH$, (b) said triazolyl moiety is substituted on the nitrogen with an alkyl group, (c) said triazolyl moiety is substituted on the nitrogen with an alkyl group, and on the carbon with an alkyl group, (d) said triazolyl moiety is substituted on the nitrogen with a $-CH_3$ group, (e) said triazolyl moiety is substituted on the nitrogen with one $-CH_3$ group, and on the carbon with one $-CH_3$ group, (f) said triazolyl moiety is substituted on the carbon with a $-NH_2$ group, or (g) said triazolyl moiety is substituted on the nitrogen with a $-CH_2CH_2OCH_3$ group; and wherein said phenyl moiety is optionally substituted with halo.

In another embodiment of this invention R^5 is a substituted triazolyl-phenyl-group wherein (a) said triazolyl moiety is substituted on the nitrogen with a substituent selected from the group consisting of: $-CH_2COH(CH_3)_2$ and $-CH_2CH_2OH$, (b) said triazolyl moiety is substituted on the nitrogen with an alkyl group, (c) said triazolyl moiety is substituted on the nitrogen with an alkyl group, and on the carbon with an alkyl group, (d) said triazolyl moiety is substituted on the nitrogen with a $-CH_3$ group, (e) said triazolyl moiety is substituted on the nitrogen with one $-CH_3$ group, and on the carbon with one $-CH_3$ group, (f) said triazolyl moiety is substituted on the carbon with a $-NH_2$ group, or (g) said triazolyl moiety is substituted on the nitrogen with a $-CH_2CH_2OCH_3$ group; and wherein said phenyl moiety is substituted with halo.

In another embodiment of this invention R^5 is a substituted triazolyl-phenyl-group wherein (a) said triazolyl moiety is substituted on the nitrogen with a substituent

selected from the group consisting of: $-CH_2COH(CH_3)_2$ and $-CH_2CH_2OH$, (b) said triazolyl moiety is substituted on the nitrogen with an alkyl group, (c) said triazolyl moiety is substituted on the nitrogen with an alkyl group, and on the carbon with an alkyl group, (d) said triazolyl moiety is substituted on the nitrogen with a $-CH_3$ group, (e) said triazolyl moiety is substituted on the nitrogen with one $-CH_3$ group, and on the carbon with one $-CH_3$ group, (f) said triazolyl moiety is substituted on the carbon with a $-NH_2$ group, or (g) said triazolyl moiety is substituted on the nitrogen with a $-CH_2CH_2OCH_3$ group; and wherein said phenyl moiety is unsubstituted.

In another embodiment of this invention R^5 is a substituted triazolyl-phenyl- group wherein (a) said triazolyl moiety is optionally substituted on the nitrogen with a substituent selected from the group consisting of: $-CH_2COH(CH_3)_2$ and $-CH_2CH_2OH$, (b) said triazolyl moiety is optionally substituted on the nitrogen with an alkyl group, (c) said triazolyl moiety is optionally substituted on the nitrogen with an alkyl group, and on the carbon with an alkyl group, (d) said triazolyl moiety is optionally substituted on the nitrogen with a $-CH_3$ group, (e) said triazolyl moiety is optionally substituted on the nitrogen with one $-CH_3$ group, and on the carbon with one $-CH_3$ group, (f) said triazolyl moiety is optionally substituted on the carbon with a $-NH_2$ group, or (g) said triazolyl moiety is optionally substituted on the nitrogen with a $-CH_2CH_2OCH_3$ group; and wherein said phenyl moiety is optionally substituted with alkoxy.

In another embodiment of this invention R^5 is a substituted triazolyl-phenyl- group wherein (a) said triazolyl moiety is optionally substituted on the nitrogen with a substituent selected from the group consisting of: $-CH_2COH(CH_3)_2$ and $-CH_2CH_2OH$, (b) said triazolyl moiety is optionally substituted on the nitrogen with an alkyl group, (c) said triazolyl moiety is optionally substituted on the nitrogen with an alkyl group, and on the carbon with an alkyl group, (d) said triazolyl moiety is optionally substituted on the nitrogen with a $-CH_3$ group, (e) said triazolyl moiety is optionally substituted on the nitrogen with one $-CH_3$ group, and on the carbon with one $-CH_3$ group, (f) said triazolyl moiety is optionally substituted on the carbon with a $-NH_2$ group, or (g) said triazolyl moiety is optionally substituted on the nitrogen with a $-CH_2CH_2OCH_3$ group; and wherein said phenyl moiety is substituted with alkoxy.

In another embodiment of this invention R^5 is a substituted triazolyl-phenyl- group wherein (a) said triazolyl moiety is substituted on the nitrogen with a substituent selected from the group consisting of: $-CH_2COH(CH_3)_2$ and $-CH_2CH_2OH$, (b) said triazolyl moiety is substituted on the nitrogen with an alkyl group, (c) said triazolyl

moiety is substituted on the nitrogen with an alkyl group, and on the carbon with an alkyl group, (d) said triazolyl moiety is substituted on the nitrogen with a $-CH_3$ group, (e) said triazolyl moiety is substituted on the nitrogen with one $-CH_3$ group, and on the carbon with one $-CH_3$ group, (f) said triazolyl moiety is substituted on the carbon with a $-NH_2$ group, or (g) said triazolyl moiety is substituted on the nitrogen with a $-CH_2CH_2OCH_3$ group; and wherein said phenyl moiety is optionally substituted with alkoxy.

In another embodiment of this invention R^5 is a substituted triazolyl-phenyl- group wherein (a) said triazolyl moiety is substituted on the nitrogen with a substituent selected from the group consisting of: $-CH_2COH(CH_3)_2$ and $-CH_2CH_2OH$, (b) said triazolyl moiety is substituted on the nitrogen with an alkyl group, (c) said triazolyl moiety is substituted on the nitrogen with an alkyl group, and on the carbon with an alkyl group, (d) said triazolyl moiety is substituted on the nitrogen with a $-CH_3$ group, (e) said triazolyl moiety is substituted on the nitrogen with one $-CH_3$ group, and on the carbon with one $-CH_3$ group, (f) said triazolyl moiety is substituted on the carbon with a $-NH_2$ group, or (g) said triazolyl moiety is substituted on the nitrogen with a $-CH_2CH_2OCH_3$ group; and wherein said phenyl moiety is substituted with alkoxy.

In another embodiment of this invention R^5 is a substituted triazolyl-thienyl- group wherein (a) said triazolyl moiety is optionally substituted on the nitrogen with a substituent selected from the group consisting of: $-CH_2COH(CH_3)_2$ and $-CH_2CH_2OH$, (b) said triazolyl moiety is optionally substituted on the nitrogen with an alkyl group, (c) said triazolyl moiety is optionally substituted on the nitrogen with an alkyl group, and on the carbon with an alkyl group, (d) said triazolyl moiety is optionally substituted on the nitrogen with a $-CH_3$ group, (e) said triazolyl moiety is optionally substituted on the nitrogen with one $-CH_3$ group, and on the carbon with one $-CH_3$ group, (f) said triazolyl moiety is optionally substituted on the carbon with a $-NH_2$ group, or (g) said triazolyl moiety is optionally substituted on the nitrogen with a $-CH_2CH_2OCH_3$ group; and wherein said thienyl moiety is optionally substituted with halo.

In another embodiment of this invention R^5 is a substituted triazolyl-thienyl- group wherein (a) said triazolyl moiety is optionally substituted on the nitrogen with a substituent selected from the group consisting of: $-CH_2COH(CH_3)_2$ and $-CH_2CH_2OH$, (b) said triazolyl moiety is optionally substituted on the nitrogen with an alkyl group, (c) said triazolyl moiety is optionally substituted on the nitrogen with an alkyl group, and on the carbon with an alkyl group, (d) said triazolyl moiety is optionally substituted on

the nitrogen with a $-CH_3$ group, (e) said triazolyl moiety is optionally substituted on the nitrogen with one $-CH_3$ group, and on the carbon with one $-CH_3$ group, (f) said triazolyl moiety is optionally substituted on the carbon with a $-NH_2$ group, or (g) said triazolyl moiety is optionally substituted on the nitrogen with a $-CH_2CH_2OCH_3$ group; and wherein said thienyl moiety is substituted with halo.

In another embodiment of this invention R^5 is a substituted triazolyl-thienyl-group wherein (a) said triazolyl moiety is substituted on the nitrogen with a substituent selected from the group consisting of: $-CH_2COH(CH_3)_2$ and $-CH_2CH_2OH$, (b) said triazolyl moiety is substituted on the nitrogen with an alkyl group, (c) said triazolyl moiety is substituted on the nitrogen with an alkyl group, and on the carbon with an alkyl group, (d) said triazolyl moiety is substituted on the nitrogen with a $-CH_3$ group, (e) said triazolyl moiety is substituted on the nitrogen with one $-CH_3$ group, and on the carbon with one $-CH_3$ group, (f) said triazolyl moiety is substituted on the carbon with a $-NH_2$ group, or (g) said triazolyl moiety is substituted on the nitrogen with a $-CH_2CH_2OCH_3$ group; and wherein said thienyl moiety is optionally substituted with halo.

In another embodiment of this invention R^5 is a substituted triazolyl-thienyl-group wherein (a) said triazolyl moiety is substituted on the nitrogen with a substituent selected from the group consisting of: $-CH_2COH(CH_3)_2$ and $-CH_2CH_2OH$, (b) said triazolyl moiety is substituted on the nitrogen with an alkyl group, (c) said triazolyl moiety is substituted on the nitrogen with an alkyl group, and on the carbon with an alkyl group, (d) said triazolyl moiety is substituted on the nitrogen with a $-CH_3$ group, (e) said triazolyl moiety is substituted on the nitrogen with one $-CH_3$ group, and on the carbon with one $-CH_3$ group, (f) said triazolyl moiety is substituted on the carbon with a $-NH_2$ group, or (g) said triazolyl moiety is substituted on the nitrogen with a $-CH_2CH_2OCH_3$ group; and wherein said thienyl moiety is substituted with halo.

In another embodiment of this invention R^5 is a substituted triazolyl-thienyl-group wherein (a) said triazolyl moiety is substituted on the nitrogen with a substituent selected from the group consisting of: $-CH_2COH(CH_3)_2$ and $-CH_2CH_2OH$, (b) said triazolyl moiety is substituted on the nitrogen with an alkyl group, (c) said triazolyl moiety is substituted on the nitrogen with an alkyl group, and on the carbon with an alkyl group, (d) said triazolyl moiety is substituted on the nitrogen with a $-CH_3$ group, (e) said triazolyl moiety is substituted on the nitrogen with one $-CH_3$ group, and on the carbon with one $-CH_3$ group, (f) said triazolyl moiety is substituted on the carbon with

a $-NH_2$ group, or (g) said triazolyl moiety is substituted on the nitrogen with a $-CH_2CH_2OCH_3$ group; and wherein said thienyl moiety is unsubstituted.

In another embodiment of this invention R^5 is a substituted triazolyl-thienyl- group wherein (a) said triazolyl moiety is optionally substituted on the nitrogen with a substituent selected from the group consisting of: $-CH_2COH(CH_3)_2$, and $-CH_2CH_2OH$, (b) said triazolyl moiety is optionally substituted on the nitrogen with an alkyl group, (c) said triazolyl moiety is optionally substituted on the nitrogen with an alkyl group, and on the carbon with an alkyl group, (d) said triazolyl moiety is optionally substituted on the nitrogen with a $-CH_3$ group, (e) said triazolyl moiety is optionally substituted on the nitrogen with one $-CH_3$ group, and on the carbon with one $-CH_3$ group, (f) said triazolyl moiety is optionally substituted on the carbon with a $-NH_2$ group, or (g) said triazolyl moiety is optionally substituted on the nitrogen with a $-CH_2CH_2OCH_3$ group; and wherein said thienyl moiety is optionally substituted with alkoxy.

In another embodiment of this invention R^5 is a substituted triazolyl-thienyl- group wherein (a) said triazolyl moiety is optionally substituted on the nitrogen with a substituent selected from the group consisting of: $-CH_2COH(CH_3)_2$ and $-CH_2CH_2OH$, (b) said triazolyl moiety is optionally substituted on the nitrogen with an alkyl group, (c) said triazolyl moiety is optionally substituted on the nitrogen with an alkyl group, and on the carbon with an alkyl group, (d) said triazolyl moiety is optionally substituted on the nitrogen with a $-CH_3$ group, (e) said triazolyl moiety is optionally substituted on the nitrogen with one $-CH_3$ group, and on the carbon with one $-CH_3$ group, (f) said triazolyl moiety is optionally substituted on the carbon with a $-NH_2$ group, or (g) said triazolyl moiety is optionally substituted on the nitrogen with a $-CH_2CH_2OCH_3$ group; and wherein said thienyl moiety is substituted with alkoxy.

In another embodiment of this invention R^5 is a substituted triazolyl-thienyl- group wherein (a) said triazolyl moiety is substituted on the nitrogen with a substituent selected from the group consisting of: $-CH_2COH(CH_3)_2$ and $-CH_2CH_2OH$, (b) said triazolyl moiety is substituted on the nitrogen with an alkyl group, (c) said triazolyl moiety is substituted on the nitrogen with an alkyl group, and on the carbon with an alkyl group, (d) said triazolyl moiety is substituted on the nitrogen with a $-CH_3$ group, (e) said triazolyl moiety is substituted on the nitrogen with one $-CH_3$ group, and on the carbon with one $-CH_3$ group, (f) said triazolyl moiety is substituted on the carbon with a $-NH_2$ group, or (g) said triazolyl moiety is substituted on the nitrogen with a

$-CH_2CH_2OCH_3$ group; and wherein said thienyl moiety is optionally substituted with alkoxy.

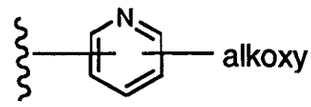
In another embodiment of this invention R^5 is a substituted triazolyl-thienyl-group wherein (a) said triazolyl moiety is substituted on the nitrogen with a substituent selected from the group consisting of: $-CH_2COH(CH_3)_2$, and $-CH_2CH_2OH$, (b) said triazolyl moiety is substituted on the nitrogen with an alkyl group, (c) said triazolyl moiety is substituted on the nitrogen with an alkyl group, and on the carbon with an alkyl group, (d) said triazolyl moiety is substituted on the nitrogen with a $-CH_3$ group, (e) said triazolyl moiety is substituted on the nitrogen with one $-CH_3$ group, and on the carbon with one $-CH_3$ group, (f) said triazolyl moiety is substituted on the carbon with a $-NH_2$ group, or (g) said triazolyl moiety is substituted on the nitrogen with a $-CH_2CH_2OCH_3$ group; and wherein said thienyl moiety is substituted with alkoxy.

Other embodiments of the invention are described below. The embodiments have been numbered for ease of reference.

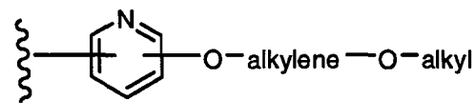
Embodiment No. 1 is directed to compounds of formula 1.0 wherein R^2 is a $-O-(C_1-C_2)$alkyl group, and R^1 is substituted pyridyl.

Embodiment No. 2 is directed to compounds of formula 1.0 wherein R^2 is a $-O-(C_1-C_2)$alkyl group, and R^1 is pyridyl substituted with one substituent.

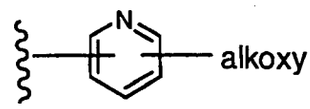
Embodiment No. 3 is directed to compounds of formula 1.0 wherein R^2 is a $-O-(C_1-C_2)$alkyl group, and R^1 is selected from the group consisting of:



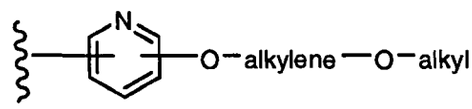
and



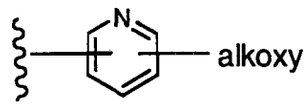
Embodiment No. 4 is directed to compounds of formula 1.0 wherein R^2 is a $-O-(C_1-C_2)$alkyl group, and R^1 is:



Embodiment No. 5 is directed to compounds of formula 1.0 wherein R^2 is a $-O-(C_1-C_2)$alkyl group, and R^1 is:

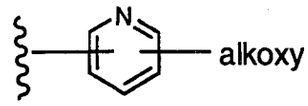


Embodiment No. 6 is directed to compounds of formula 1.0 wherein R^2 is a $-O-(C_1-C_2)$alkyl group, and R^1 is:



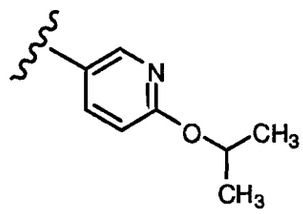
wherein said alkoxy group is $-OCH(CH_3)_2$.

Embodiment No. 7 is directed to compounds of formula 1.0 wherein, R^2 is a $-O-(C_1-C_2)$alkyl group, and R^1 is:

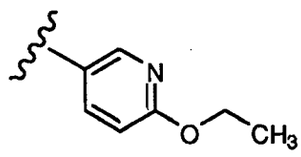


wherein said alkoxy group is $-OC_2H_5$.

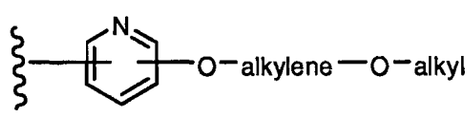
Embodiment No. 8 is directed to compounds of formula 1.0 wherein R^2 is a $-O-(C_1-C_2)$alkyl group, and R^1 is:



Embodiment No. 9 is directed to compounds of formula 1.0 wherein R^2 is a $-O-(C_1-C_2)$alkyl group, and R^1 is:

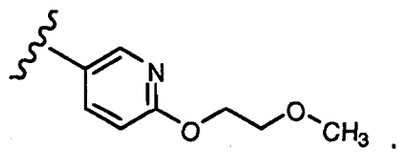


Embodiment No. 10 is directed to compounds of formula 1.0 wherein z is 1, R^2 is a $-O-(C_1-C_2)$alkyl group, and R^1 is:



wherein said –O-alkylene-O-alkyl group is $-OCH_2CH_2OCH_3$.

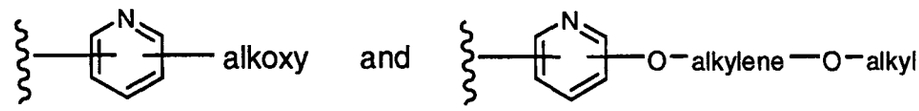
Embodiment No. 11 is directed to compounds of formula 1.0 wherein R^2 is a $-O-(C_1-C_2)$alkyl group, and R^1 is:



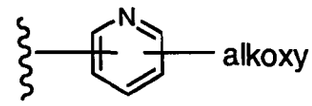
Embodiment No. 12 is directed to compounds of formula 1.0 wherein R^2 is $-OCH_3$, and R^1 is substituted pyridyl.

Embodiment No. 13 is directed to compounds of formula 1.0 wherein R^2 is $-OCH_3$, and R^1 is pyridyl substituted with one substituent.

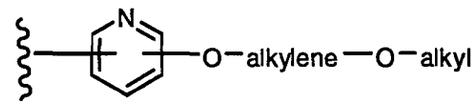
Embodiment No. 14 is directed to compounds of formula 1.0 wherein R^2 is $-OCH_3$, and R^1 is selected from the group consisting of:



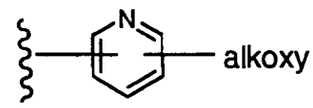
Embodiment No. 15 is directed to compounds of formula 1.0 wherein R^2 is $-OCH_3$, and R^1 is:



Embodiment No. 16 is directed to compounds of formula 1.0 wherein R^2 is $-OCH_3$, and R^1 is:

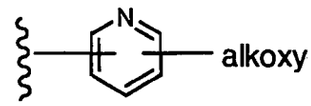


Embodiment No. 17 is directed to compounds of formula 1.0 wherein R^2 is $-OCH_3$, and R^1 is:



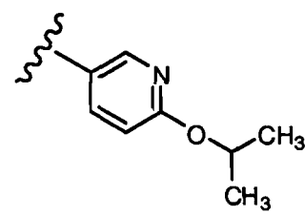
wherein said alkoxy group is $-OCH(CH_3)_2$.

Embodiment No. 18 is directed to compounds of formula 1.0 wherein R^2 is $-OCH_3$, and R^1 is:

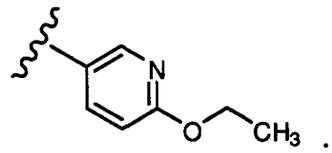


wherein said alkoxy group is $-OC_2H_5$.

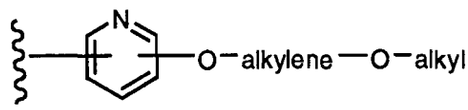
Embodiment No. 19 is directed to compounds of formula 1.0 wherein R^2 is $-OCH_3$, and R^1 is:



Embodiment No. 20 is directed to compounds of formula 1.0 wherein R^2 is $-OCH_3$, and R^1 is:

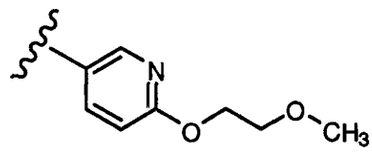


Embodiment No. 21 is directed to compounds of formula 1.0 wherein R^2 is $-OCH_3$, and R^1 is:



wherein said –O-alkylene-O-alkyl group is $-OCH_2CH_2OCH_3$.

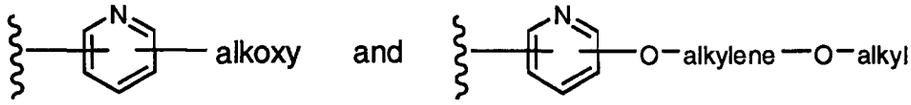
Embodiment No. 22 is directed to compounds of formula 1.0 wherein R^2 is $-OCH_3$, and R^1 is:



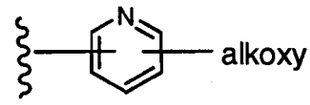
Embodiment No. 23 is directed to compounds of formula 1.0 wherein R^2 is a $-S-(C_1-C_2)$alkyl group, and R^1 is substituted pyridyl.

Embodiment No. 24 is directed to compounds of formula 1.0 wherein R^2 is a $-S-(C_1-C_2)$alkyl group, and R^1 is pyridyl substituted with one substituent.

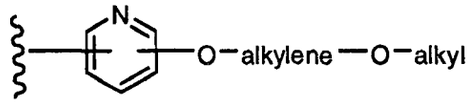
Embodiment No. 25 is directed to compounds of formula 1.0 wherein R^2 is a $-S-(C_1-C_2)$alkyl group, and R^1 is selected from the group consisting of:



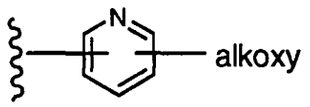
Embodiment No. 26 is directed to compounds of formula 1.0 wherein R^2 is a $-S-(C_1-C_2)$alkyl group, and R^1 is:



Embodiment No. 27 is directed to compounds of formula 1.0 wherein R^2 is a $-S-(C_1-C_2)$alkyl group, and R^1 is:

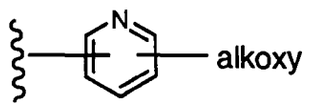


Embodiment No. 28 is directed to compounds of formula 1.0 wherein R^2 is a –S-(C_1-C_2)alkyl group, and R^1 is:



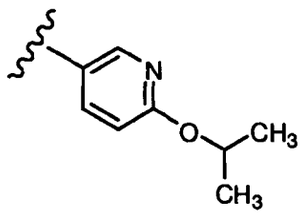
wherein said alkoxy group is $-OCH(CH_3)_2$.

Embodiment No. 29 is directed to compounds of formula 1.0 wherein R^2 is a –S-(C_1-C_2)alkyl group, and R^1 is:



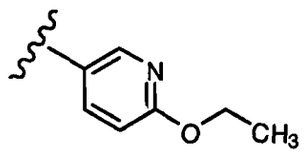
wherein said alkoxy group is $-OC_2H_5$.

Embodiment No. 30 is directed to compounds of formula 1.0 wherein R^2 is a –S-(C_1-C_2)alkyl group, and R^1 is:



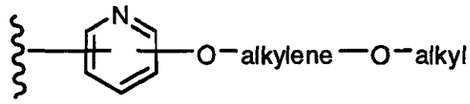
.

Embodiment No. 31 is directed to compounds of formula 1.0 wherein R^2 is a –S-(C_1-C_2)alkyl group, and R^1 is:



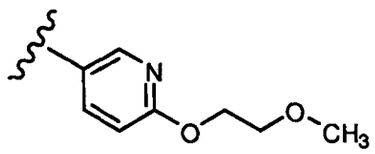
.

Embodiment No. 32 is directed to compounds of formula 1.0 wherein R^2 is a –S-(C_1-C_2)alkyl group, and R^1 is:



wherein said –O-alkylene-O-alkyl group is $-OCH_2CH_2OCH_3$.

Embodiment No. 33 is directed to compounds of formula 1.0 wherein R^2 is a –S-(C_1-C_2)alkyl group, and R^1 is:

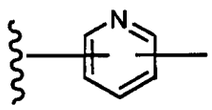


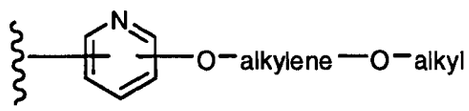
.

Embodiment No. 34 is directed to compounds of formula 1.0 wherein R^2 is $-SCH_3$, and R^1 is substituted pyridyl.

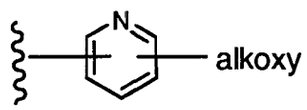
Embodiment No. 35 is directed to compounds of formula 1.0 wherein R^2 is $-SCH_3$, and R^1 is pyridyl substituted with one substituent.

Embodiment No. 36 is directed to compounds of formula 1.0 wherein R^2 is $-SCH_3$, and R^1 is selected from the group consisting of:

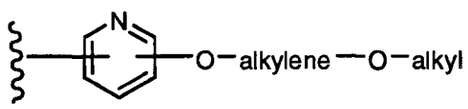


and


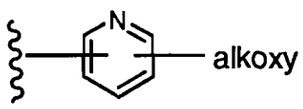
Embodiment No. 37 is directed to compounds of formula 1.0 wherein R^2 is $-SCH_3$, and R^1 is:



Embodiment No. 38 is directed to compounds of formula 1.0 wherein R^2 is $-SCH_3$, and R^1 is:

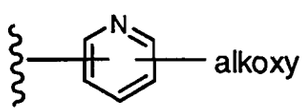


Embodiment No. 39 is directed to compounds of formula 1.0 wherein R^2 is $-SCH_3$, and R^1 is:



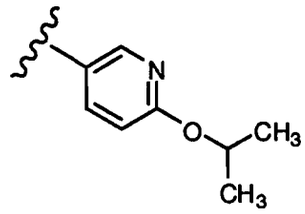
wherein said alkoxy group is $-OCH(CH_3)_2$.

Embodiment No. 40 is directed to compounds of formula 1.0 wherein R^2 is $-SCH_3$, and R^1 is:

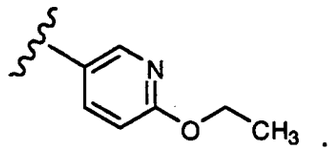


wherein said alkoxy group is $-OC_2H_5$.

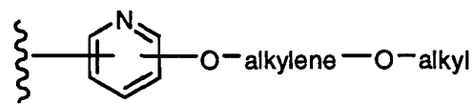
Embodiment No. 41 is directed to compounds of formula 1.0 wherein R^2 is $-SCH_3$, and R^1 is:



Embodiment No. 42 is directed to compounds of formula 1.0 wherein R^2 is $-SCH_3$, and R^1 is:

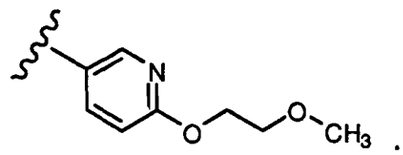


Embodiment No. 43 is directed to compounds of formula 1.0 wherein R^2 is $-SCH_3$, and R^1 is:

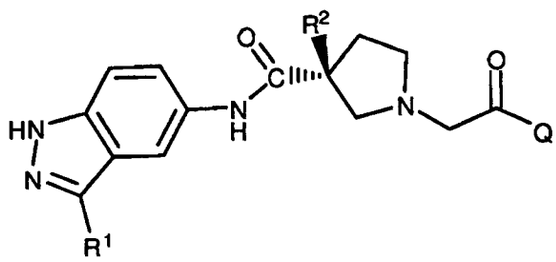


wherein said –O-alkylene-O-alkyl group is $-OCH_2CH_2OCH_3$.

Embodiment No. 44 is directed to compounds of formula 1.0 wherein R^2 is $-SCH_3$, and R^1 is:



Embodiment No. 45 is directed to compounds of formula 1.0 having the formula 1.1:



(1.1)

Embodiment No. 46 is directed to any one of Embodiment Numbers 1 to 44 wherein the compound of formula 1.0 is a compound of formula 1.1.

Other embodiments of the invention directed to the R^5 substituent are described below. The language "as described in any one of Embodiment Numbers 1 to 46" means that the embodiment being described is applicable to each one of

Embodiment Numbers 1 to 46. For example, another embodiment of this invention is directed to compounds described in Embodiment No. 1 wherein R^5 is as described in any one of the paragraphs below. In another example, another embodiment of this invention is directed to the compounds described in Embodiment No.2 wherein R^5 is as described in any one of the paragraphs below, etc.

Thus, other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein R^5 is a substituted triazolyl-phenyl- wherein the triazolyl moiety is substituted with one or two alkyl groups selected from the group consisting of: -C_1-C_6alkyl, -C_1-C_4alkyl, -C_1-C_2alkyl, and –CH_3. .

Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein R^5 is a substituted triazolyl-phenyl- wherein the triazolyl moiety is substituted with one or two alkyl groups selected from the group consisting of: -C_1-C_4alkyl, -C_1-C_2alkyl, and –CH_3. Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein R^5 is a substituted triazolyl-phenyl- wherein the triazolyl moiety is substituted with one or two –CH_3 groups.

Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein R^5 is a substituted triazolyl-phenyl- wherein the triazolyl moiety is substituted on the nitrogen with an alkyl group selected from the group consisting of: -C_1-C_4alkyl, -C_1-C_2alkyl, and –CH_3. Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein R^5 is a substituted triazolyl-phenyl- wherein the triazolyl moiety is substituted on the nitrogen with –CH_3 group.

Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein R^5 is a substituted triazolyl-phenyl- wherein the triazolyl moiety is substituted on the nitrogen with an -alkylene-O-alkyl group selected from the group consisting of: -C_2-C_4alkylene-O-C_1-C_6alkyl, -C_2alkylene-O-C_1-C_2alkyl, -C_2-C_4alkylene-O-CH_3, and –$CH_2CH_2OCH_3$.

Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein R^5 is a substituted triazolyl-phenyl- wherein the triazolyl moiety is substituted on the nitrogen with an -alkylene-O-alkyl group selected from the group consisting of: -C_2alkylene-O-C_1-

C_2alkyl, and $-CH_2CH_2OCH_3$. Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein R^5 is a substituted triazolyl-phenyl- wherein the triazolyl moiety is substituted on the nitrogen with $-CH_2CH_2OCH_3$.

Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein R^5 is a substituted triazolyl-phenyl- wherein the triazolyl moiety is substituted on the nitrogen with a hydroxy substituted alkyl group selected from the group consisting of: hydroxy substituted $-C_1$-C_4alkyl, hydroxy substituted $-C_1$-C_2alkyl, and hydroxy substituted $-CH_3$.

Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein R^5 is a substituted triazolyl-phenyl- wherein the triazolyl moiety is substituted on the nitrogen with a hydroxy substituted alkyl group selected from the group consisting of: $CH_2COH(CH_3)_2$, and $-CH_2CH_2OH$.

Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein the optional halo substituents for the phenyl moiety of R^5 are independently selected from the group consisting of: Cl, F and Br.

Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein the optional halo substituents for the phenyl moiety of R^5 are F.

Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein the optional halo substituent for the phenyl moiety of R^5 is one F.

Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein R^5 is a substituted triazolyl-phenyl- group wherein (a) said triazolyl moiety is optionally substituted on the nitrogen with a substituent selected from the group consisting of: $-CH_2COH(CH_3)_2$ and $-CH_2CH_2OH$, (b) said triazolyl moiety is optionally substituted on the nitrogen with an alkyl group, (c) said triazolyl moiety is optionally substituted on the nitrogen with an alkyl group, and on the carbon with an alkyl group, (d) said triazolyl moiety is optionally substituted on the nitrogen with a $-CH_3$ group, (e) said triazolyl moiety is optionally substituted on the nitrogen with one $-CH_3$ group, and on the carbon with one $-CH_3$ group, (f) said triazolyl moiety is optionally substituted on the carbon with a

$-NH_2$ group, or (g) said triazolyl moiety is optionally substituted on the nitrogen with a $-CH_2CH_2OCH_3$ group; and wherein said phenyl moiety is optionally substituted with halo (e.g., one halo, such as for example, F).

Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein R^5 is a substituted triazolyl-phenyl- group wherein (a) said triazolyl moiety is optionally substituted on the nitrogen with a substituent selected from the group consisting of: $-CH_2COH(CH_3)_2$ and $-CH_2CH_2OH$, (b) said triazolyl moiety is optionally substituted on the nitrogen with an alkyl group, (c) said triazolyl moiety is optionally substituted on the nitrogen with an alkyl group, and on the carbon with an alkyl group, (d) said triazolyl moiety is optionally substituted on the nitrogen with a $-CH_3$ group, (e) said triazolyl moiety is optionally substituted on the nitrogen with one $-CH_3$ group, and on the carbon with one $-CH_3$ group, (f) said triazolyl moiety is optionally substituted on the carbon with a $-NH_2$ group, or (g) said triazolyl moiety is optionally substituted on the nitrogen with a $-CH_2CH_2OCH_3$ group; and wherein said phenyl moiety is substituted with halo (e.g., one halo, such as for example, F).

Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein R^5 is a substituted triazolyl-phenyl- group wherein (a) said triazolyl moiety is substituted on the nitrogen with a substituent selected from the group consisting of: $-CH_2COH(CH_3)_2$ and $-CH_2CH_2OH$, (b) said triazolyl moiety is substituted on the nitrogen with an alkyl group, (c) said triazolyl moiety is substituted on the nitrogen with an alkyl group, and on the carbon with an alkyl group, (d) said triazolyl moiety is substituted on the nitrogen with a $-CH_3$ group, (e) said triazolyl moiety is substituted on the nitrogen with one $-CH_3$ group, and on the carbon with one $-CH_3$ group, (f) said triazolyl moiety is substituted on the carbon with a $-NH_2$ group, or (g) said triazolyl moiety is substituted on the nitrogen with a$-CH_2CH_2OCH_3$ group; and wherein said phenyl moiety is optionally substituted with halo (e.g., one halo, such as for example, F).

Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein R^5 is a substituted triazolyl-phenyl- group wherein (a) said triazolyl moiety is substituted on the nitrogen with a substituent selected from the group consisting of: $-CH_2COH(CH_3)_2$ and $-CH_2CH_2OH$, (b) said triazolyl moiety is substituted on the nitrogen with an alkyl group, (c) said triazolyl moiety is substituted on the nitrogen with an alkyl group, and on the

carbon with an alkyl group, (d) said triazolyl moiety is substituted on the nitrogen with a $-CH_3$ group, (e) said triazolyl moiety is substituted on the nitrogen with one $-CH_3$ group, and on the carbon with one $-CH_3$ group, (f) said triazolyl moiety is substituted on the carbon with a $-NH_2$ group, or (g) said triazolyl moiety is substituted on the nitrogen with a$-CH_2CH_2OCH_3$ group; and wherein said phenyl moiety is substituted with halo (e.g., one halo, such as for example, F).

Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein the optional substituents for the phenyl moiety of R^5 are independently selected from the group consisting of: alkoxy.

Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein the optional substituents for the phenyl moiety of R^5 are $-OCH_3$.

Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein the optional substituent for the phenyl moiety of R^5 is one $-OCH_3$.

Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein R^5 is a substituted triazolyl-phenyl- group wherein (a) said triazolyl moiety is optionally substituted on the nitrogen with a substituent selected from the group consisting of: $-CH_2COH(CH_3)_2$, and $-CH_2CH_2OH$, (b) said triazolyl moiety is optionally substituted on the nitrogen with an alkyl group, (c) said triazolyl moiety is optionally substituted on the nitrogen with an alkyl group, and on the carbon with an alkyl group, (d) said triazolyl moiety is optionally substituted on the nitrogen with a $-CH_3$ group, (e) said triazolyl moiety is optionally substituted on the nitrogen with one $-CH_3$ group, and on the carbon with one $-CH_3$ group, (f) said triazolyl moiety is optionally substituted on the carbon with a $-NH_2$ group, or (g) said triazolyl moiety is optionally substituted on the nitrogen with a $-CH_2CH_2OCH_3$ group; and wherein said phenyl moiety is optionally substituted with alkoxy (e.g., one $-OCH_3$).

Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein R^5 is a substituted triazolyl-phenyl- group wherein (a) said triazolyl moiety is optionally substituted on the nitrogen with a substituent selected from the group consisting of: $-CH_2COH(CH_3)_2$, and $-CH_2CH_2OH$, (b) said triazolyl moiety is optionally substituted on the nitrogen with

an alkyl group, (c) said triazolyl moiety is optionally substituted on the nitrogen with an alkyl group, and on the carbon with an alkyl group, (d) said triazolyl moiety is optionally substituted on the nitrogen with a $-CH_3$ group, (e) said triazolyl moiety is optionally substituted on the nitrogen with one $-CH_3$ group, and on the carbon with one $-CH_3$ group, (f) said triazolyl moiety is optionally substituted on the carbon with a $-NH_2$ group, or (g) said triazolyl moiety is optionally substituted on the nitrogen with a $-CH_2CH_2OCH_3$ group; and wherein said phenyl moiety is substituted with alkoxy (e.g., one $-OCH_3$).

Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein R^5 is a substituted triazolyl-phenyl- group wherein (a) said triazolyl moiety is substituted on the nitrogen with a substituent selected from the group consisting of: $-CH_2COH(CH_3)_2$, and $-CH_2CH_2OH$, (b) said triazolyl moiety is substituted on the nitrogen with an alkyl group, (c) said triazolyl moiety is substituted on the nitrogen with an alkyl group, and on the carbon with an alkyl group, (d) said triazolyl moiety is substituted on the nitrogen with a $-CH_3$ group, (e) said triazolyl moiety is substituted on the nitrogen with one $-CH_3$ group, and on the carbon with one $-CH_3$ group, (f) said triazolyl moiety is substituted on the carbon with a $-NH_2$ group, or (g) said triazolyl moiety is substituted on the nitrogen with a$-CH_2CH_2OCH_3$ group; and wherein said phenyl moiety is optionally substituted with alkoxy (e.g., one $-OCH_3$).

Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein R^5 is a substituted triazolyl-phenyl- group wherein (a) said triazolyl moiety is substituted on the nitrogen with a substituent selected from the group consisting of: $-CH_2COH(CH_3)_2$, and $-CH_2CH_2OH$, (b) said triazolyl moiety is substituted on the nitrogen with an alkyl group, (c) said triazolyl moiety is substituted on the nitrogen with an alkyl group, and on the carbon with an alkyl group, (d) said triazolyl moiety is substituted on the nitrogen with a $-CH_3$ group, (e) said triazolyl moiety is substituted on the nitrogen with one $-CH_3$ group, and on the carbon with one $-CH_3$ group, (f) said triazolyl moiety is substituted on the carbon with a $-NH_2$ group, or (g) said triazolyl moiety is substituted on the nitrogen with a$-CH_2CH_2OCH_3$ group; and wherein said phenyl moiety is substituted with alkoxy (e.g., one $-OCH_3$).

Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein R^5 is a substituted

triazolyl-phenyl- group wherein (a) said triazolyl moiety is substituted on the nitrogen with a substituent selected from the group consisting of: $-CH_2COH(CH_3)_2$, and $-CH_2CH_2OH$, (b) said triazolyl moiety is substituted on the nitrogen with an alkyl group, (c) said triazolyl moiety is substituted on the nitrogen with an alkyl group, and on the carbon with an alkyl group, (d) said triazolyl moiety is substituted on the nitrogen with a $-CH_3$ group, (e) said triazolyl moiety is substituted on the nitrogen with one $-CH_3$ group, and on the carbon with one $-CH_3$ group, (f) said triazolyl moiety is substituted on the carbon with a $-NH_2$ group, or (g) said triazolyl moiety is substituted on the nitrogen with a$-CH_2CH_2OCH_3$ group; and wherein said phenyl moiety is unsubstituted.

Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein said substituted R^5 moiety is a substituted triazolyl-phenyl group wherein said triazolyl moiety is substituted with: (a) one substituent selected from the group consisting of: $-CH_2COH(CH_3)_2$, and $-CH_2CH_2OH$, (b) one alkyl group, (c) two alkyl groups, (d) one $-CH_3$ group, (e) two $-CH_3$ groups, (f) one $-NH_2$ group, or (g) one $-CH_2CH_2OCH_3$ group.

Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein R^5 is a substituted triazolyl-thienyl- wherein the triazolyl moiety is substituted with one or two alkyl groups selected from the group consisting of: $-C_1$-C_6alkyl, $-C_1$-C_4alkyl, $-C_1$-C_2alkyl, and $-CH_3$.

Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein R^5 is a substituted triazolyl-thienyl- wherein the triazolyl moiety is substituted with one or two alkyl groups selected from the group consisting of: $-C_1$-C_4alkyl, $-C_1$-C_2alkyl, and $-CH_3$. Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein R^5 is a substituted triazolyl-thienyl- wherein the triazolyl moiety is substituted with one or two $-CH_3$ groups.

Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein R^5 is a substituted triazolyl-thienyl- wherein the triazolyl moiety is substituted on the nitrogen with an alkyl group selected from the group consisting of: $-C_1$-C_4alkyl, $-C_1$-C_2alkyl, and $-CH_3$. Other embodiments of this invention are directed to compounds of formula 1.0 as

described in any one of Embodiment Numbers 1 to 46 wherein R^5 is a substituted triazolyl-thienyl- wherein the triazolyl moiety is substituted on the nitrogen with $-CH_3$.

Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein R^5 is a substituted triazolyl-thienyl- wherein the triazolyl moiety is substituted on the nitrogen with an -alkylene-O-alkyl group selected from the group consisting of: -C_2-C_4alkylene-O-C_1-C_6alkyl, -C_2alkylene-O-C_1-C_2alkyl, -C_2-C_4alkylene-O-CH_3, and $-CH_2CH_2OCH_3$.

Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein R^5 is a substituted triazolyl-thienyl- wherein the triazolyl moiety is substituted on the nitrogen with an -alkylene-O-alkyl group selected from the group consisting of: -C_2alkylene-O-C_1-C_2alkyl, and$-CH_2CH_2OCH_3$. Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein R^5 is a substituted triazolyl-thienyl- wherein the triazolyl moiety is substituted on the nitrogen with $-CH_2CH_2OCH_3$.

Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein R^5 is a substituted triazolyl-thienyl- wherein the triazolyl moiety is substituted on the nitrogen with a hydroxy substituted alkyl group selected from the group consisting of: hydroxy substituted -C_1-C_4alkyl, hydroxy substituted -C_1-C_2alkyl, and hydroxy substituted -CH_3.

Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein R^5 is a substituted triazolyl-thienyl- wherein the triazolyl moiety is substituted on the nitrogen with a hydroxy substituted alkyl group selected from the group consisting of: $CH_2COH(CH_3)_2$, and -CH_2CH_2OH.

Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein the optional halo substituents for the thienyl moiety of R^5 are independently selected from the group consisting of: Cl, F and Br.

Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein the optional halo substituents for the thienyl moiety of R^5 are F.

Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein the optional halo substituent for the thienyl moiety of R^5 is one F.

Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein R^5 is a substituted triazolyl-thienyl- group wherein (a) said triazolyl moiety is optionally substituted on the nitrogen with a substituent selected from the group consisting of: $-CH_2COH(CH_3)_2$, and $-CH_2CH_2OH$, (b) said triazolyl moiety is optionally substituted on the nitrogen with an alkyl group, (c) said triazolyl moiety is optionally substituted on the nitrogen with an alkyl group, and on the carbon with an alkyl group, (d) said triazolyl moiety is optionally substituted on the nitrogen with a $-CH_3$ group, (e) said triazolyl moiety is optionally substituted on the nitrogen with one $-CH_3$ group, and on the carbon with one $-CH_3$ group, (f) said triazolyl moiety is optionally substituted on the carbon with a $-NH_2$ group, or (g) said triazolyl moiety is optionally substituted on the nitrogen with a $-CH_2CH_2OCH_3$ group; and wherein said thienyl moiety is optionally substituted with halo (e.g., one halo, such as for example, F).

Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein R^5 is a substituted triazolyl-thienyl- group wherein (a) said triazolyl moiety is optionally substituted on the nitrogen with a substituent selected from the group consisting of:$-CH_2COH(CH_3)_2$, $-CH_2CH_2OH$, (b) said triazolyl moiety is optionally substituted on the nitrogen with an alkyl group, (c) said triazolyl moiety is optionally substituted on the nitrogen with an alkyl group, and on the carbon with an alkyl group, (d) said triazolyl moiety is optionally substituted on the nitrogen with a $-CH_3$ group, (e) said triazolyl moiety is optionally substituted on the nitrogen with one $-CH_3$ group, and on the carbon with one $-CH_3$ group, (f) said triazolyl moiety is optionally substituted on the carbon with a $-NH_2$ group, or (g) said triazolyl moiety is optionally substituted on the nitrogen with a $-CH_2CH_2OCH_3$ group; and wherein said thienyl moiety is substituted with halo (e.g., one halo, such as for example, F).

Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein R^5 is a substituted triazolyl-thienyl- group wherein (a) said triazolyl moiety is substituted on the nitrogen with a substituent selected from the group consisting of: $-CH_2COH(CH_3)_2$, and $-CH_2CH_2OH$, (b) said triazolyl moiety is substituted on the nitrogen with an alkyl group,

(c) said triazolyl moiety is substituted on the nitrogen with an alkyl group, and on the carbon with an alkyl group, (d) said triazolyl moiety is substituted on the nitrogen with a $-CH_3$ group, (e) said triazolyl moiety is substituted on the nitrogen with one $-CH_3$ group, and on the carbon with one $-CH_3$ group, (f) said triazolyl moiety is substituted on the carbon with a $-NH_2$ group, or (g) said triazolyl moiety is substituted on the nitrogen with a$-CH_2CH_2OCH_3$ group; and wherein said thienyl moiety is optionally substituted with halo (e.g., one halo, such as for example, F).

Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein R^5 is a substituted triazolyl-thienyl- group wherein (a) said triazolyl moiety is substituted on the nitrogen with a substituent selected from the group consisting of: $-CH_2COH(CH_3)_2$, and $-CH_2CH_2OH$, (b) said triazolyl moiety is substituted on the nitrogen with an alkyl group, (c) said triazolyl moiety is substituted on the nitrogen with an alkyl group, and on the carbon with an alkyl group, (d) said triazolyl moiety is substituted on the nitrogen with a $-CH_3$ group, (e) said triazolyl moiety is substituted on the nitrogen with one $-CH_3$ group, and on the carbon with one $-CH_3$ group, (f) said triazolyl moiety is substituted on the carbon with a $-NH_2$ group, or (g) said triazolyl moiety is substituted on the nitrogen with a$-CH_2CH_2OCH_3$ group; and wherein said thienyl moiety is substituted with halo (e.g., one halo, such as for example, F).

Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein R^5 is a substituted triazolyl-thienyl- group wherein (a) said triazolyl moiety is substituted on the nitrogen with a substituent selected from the group consisting of: $-CH_2COH(CH_3)_2$, and $-CH_2CH_2OH$, (b) said triazolyl moiety is substituted on the nitrogen with an alkyl group, (c) said triazolyl moiety is substituted on the nitrogen with an alkyl group, and on the carbon with an alkyl group, (d) said triazolyl moiety is substituted on the nitrogen with a $-CH_3$ group, (e) said triazolyl moiety is substituted on the nitrogen with one $-CH_3$ group, and on the carbon with one $-CH_3$ group, (f) said triazolyl moiety is substituted on the carbon with a $-NH_2$ group, or (g) said triazolyl moiety is substituted on the nitrogen with a$-CH_2CH_2OCH_3$ group; and wherein said thienyl moiety is unsubstituted.

Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein said substituted R^5 moiety is a substituted triazolyl-thienyl group wherein said triazolyl moiety is substituted with: (a) one substituent selected from the group consisting of:

$-CH_2COH(CH_3)_2$, and $-CH_2CH_2OH$, (b) one alkyl group, (c) two alkyl groups, (d) one $-CH_3$ group, (e) two $-CH_3$ groups, (f) one $-NH_2$ group, or (g) one $-CH_2CH_2OCH_3$ group.

Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein the optional substituents for the thienyl moiety of R^5 are independently selected from the group consisting of: alkoxy.

Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein the optional substituents for the thienyl moiety of R^5 are $-OCH_3$.

Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein the optional substituent for the thienyl moiety of R^5 is one $-OCH_3$.

Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein R^5 is a substituted triazolyl-thienyl- group wherein (a) said triazolyl moiety is optionally substituted on the nitrogen with a substituent selected from the group consisting of: $-CH_2COH(CH_3)_2$, and $-CH_2CH_2OH$, (b) said triazolyl moiety is optionally substituted on the nitrogen with an alkyl group, (c) said triazolyl moiety is optionally substituted on the nitrogen with an alkyl group, and on the carbon with an alkyl group, (d) said triazolyl moiety is optionally substituted on the nitrogen with a $-CH_3$ group, (e) said triazolyl moiety is optionally substituted on the nitrogen with one $-CH_3$ group, and on the carbon with one $-CH_3$ group, (f) said triazolyl moiety is optionally substituted on the carbon with a $-NH_2$ group, or (g) said triazolyl moiety is optionally substituted on the nitrogen with a $-CH_2CH_2OCH_3$ group; and wherein said thienyl moiety is optionally substituted with alkoxy (e.g., one $-OCH_3$).

Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein R^5 is a substituted triazolyl-thienyl- group wherein (a) said triazolyl moiety is optionally substituted on the nitrogen with a substituent selected from the group consisting of: $-CH_2COH(CH_3)_2$, and $-CH_2CH_2OH$, (b) said triazolyl moiety is optionally substituted on the nitrogen with an alkyl group, (c) said triazolyl moiety is optionally substituted on the nitrogen with an alkyl group, and on the carbon with an alkyl group, (d) said triazolyl moiety is optionally substituted on the nitrogen with a $-CH_3$ group, (e) said triazolyl moiety is

optionally substituted on the nitrogen with one $-CH_3$ group, and on the carbon with one $-CH_3$ group, (f) said triazolyl moiety is optionally substituted on the carbon with a $-NH_2$ group, or (g) said triazolyl moiety is optionally substituted on the nitrogen with a $-CH_2CH_2OCH_3$ group; and wherein said thienyl moiety is substituted with alkoxy (e.g., one $-OCH_3$).

Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein R^5 is a substituted triazolyl-thienyl- group wherein (a) said triazolyl moiety is substituted on the nitrogen with a substituent selected from the group consisting of: $-CH_2COH(CH_3)_2$, and $-CH_2CH_2OH$, (b) said triazolyl moiety is substituted on the nitrogen with an alkyl group, (c) said triazolyl moiety is substituted on the nitrogen with an alkyl group, and on the carbon with an alkyl group, (d) said triazolyl moiety is substituted on the nitrogen with a $-CH_3$ group, (e) said triazolyl moiety is substituted on the nitrogen with one $-CH_3$ group, and on the carbon with one $-CH_3$ group, (f) said triazolyl moiety is substituted on the carbon with a $-NH_2$ group, or (g) said triazolyl moiety is substituted on the nitrogen with a$-CH_2CH_2OCH_3$ group; and wherein said thienyl moiety is optionally substituted with alkoxy (e.g., one $-OCH_3$).

Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein R^5 is a substituted triazolyl-thienyl- group wherein (a) said triazolyl moiety is substituted on the nitrogen with a substituent selected from the group consisting of: $-CH_2COH(CH_3)_2$, and $-CH_2CH_2OH$, (b) said triazolyl moiety is substituted on the nitrogen with an alkyl group, (c) said triazolyl moiety is substituted on the nitrogen with an alkyl group, and on the carbon with an alkyl group, (d) said triazolyl moiety is substituted on the nitrogen with a $-CH_3$ group, (e) said triazolyl moiety is substituted on the nitrogen with one $-CH_3$ group, and on the carbon with one $-CH_3$ group, (f) said triazolyl moiety is substituted on the carbon with a $-NH_2$ group, or (g) said triazolyl moiety is substituted on the nitrogen with a$-CH_2CH_2OCH_3$ group; and wherein said thienyl moiety is substituted with alkoxy (e.g., one $-OCH_3$).

Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein R^5 is a substituted triazolyl-pyridyl- wherein the triazolyl moiety is substituted with one or two alkyl groups selected from the group consisting of: $-C_1$-C_6alkyl, $-C_1$-C_4alkyl, $-C_1$-C_2alkyl, and $-CH_3$.

Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein R^5 is a substituted triazolyl-pyridyl- wherein the triazolyl moiety is substituted with one or two alkyl groups selected from the group consisting of: -C_1-C_4alkyl, -C_1-C_2alkyl, and –CH_3. Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein R^5 is a substituted triazolyl-pyridyl- wherein the triazolyl moiety is substituted with one or two –CH_3 groups.

Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein R^5 is a substituted triazolyl-pyridyl- wherein the triazolyl moiety is substituted on the nitrogen with an alkyl group selected from the group consisting of: -C_1-C_4alkyl, -C_1-C_2alkyl, and –CH_3. Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein R^5 is a substituted triazolyl-pyridyl- wherein the triazolyl moiety is substituted on the nitrogen with –CH_3.

Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein R^5 is a substituted triazolyl-pyridyl- wherein the triazolyl moiety is substituted on the nitrogen with an -alkylene-O-alkyl group selected from the group consisting of: -C_2-C_4alkylene-O-C_1-C_6alkyl, -C_2alkylene-O-C_1-C_2alkyl, -C_2-C_4alkylene-O-CH_3, and –$CH_2CH_2OCH_3$.

Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein R^5 is a substituted triazolyl-pyridyl- wherein the triazolyl moiety is substituted on the nitrogen with an -alkylene-O-alkyl group selected from the group consisting of: -C_2alkylene-O-C_1-C_2alkyl, and –$CH_2CH_2OCH_3$. Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein R^5 is a substituted triazolyl-pyridyl- wherein the triazolyl moiety is substituted on the nitrogen with –$CH_2CH_2OCH_3$.

Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein R^5 is a substituted triazolyl-pyridyl- wherein the triazolyl moiety is substituted on the nitrogen with a hydroxy substituted alkyl group selected from the group consisting of: hydroxy substituted -C_1-C_4alkyl, hydroxy substituted -C_1-C_2alkyl, and hydroxy substituted -CH_3.

Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein R^5 is a substituted

triazolyl-pyridyl- wherein the triazolyl moiety is substituted on the nitrogen with a hydroxy substituted alkyl group selected from the group consisting of: $CH_2COH(CH_3)_2$, and $-CH_2CH_2OH$.

Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein R^5 is a substituted triazolyl-pyridyl- group wherein (a) said triazolyl moiety is optionally substituted on the nitrogen with a substituent selected from the group consisting of: $-CH_2COH(CH_3)_2$, and $-CH_2CH_2OH$, (b) said triazolyl moiety is optionally substituted on the nitrogen with an alkyl group, (c) said triazolyl moiety is optionally substituted on the nitrogen with an alkyl group, and on the carbon with an alkyl group, (d) said triazolyl moiety is optionally substituted on the nitrogen with a $-CH_3$ group, (e) said triazolyl moiety is optionally substituted on the nitrogen with one $-CH_3$ group, and on the carbon with one $-CH_3$ group, (f) said triazolyl moiety is optionally substituted on the carbon with a $-NH_2$ group, or (g) said triazolyl moiety is optionally substituted on the nitrogen with a $-CH_2CH_2OCH_3$ group; and wherein said pyridyl moiety is unsubstitued.

Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein R^5 is a substituted triazolyl-pyridyl- group wherein (a) said triazolyl moiety is substituted on the nitrogen with a substituent selected from the group consisting of: $-CH_2COH(CH_3)_2$, and $-CH_2CH_2OH$, (b) said triazolyl moiety is substituted on the nitrogen with an alkyl group, (c) said triazolyl moiety is substituted on the nitrogen with an alkyl group, and on the carbon with an alkyl group, (d) said triazolyl moiety is substituted on the nitrogen with a $-CH_3$ group, (e) said triazolyl moiety is substituted on the nitrogen with one $-CH_3$ group, and on the carbon with one $-CH_3$ group, (f) said triazolyl moiety is substituted on the carbon with a $-NH_2$ group, or (g) said triazolyl moiety is substituted on the nitrogen with a$-CH_2CH_2OCH_3$ group; and wherein said pyridyl moiety is unsubstitued.

Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein R^5 is a substituted triazolyl-thiazolyl- wherein the triazolyl moiety is substituted with one or two alkyl groups selected from the group consisting of: $-C_1$-C_6alkyl, $-C_1$-C_4alkyl, $-C_1$-C_2alkyl, and $-CH_3$.

Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein R^5 is a substituted triazolyl-thiazolyl- wherein the triazolyl moiety is substituted with one or two alkyl

groups selected from the group consisting of: -C_1-C_4alkyl, -C_1-C_2alkyl, and –CH_3. Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein R^5 is a substituted triazolyl-thiazolyl- wherein the triazolyl moiety is substituted with one or two –CH_3 groups.

Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein R^5 is a substituted triazolyl-thiazolyl- wherein the triazolyl moiety is substituted on the nitrogen with an alkyl group selected from the group consisting of: -C_1-C_4alkyl, -C_1-C_2alkyl, and –CH_3. Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein R^5 is a substituted triazolyl-thiazolyl- wherein the triazolyl moiety is substituted on the nitrogen with –CH_3.

Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein R^5 is a substituted triazolyl-thiazolyl- wherein the triazolyl moiety is substituted on the nitrogen with an -alkylene-O-alkyl group selected from the group consisting of: -C_2-C_4alkylene-O-C_1-C_6alkyl, -C_2alkylene-O-C_1-C_2alkyl, -C_2-C_4alkylene-O-CH_3, and –$CH_2CH_2OCH_3$.

Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein R^5 is a substituted triazolyl-thiazolyl- wherein the triazolyl moiety is substituted on the nitrogen with an -alkylene-O-alkyl group selected from the group consisting of: -C_2alkylene-O-C_1-C_2alkyl, and –$CH_2CH_2OCH_3$. Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein R^5 is a substituted triazolyl-thiazolyl- wherein the triazolyl moiety is substituted on the nitrogen with –$CH_2CH_2OCH_3$.

Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein R^5 is a substituted triazolyl-thiazolyl- wherein the triazolyl moiety is substituted on the nitrogen with a hydroxy substituted alkyl group selected from the group consisting of: hydroxy substituted -C_1-C_4alkyl, hydroxy substituted -C_1-C_2alkyl, and hydroxy substituted -CH_3.

Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein R^5 is a substituted triazolyl-thiazolyl- wherein the triazolyl moiety is substituted on the nitrogen with a

hydroxy substituted alkyl group selected from the group consisting of: $CH_2COH(CH_3)_2$, and $-CH_2CH_2OH$.

Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein R^5 is a substituted triazolyl-thiazolyl- group wherein (a) said triazolyl moiety is optionally substituted on the nitrogen with a substituent selected from the group consisting of: $-CH_2COH(CH_3)_2$, and $-CH_2CH_2OH$, (b) said triazolyl moiety is optionally substituted on the nitrogen with an alkyl group, (c) said triazolyl moiety is optionally substituted on the nitrogen with an alkyl group, and on the carbon with an alkyl group, (d) said triazolyl moiety is optionally substituted on the nitrogen with a $-CH_3$ group, (e) said triazolyl moiety is optionally substituted on the nitrogen with one $-CH_3$ group, and on the carbon with one $-CH_3$ group, (f) said triazolyl moiety is optionally substituted on the carbon with a $-NH_2$ group, or (g) said triazolyl moiety is optionally substituted on the nitrogen with a $-CH_2CH_2OCH_3$ group; and wherein said thiazolyl moiety is unsubstitued.

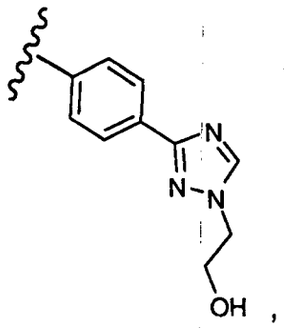
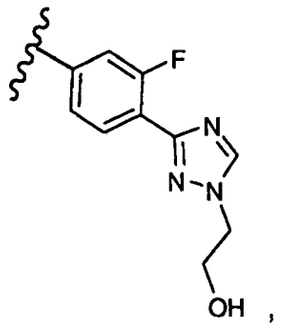
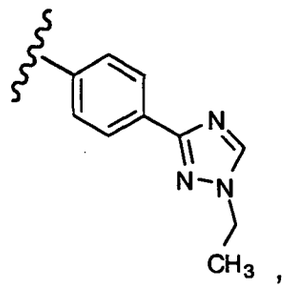
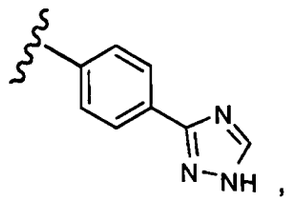
Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein R^5 is a substituted triazolyl-thiazolyl- group wherein (a) said triazolyl moiety is substituted on the nitrogen with a substituent selected from the group consisting of: $-CH_2COH(CH_3)_2$, and $-CH_2CH_2OH$, (b) said triazolyl moiety is substituted on the nitrogen with an alkyl group, (c) said triazolyl moiety is substituted on the nitrogen with an alkyl group, and on the carbon with an alkyl group, (d) said triazolyl moiety is substituted on the nitrogen with a $-CH_3$ group, (e) said triazolyl moiety is substituted on the nitrogen with one $-CH_3$ group, and on the carbon with one $-CH_3$ group, (f) said triazolyl moiety is substituted on the carbon with a $-NH_2$ group, or (g) said triazolyl moiety is substituted on the nitrogen with a$-CH_2CH_2OCH_3$ group; and wherein said thiazolyl moiety is unsubstitued.

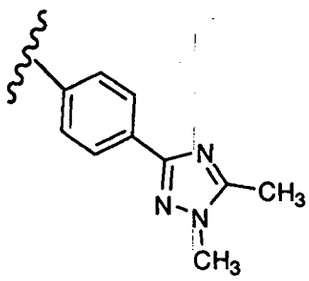
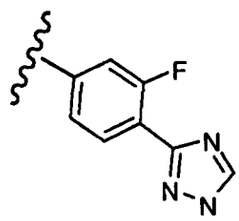
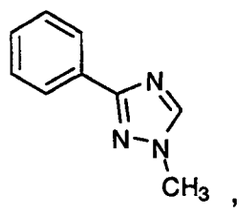
Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein R^5 is a substituted pyradizinyl-thienyl- wherein the pyridazinyl moiety is substituted with 1 or 2 groups indepenendently selected from the group consisting of alkyl (e.g., methyl) and =O, and said thienyl moiety is unsubstituted.

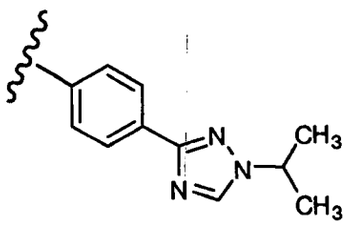
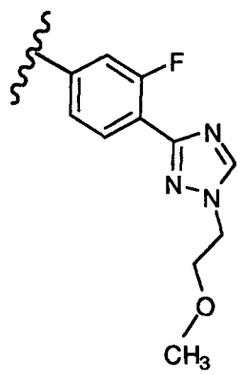
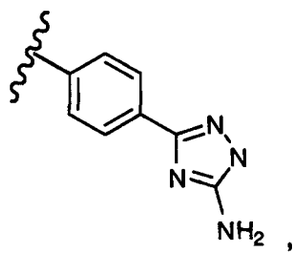
Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein R^5 is a substituted

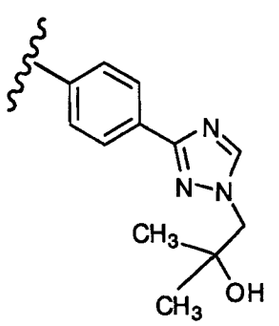
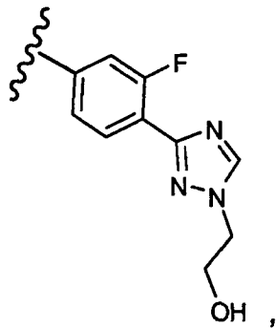
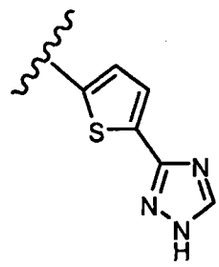
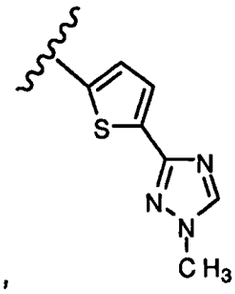
pyradizinyl-thienyl- wherein the pyridazinyl moiety is substituted with an =O moiety, or said pyridazinyl group is substituted with an alkyl (e.g., methyl), or said pyridazinyl is substituted with an =O moiety and an an alkyl (e.g., methyl), and said thienyl moiety is unsubstituted.

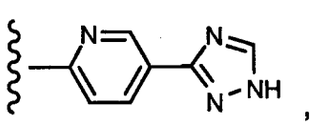
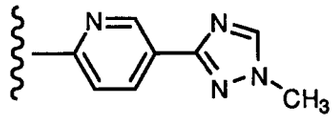
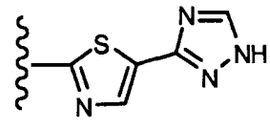
Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein R^5 is selected from the group consisting of:


,

,

,

,

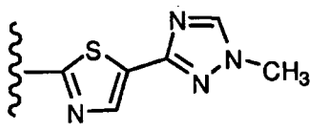
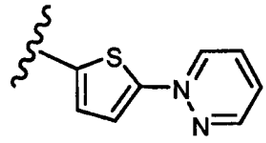
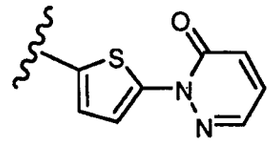

,

,

,

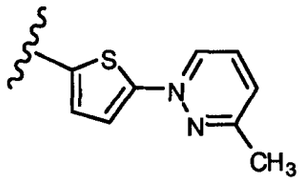
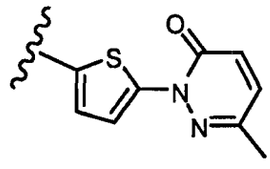

,

,

.


,

,

,

,

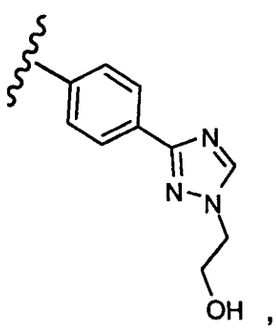
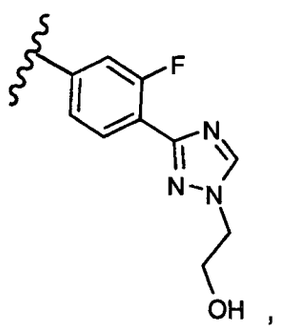
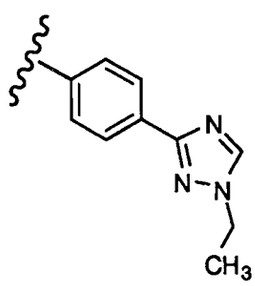
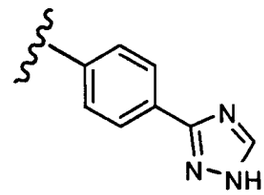

,

,

,

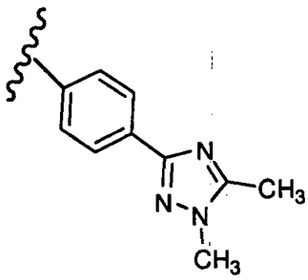
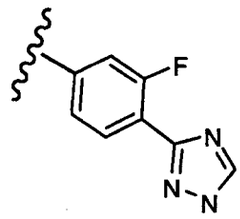
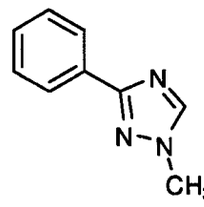
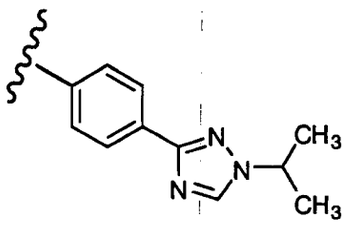
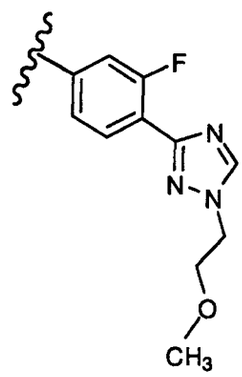
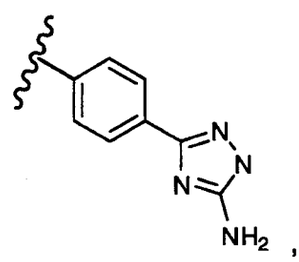
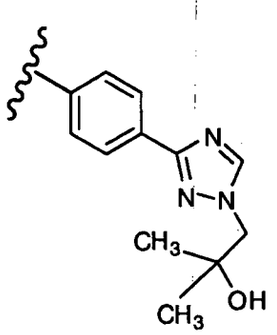
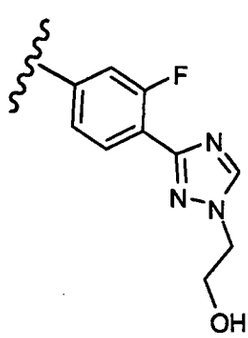
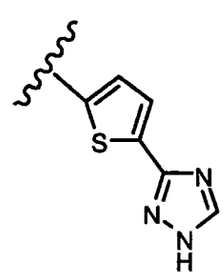
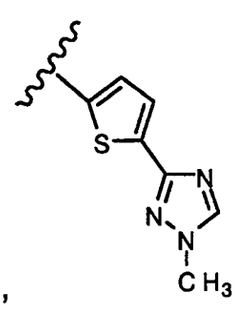
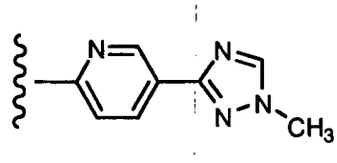
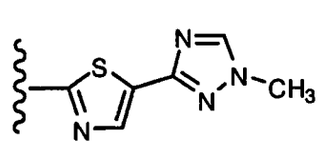
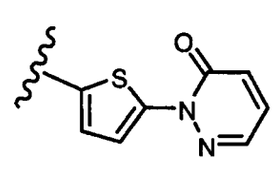
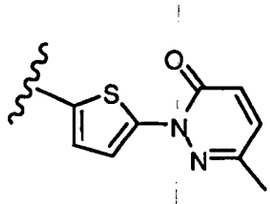
5


,

,

,


, and

.

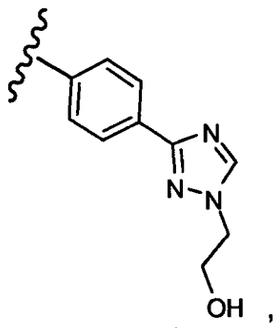
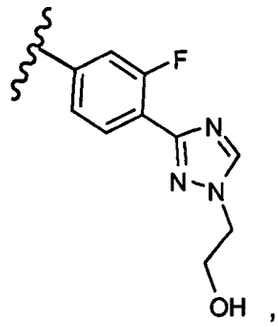
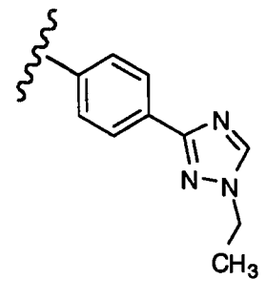
10 Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein R^5 is selected from the group consisting of:

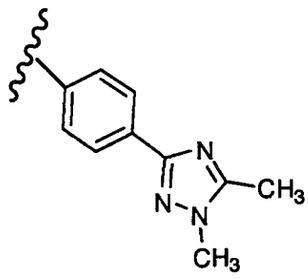
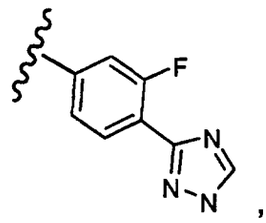
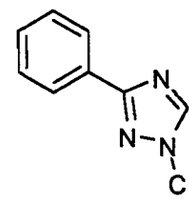

,

,

,

,

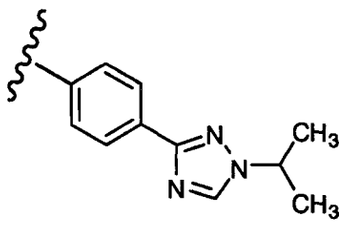
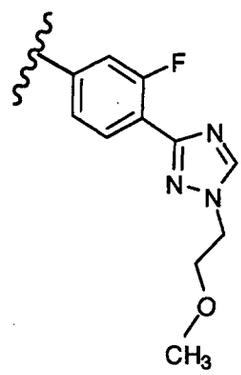
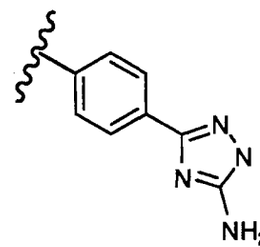













and


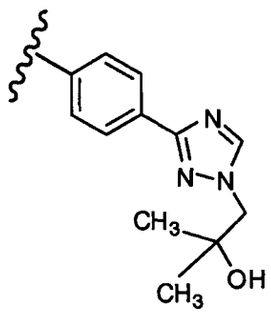
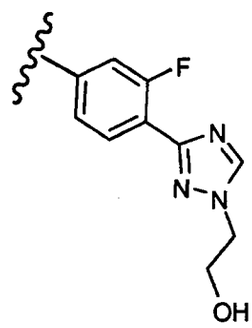
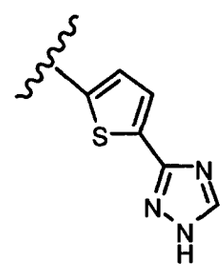
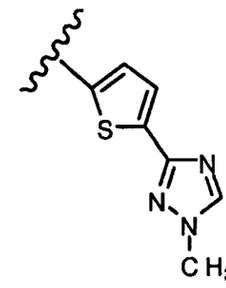
.

Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein R^5 is selected from the group consisting of:

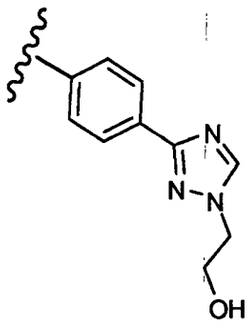
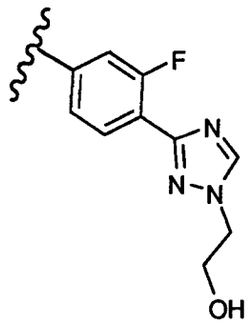
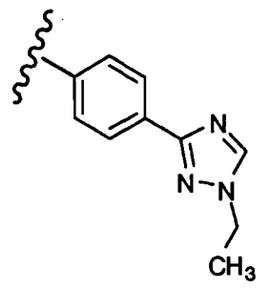

,

,

,

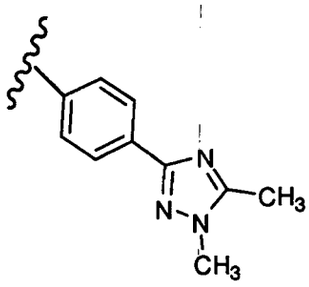
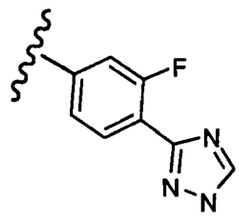
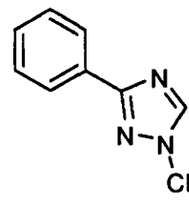

,

,

,

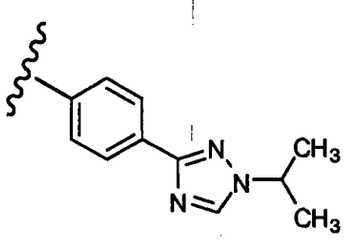
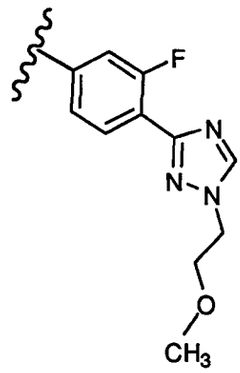
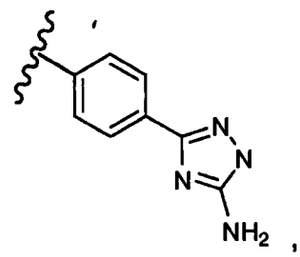

,

,

,

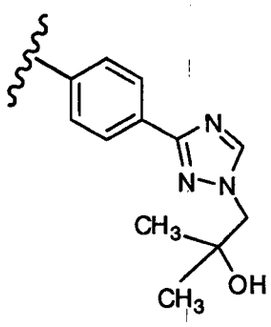
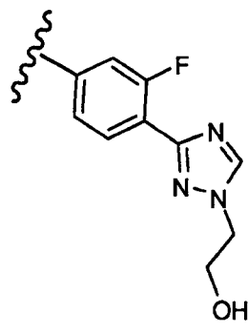
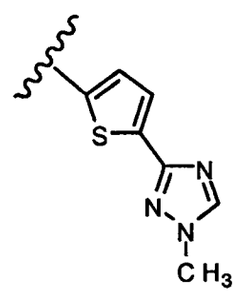

,

,

and

.

Other embodiments of this invention are directed to compounds of formula 1.0 as described in any one of Embodiment Numbers 1 to 46 wherein R^5 is selected from the group consisting of:

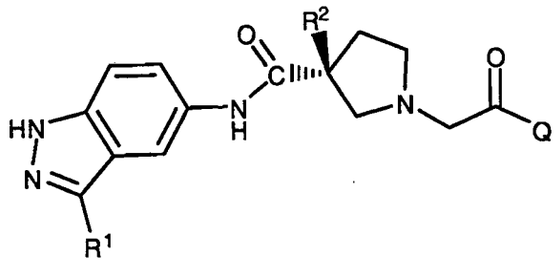




, and .

Other embodiments of this invention are directed to compounds of formula 1.1:

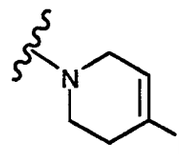


(1.1)

wherein:

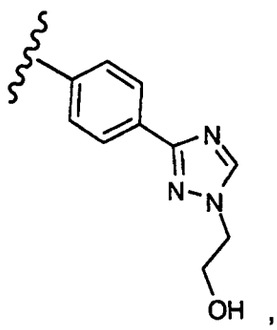
R^1 and R^2 are as defined in any one of embodiment numbers 1 to 44,

Q is:

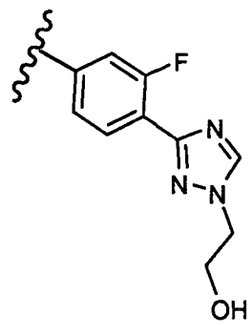


; and

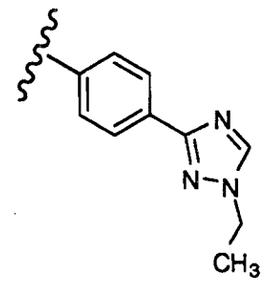
R^5 is selected from the group consisting of:



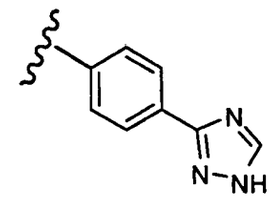
,



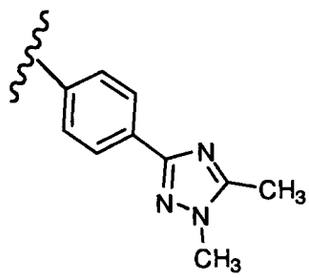
,



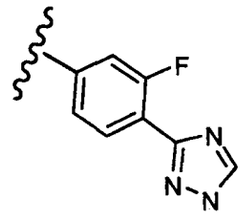
,



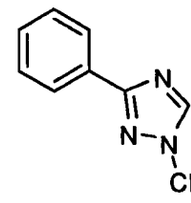
,



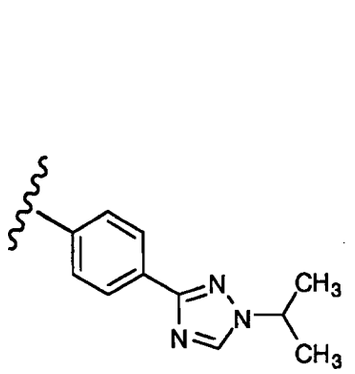
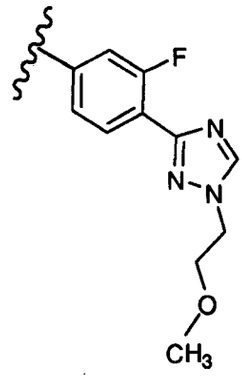
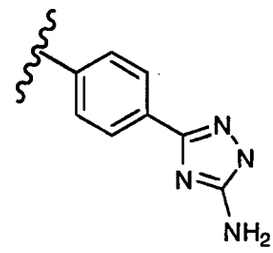
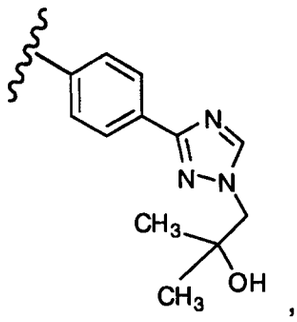
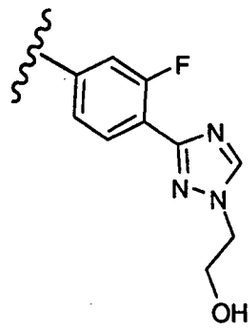
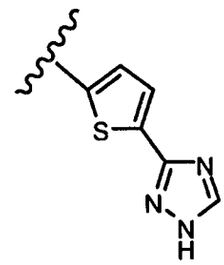
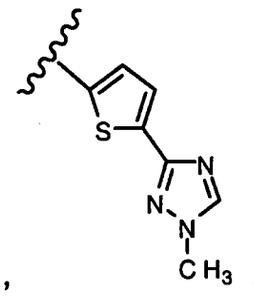
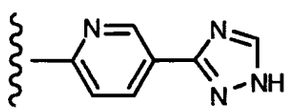
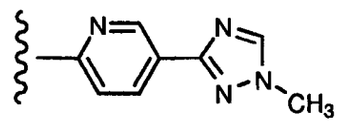
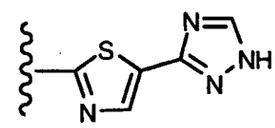
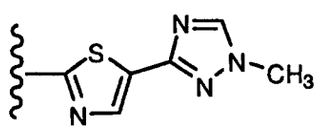
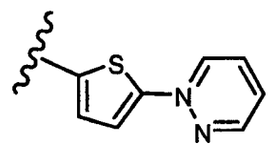
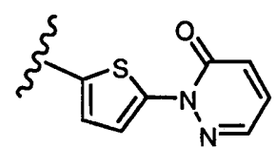
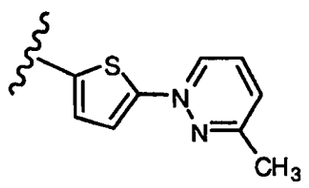
,



,



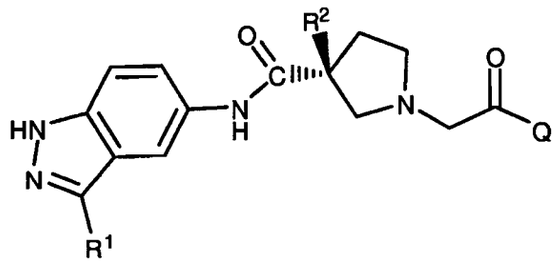
,

, and

.

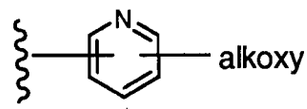
Other embodiments of this invention are directed to compounds of formula 1.1:



(1.1)

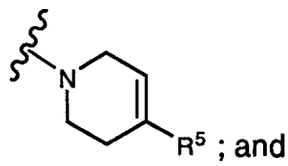
wherein:

R^2 is a –O-(C_1-C_2)alkyl group, and R^1 is:



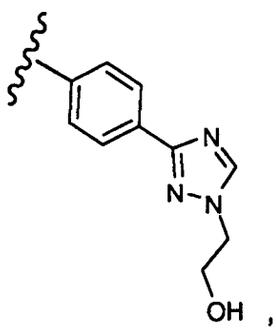
,

Q is:

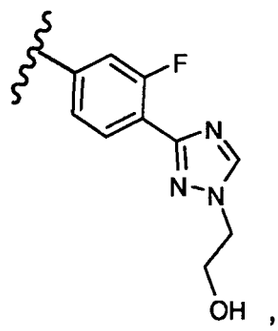


; and

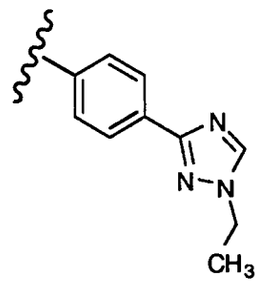
R^5 is selected from the group consisting of:



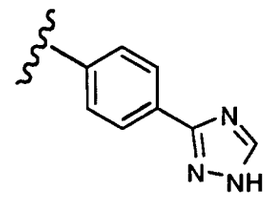
,



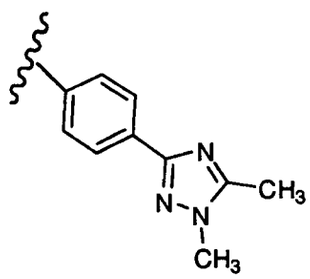
,



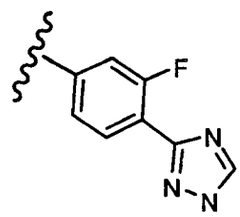
,



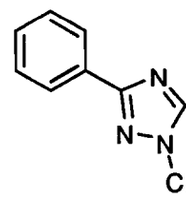
,



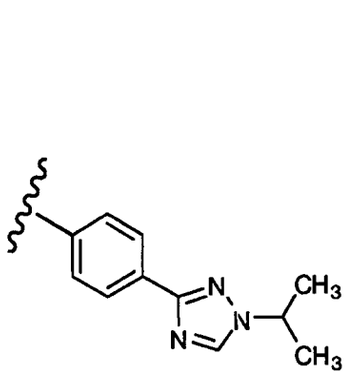
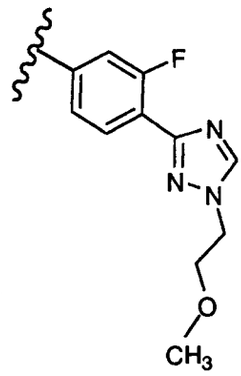
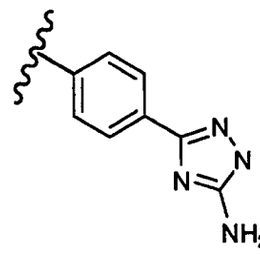
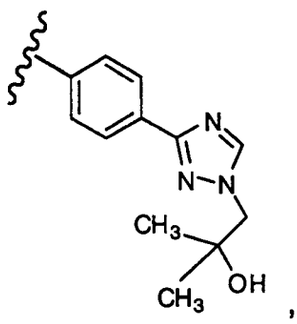
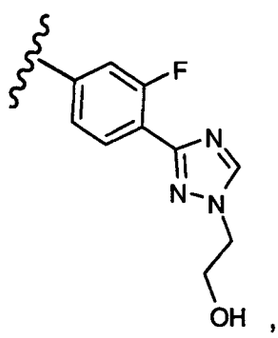
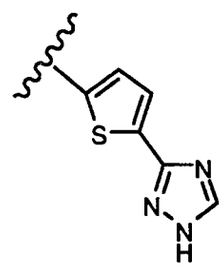
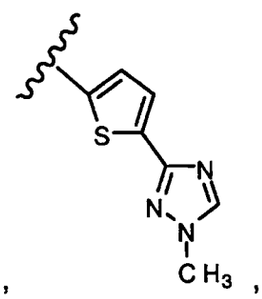
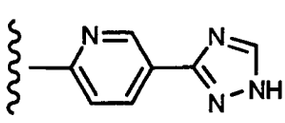
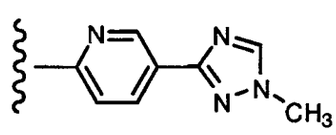
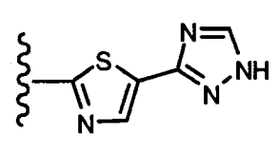
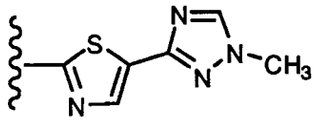
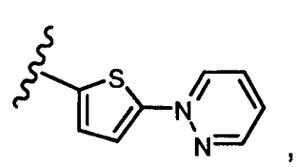
,

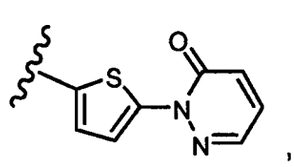
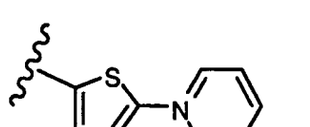


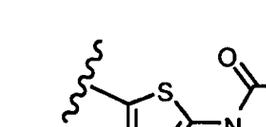
,

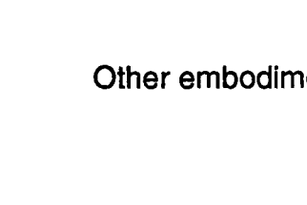
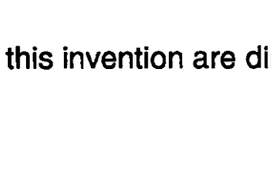


,

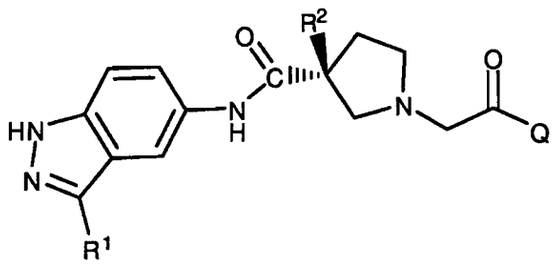





, and .

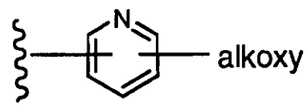
Other embodiments of this invention are directed to compounds of formula 1.1:



(1.1)

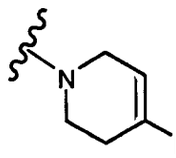
wherein:

R^2 is a –S-(C_1-C_2)alkyl group, and R^1 is:



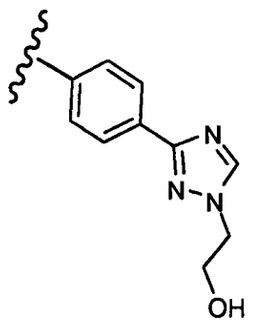
,

Q is:

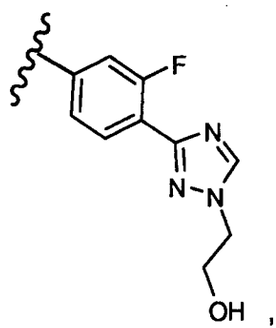


; and

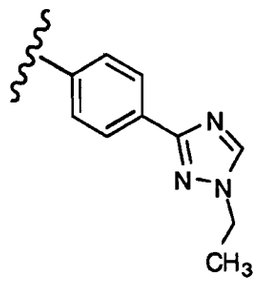
R^5 is selected from the group consisting of:



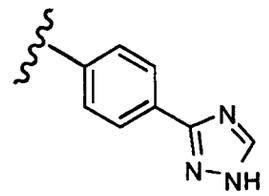
,



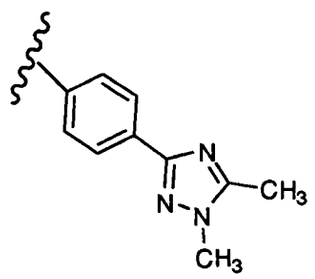
,



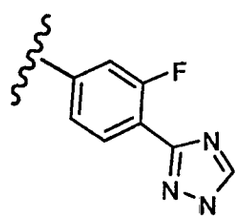
,



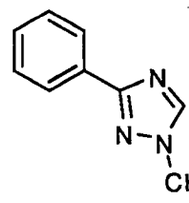
,



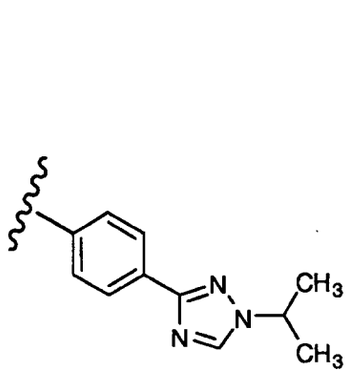
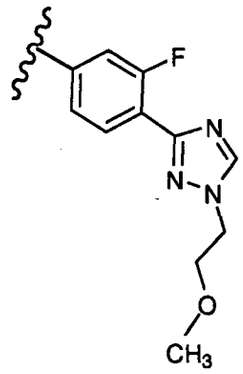
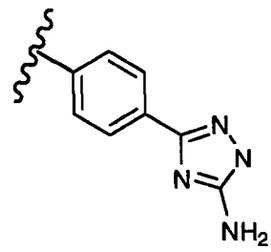
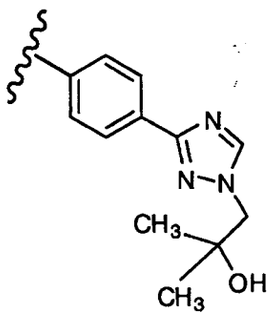
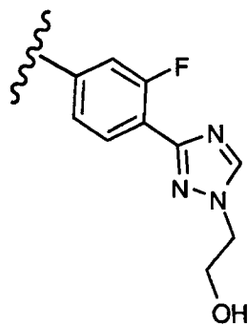
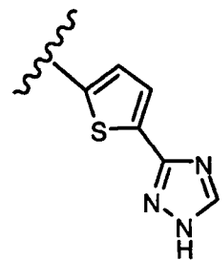
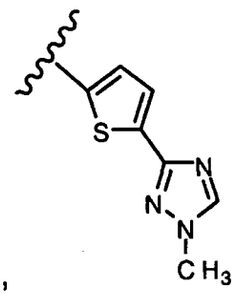
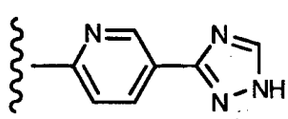
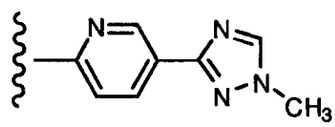
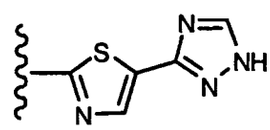
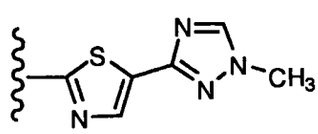
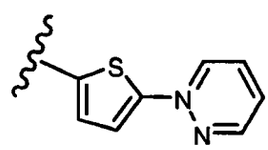
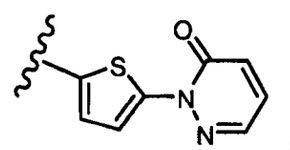
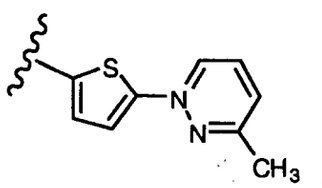
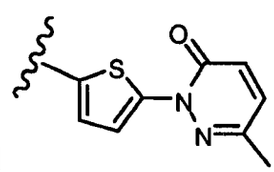
,



,



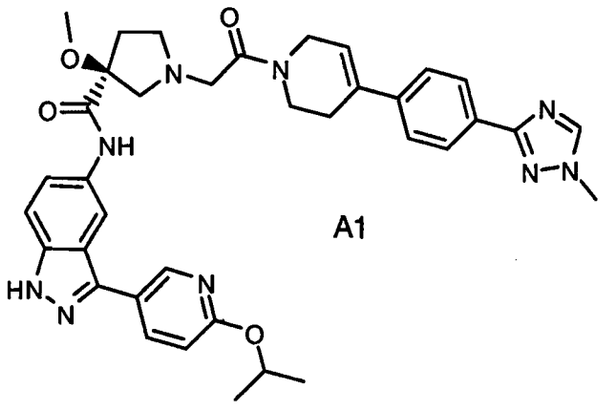
,

and .

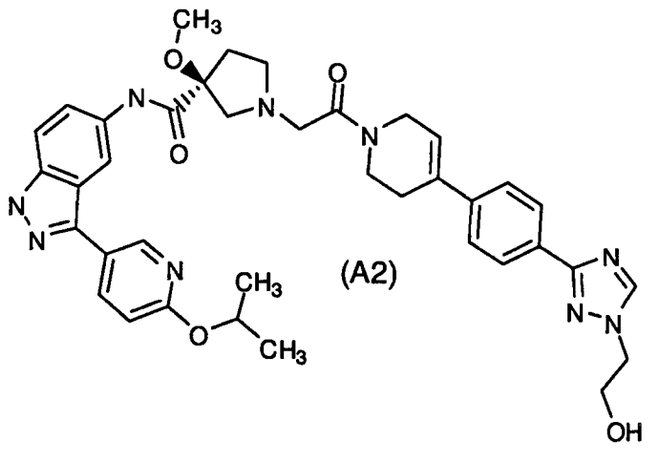
Other embodiments of this invention are directed to any one of the embodiments above (for example, any one of embodiment numbers 1 to 46, or any one of the embodiments following embodiment number 46) wherein one or more hydrogen atoms are deuterium.

Representative compounds of this invention include, but are not limited to:



A1

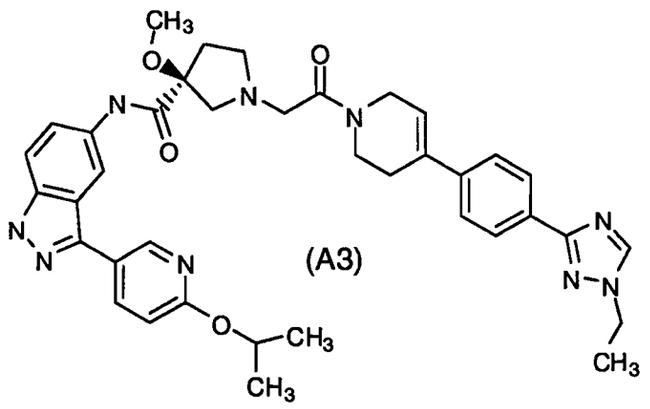
,



(A2)

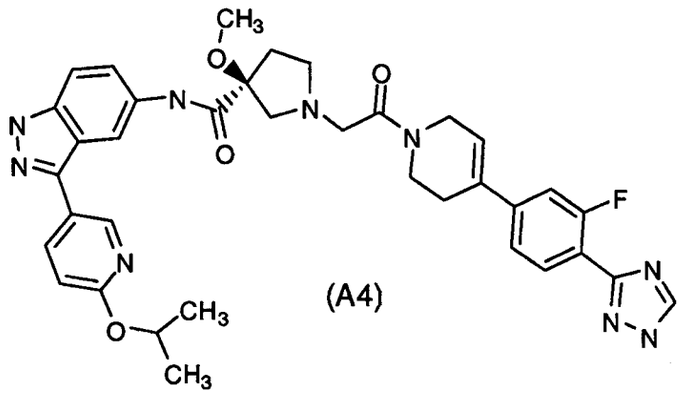
,

5



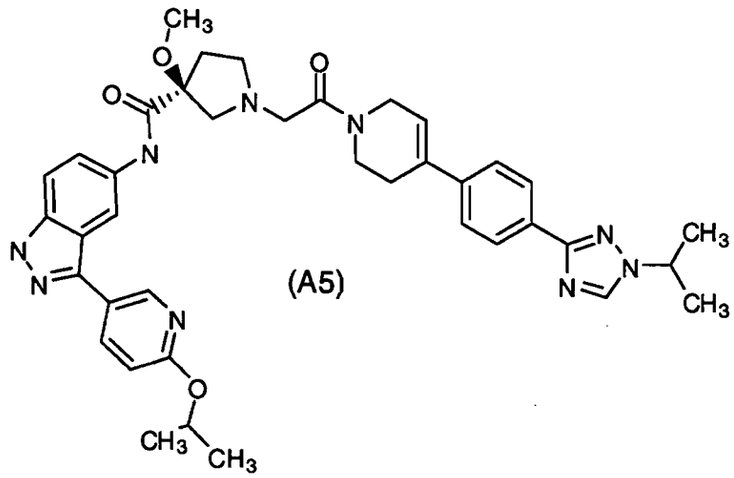
(A3)

,



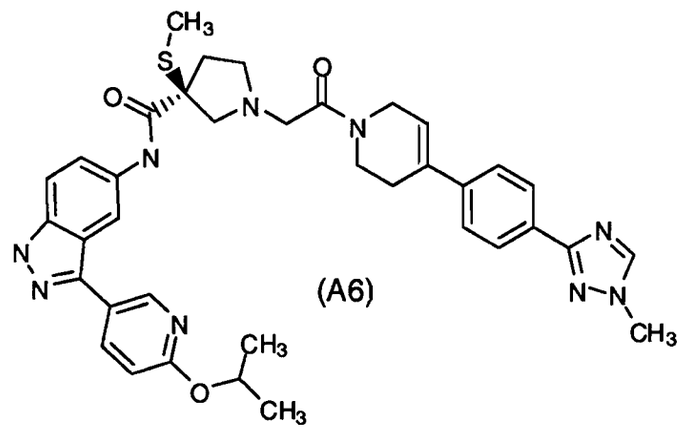
(A4)

,



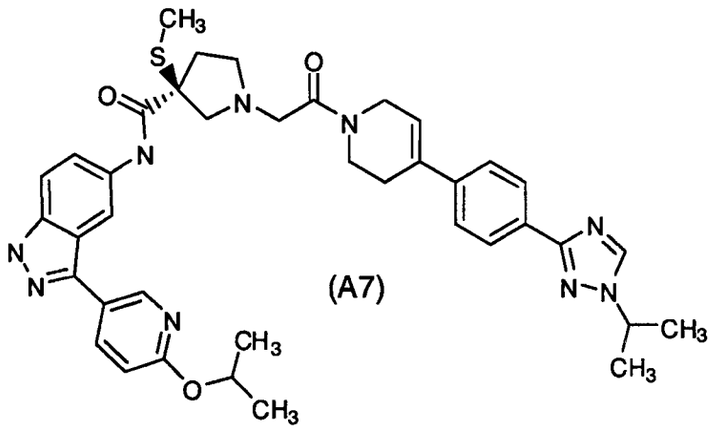
(A5)

,



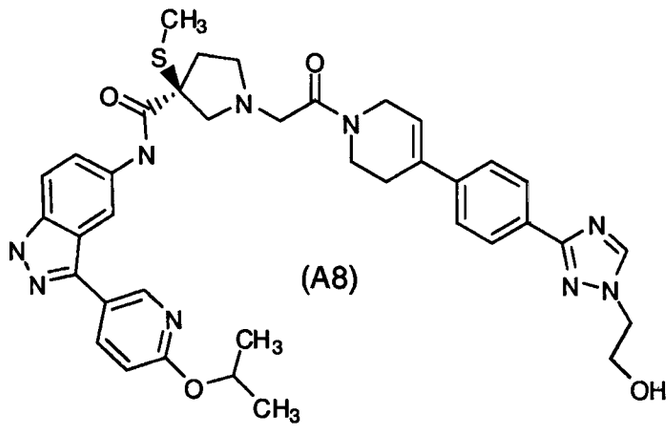
(A6)

,



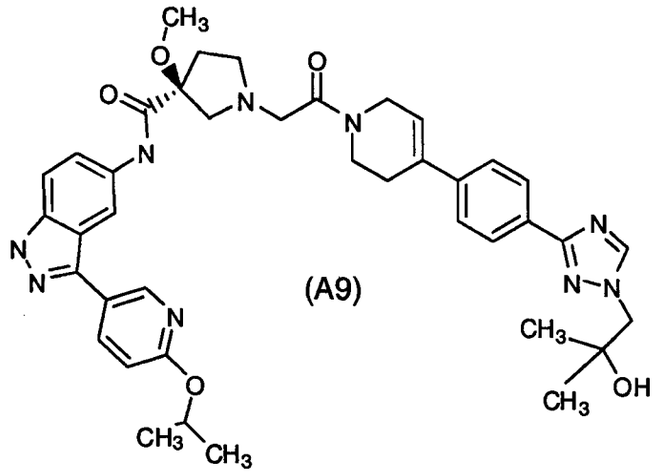
(A7)

,



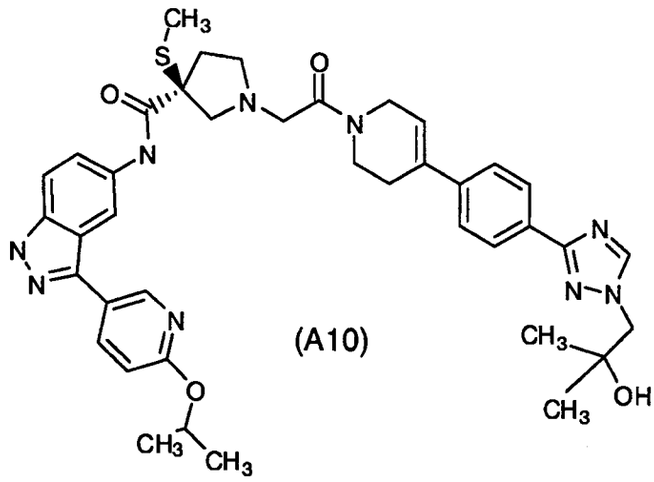
(A8)

,

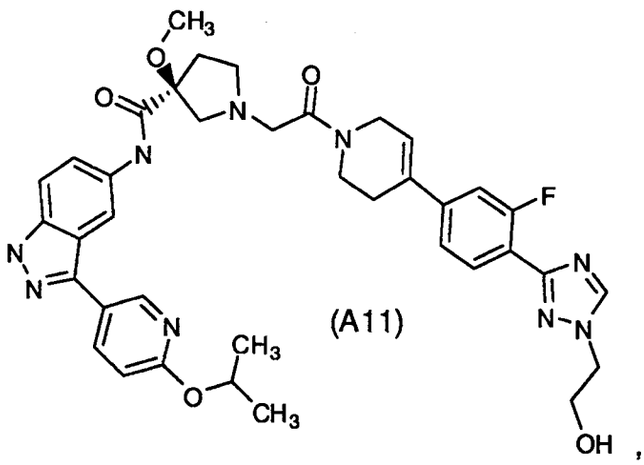


(A9)

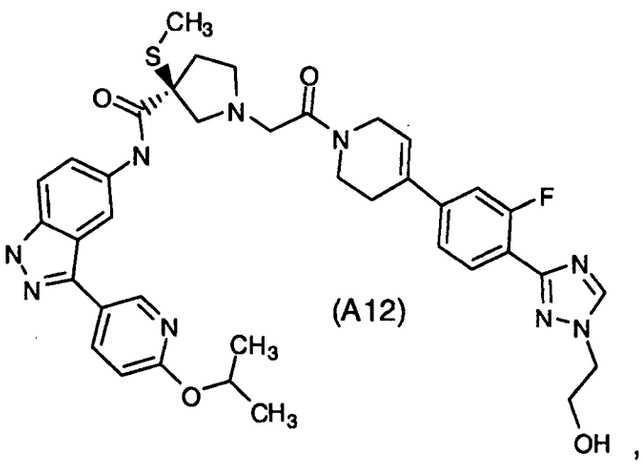
,



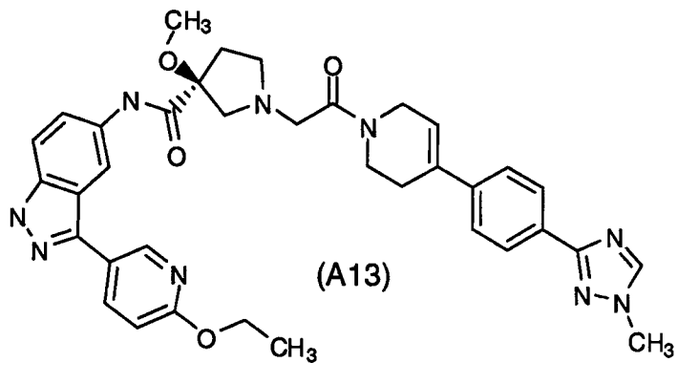
(A10),



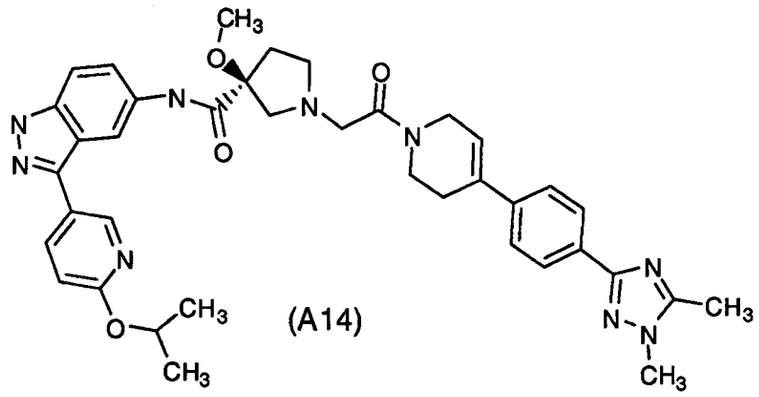
(A11),



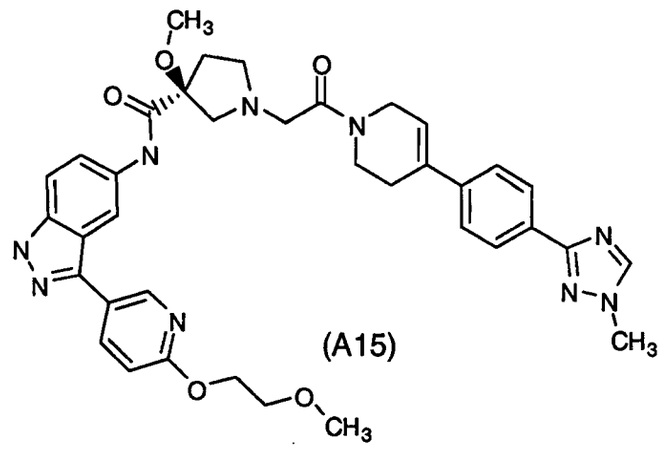
(A12),



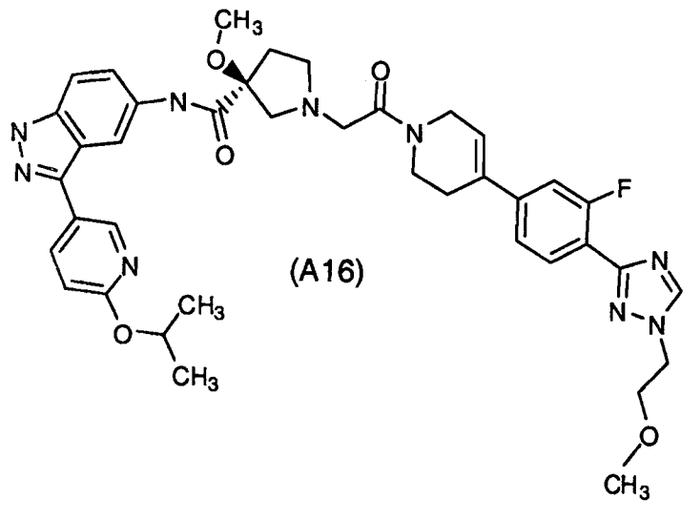
(A13) ,



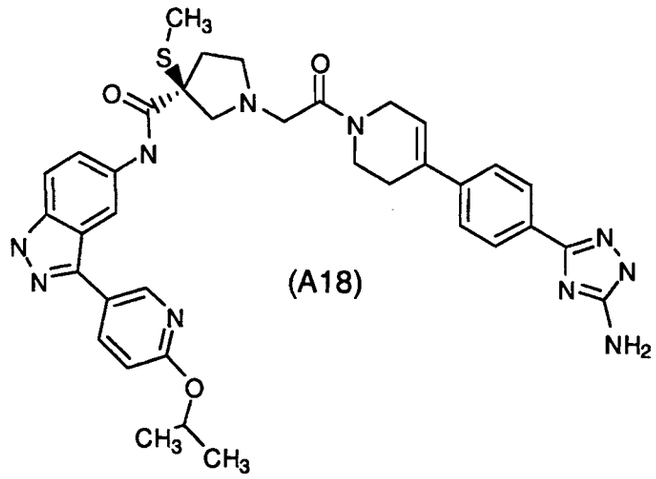
(A14) ,



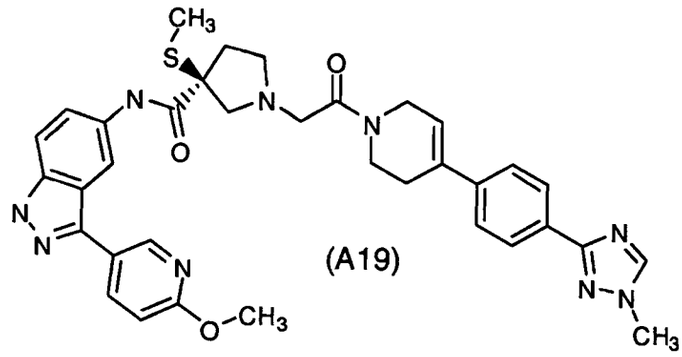
(A15) ,



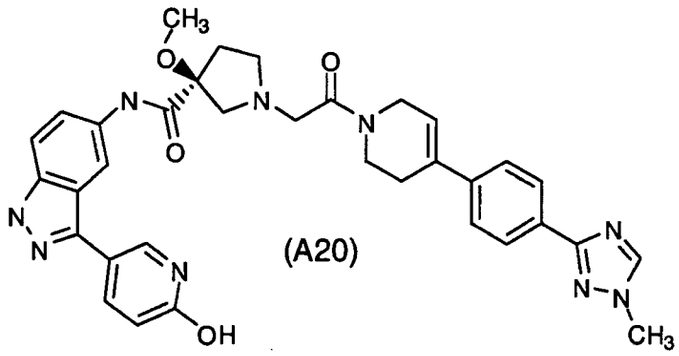
(A16),



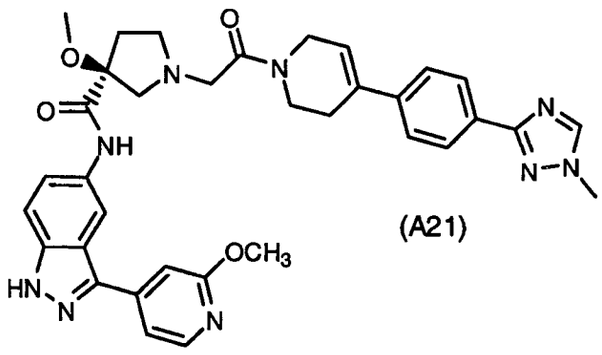
(A18),



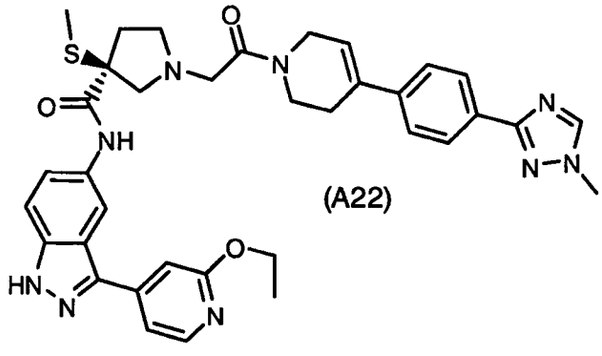
(A19),



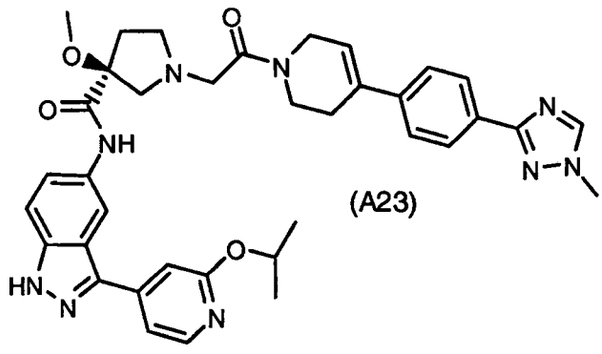
(A20) ,



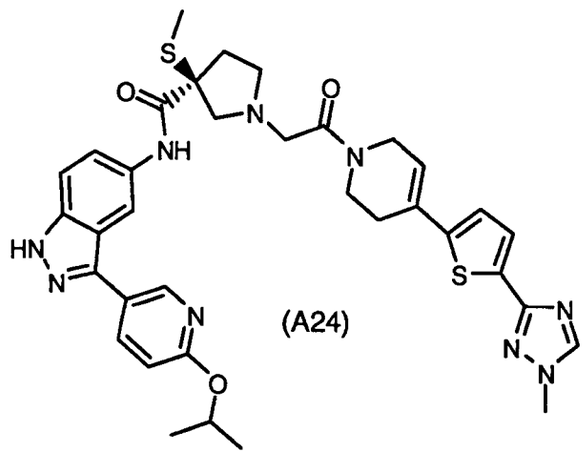
(A21) ,



(A22) ,

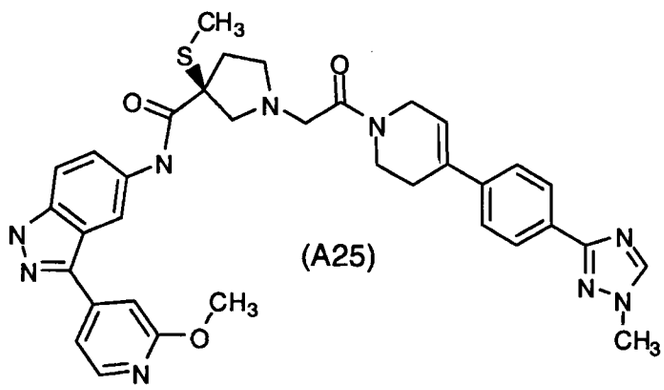


(A23) ,



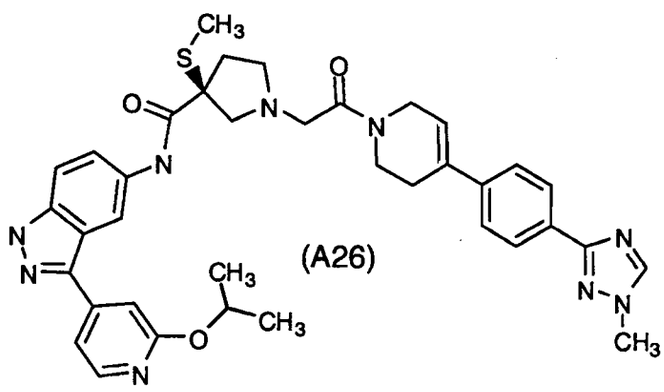
(A24)

,



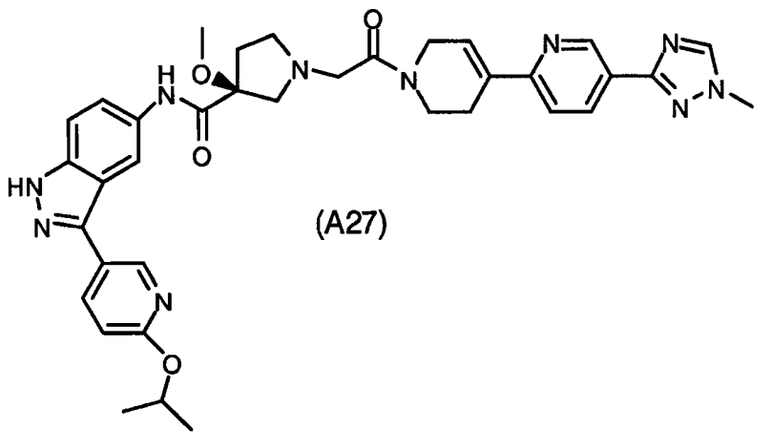
(A25)

,



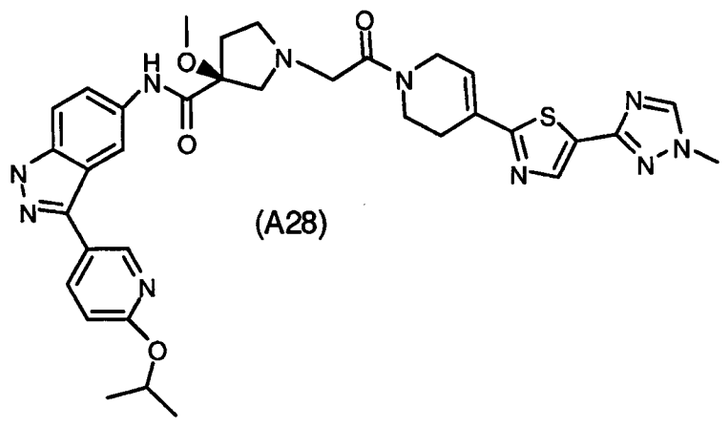
(A26)

,



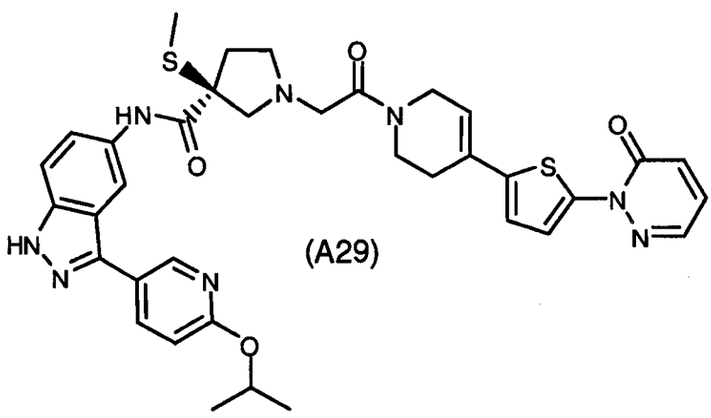
(A27)

,



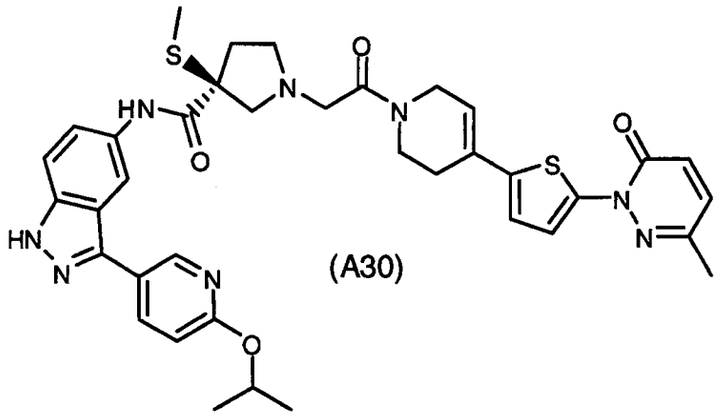
(A28)

,



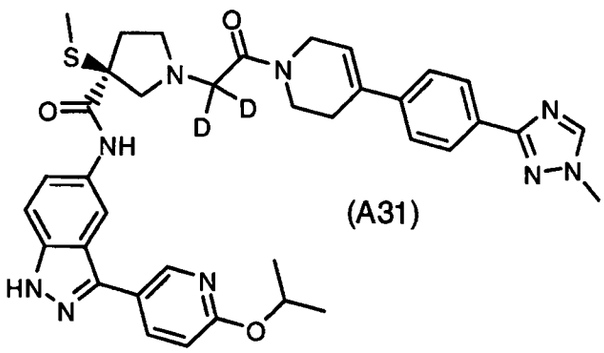
(A29)

,



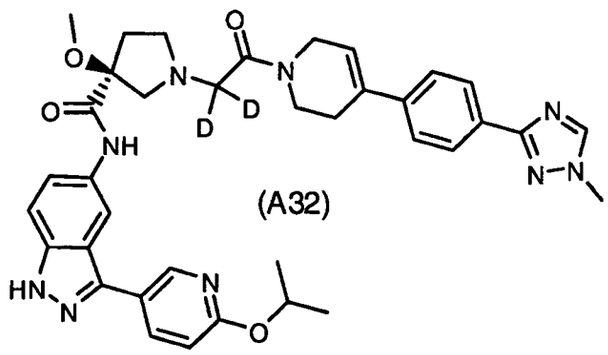
(A30)

,



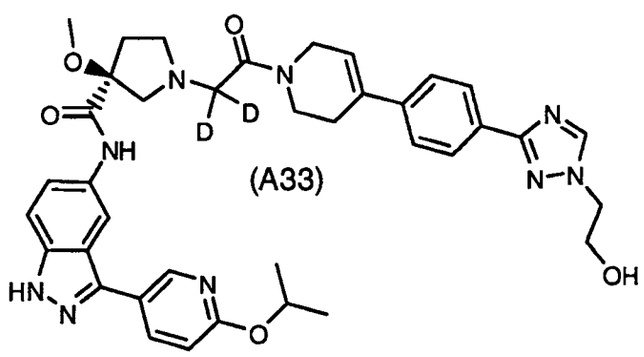
(A31)

,



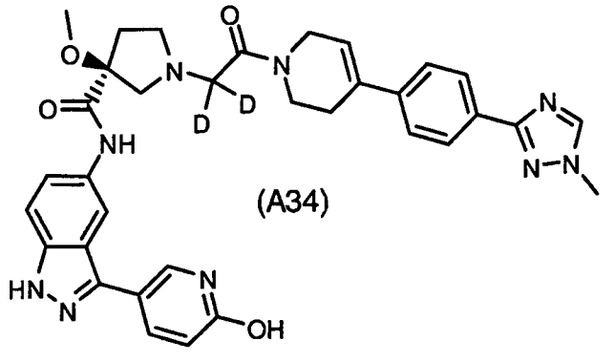
(A32)

,

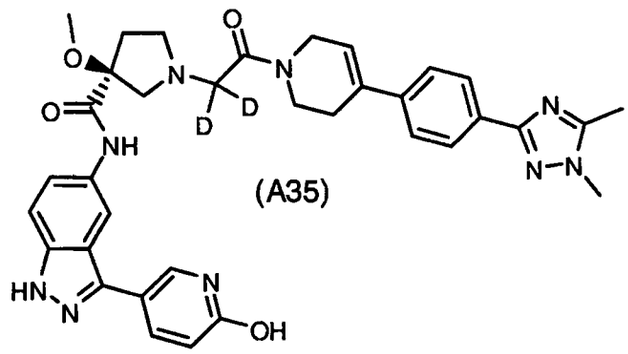


(A33)

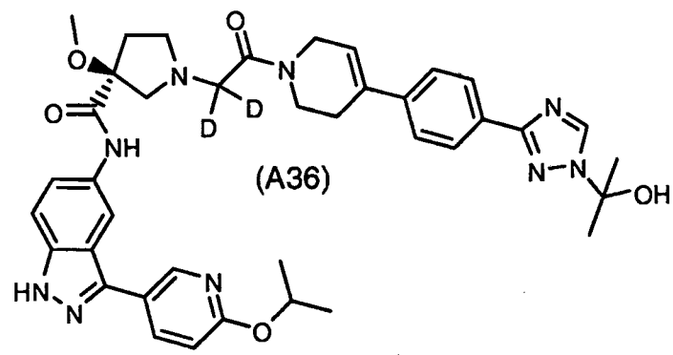
,



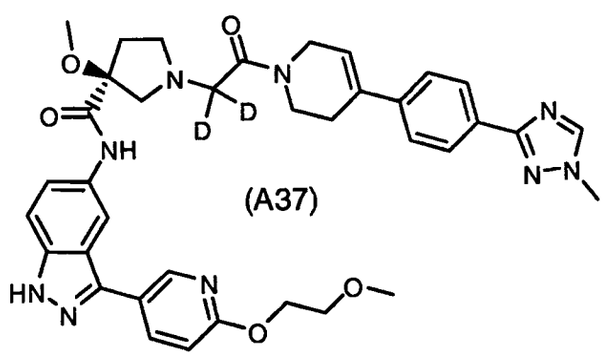
(A34)



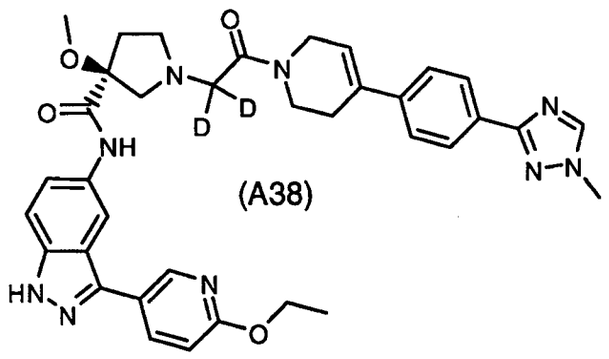
(A35)



(A36)

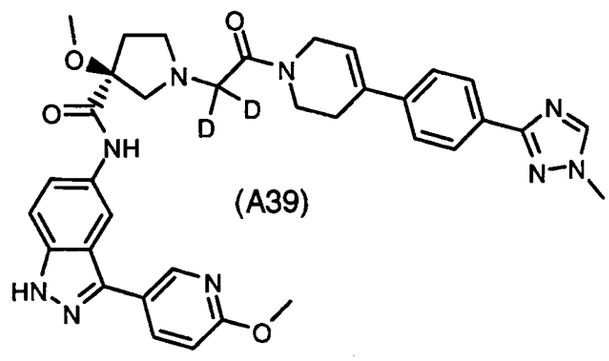


(A37)



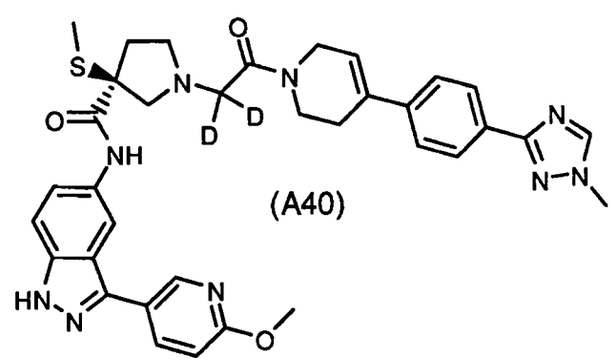
(A38)

,



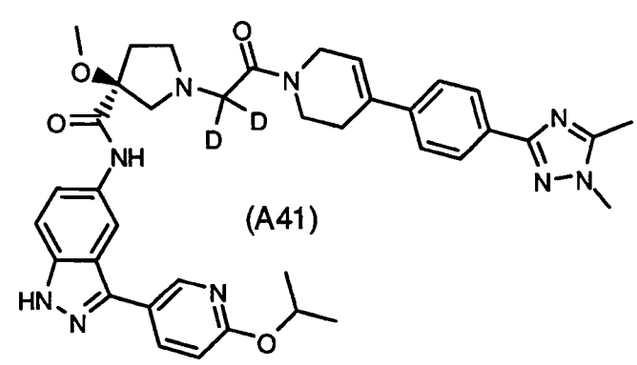
(A39)

,



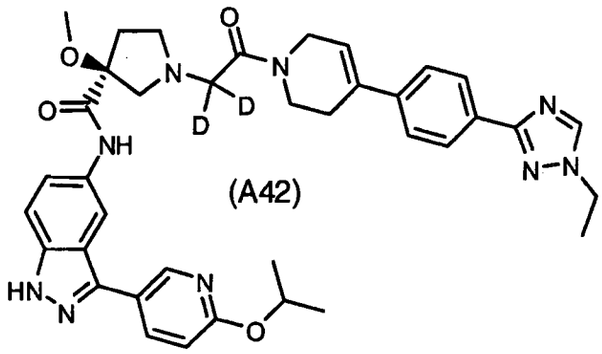
(A40)

,



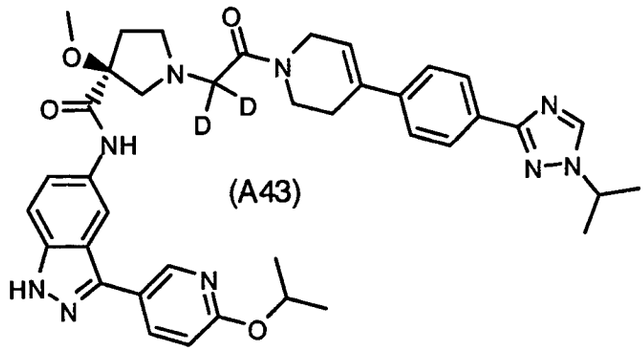
(A41)

,



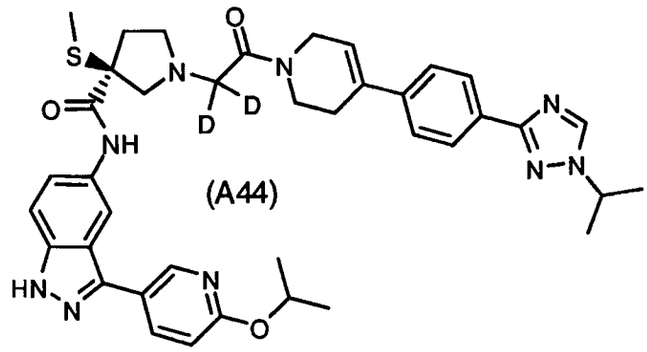
(A42)

,



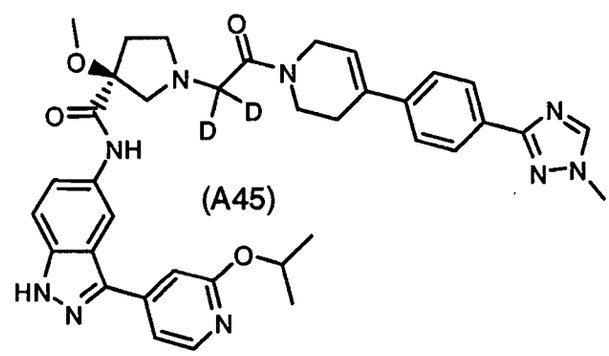
(A43)

,



(A44)

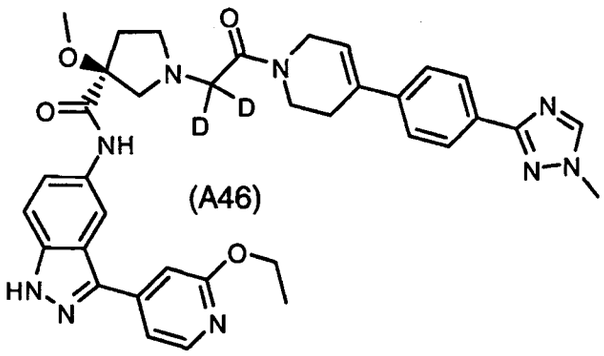
,



(A45)

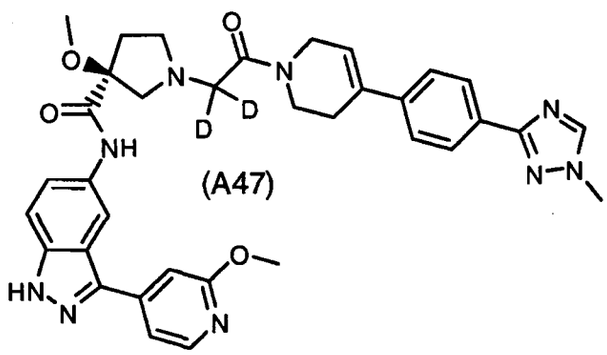
,

62



(A46)

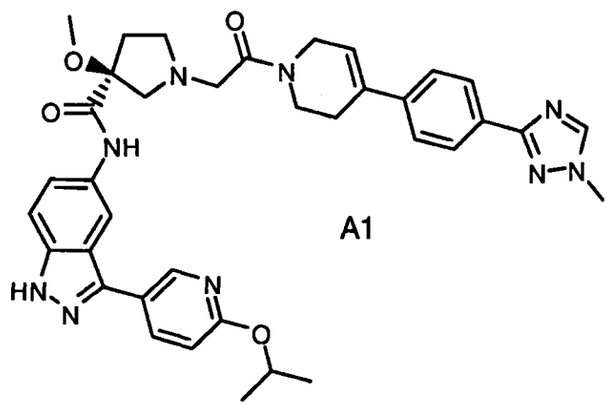
, and



(A47)

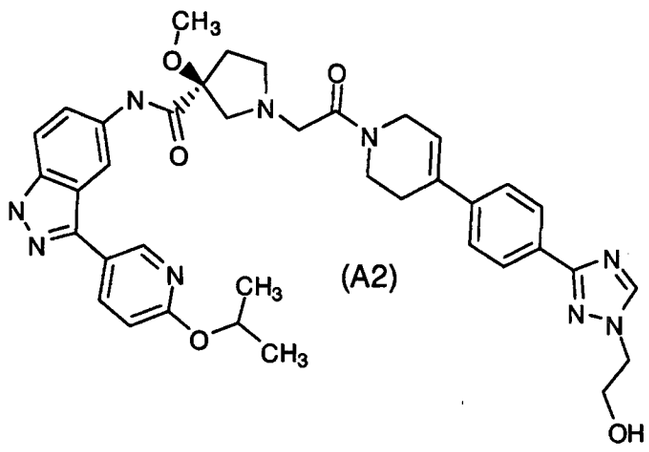
.

Representative compounds of this invention include, but are not limited to:

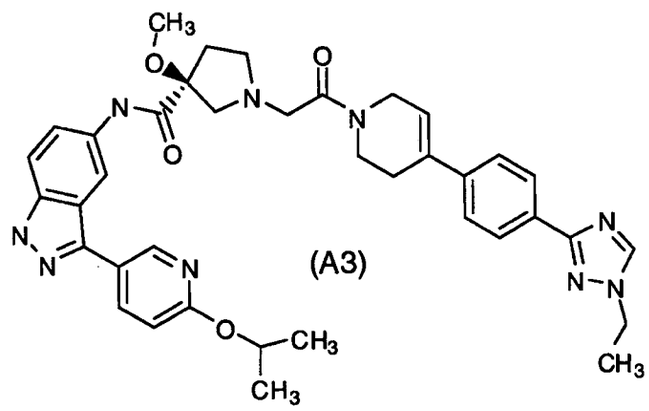


A1

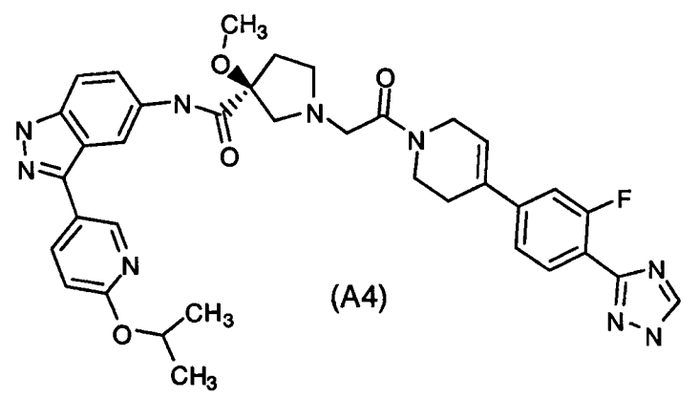
,



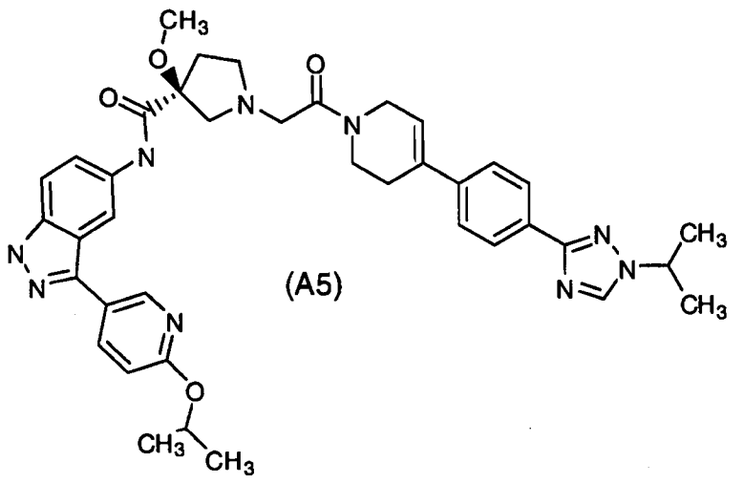
(A2),



(A3),

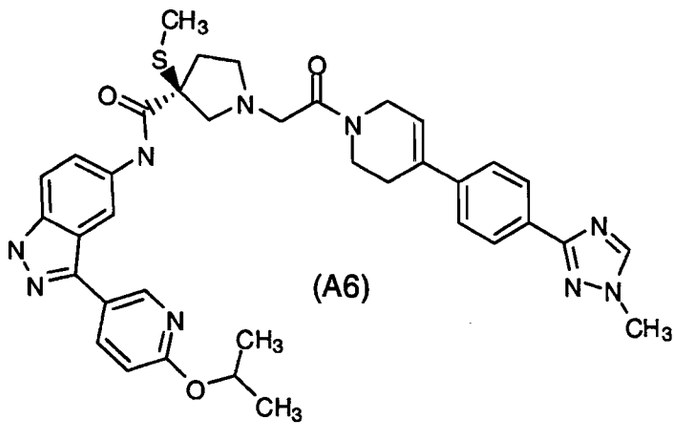


(A4),



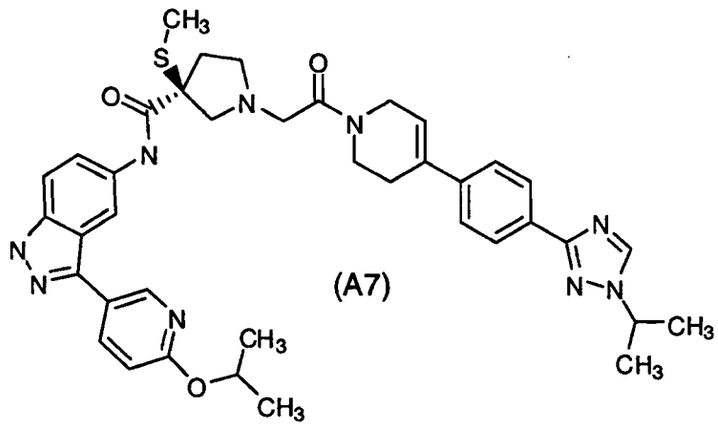
(A5)

,



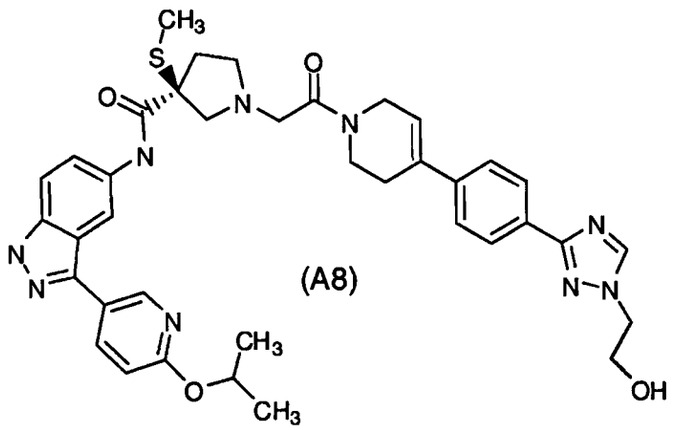
(A6)

,



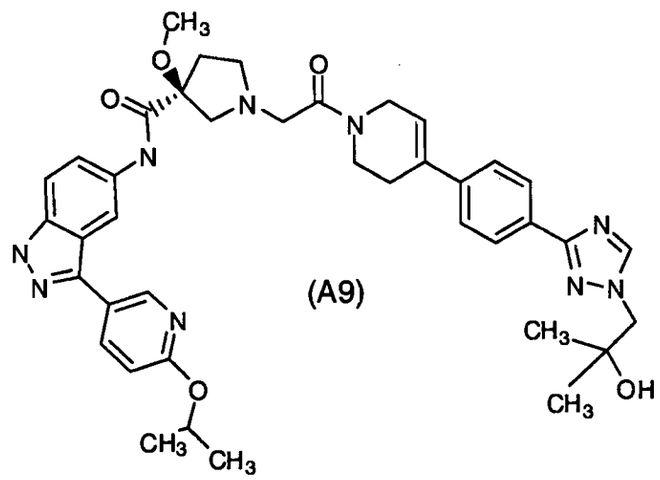
(A7)

,



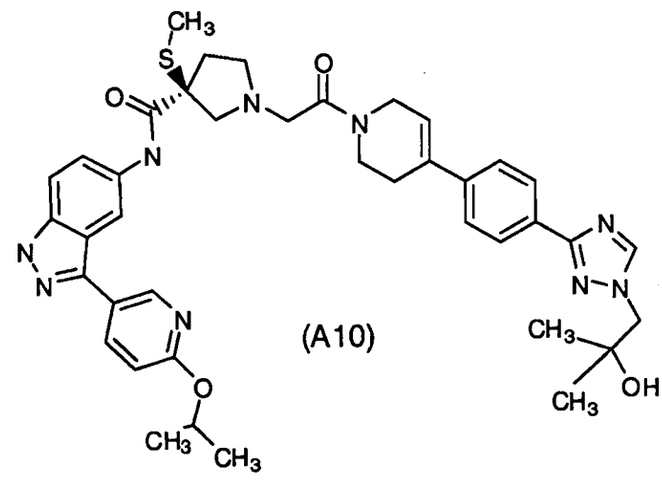
(A8)

,



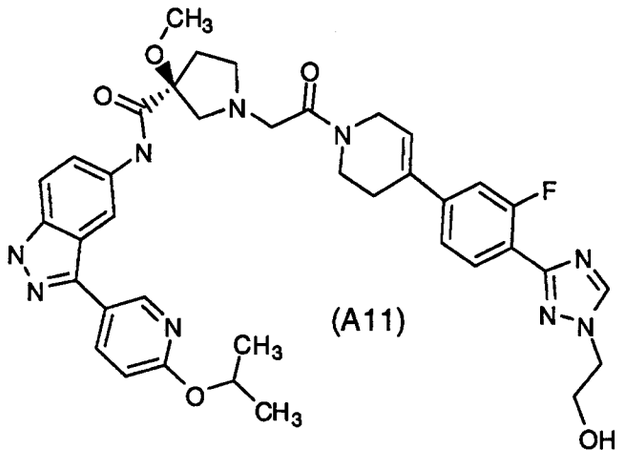
(A9)

,

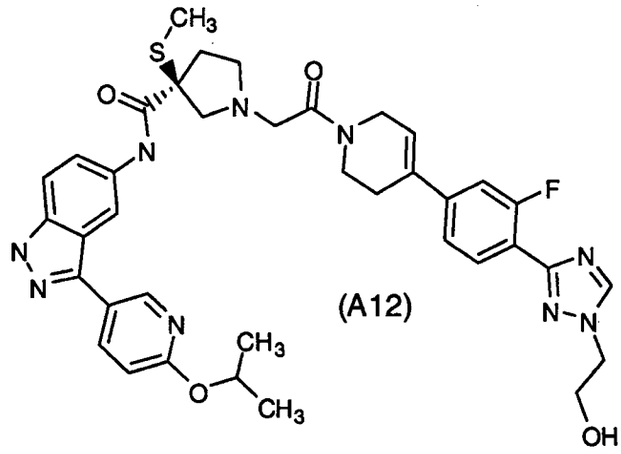


(A10)

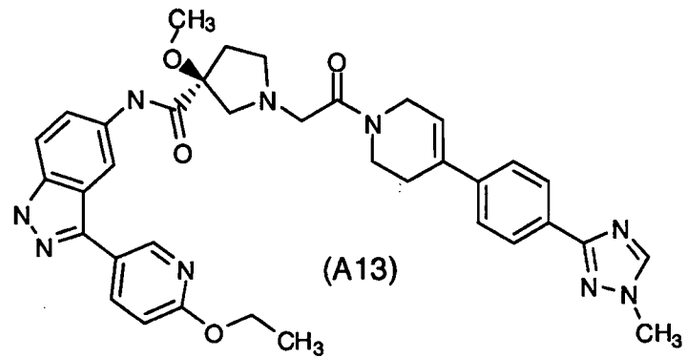
,



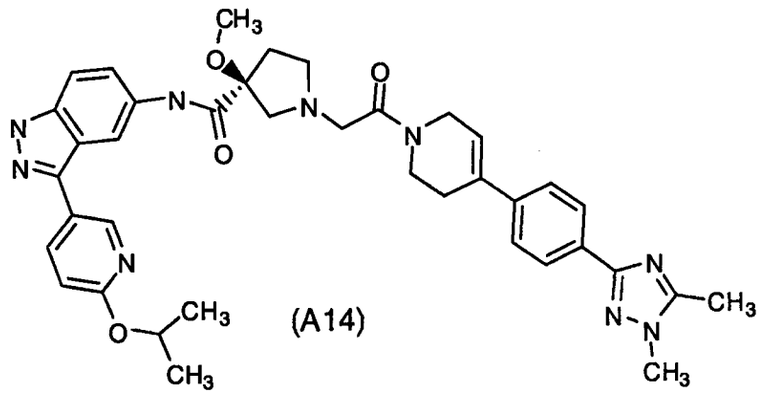
(A11) ,



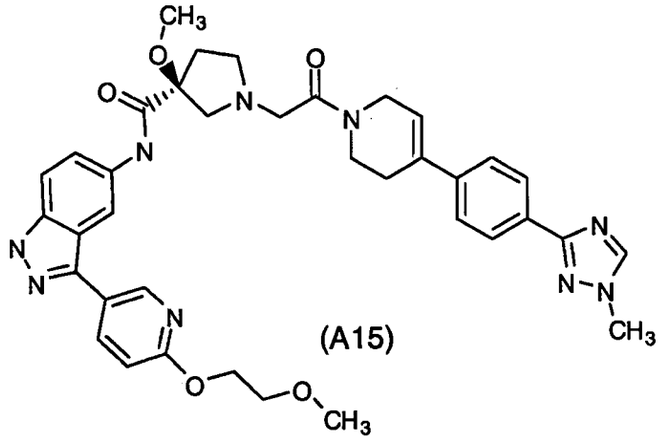
(A12) ,



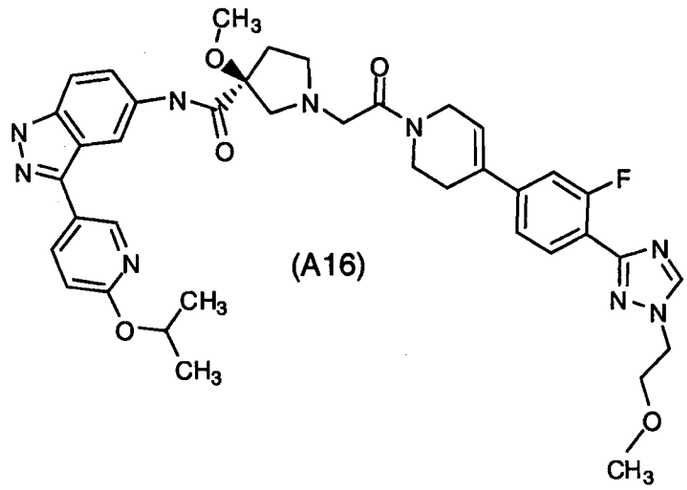
(A13) ,



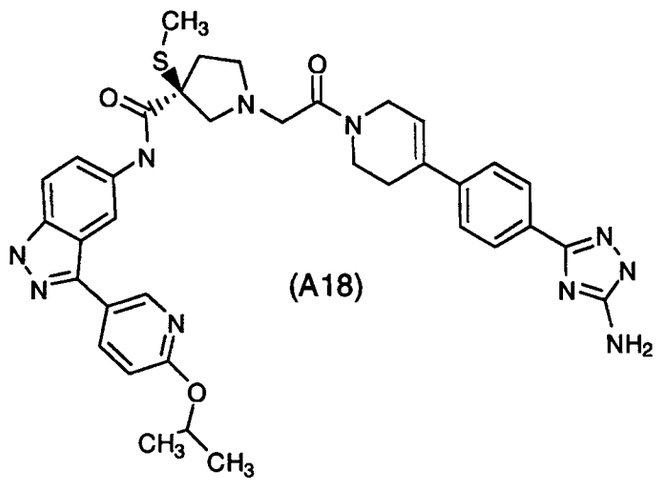
(A14) ,



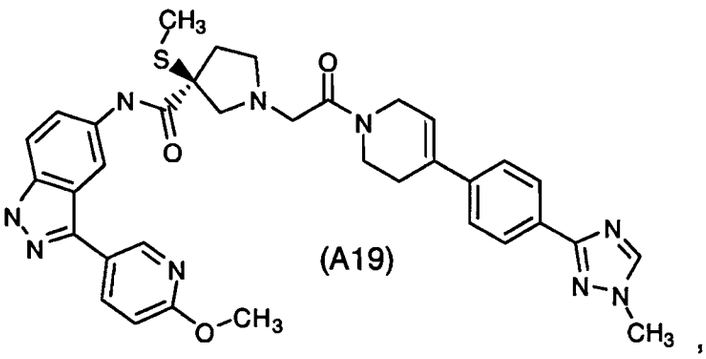
(A15) ,



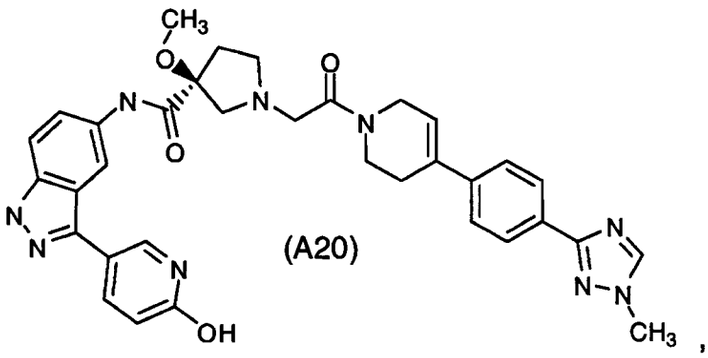
(A16) ,



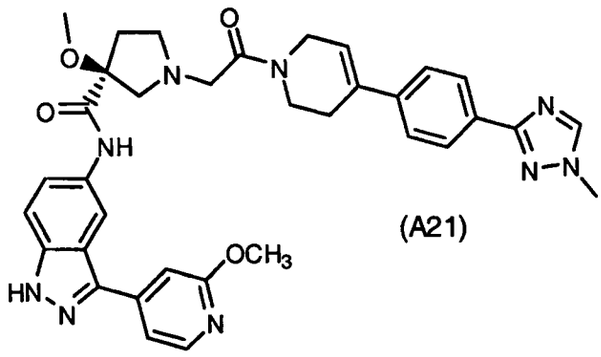
(A18) ,



(A19) ,

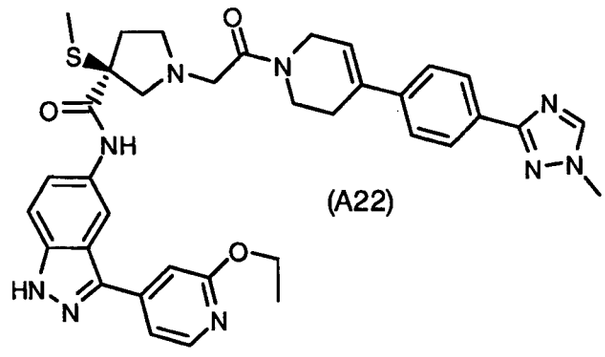


(A20) ,



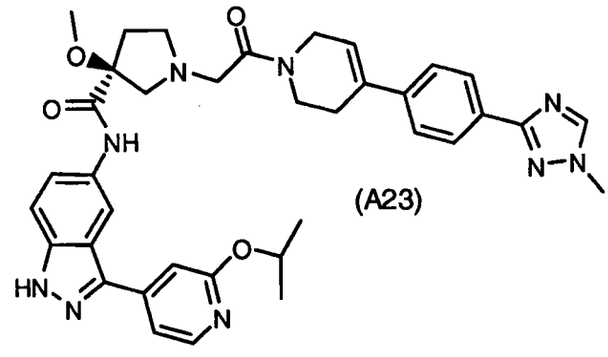
(A21)

,



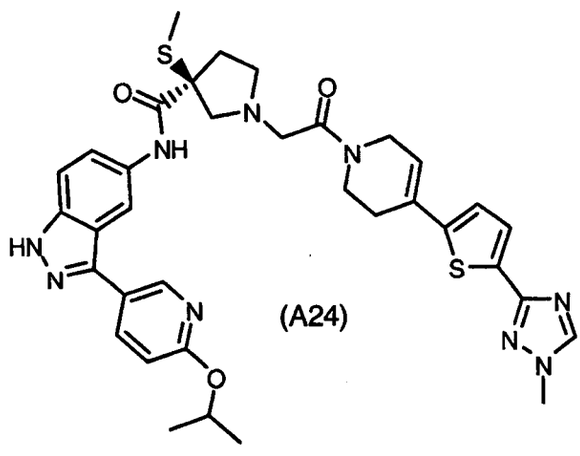
(A22)

,



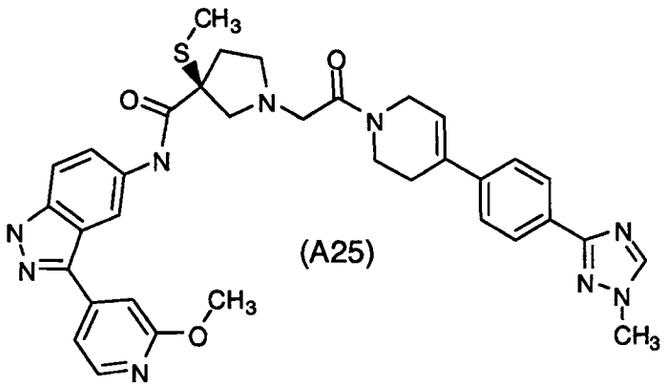
(A23)

,

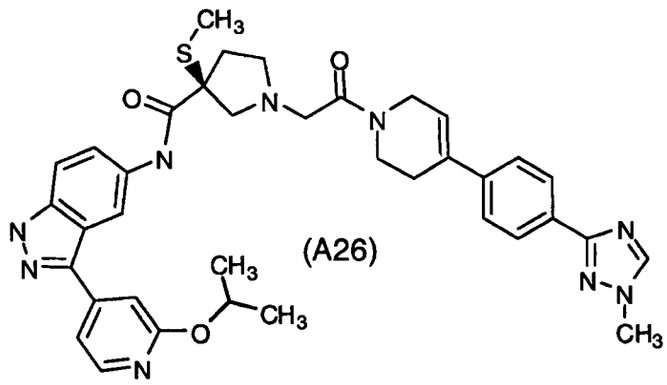


(A24)

,

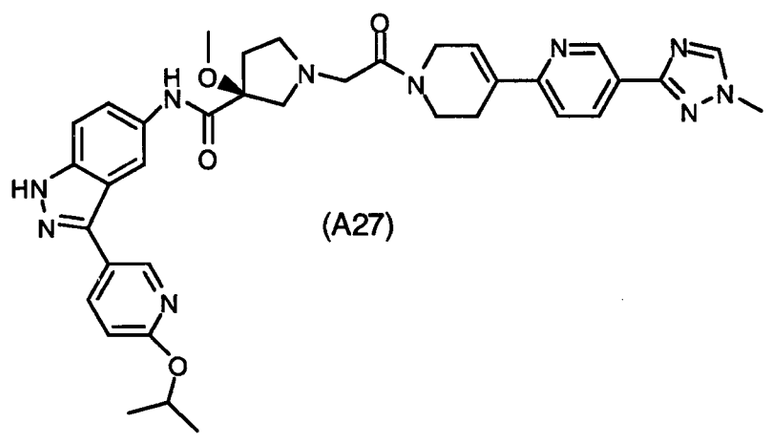


(A25),

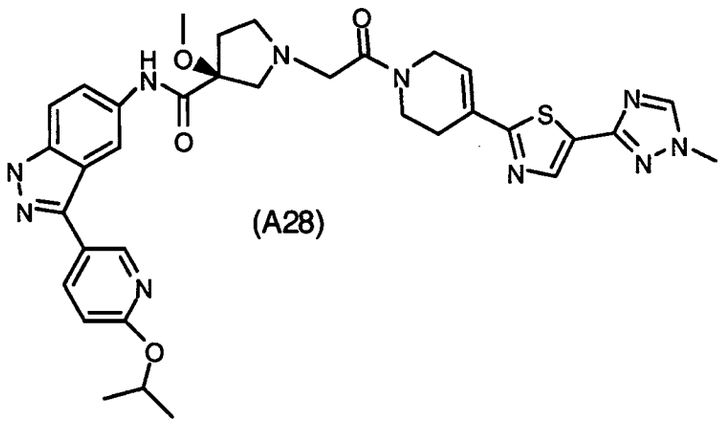


(A26),

5

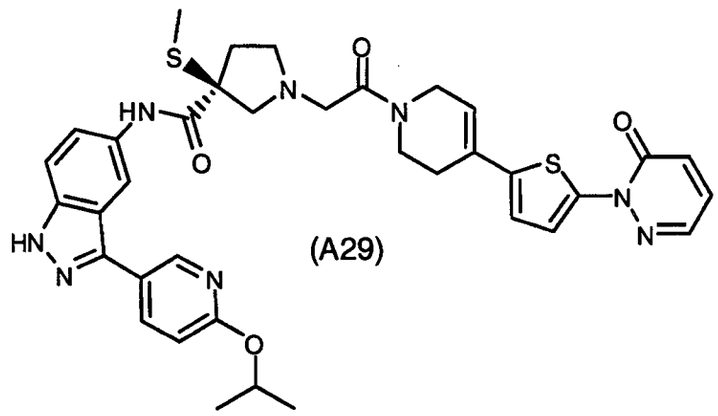


(A27),



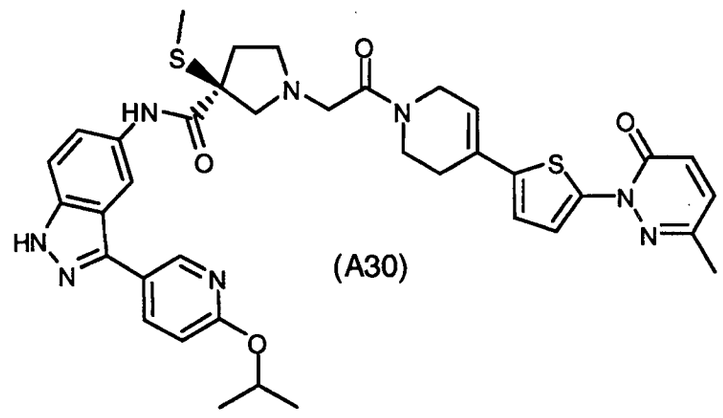
(A28)

,



(A29)

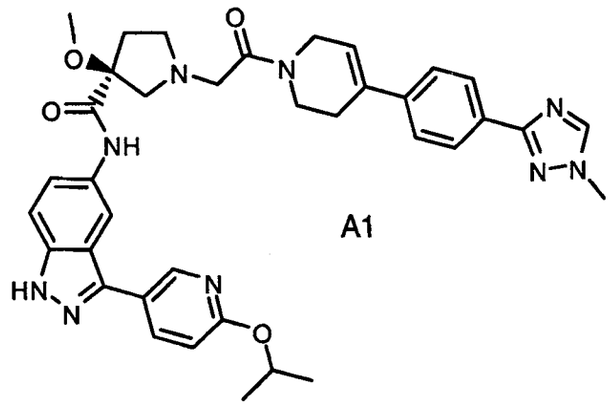
, and



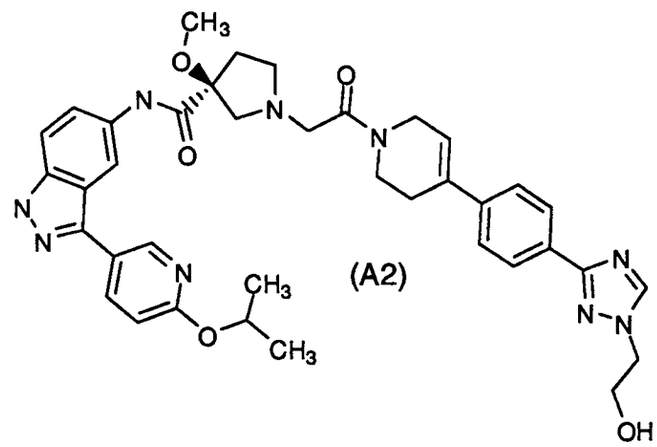
(A30)

.

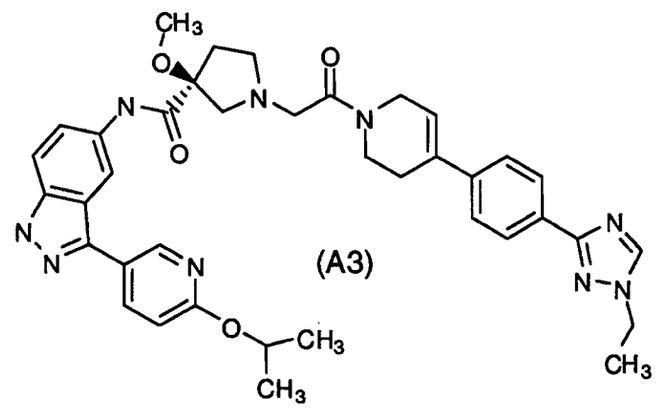
Representative compounds of this invention include, but are not limited to:



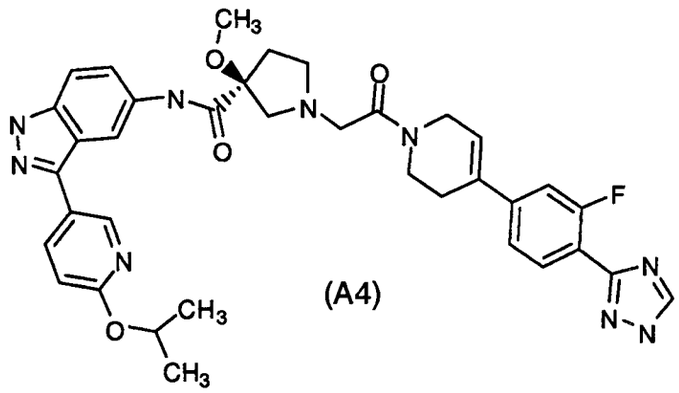
A1 ,



(A2) ,

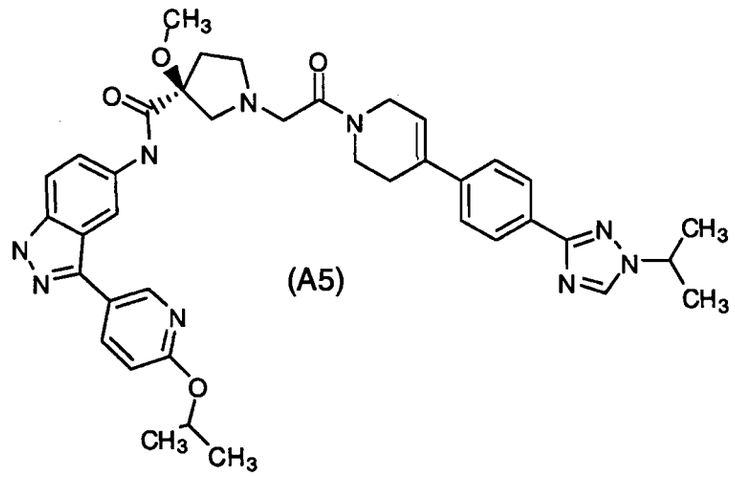


(A3) ,



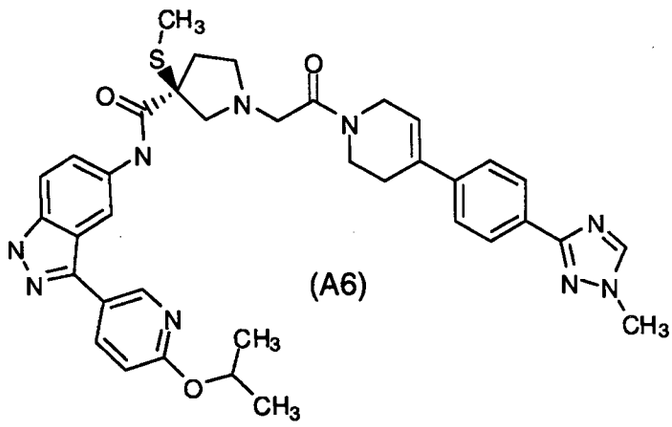
(A4)

,



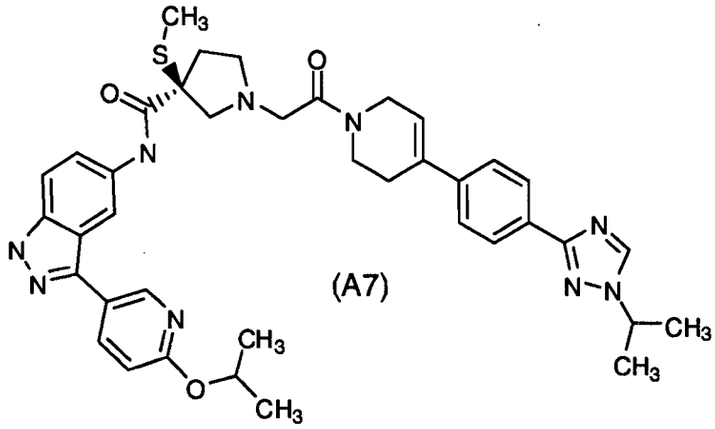
(A5)

,

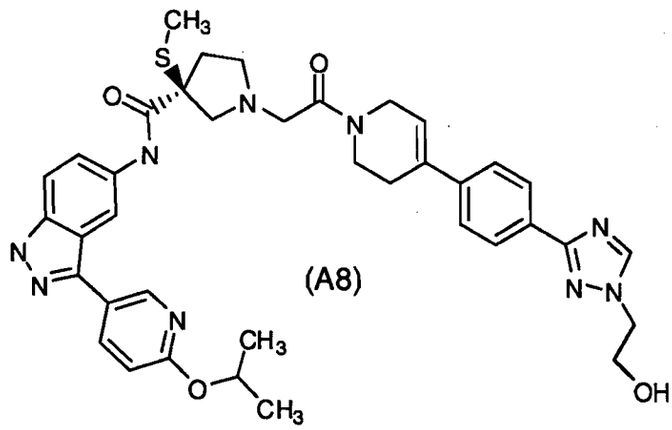


(A6)

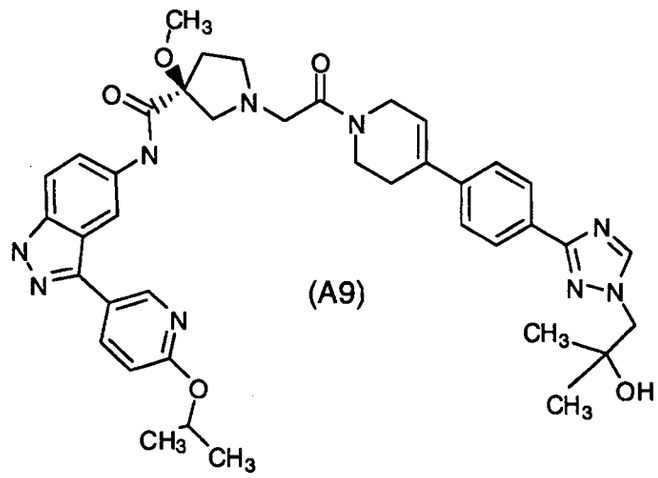
,



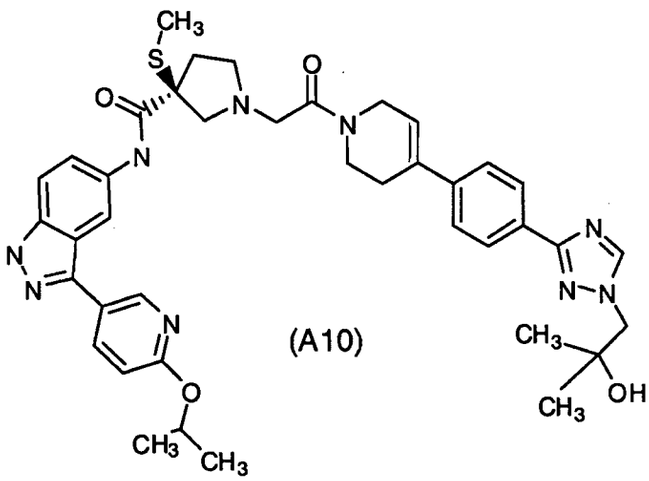
(A7),



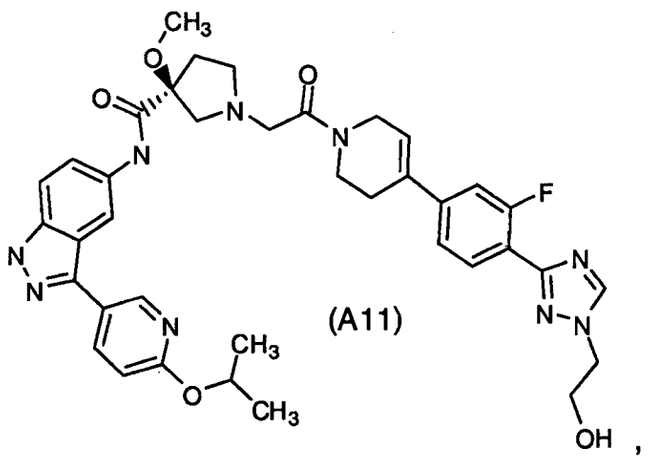
(A8),



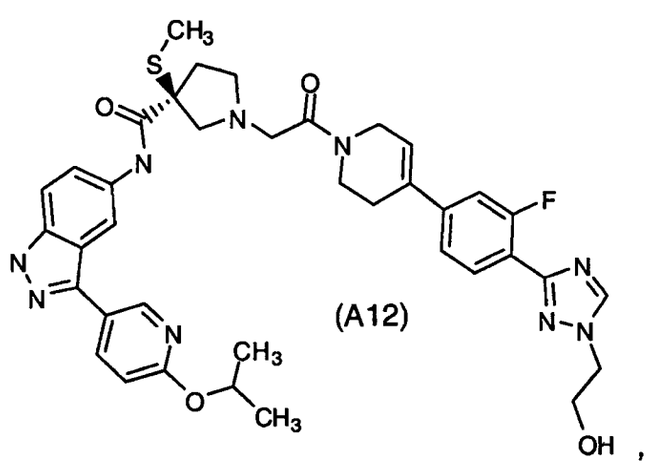
(A9),



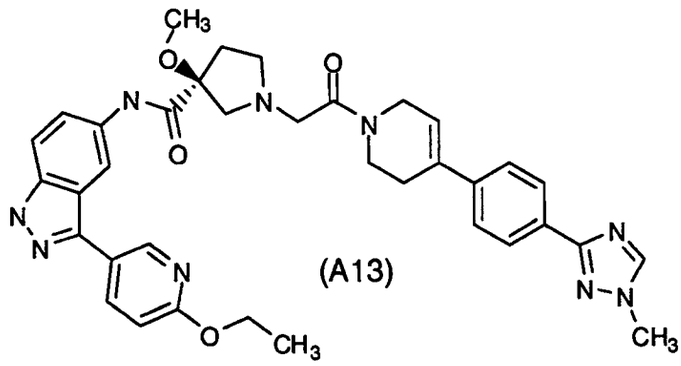
(A10)



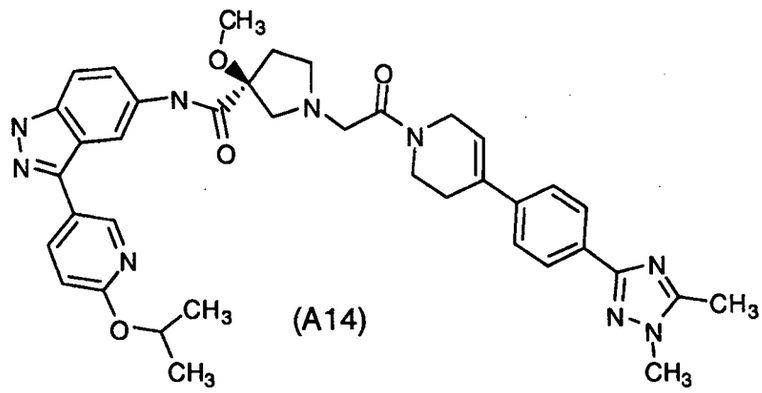
(A11),



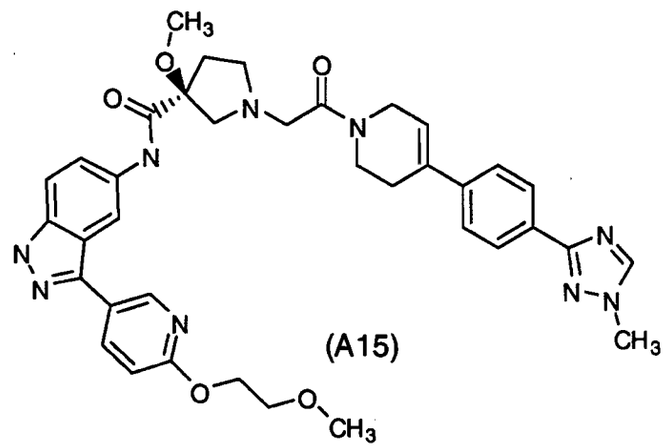
(A12),



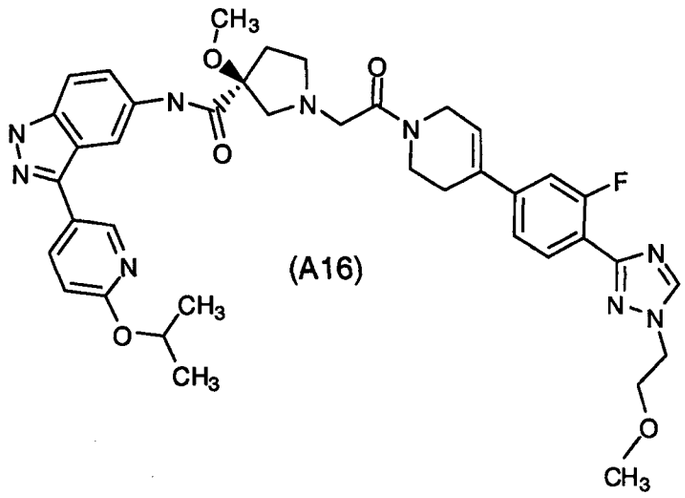
(A13),



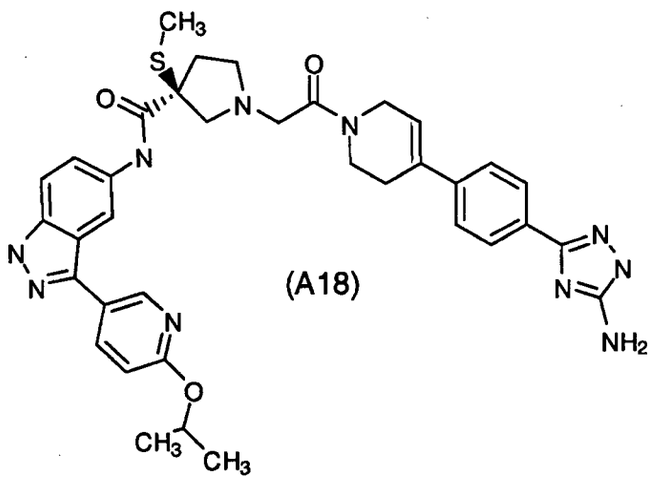
(A14),



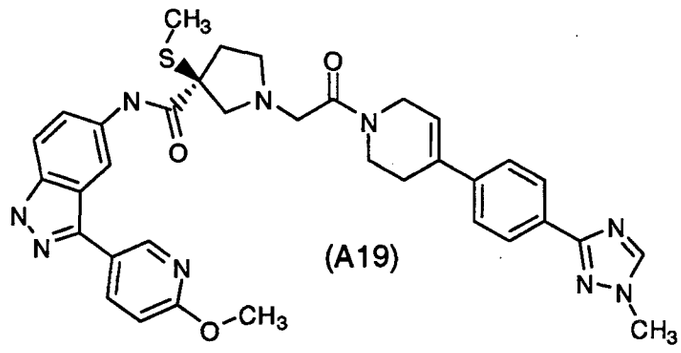
(A15),



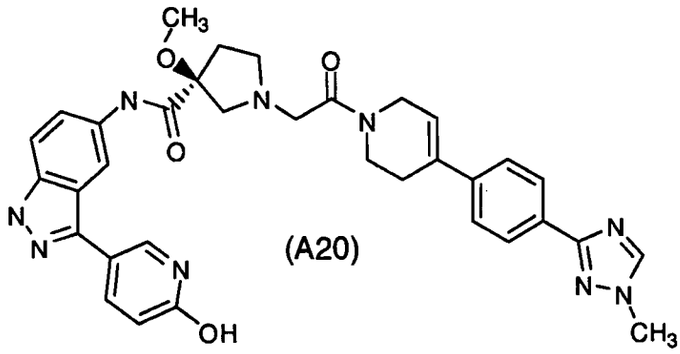
(A16)



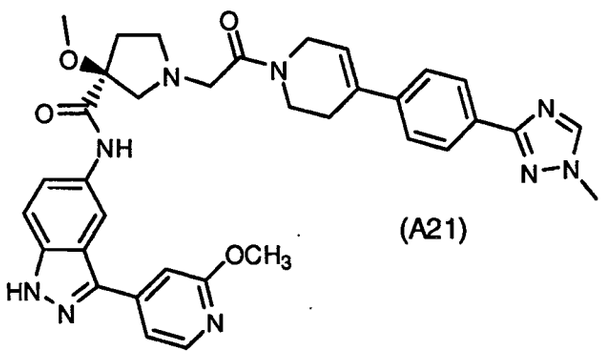
(A18)



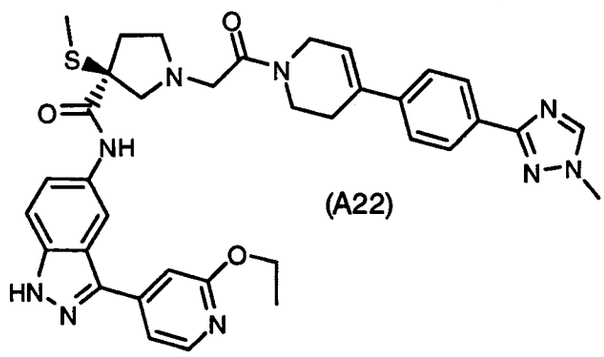
(A19)



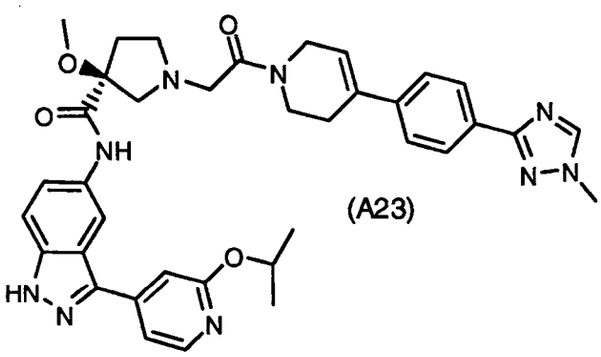
(A20),



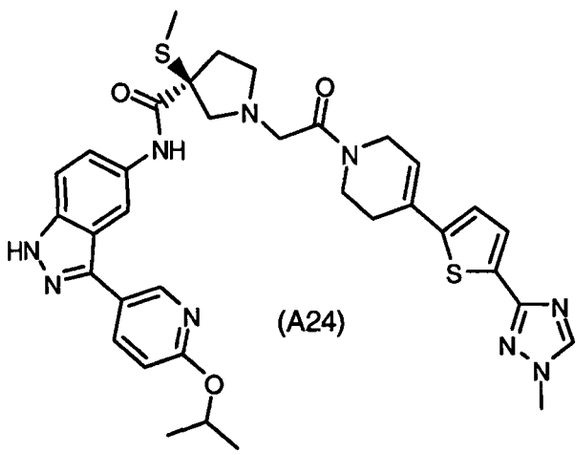
(A21),



(A22),

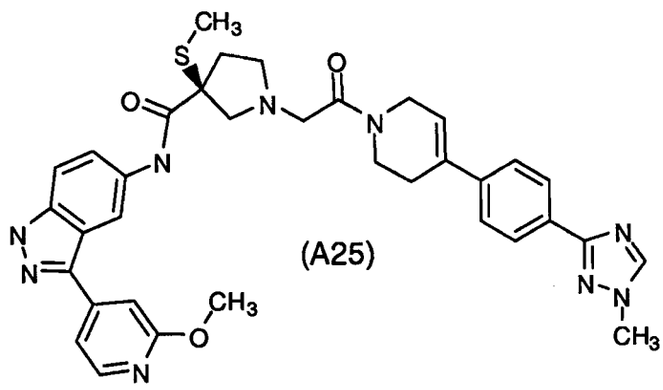


(A23),



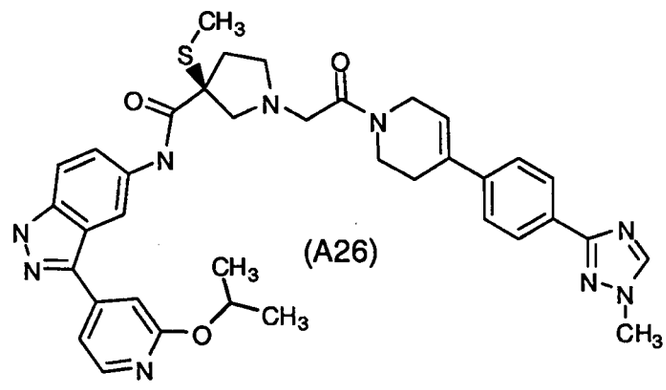
(A24)

,



(A25)

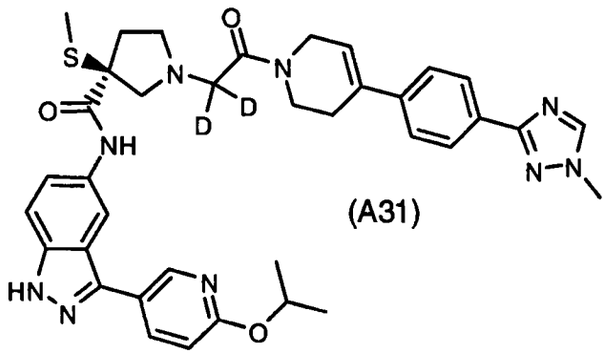
, and



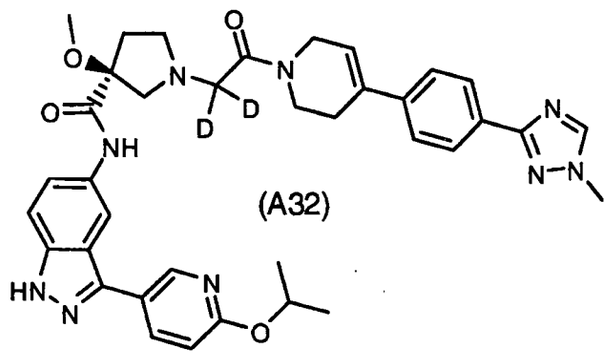
(A26)

.

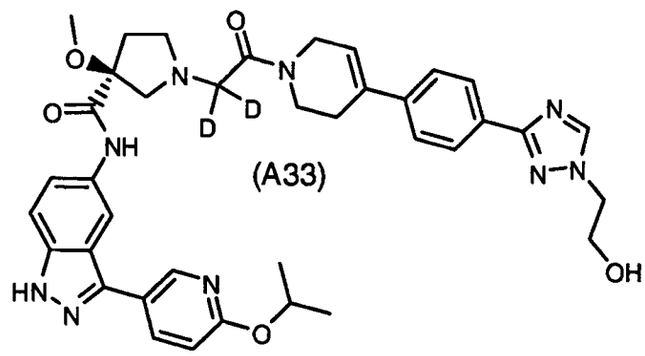
Representative compounds of this invention wherein hydrogen has been replaced by deuterium include, but are not limited to:



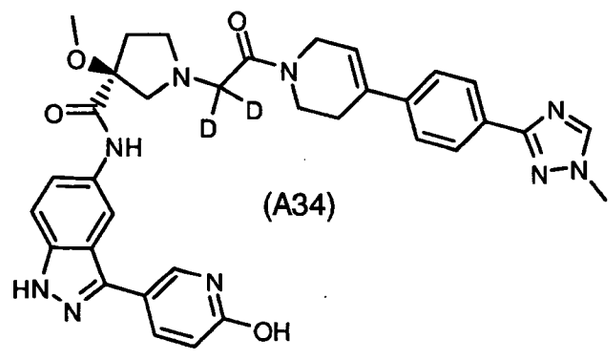
(A31)



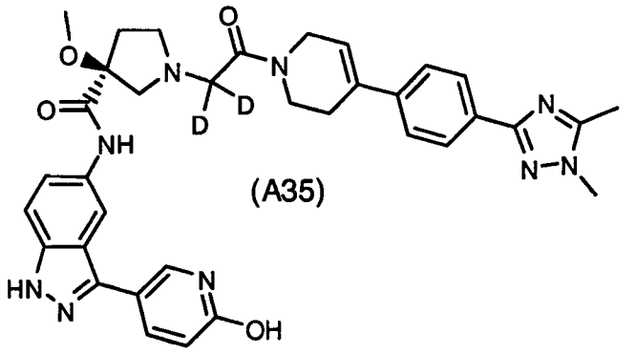
(A32)



(A33)

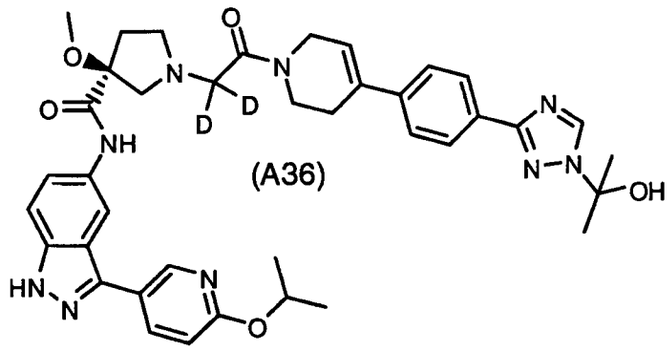


(A34)



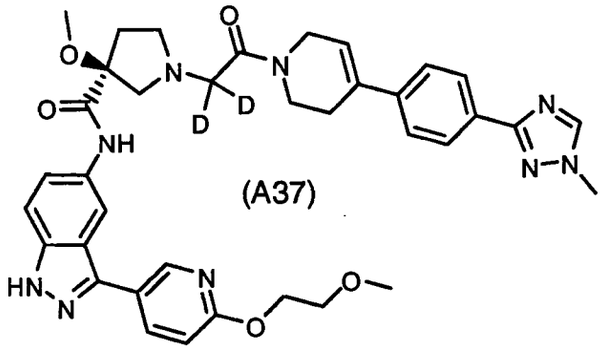
(A35)

,



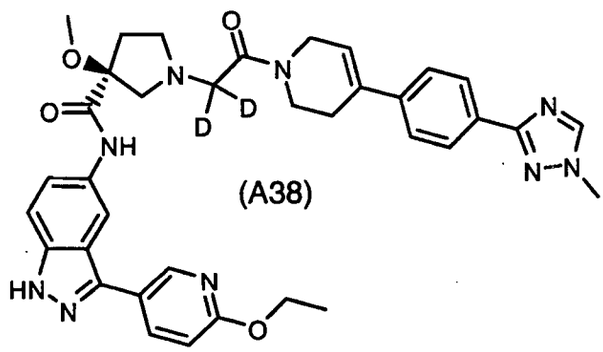
(A36)

,



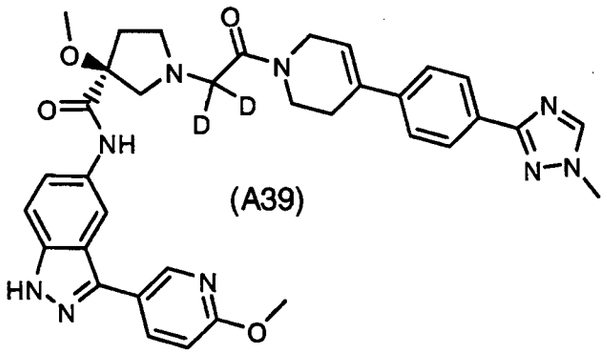
(A37)

,

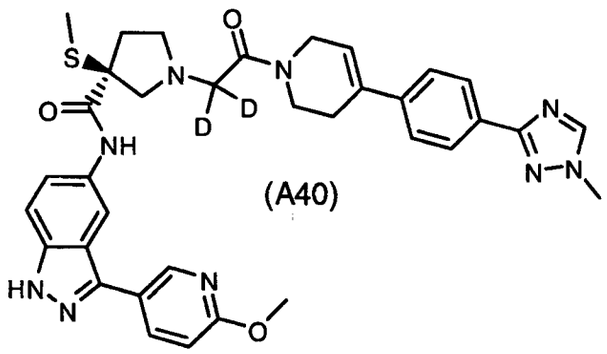


(A38)

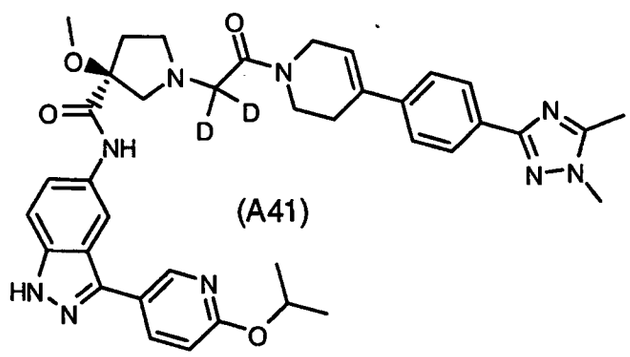
,



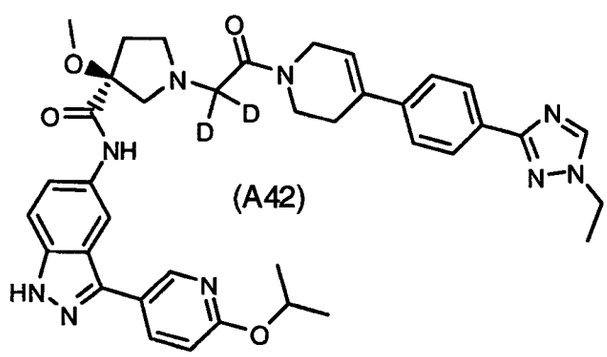
(A39)



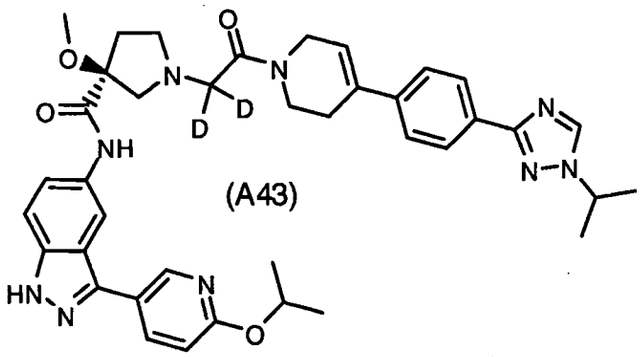
(A40)



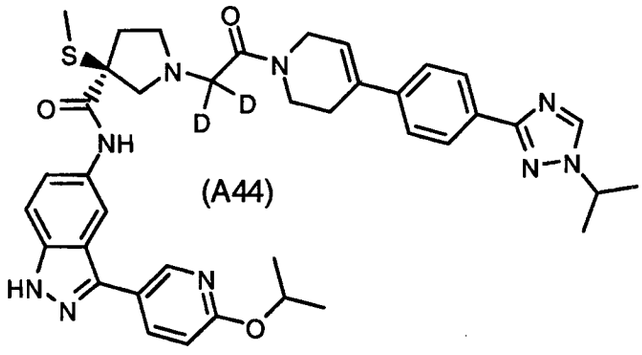
(A41)



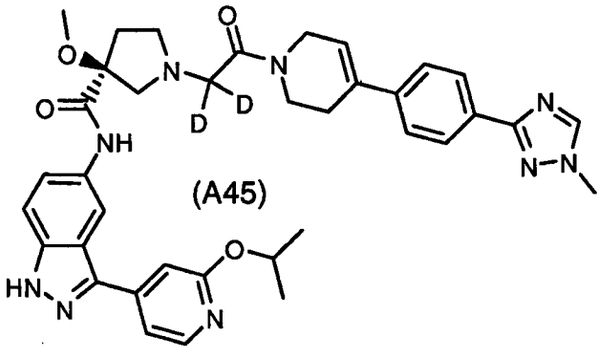
(A42)



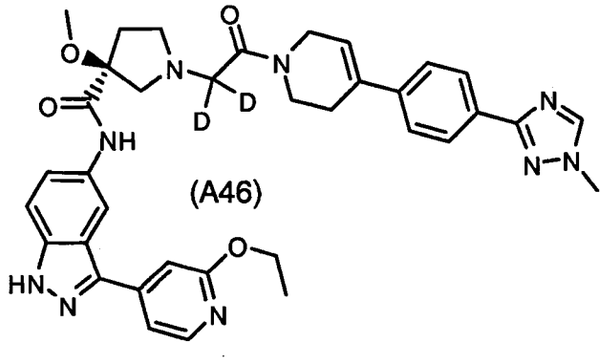
(A43)



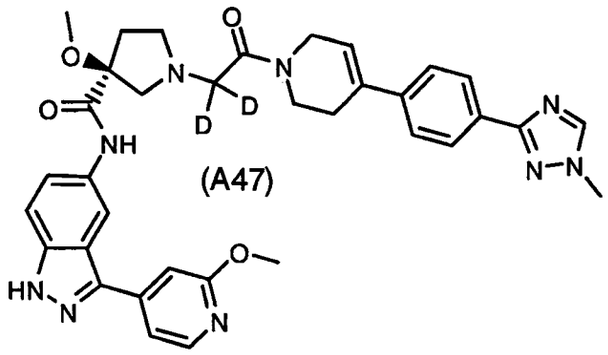
(A44)



(A45)

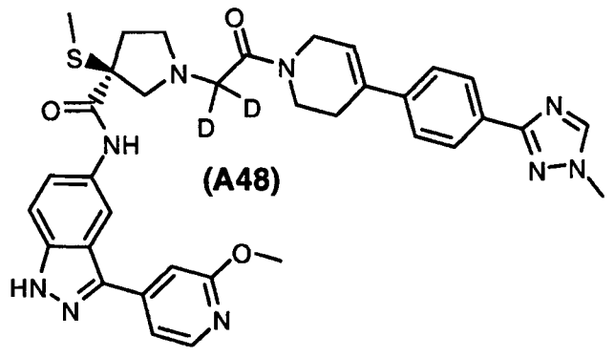


(A46)



(A47)

and



(A48)

Another embodiment of this invention is directed to compound A1.
Another embodiment of this invention is directed to compound A2.
Another embodiment of this invention is directed to compound A3.
Another embodiment of this invention is directed to compound A4.
Another embodiment of this invention is directed to compound A5.
Another embodiment of this invention is directed to compound A6.
Another embodiment of this invention is directed to compound A7.
Another embodiment of this invention is directed to compound A8.
Another embodiment of this invention is directed to compound A9.
Another embodiment of this invention is directed to compound A10.
Another embodiment of this invention is directed to compound A11.
Another embodiment of this invention is directed to compound A12.
Another embodiment of this invention is directed to compound A13.
Another embodiment of this invention is directed to compound A14.
Another embodiment of this invention is directed to compound A15.
Another embodiment of this invention is directed to compound A16.
Another embodiment of this invention is directed to compound A18.

Another embodiment of this invention is directed to compound A19.

Another embodiment of this invention is directed to compound A20.

Another embodiment of this invention is directed to compound A21.

Another embodiment of this invention is directed to compound A22.

Another embodiment of this invention is directed to compound A23.

Another embodiment of this invention is directed to compound A24.

Another embodiment of this invention is directed to compound A25.

Another embodiment of this invention is directed to compound A26.

Another embodiment of this invention is directed to compound A27.

Another embodiment of this invention is directed to compound A28.

Another embodiment of this invention is directed to compound A29.

Another embodiment of this invention is directed to compound A30.

Another embodiment of this invention is directed to compound A31.

Another embodiment of this invention is directed to compound A32.

Another embodiment of this invention is directed to compound A33.

Another embodiment of this invention is directed to compound A34.

Another embodiment of this invention is directed to compound A35.

Another embodiment of this invention is directed to compound A36.

Another embodiment of this invention is directed to compound A37.

Another embodiment of this invention is directed to compound A38.

Another embodiment of this invention is directed to compound A39.

Another embodiment of this invention is directed to compound A40.

Another embodiment of this invention is directed to compound A41.

Another embodiment of this invention is directed to compound A42.

Another embodiment of this invention is directed to compound A43.

Another embodiment of this invention is directed to compound A44.

Another embodiment of this invention is directed to compound A45.

Another embodiment of this invention is directed to compound A46.

Another embodiment of this invention is directed to compound A47.

Another embodiment of this invention is directed to compound A48.

Another embodiment of this invention is directed to a pharmaceutically acceptable salt of compound A1.

Another embodiment of this invention is directed to a pharmaceutically acceptable salt of compound A2.

Another embodiment of this invention is directed to a pharmaceutically acceptable salt of compound A3.

Another embodiment of this invention is directed to a pharmaceutically acceptable salt of compound A4.

Another embodiment of this invention is directed to a pharmaceutically acceptable salt of compound A5.

Another embodiment of this invention is directed to a pharmaceutically acceptable salt of compound A6.

Another embodiment of this invention is directed to a pharmaceutically acceptable salt of compound A7.

Another embodiment of this invention is directed to a pharmaceutically acceptable salt of compound A8.

Another embodiment of this invention is directed to a pharmaceutically acceptable salt of compound A9.

Another embodiment of this invention is directed to a pharmaceutically acceptable salt of compound A10.

Another embodiment of this invention is directed to a pharmaceutically acceptable salt of compound A11.

Another embodiment of this invention is directed to a pharmaceutically acceptable salt of compound A12.

Another embodiment of this invention is directed to a pharmaceutically acceptable salt of compound A13.

Another embodiment of this invention is directed to a pharmaceutically acceptable salt of compound A14.

Another embodiment of this invention is directed to a pharmaceutically acceptable salt of compound A15.

Another embodiment of this invention is directed to a pharmaceutically acceptable salt of compound A16.

Another embodiment of this invention is directed to a pharmaceutically acceptable salt of compound A18.

Another embodiment of this invention is directed to a pharmaceutically acceptable salt of compound A19.

Another embodiment of this invention is directed to a pharmaceutically acceptable salt of compound A20.

Another embodiment of this invention is directed to a pharmaceutically acceptable salt of compound A21.

Another embodiment of this invention is directed to a pharmaceutically acceptable salt of compound A22.

Another embodiment of this invention is directed to a pharmaceutically acceptable salt of compound A23.

Another embodiment of this invention is directed to a pharmaceutically acceptable salt of compound A24.

Another embodiment of this invention is directed to a pharmaceutically acceptable salt of compound A25.

Another embodiment of this invention is directed to a pharmaceutically acceptable salt of compound A26.

Another embodiment of this invention is directed to a pharmaceutically acceptable salt of compound A27.

Another embodiment of this invention is directed to a pharmaceutically acceptable salt of compound A28.

Another embodiment of this invention is directed to a pharmaceutically acceptable salt of compound A29.

Another embodiment of this invention is directed to a pharmaceutically acceptable salt of compound A30.

Another embodiment of this invention is directed to a pharmaceutically acceptable salt of compound A31.

Another embodiment of this invention is directed to a pharmaceutically acceptable salt of compound A32.

Another embodiment of this invention is directed to a pharmaceutically acceptable salt of compound A33.

Another embodiment of this invention is directed to a pharmaceutically acceptable salt of compound A34.

Another embodiment of this invention is directed to a pharmaceutically acceptable salt of compound A35.

Another embodiment of this invention is directed to a pharmaceutically acceptable salt of compound A36.

Another embodiment of this invention is directed to a pharmaceutically acceptable salt of compound A37.

Another embodiment of this invention is directed to a pharmaceutically acceptable salt of compound A38.

Another embodiment of this invention is directed to a pharmaceutically acceptable salt of compound A39.

Another embodiment of this invention is directed to a pharmaceutically acceptable salt of compound A40.

Another embodiment of this invention is directed to a pharmaceutically acceptable salt of compound A41.

Another embodiment of this invention is directed to a pharmaceutically acceptable salt of compound A42.

Another embodiment of this invention is directed to a pharmaceutically acceptable salt of compound A43.

Another embodiment of this invention is directed to a pharmaceutically acceptable salt of compound A44.

Another embodiment of this invention is directed to a pharmaceutically acceptable salt of compound A45.

Another embodiment of this invention is directed to a pharmaceutically acceptable salt of compound A46.

Another embodiment of this invention is directed to a pharmaceutically acceptable salt of compound A47.

Another embodiment of this invention is directed to a pharmaceutically acceptable salt of compound A48.

Another embodiment of this invention is directed to a solvate of compound A1.

Another embodiment of this invention is directed to a solvate of compound A2.

Another embodiment of this invention is directed to solvate of compound A3.

Another embodiment of this invention is directed to solvate of compound A4.

Another embodiment of this invention is directed to a solvate of compound A5.

Another embodiment of this invention is directed to a solvate of compound A6.

Another embodiment of this invention is directed to a solvate of compound A7.

Another embodiment of this invention is directed to a solvate of compound A8.

Another embodiment of this invention is directed to a solvate of compound A9.

Another embodiment of this invention is directed to a solvate of compound A10.

Another embodiment of this invention is directed to solvate of compound A11.

Another embodiment of this invention is directed to a solvate of compound A12.

Another embodiment of this invention is directed to a solvate of compound A13.

Another embodiment of this invention is directed to a solvate of compound A14.

Another embodiment of this invention is directed to a solvate of compound A15.

Another embodiment of this invention is directed to a solvate of compound A16.

Another embodiment of this invention is directed to a solvate of compound A18.

Another embodiment of this invention is directed to a solvate of compound A19.

Another embodiment of this invention is directed to a solvate of compound A20.

Another embodiment of this invention is directed to a solvate of compound A21.

Another embodiment of this invention is directed to a solvate of compound A22.

Another embodiment of this invention is directed to a solvate of compound A23.

Another embodiment of this invention is directed to a solvate of compound A24.

Another embodiment of this invention is directed to a solvate of compound A25.

Another embodiment of this invention is directed to a solvate of compound A26.

Another embodiment of this invention is directed to a solvate of compound A27.

Another embodiment of this invention is directed to a solvate of compound A28.

Another embodiment of this invention is directed to a solvate of compound A29.

Another embodiment of this invention is directed to a solvate of compound A30.

Another embodiment of this invention is directed to a solvate of compound A31.

Another embodiment of this invention is directed to a solvate of compound A32.

Another embodiment of this invention is directed to a solvate of compound A33.

Another embodiment of this invention is directed to a solvate of compound A34.

Another embodiment of this invention is directed to a solvate of compound A35.

Another embodiment of this invention is directed to a solvate of compound A36.

Another embodiment of this invention is directed to a solvate of compound A37.

Another embodiment of this invention is directed to a solvate of compound A38.

Another embodiment of this invention is directed to a solvate of compound A39.

Another embodiment of this invention is directed to a solvate of compound A40.

Another embodiment of this invention is directed to a solvate of compound A41.

Another embodiment of this invention is directed to a solvate of compound A42.

Another embodiment of this invention is directed to a solvate of compound A43.

Another embodiment of this invention is directed to a solvate of compound A44.

Another embodiment of this invention is directed to a solvate of compound A45.

Another embodiment of this invention is directed to a solvate of compound A46.

Another embodiment of this invention is directed to a solvate of compound A47.

Another embodiment of this invention is directed to a solvate of compound A48.

Other embodiments of this invention are directed to any one of the embodiments of formula 1.0 wherein the compound is in pure and isolated form.

Other embodiments of this invention are directed to any one of the embodiments of formula 1.0 wherein the compound is in pure form.

Other embodiments of this invention are directed to any one of the embodiments of formula 1.0 wherein the compound is in isolated form.

Other embodiments of this invention are directed to any one of the compounds of A1 to A16 and A18 to A48 in pure and isolated form.

Other embodiments of this invention are directed to any one of the compounds of A1 to A16 and A18 to A30 in pure and isolated form.

Other embodiments of this invention are directed to any one of the compounds of A1 to A16 and A18 to A26 in pure and isolated form.

Other embodiments of this invention are directed to any one of the compounds of A31 to A48 in pure and isolated form.

Other embodiments of this invention are directed to any one of the compounds of A1 to A16 and A18 to A48 in pure form.

Other embodiments of this invention are directed to any one of the compounds of A1 to A16 and A18 to A30 in pure form.

Other embodiments of this invention are directed to any one of the compounds of A1 to A16 and A18 to A26 in pure form.

Other embodiments of this invention are directed to any one of the compounds of A31 to A48 in pure.

Other embodiments of this invention are directed to any one of the compounds of A1 to A16 and A18 to A48 in isolated form.

Other embodiments of this invention are directed to any one of the compounds of A1 to A16 and A18 to A30 in isolated form.

Other embodiments of this invention are directed to any one of the compounds of A1 to A16 and A18 to A26 in isolated form.

Other embodiments of this invention are directed to any one of the compounds of A31 to A48 in isolated form.

Another embodiment of this invention 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 of formula 1.1) and a pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a compound of formula 1.0 (preferably of formula 1.1) and a pharmaceutically acceptable carrier.

Another embodiment of this invention 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) selected from the group consisting of: A1 to A16 and A18 to A48, and a pharmaceutically acceptable carrier.

Another embodiment of this invention 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) selected from the group consisting of: A1 to A16 and A18 to A30, and a pharmaceutically acceptable carrier.

Another embodiment of this invention 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) selected from the group consisting of: A1 to A16 and A18 to A26, and a pharmaceutically acceptable carrier.

Another embodiment of this invention 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) selected from the group consisting of: A31 to A48, and a pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a compound selected from the group consisting of: A1 to A16 and A18 to A48, and a pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a compound selected from the group consisting of: A1 to A16 and A18 to A30, and a pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a compound selected from the group consisting of: A1 to A16 and A18 to A26, and a pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a compound selected from the group consisting of: A31 to A48, and a pharmaceutically acceptable carrier.

Another embodiment of this invention 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 of formula 1.1), at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) other active pharmaceutically active ingredient, and a pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a compound of formula 1.0 (preferably of formula 1.1), another active pharmaceutically active ingredient, and a pharmaceutically acceptable carrier.

Another embodiment of this invention 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) selected from the group consisting of: A1 to A16 and A18 to A48, at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) other active pharmaceutically active ingredient, and a pharmaceutically acceptable carrier.

Another embodiment of this invention 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) selected from the group consisting of: A1 to A16 and A18 to A30, at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) other active pharmaceutically active ingredient, and a pharmaceutically acceptable carrier.

Another embodiment of this invention 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) selected from the group consisting of: A1 to A16 and A18 to A26, at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) other active pharmaceutically active ingredient, and a pharmaceutically acceptable carrier.

Another embodiment of this invention 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) selected from the group consisting of: A31 to A48, at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) other active pharmaceutically active ingredient, and a pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a compound selected from the group

consisting of: A1 to A16 and A18 to A48, another active pharmaceutically active ingredient, and a pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a compound selected from the group consisting of: A1 to A16 and A18 to A30, another active pharmaceutically active ingredient, and a pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a compound selected from the group consisting of: A1 to A16 and A18 to A26, another active pharmaceutically active ingredient, and a pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a compound selected from the group consisting of: A31 to A48, another active pharmaceutically active ingredient, and a pharmaceutically acceptable carrier.

Another embodiment of this invention 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 of formula 1.1), at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) chemotherapeutic agent, and a pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a compound of formula 1.0 (preferably of formula 1.1), a chemotherapeutic agent, and a pharmaceutically acceptable carrier.

Another embodiment of this invention 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) selected from the group consisting of: A1 to A16 and A18 to A48, at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) chemotherapeutic agent, and a pharmaceutically acceptable carrier.

Another embodiment of this invention 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) selected from the group consisting of: A1 to A16 and A18 to A30, at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) chemotherapeutic agent, and a pharmaceutically acceptable carrier.

Another embodiment of this invention 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) selected from the group consisting of: A1 to A16 and A18 to A26, at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) chemotherapeutic agent, and a pharmaceutically acceptable carrier.

Another embodiment of this invention 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) selected from the group consisting of: A31 to A48, at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) chemotherapeutic agent, and a pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a compound selected from the group consisting of: A1 to A16 and A18 to A48, a chemotherapeutic agent, and a pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a compound selected from the group consisting of: A1 to A16 and A18 to A30, a chemotherapeutic agent, and a pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a compound selected from the group consisting of: A1 to A16 and A18 to A26, a chemotherapeutic agent, and a pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a compound selected from the group consisting of: A31 to A48, a chemotherapeutic agent, and a pharmaceutically acceptable carrier.

Another embodiment of this invention 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 of formula 1.6).

Another embodiment of this invention 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 of formula 1.6).

Another embodiment of this invention 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 A1 to A16 and A18 to A48.

Another embodiment of this invention 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 A1 to A16 and A18 to A30.

Another embodiment of this invention 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 A1 to A16 and A18 to A26.

Another embodiment of this invention 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 A31 to A48.

Another embodiment of this invention 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 A1 to A16 and A18 to A48.

Another embodiment of this invention 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 A1 to A16 and A18 to A30.

Another embodiment of this invention 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 A1 to A16 and A18 to A26.

Another embodiment of this invention 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 A31 to A48.

Another embodiment of this invention 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, and an effective amount of at least one (1, 2 or 3, or 1 or 2, or 1, and usually 1) chemotherapeutic agent.

Another embodiment of this invention 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, and an effective amount of at least one (1, 2 or 3, or 1 or 2, or 1, and usually 1) chemotherapeutic agent.

Another embodiment of this invention 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 A1 to A16 and A18 to A48, and an effective amount of at least one (1, 2 or 3, or 1 or 2, or 1, and usually 1) chemotherapeutic agent.

Another embodiment of this invention 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 A1 to A16 and A18 to A30, and an effective amount of at least one (1, 2 or 3, or 1 or 2, or 1, and usually 1) chemotherapeutic agent.

Another embodiment of this invention 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 A1 to A16 and A18 to A26, and an effective amount of at least one (1, 2 or 3, or 1 or 2, or 1, and usually 1) chemotherapeutic agent.

Another embodiment of this invention 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 A31 to A48, and an effective amount of at least one (1, 2 or 3, or 1 or 2, or 1, and usually 1) chemotherapeutic agent.

Another embodiment of this invention 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 A1 to A16 and A18 to A48, and an effective amount of at least one (1, 2 or 3, or 1 or 2, or 1, and usually 1) chemotherapeutic agent.

Another embodiment of this invention 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 A1 to A16 and A18 to A30, and an effective amount of at least one (1, 2 or 3, or 1 or 2, or 1, and usually 1) chemotherapeutic agent.

Another embodiment of this invention 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 A1 to A16 and A18 to A26, and an effective amount of at least one (1, 2 or 3, or 1 or 2, or 1, and usually 1) chemotherapeutic agent.

Another embodiment of this invention 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 A31 to A48, and an effective amount of at least one (1, 2 or 3, or 1 or 2, or 1, and usually 1) chemotherapeutic agent.

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.

Thus, another embodiment of this invention is directed to 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.

Another embodiment of this invention is directed to 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, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

Another embodiment of this invention is directed to 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.

Another embodiment of this invention is directed to 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, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

Another embodiment of this invention is directed to 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, wherein said cancer is selected from the group consisting of: melanoma, pancreatic cancer, thryroid cancer, colorectal cancer, lung cancer, breast cancer, and ovarian cancer.

Another embodiment of this invention is directed to 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, 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.

Another embodiment of this invention is directed to 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, wherein said cancer is selected from the group consisting of: melanoma, pancreatic cancer, thryroid cancer, colorectal cancer, lung cancer, breast cancer, and ovarian cancer.

Another embodiment of this invention is directed to 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, 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.

Another embodiment of this invention is directed to 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.

Another embodiment of this invention is directed to 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, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

Another embodiment of this invention is directed to 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.

Another embodiment of this invention is directed to 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, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

Another embodiment of this invention is directed to 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.

Another embodiment of this invention is directed to 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, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

Another embodiment of this invention is directed to 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.

Another embodiment of this invention is directed to 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, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

Another embodiment of this invention is directed to 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.

Another embodiment of this invention is directed to 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, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

Another embodiment of this invention is directed to 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.

Another embodiment of this invention is directed to 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, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

Another embodiment of this invention is directed to 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.

Another embodiment of this invention is directed to 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, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

Another embodiment of this invention is directed to 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.

Another embodiment of this invention is directed to 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, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

Another embodiment of this invention is directed to 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.

Another embodiment of this invention is directed to 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, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

Another embodiment of this invention is directed to 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.

Another embodiment of this invention is directed to 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, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

Another embodiment of this invention is directed to 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.

Another embodiment of this invention is directed to 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, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

Another embodiment of this invention is directed to 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.

Another embodiment of this invention is directed to 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, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

Another embodiment of this invention is directed to 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.

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

Another embodiment of this invention is directed to 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.

Another embodiment of this invention is directed to 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, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

Other embodiments of this invention are directed to 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 in combination with hormonal therapies (i.e., antihormonal agents).

Other embodiments of this invention are directed to 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 in combination with hormonal therapies (i.e., antihormonal agents).

Other embodiments of this invention are directed to 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 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.

Other embodiments of this invention are directed to 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 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, other embodiment of this invention are directed to 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 in combination with hormonal therapies (i.e., antihormonal agents).

Other embodiments of this invention are directed to 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 in combination with hormonal therapies (i.e., antihormonal agents).

Other embodimenst of this invention are directed to 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 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.

Other embodiments of this invention are directed to 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 in cornbination 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.

Another embodiment of this invention is directed to 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.

Another embodiment of this invention is directed to 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, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

Another embodiment of this invention is directed to 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.

Another embodiment of this invention is directed to 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, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

Another embodiment of this invention is directed to 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, in combination with an effective amount of a chemotherapeutic agent wherein said chemotherapeutic agent is temozolomide.

Another embodiment of this invention is directed to 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, in combination with an effective amount of a chemotherapeutic agent, wherein said chemotherapeutic agent is temozolomide.

Another embodiment of this invention is directed to 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.

Another embodiment of this invention is directed to 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, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

Another embodiment of this invention is directed to 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.

Another embodiment of this invention is directed to 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, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

Another embodiment of this invention is directed to 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.

Another embodiment of this invention is directed to 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, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

Another embodiment of this invention is directed to 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.

Another embodiment of this invention is directed to 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, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

Another embodiment of this invention is directed to 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.

Another embodiment of this invention is directed to 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, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

Another embodiment of this invention is directed to 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.

Another embodiment of this invention is directed to 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, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

Another embodiment of this invention is directed to 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.

Another embodiment of this invention is directed to 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, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

Another embodiment of this invention is directed to 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.

Another embodiment of this invention is directed to 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, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

Another embodiment of this invention is directed to 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.

Another embodiment of this invention is directed to 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, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

Another embodiment of this invention is directed to 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.

Another embodiment of this invention is directed to 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, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

Another embodiment of this invention is directed to 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.

Another embodiment of this invention is directed to 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, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

Another embodiment of this invention is directed to 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.

Another embodiment of this invention is directed to 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, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

Another embodiment of this invention is directed to 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.

Another embodiment of this invention is directed to 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, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

Another embodiment of this invention is directed to 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.

Another embodiment of this invention is directed to 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, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

Another embodiment of this invention is directed to 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.

Another embodiment of this invention is directed to 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, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

Another embodiment of this invention is directed to 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.

Another embodiment of this invention is directed to 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, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

Another embodiment of this invention is directed to 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.

Another embodiment of this invention is directed to 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, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

Another embodiment of this invention is directed to 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.

Another embodiment of this invention is directed to 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, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

Another embodiment of this invention is directed to 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.

Another embodiment of this invention is directed to 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, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

Another embodiment of this invention is directed to 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.

Another embodiment of this invention is directed to 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, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

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 166 (Novartis), EKB 569 (Wyeth-Ayerst), GW 572016 (GlaxoSmithKline), CI 1033 (Pfizer Global Research and Development), trastuzrnab-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 αVβ3 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:

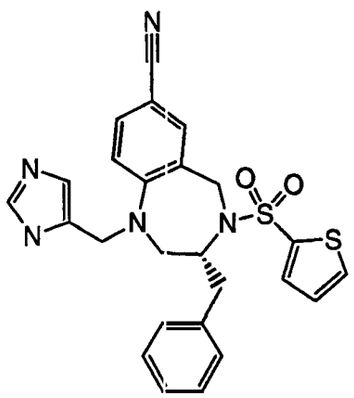
(a) Sarasar® brand of lonifarnib (i.e., 4-[2-[4-(3,10-dibromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-*b*]byridin-11-yl)-1-piperidinyl)-2-oxoethyl]-1-piperidinecarboxamide, see for example, U.S. 5,874,442 issued February 23, 1999, and U.S. 6,632,455 issued October 14, 2003 the disclosures of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

91

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), the Physician's Desk Reference, 57th Edition, 2003 (published by Thompson PDR, Montvale, NJ 07645-1742); and the Physician's Desk Reference, 60th Edition, 2006 (published by

Thompson PDR, Montvale, NJ 07645-1742); the disclosures of which are 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 directed to any one of the method of treating cancer embodiments wherein the compounds of formula 1.0 and the chemotherapeutic agents are administered as a pharmaceutical composition comprising an effective amount of the compounds of formula 1.0, an effective amount of the chemotherapeutic agents, and a pharmaceutically acceptable carrier.

Other embodiments of this invention are directed to any one of the method of treating cancer embodiments wherein a chemotherapeutic agent is used wherein the 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.

Other embodiments of this invention are directed to any one of the method of treating cancer embodiments wherein a chemotherapeutic agent is used wherein the the chemotherapeutic agent is selected from the group consisting of: paclitaxel, docetaxel, carboplatin, cisplatin, navelbine, gemcitabine, and Herceptin.

Other embodiments of this invention are directed to any one of the method of treating cancer embodiments wherein a chemotherapeutic agent is used wherein the the chemotherapeutic agent is selected from the group consisting of: Cyclophasphamide, 5-Fluorouracil, Temozolomide, Vincristine, Cisplatin, Carboplatin, and Gemcitabine.

Other embodiments of this invention are directed to any one of the method of treating cancer embodiments wherein a chemotherapeutic agent is used wherein the 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, 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, 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, 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, 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 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 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, 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 $\alpha V\beta 3$ 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, 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, 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, (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, (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, (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, (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, 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, 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, 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, (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, (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 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.

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, 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, (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, 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, (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, 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, 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, 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, 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 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, 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 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 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 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 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 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 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 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 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 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 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 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 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 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 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 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 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, 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

qq

effective amounts of the compound of formula 1.0, 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, 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, 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, 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, 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, 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 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 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, 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, (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, 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, 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, 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, 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, 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, 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, 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 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 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 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 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 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 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 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 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 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 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, 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 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, 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; 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; 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; 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; 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; 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; (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; (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; (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; (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; (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 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 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 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 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 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 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 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 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 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 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 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, 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, 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, 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, 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, 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, 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, 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, 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, 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, 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, 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, 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, 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, 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, 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, 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, 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, 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, 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, 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, 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, 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, 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, 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, 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, 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, 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, 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, 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, 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, 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, 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, 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, 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, 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, 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, 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, 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, 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, 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, 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, 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, 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, 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, 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, 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, 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, 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, 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, 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, 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, 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, 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, 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, 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, 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, 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, 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, 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 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 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 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 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 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, 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 1.0 (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, 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, 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, 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, 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, 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 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, 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 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 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 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 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 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 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 being dosed twice a day at 100 mg per dose. Examples also include the compound of formula 1.0 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 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 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 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 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 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 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 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 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 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 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, 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 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 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 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 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 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 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 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 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 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 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 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 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 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 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 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 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, 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, 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 the invention can be made according to the processes described in US 2007/0191604 published August 16, 2007, U.S. Serial No. 11/810282 filed June 5, 2007, as well as the processes described below. The disclosures of US

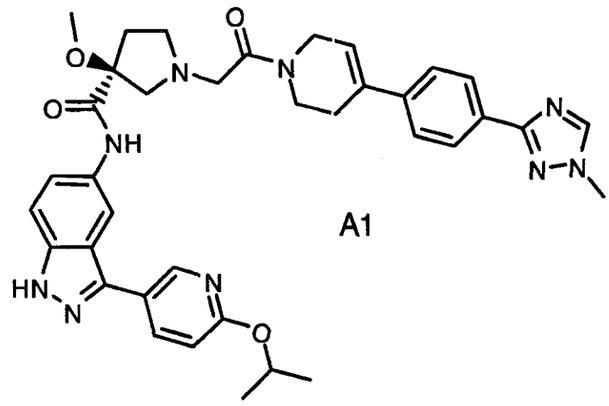
2007/0191604 and U.S. Serial No. 11/810282 are incorporated herein by reference thereto.

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

110

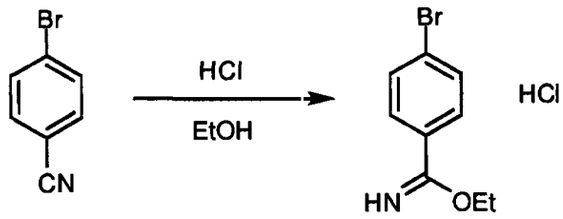
Example 1

Synthesis of 3-Methoxy-1-(2-{4-[4-(1-methyl-1H-[1,2,4]triazol-3-yl)-phenyl]-3,6-dihydro-2H-pyridin-1-yl}-2-oxo-ethyl)-pyrrolidine-3-carboxylic acid [3-(6-isopropoxy-pyridin-3-yl)-1H-indazol-5-yl]-amide



A1

Synthesis of 2-chloro-1-{4-[4-(1-methyl-1*H*-[1,2,4]triazol-3-yl)-phenyl]-3,6-dihydro-2*H*-pyridin-1-yl}-ethanone

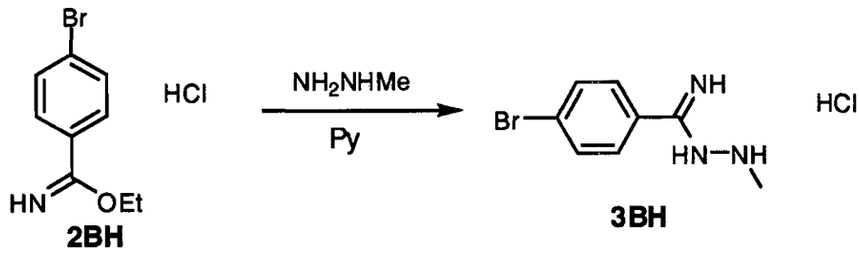


1BH **2BH**

Step 1: Preparation of 4-bromo-benzimidic acid ethyl ester

4-Bromo-benzonitrile (5g) was suspended in absolute EtOH (100 ml) and cooled to 0-5 ^{0} C. HCl gas was bubbled through, initially vigorously for several minutes and later slowly for 5 hours. The resulting solution was allowed to stir overnight. Most of solvent was removed and the precipitate was filtered, washed with EtOH twice and dried to afford compound **2BH** (4.1 g) as white solid.

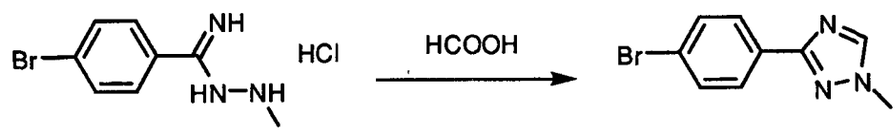
Step 2: Preparation of Compound 3BH



2BH **3BH**

The 4-bromo-benzimidic acid ethyl ester (2.12g, 8 mmols) was dissolved in pyridine (20 ml). Methylhydrazine (640 µl, 12 mmols) was added with stirring and the resulting mixture was allowed to stir overnight. The reaction mixture was concentrated under reduced preessure, and added ether, filtered, washed with ether three times and dried to provide the compound **3BH** (2.2 g).

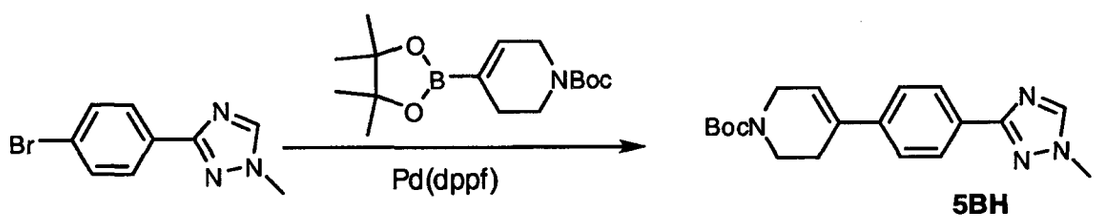
Step 3: Preparation of 3-(4-bromo-phenyl)-1-methyl-*1H*-[1, 2, 4]triazole



3BH **4BH**

A mixture of compound **3BH** (2.2 g) in formic acid (30 ml) was refluxed overnight and concentrated. The residue was treated with sat. $NaHCO_3$, and extracted with EtOAc three times. The combined organics were dried over $MgSO_4$. After concentration, compound **4BH** was obtained as colorless crystals (1.39 g). (Note: it was found that the reaction can be done in just two hours. In large scale synthesis, use 10% NaOH to replace $NaHCO_3$).

Step 4: Preparation of 4-[4-(1-methyl-*1H*-[1,2,4]triazol-3-yl)-phenyl]-3,6-dihydro-*2H*-pyridine-1-carboxylic acid *tert*-butyl ester

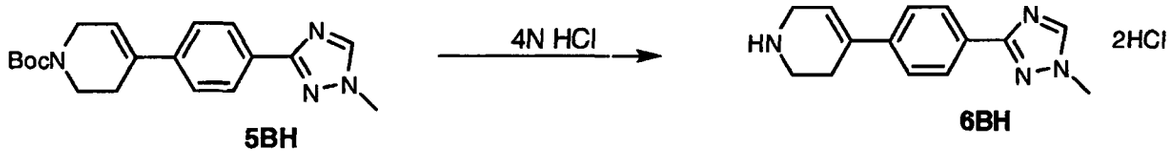


4BH **5BH**

To a large pressure flask were charged compound **4BH** (13.3 g, 55.9 mmols), 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester (19 g, 61.5 mmols), [1,1'-bis(diphenylphosphino)-

ferrocene]dichloropalladium(II), complex with dichloromethane(1:1) (2.3 g, 2.8 mmols), K_2CO_3 (23.2 g, 168 mmols) and DME/water (5:1, 120 ml). The mixture was briefly degassed with Ar for ~0.5 minute, capped and stirred at 80C overnight. After cooling, the reaction mixture was diluted with EtOAc and brine. Organic layer was isolated, and dried ($MgSO_4$). After concentration, the residue was purified on silica gel. Elution with MeOH/EtOAc (0-10%) gave the desired product **5BH** (13.9 g, 73%).

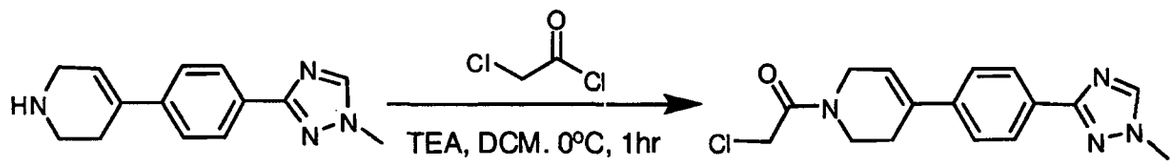
Step 5: Preparation of 4-[4-(1-methyl-1*H*-[1,2,4]triazol-3-yl)-phenyl]-1,2,3,6-tetrahydro-pyridine hydrochloride



5BH **6BH**

The Boc group can be removed by treating compound **5BH** with 4N HCl in dioxane at rt for two hours. Removal of solvent under vacuum gave compound **6BH**.

Step 6: Preparation of 2-chloro-1-{4-[4-(1-methyl-1*H*-[1,2,4]triazol-3-yl)-phenyl]-3,6-dihydro-2*H*-pyridin-1-yl}-ethanone

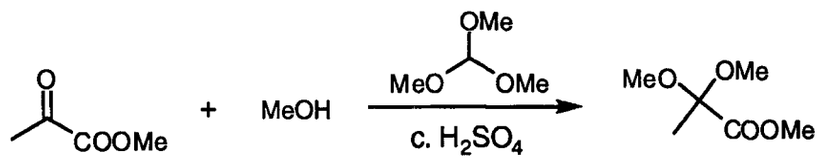


6BH .2HCl **7BH**

To a cold (0 °C) solution of 4-[4-(1-methyl-1*H*-[1,2,4]triazol-3-yl)-phenyl]-1,2,3,6-tetrahydro-pyridine **6BH** (13.7g, 44mmol) in dichloromethane (450ml) was added TEA (37ml, 264mmol) dropwise. After stirred at 0 °C for 10min, chloroacetyl chloride (10.5 ml, 132 mmols) was added to the reaction mixture. The resulting mixture was stirred at 0 °C for 1hr., and quenched with water (165ml). The reaction mixture was diluted with dichloromethane (600ml). The organic layer was separated and washed with brine, dried over $MgSO_4$. Reaction mixture was concentrated to ~50ml, ether was added and the solid was filtered out to get the desired product **7BH** (8.74g).

Synthesis of 3-Methoxy-pyrrolidine-3-carboxylic acid methyl ester

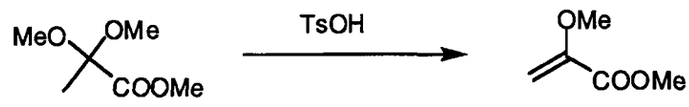
Step 1: Preparation of methyl α, α-dimethoxypropionate



8BH

The procedure by Ernest Wenkert, et al. (JACS, **1983**, *105*, 2021-2029) was followed. A solution of methyl pyruvate (44g), trimethyl orthoformate (62 ml), concentrated H_2SO_4 (0.2 ml) in MeOH (120 ml) was refluxed for 4 hours. In the next one hour period, solvent (about 80 ml) was distilled out. The reaction mixture was cooled to 10 °C, poured into a KOH solution (1.2 g KOH in 600 ml water), and extracted with ether (3x). Combined ether extracts were washed with brine and dried ($MgSO_4$). After concentration, the residue was distilled under vacuum to provide the acetal (**8BH**) (40g, 62%, 40-43C/1 torr).

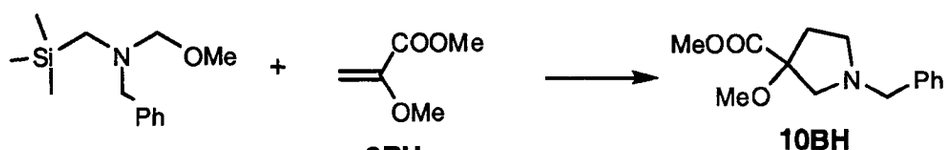
Step 2: Preparation of 2-methoxyacrylate



8BH **9BH**

The procedure by Ernest Wenkert, et al. (JACS, **1983**, *105*, 2021-2029) was followed. To a one neck flask was charged α, α-dimethoxypropionate (**8BH**) (150 g) and Tolunesulfonic acid monohydrate (3g) and a short path distillation head was attached. The mixture was heated at 140 °C (oil bath temperature) and methanol began to come out first. The product (76 g) of (**9BH**) was then distilled out later after oil bath temperature was raised over 190 °C.

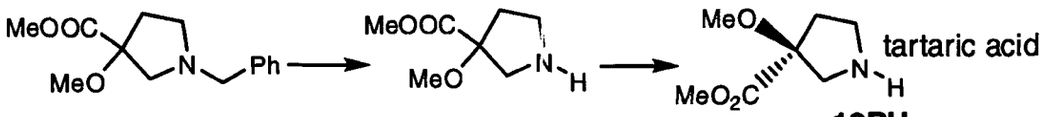
Step 3: Preparation of 1-benzyl-3-methoxy-pyrrolidine-3-carboxylic acid methyl ester



9BH **10BH**

To a stirred solution of methyl 2-methoxyacrylate (20.8 g, 179 mmols) and *N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)benzylamine (55 ml, 215 mmols) in dichloromethane (160 ml) was added at 0 °C a solution of trifluoroacetic acid (2ml) in dichloromethane (10 ml). The resulting solution was warmed to room temperature and stirred overnight. After concentration, the crude product was purified by column chromatography on silica gel eluting with a solution of ethyl acetate/hexanes/Et_3N (1000:3000:4 to 1000:1000:3) to give the title compound (**10BH**) (17.7 mg, 40 %). (Note: adding Et_3N is essential to ensure sharp separation.)

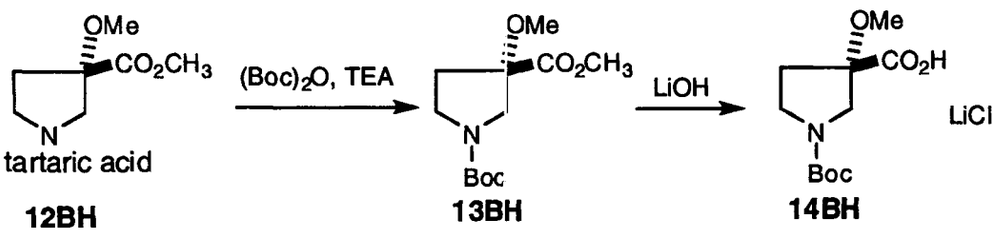
Step 4: Preparation of 3-methoxy-pyrrolidine-3-carboxylic acid methyl ester tartaric acid salt



10BH **11BH** **12BH**

2.49 gm of 1-benzyl-3-methoxy-pyrrolidine-3-carboxylic acid methyl ester (**10BH**) was hydrogenated in ethanol using 10% Pd/C at 55 psi hydrogen for 24 hrs. Filtration of the Pd/C followed by evaporation of the ethanol 1.6 gm of crude de-benzylated product (**11BH**). The crude product was dissolved in 95 ml of methanol and 1.35 gm of L-tartaric acid added. After 24 hrs, the crystals were filtered and re-crystallized from methanol to give 13.4 grams of title product (**12BH**).

Step 5: Preparation of 3-Methoxy-pyrrolidine-1,3-dicarboxylic acid 1-tert-butyl ester



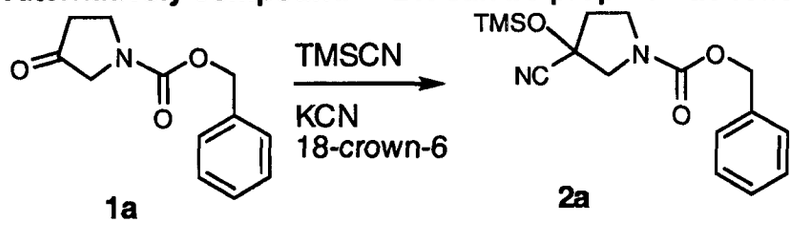
12BH **13BH** **14BH**

To a cold (0°C) solution of **12BH** (28 g, 90.52 mmol) in dry CH_2Cl_2 (250 mL) was added triethylamine (31.5 mL, 226.32 mmol, 2.5 equiv) followed by $(Boc)_2O$ (25.7 g, 117.68 mmol, 1.3 equiv). The resulting mixture was stirred from 0°C to rt for overnight then diluted with CH_2Cl_2, which was washed with saturated aqueous $NaHCO_3$ solution and brine, dried ($MgSO_4$) and concentrated. Chromatograph on

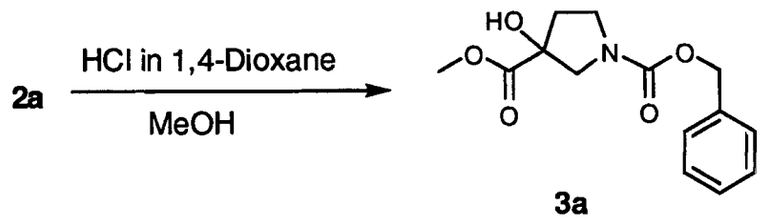
silica gel (hexanes/ethyl acetate, 4:1) gave **13BH** (23.5 mg, 90.52 mmol, 100%) as a colorless oil.

To a stirred solution of **13BH** (23.5 mg, 90.52 mmol) in THF/MeOH (175 mL/175 mL) was added 135 mL of LiOH (1M in H_2O, 135 mmol, 1.5 equiv). The reaction mixture was stirred at rt for overnight, to which 135 mL of 1N HCl was added. The resulting mixture was stirred for additional 15 min and concentrated, azeotroped with dioxane (150 mL x 3) to give **14BH** (42.32 g) as a white solid, which can be used in the next step without further purification.

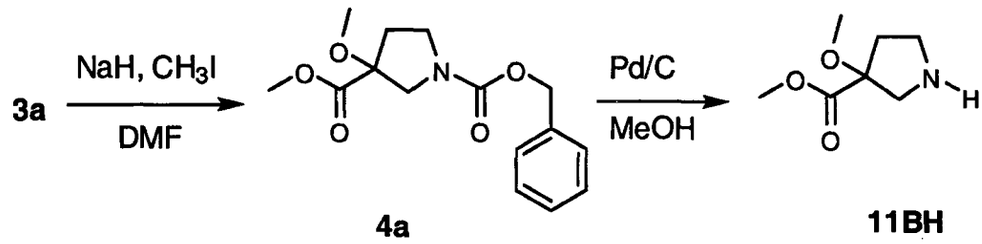
Alternatively compound 11BH can be prepared as follows:



1a **2a**



3a



4a **11BH**

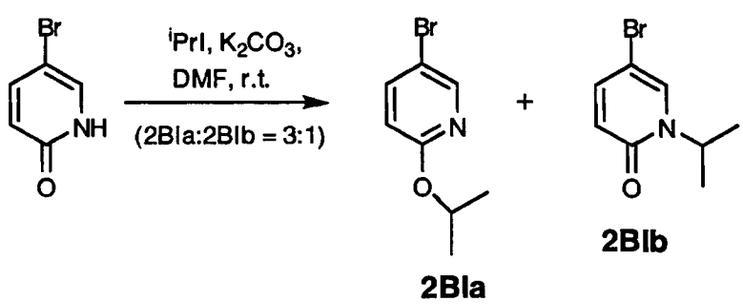
To an ice cold solution of 3-Oxo-pyrrolidine-1-carboxylic acid benzyl ester **1a** (250g, 1.14 mol) in 3.5L anhydrous dichloromethane was added KCN (7.5g, 0.12 mol), followed by 18-crown-6 (30g, 0.11 mol), though not completely dissolved, was added TMSCN (183 mL, 1.37 mol) slowly over a period of 20 min. The reaction was stirred at ambient temperature for 1 overnight. A semi-saturated $NaHCO_3$ solution (2L) was added at 15°C, stirred for 10 min and then the organic layer was separated, dried over magnesium sulfate, filtered and evaporated to give 3-Cyano-3-trimethylsilanyloxy-pyrrolidine-1-carboxylic acid benzyl ester **2a**, 422 g (>100%).

3-Cyano-3-trimethylsilanyloxy-pyrrolidine-1-carboxylic acid benzyl ester **2a** (422 g) in 4L of anhydrous MeOH, was added 2.2 L of 4N HCl in dioxane. The reaction was refluxed for 13 h and stirred at ambient temperature for 1 overnight. Solvents were removed, suspended in 5 L of CH_2Cl_2, washed with 4+3L of water, adjusted the pH to 6-7 with aq. $NaHCO_3$, dried over magnesium sulfate, filtered and evaporated to give 3-Hydroxy-pyrrolidine-1,3-dicarboxylic acid 1-benzyl ester 3-methyl ester **3a**, 278 g (2 steps, 87%).

To a suspension of NaH (52g, 1.3 mol) in 2.2 L of anhydrous DMF at 8°C, was added a solution of 3-Hydroxy-pyrrolidine-1,3-dicarboxylic acid 1-benzyl ester 3-methyl ester **3a** (278 g, 1.0 mol) in 700 DMF, keeping the reaction temperature below 11°C. After complete addition (~20 min), ice bath was removed, stirred at 16-18°C for 1 h, and then at ambient temperature for 1h. Cooled back to 15°C, added MeI (81 mL, 1.3 mol) slowly. Reaction mixture was stirred at ambient temperature for 1 overnight. The reaction mixture was then poured in a cold water (4L) and then extracted with Et_2O(6L) and EtOAc(2L), washed the organic later with water (5L), brine(700 mL), dried over magnesium sulfate, filtered and evaporated to give crude 3-Methoxy-pyrrolidine-1,3-dicarboxylic acid 1-benzyl ester 3-methyl ester **4a** 289 g (99% crude yield, contains mineral oil) (stirring/separation with pentane wash gave **4a**, 268.2 g (92%).

3-Methoxy-pyrrolidine-1,3-dicarboxylic acid 1-benzyl ester 3-methyl ester **4a** in MeOH (2200 mL), was added 14 g of 10% Pd/C (~50% in water). The reaction mixture was hydrogenated using H_2 at ~55 psi pressure (epen valve) for 1 overnight. The reaction mixture was filtered, dried to give 3-Methoxy-pyrrolidine-3-carboxylic acid methyl ester **11BH** 126 g. (overall yield of 70% for 4 steps, no column purification).

Synthesis of 3-Methoxy-pyrrolidine-3-carboxylic acid [3-(6-isopropoxy-pyridin-3-yl)-1H-indazol-5-yl]-amide

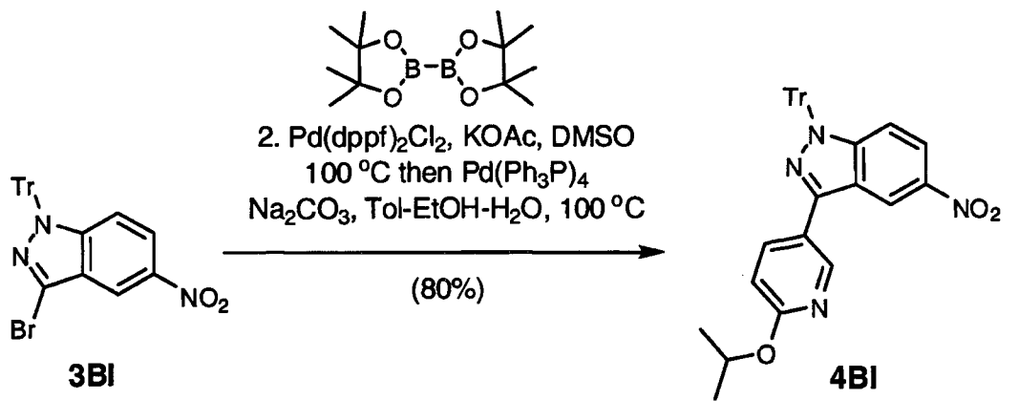


2BIa **2BIb**

Step 1:

5-bromo-1H-pyridone **1BI** (100g, 0.58 mol), potassium carbonate (238g, 1.73mol) and 2-iodopropane (86ml, 0.86mol) were stirred in DMF (1L) at r.t. for 1 day. The mixture were diluted with ethyl acetate and water, layers were separated. The separated organic layer was washed with water (X2), dried ($Mg SO_4$) and filtered. Solvents were removed in vacuum and column purification [5% ethyl acetate in hexanes] gave first the less polar 5-isopropoxypyridine **2BIa** (73g, 59%) as colourless liquid. Continuous elution with [50% ethyl acetate in hexanes] gave the more polar 5-bromo-1-isopropylpyridone **2BIb** as white solid (22g, 18%).

Step 2:

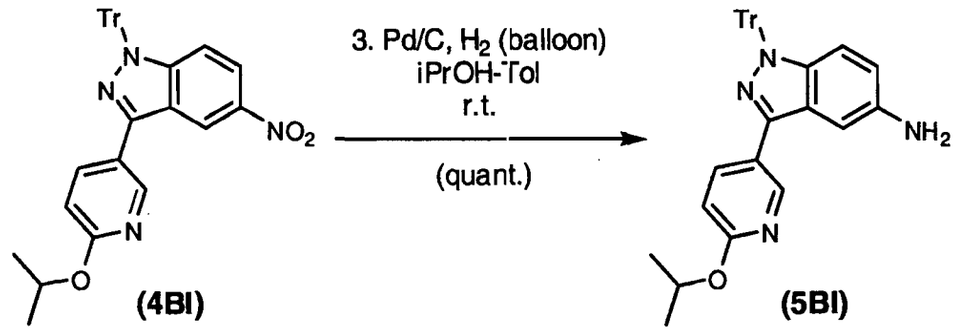


3BI **4BI**

5-isopropoxypyridine **2BIa** (10g, 0.046mol), bis(pinacolato)diboron (14.1g, 0.056mol), potassium acetate (13.6g, 0.14mol) and $PdCl_2(dppf)_2.CH_2Cl_2$ (3.78g, 0.0046mol) were weight into a 2-necked 1L flask equipped with a water condenser. DMSO (100 ml) was added and the mixture was purged with nitrogen for 15 min. The mixture was heated at 100 °C under nitrogen for 2 hr. After being cooled to r.t., water (100ml), toluene (100ml), ethanol (100ml), potassium carbonate (32g, 0.23mol) and bromoindazole **3BI** (22.4g, 0.046mol) were added. The mixture were purged with nitrogen for 10 min at r.t. and $Pd(Ph_3P)_4$ (5.35g, 0.0046mol) was added. The final mixture were heated at 100 °C for 2 hr and cooled to r.t. Water and ethyl acetate were added. Solids were filtered through Celite. Layers were separated and the separated organic layer was washed with water (X2). The combined aqueous layers were back extracted with ethyl acetate (X1). The combined organic layers were dried ($MgSO_4$), filtered and solvents were removed in vacuum. Column purification

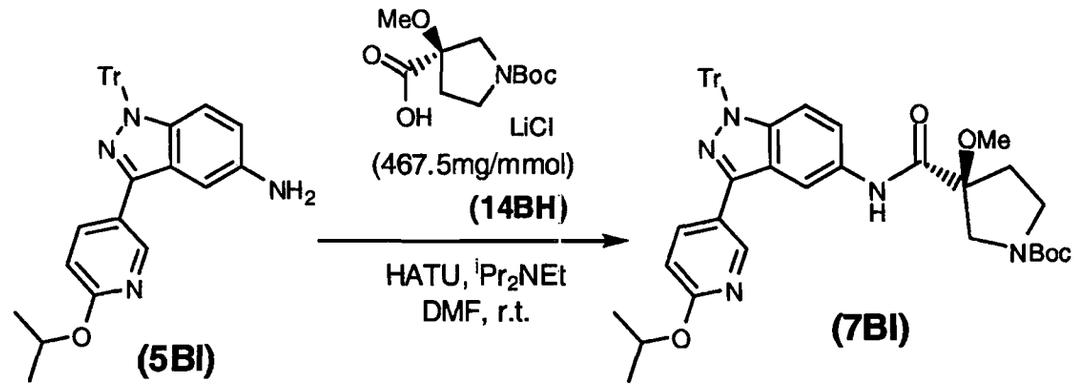
[Hexanes-ethyl acetate = 9:1 (v/v)] gave isopropoxyindazole **4BI** (20g, 80%) as yellow solid.

Step 3:



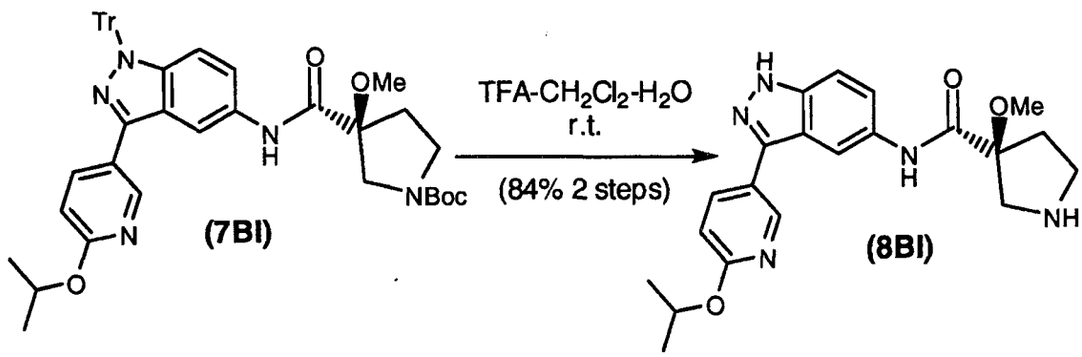
Isopropoxyindazole **4BI** (20g, 0.037mol) and Pd/C (10%, 50% wet, 7.8g, 0.0037mol) were stirred in toluene (100ml) and 2-propanol (200ml) under H_2 (balloon) at r.t. for 1 day. The solid catalyst was filtered through Celite and solvents were removed in vacuum to give aminoindazole **5BI** (quant.) as off-white solid.

Step 4:



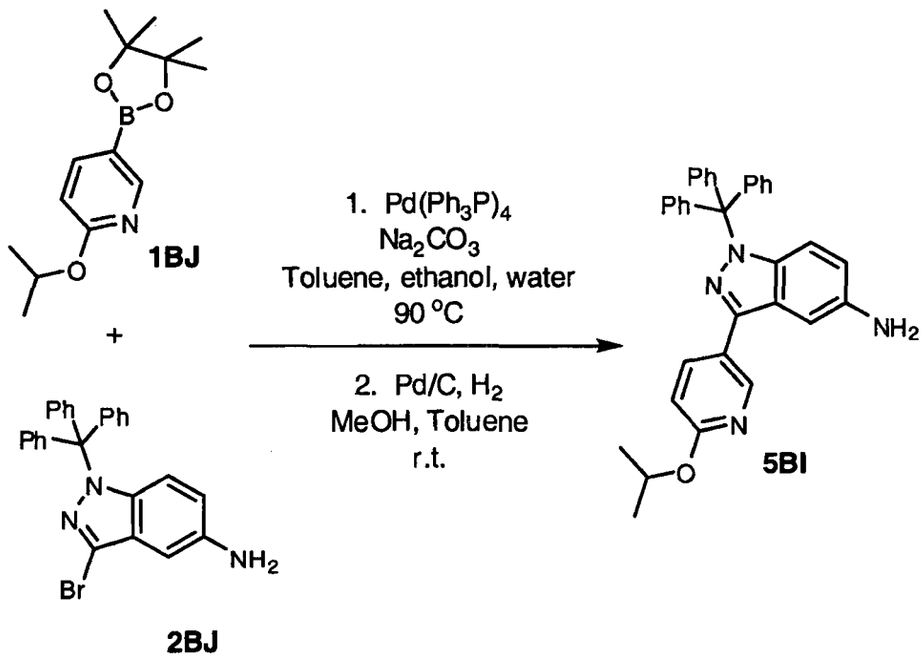
Aminoindazole **5BI** (39g, 0.076mol) and pyrrolidinecarboxylic acid **14BH** (32g, 0.069mol) were dissolved in DMF (300ml) at r.t. HATU (29g, 0.076mol) followed by $^{i}Pr_2NEt$ (14.5ml, 0.083mol) were added. The mixture was stirred at r.t. overnight and was diluted with ethyl acetate and water. Layers were separated. The separated organic layer was washed with water (X2), dried ($MgSO_4$) and filtered. Concentration in vacuum followed by column purification [hexanes – ethyl acetate = 4:1 (v/v)] gave crude **7BI** as off-white foam.

Step 5:



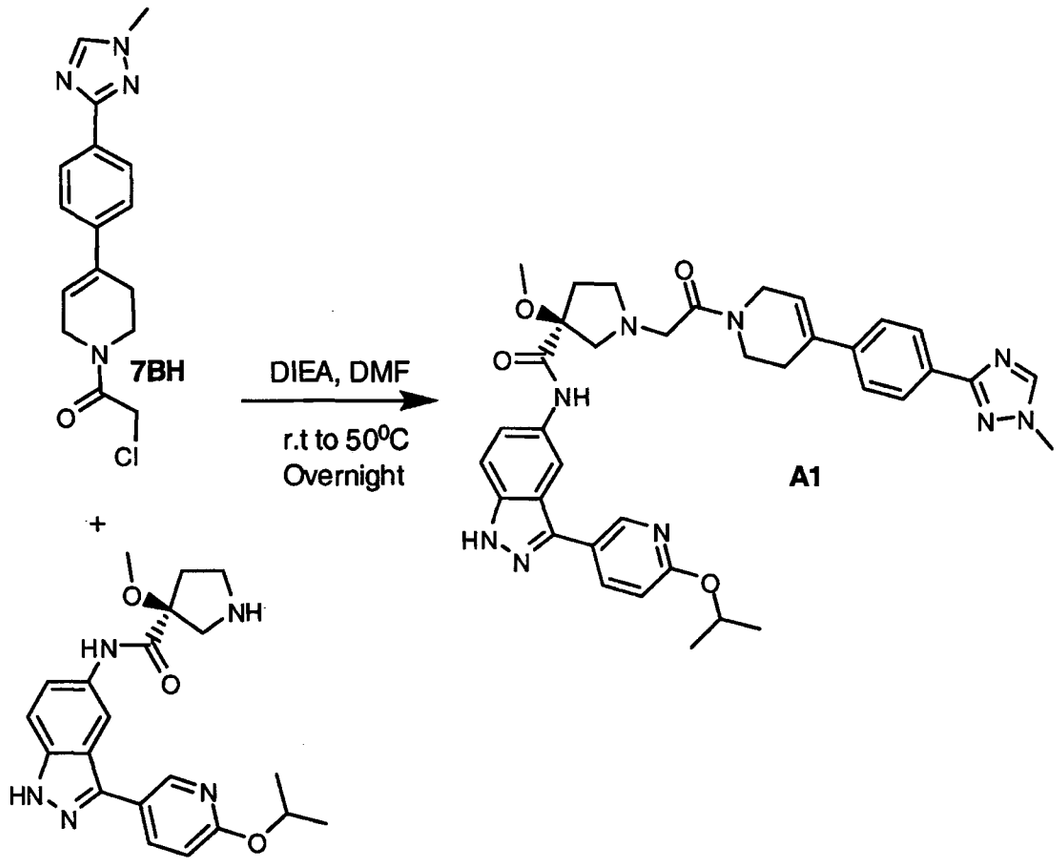
The crude **7BI** was stirred in a mixture of dichloromethane (300ml), trifluoroacetic acid (100ml) and water (50ml) at r.t. overnight. The mixture was cooled at 0 °C and quenched carefully with saturared aqueous sodium bicarbonate. Solvents were removed in vacuum. Dilute with water and ethyl acetate. Layers were separated and the separated aqueous layer was extracted with ethyl acetate (X3). The combined organic layers were dried ($MgSO_4$), filtered and solvents were removed in vacuum. Column purification [5 to 10% MeOH (7N ammonia) in dichloromethane] gave pyrrolidine **8BI** (23g, 84%) as off-white solid.

Alternatively:



Boronate **1BJ** (1.0g, 3.80mmol), bromoindazole **2BJ** (1.84g, 3.80mmol), sodium bicarbonate (1.21g, 11.4mmol) were charged into a sealed-tube. Toluene (30 ml), ethanol (30 ml) and water (15 ml) were added. The slurry was purged with nitrogen for 15 min. and $Pd(Ph_3P)_4$ (439 mg, 0.38mmol) was added in one portion. The mixture was heated in the sealed-tube at 90 °C overnight. After being cooled to r.t., water and ethyl acetate were added and the layers were separated. The separated organic layer was washed with water, dried ($MgSO_4$) and filtered. Solvents were removed in vacuum. The residue was dissolved in toluene (100ml). Methanol (100ml) followed with Pd/C (809mg, 0.38mmol, 50% wet) were added. The mixture was stirred under H_2 (balloon) overnight. The catalyst was filterd and solvents were removed in vacuum. Column purification [hexanes – ethyl acetate = 2:1 (v/v)] gave aniline **5BI** (1.2g, 61%, 2 steps) as off-white solid.

Synthesis of 3-Methoxy-1-(2-{4-[4-(1-methyl-1H-[1,2,4]triazol-3-yl)-phenyl]-3,6-dihydro-2H-pyridin-1-yl}-2-oxo-ethyl)-pyrrolidine-3-carboxylic acid [3-(6-isopropoxy-pyridin-3-yl)-1H-indazol-5-yl]-amide

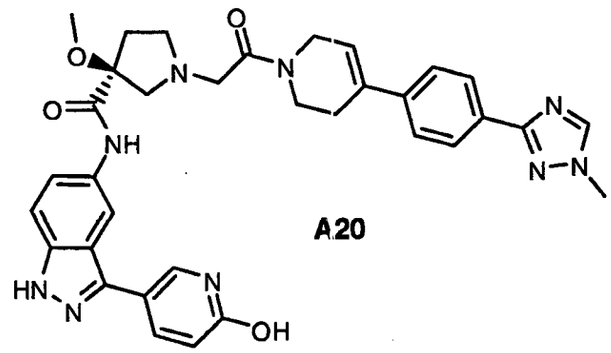


A mixture of compound **7BH** (7.88gm, 24.93mmol), compound **8BI** (9.86gm, 24.93mmol), and DIEA (26.1ml, 149.62mmol) in DMF (200ml) was stirred at room temperature for 5hr. Reaction was completed to about 89% based on the LCMS. It was then heated at 50 °C for overnight (16hr.) LCMS shows the reaction is complete. DMF was removed under reduced pressure. The crude was dissolved in 700ml of DCM and washed with 35ml of water once. Aqueous layer was extracted with 20%MeOH/DCM (2 x 120ml). The combined organic extracts were homogenized with MeOH and dried over $MgSO_4$. The solvent was removed and the crude was purified by column chromatography using 20%MeOH/EtoAc to get the desired product **A1** as a yellow solid (70%). (LCMS M+1= 674, ret. time= 2.91 min.) 1H NMR (400 MHz, CD3OD):δ 8.67 (S, 1H), 8.42 (S, 1H), 8.35 (S, 1H), 8.15-8.19 (m, 1H), 7.94(dd, 2H, J= 8.4 & 10 Hz), 7.64 (m, 1H), 7.49 (m, 3H), 6.84 (m, 1H), 6.20 (d, 1H, J= 11.2 Hz), 5.3

(m, 1H), 4.28 (s, 1H), 4.23 (m, 1H), 3.97 (s, 3H), 3.8 (m, 2H), 3.56 (d, 1H, 2.4 Hz), 3.52(d, 1H, 6.4 Hz), 3.31 (s, 3H), 3.17 (t, 1H, J= 10 Hz), 3.07 (t, 1H, J= 12 Hz), 2.81 (m, 1H), 2.81 (m, 1H), 2.65 (s, 1H), 2.58 (s, 1H), 2.43 (m, 1H), 2.17 (m, 1H), 1.32 (d, 6H, J=6.4 Hz)

Example 2

Synthesis of 3-Methoxy-1-(2-{4-[4-(1-methyl-1H-[1,2,4]triazol-3-yl)-phenyl]-3,6-dihydro-2H-pyridin-1-yl}-2-oxo-ethyl)-pyrrolidine-3-carboxylic acid [3-(6-hydroxy-pyridin-3-yl)-1H-indazol-5-yl]-amide



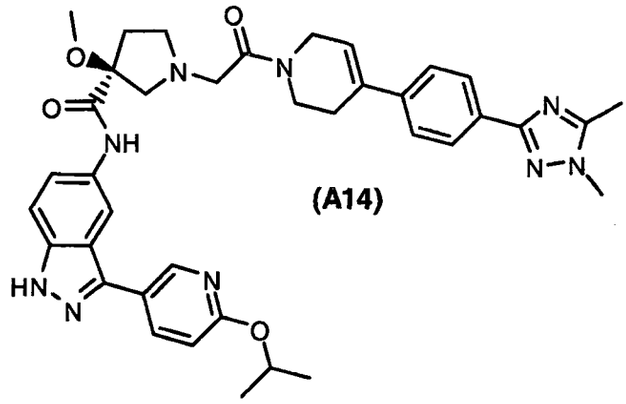
A20

The above compound (**A20**) was isolated from the decomposition of di-HCL salt of 3-Methoxy-1-(2-{4-[4-(1-methyl-1H-[1,2,4]triazol-3-yl)-phenyl]-3,6-dihydro-2H-pyridin-1-yl}-2-oxo-ethyl)-pyrrolidine-3-carboxylic acid [3-(6-isopropoxy-pyridin-3-yl)-1H-indazol-5-yl]-amide.

LCMS M+1 634, ret. time = 2.28 min. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 13.09 (br, 1H), 11.84 (br, 1H), 10.02 (s, 1H), 8.51 (s, 1H), 8.37 (s, 1H), 8.02 (dd, 1H, J=9.5 Hz & 2.5 Hz), 7.95 (m, 2H), 7.82 (d, 1H, J=1.9 Hz), 7.71 (m, 1H), 7.51 (m, 3H), 6.52 (d, 1H, J=9.5 Hz), 6.27 (m, 1H), 4.08-4.34 (m, 2H), 3.92 (s, 3H), 3.70 (m, 2H), 3.49 (m, 2H), 3.24 (s, 3H), 3.16 (d, 1H, J=5.2 Hz), 2.84-3.13 (m, 3H), 2.55-2.76 (m, 2H), 2.36 (m, 1H), 2.05 (m, 1H).

Example 3

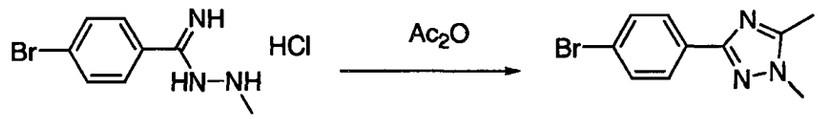
Synthesis of 1-(2-{4-[4-(1,5-Dimethyl-1H-[1,2,4]triazol-3-yl)-phenyl]-3,6-dihydro-2H-pyridin-1-yl}-2-oxo-ethyl)-3-methoxy-pyrrolidine-3-carboxylic acid [3-(6-isopropoxy-pyridin-3-yl)-1H-indazol-5-yl]-amide



(A14)

Synthesis of (S)-1-(2-(4-(4-(1,5-dimethyl-1*H*-1,2,4-triazol-3-yl)phenyl)-5,6-dihydropyridin-1(2*H*)-yl)-2-oxoethyl)-*N*-(3-(6-isopropoxypyridin-3-yl)-1*H*-indazol-5-yl)-3-methoxypyrrolidine-3-carboxamide

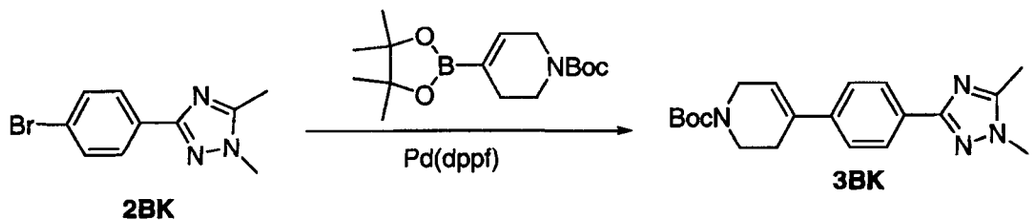
Step 1: Preparation of 3-(4-bromo-phenyl)-1, 5-dimethyl-1*H*-[1,2,4]triazole



1BK **2BK**

A mixture of 4-bromo-*N*-methylbenzimidohydrazide hydrochloride **1** (1.7 g) (prepared according to a procedure in synthesis of Sch-1499895) in acetic anhydride (10 ml) was heated at 100 °C for 0.5 hour. After cooling and concentration under reduced pressure, the residue was dissolved in EtOAc, washed with saturated $NaHCO_3$ twice, brine and dried ($MgSO_4$). After evaporation of solvent, the residue was purified on silica gel. Elution with EtOAc gave 3-(4-bromophenyl)-1, 5-dimethyl-1*H*-[1,2,4]-triazole **2BK** (1.04 g).

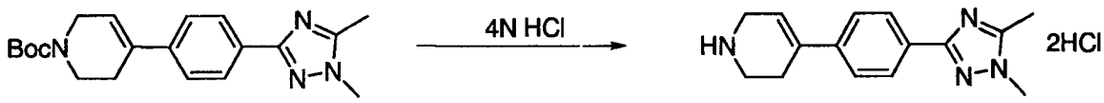
Step 2: Preparation of *tert*-butyl 4-(4-(1, 5-dimethyl-1*H*-1,2,4-triazol-3-yl)phenyl)-5,6-dihydropyridine-1(2*H*)-carboxylate



2BK **3BK**

To a pressure tube were charged compound **2BK** (252 mg, 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 (403 mg, 1.3 mmol), [1,1'-bis(diphenylphosphino)-ferrocene]dichloropalladium(II), complex with dichloromethane(1:1) (41 mg, 0.05 mmol), K_2CO_3 (410 mg, 3 mmol) and DME/water (5:1, 6 ml). The mixture was briefly degassed with Ar for ~0.5 minute, capped and stirred at 100 °C overnight. After cooling, the reaction mixture was diluted with EtOAc and brine. Organic layer was isolated, and dried ($MgSO_4$). After concentration, the residue was purified on silica gel. Elution with MeOH/EtOAc (0-10%) gave the desired product **3BK** (332 mg).

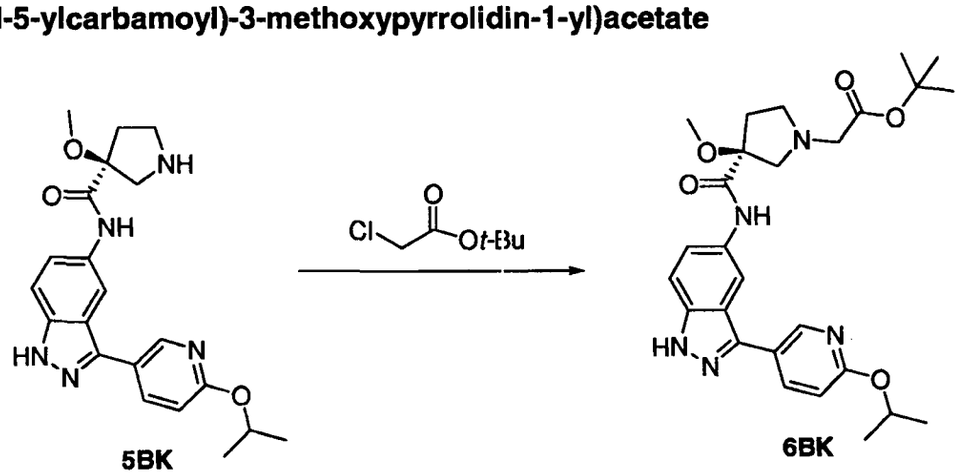
Step 3: Preparation of 4-(4-(1,5-dimethyl-1*H*-1,2,4-triazol-3-yl)phenyl)-1,2,3,6-tetrahydropyridine dihydrochloride



3BK **4BK**

The Boc group can be removed by treating compound **3BK** with 4N HCl in dioxane at rt for two hours. Removal of solvent under vacuum gave compound **4BK**.

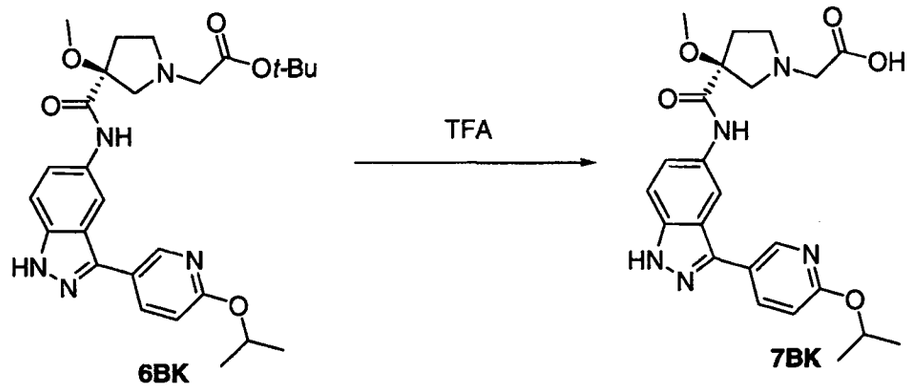
Step 4: Preparation of (S)-*tert*-butyl 2-(3-(3-(6-isopropoxypyridin-3-yl)-1*H*-indazol-5-ylcarbamoyl)-3-methoxypyrrolidin-1-yl)acetate



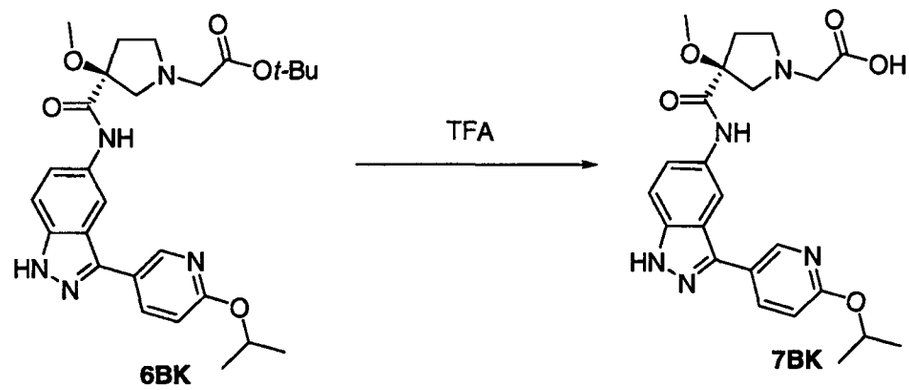
5BK **6BK**

In a solution of compound **5BK** (3.5 g, 6.6 mmol) (prepared according to a procedure in the synthesis of Sch-1499895) in acetonitrile (26 ml) was added DIEA (5.7 ml, 32.9 mmol). It was cooled to 0 °C and 0.47 ml (3.29 mmol) of *tert*-butyl chloroacetate was added dropwise. After stirring for 4hr at 0 °C, 0.47 ml (3.29 mmol)

of *tert*-butyl chloroacetate was added again. It was stirred further for 1hr at 0 ^{0}C and then warmed up to r.t. After stirring overnight at room temperature, it was dissolved in EtOAc (200 ml) and washed with $NaHCO_3$ (1 x 50ml), water (1x 50ml) and brine (1 x 50ml). The organic extracts were dried over $MgSO_4$ and the solvent was removed. The crude was purified by column chromatography using 20%MeOH/EtOAC to get the desired product **6BK** (2.4 g).

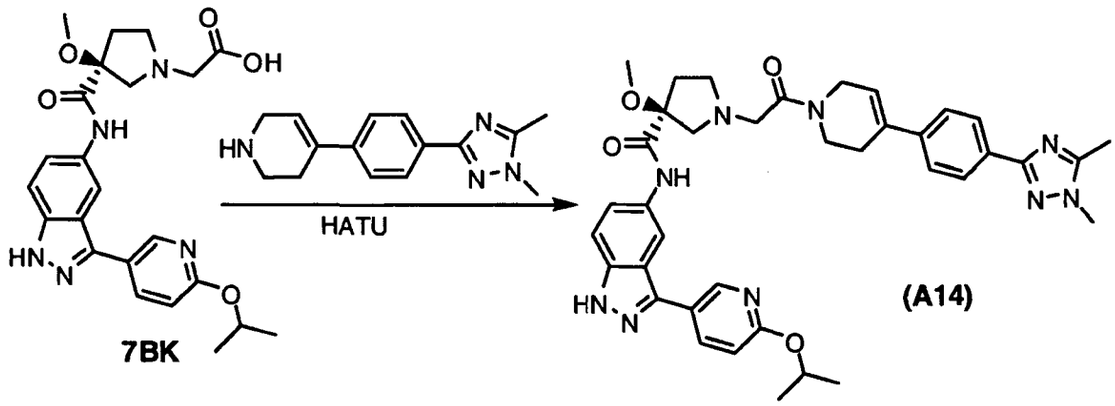


Step 5: Preparation of (S)-2-(3-(3-(6-isopropoxypyridin-3-yl)-1*H*-indazol-5-ylcarbamoyl)-3-methoxypyrrolidin-1-yl) acetic acid



Compound **6BK** (2.4 g) was treated with 40ml of TFA for 45 minutes at room temperature. TFA was removed under reduced pressure and the solid was washed with ether to get the compound **7BK** as a TFA salt (4.4 g, 95%).

Step 6: Preparation of (S)-1-(2-(4-(4-(1, 5-dimethyl-1*H*-1,2,4-triazol-3-yl)phenyl)-5,6-dihydropyridin-1(2*H*)-yl)-2-oxoethyl)-*N*-(3-(6-isopropoxypyridin-3-yl)-1*H*-indazol-5-yl)-3-methoxypyrrolidine-3-carboxamide



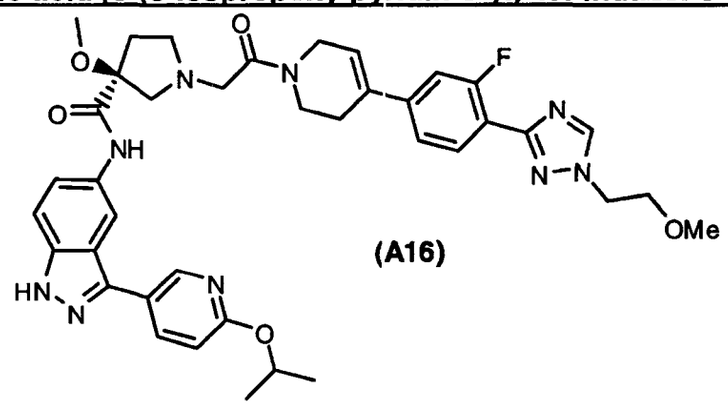
7BK **(A14)**

To a mixture of compound **7BK** (0.12 mmol), HATU (46 mg, 0.12 mmol) in DMF (2 ml) was added compound **4BK** (39 mg, 0.12 mmol) and DIEA (0.063 ml). The mixture was stirred for 20 minutes and directly purified by HPLC to give compound **A14**. Mass spectrum: LCMS M+1= 690, retention time= 3.25 minutes;

^{1}H NMR of **A14** HCl salt (400 MHz, DMSO-d_6):δ10.5 (br, 1H), 10.23 (d, J = 17.6 Hz, 1H), 8.7 (m, 1H), 8.45 (d, J = 1.2 Hz, 1H), 8.18 (m, 1H), 7.94 (m, 2H), 7.75 (dd, J = 8.8, 2.0 Hz, 1H), 7.56 (m, 3H), 6.93 (m, 1H), 6.3 (m, 1H), 5.3 (m, 1H), 4.6-4.53 (m, 2H), 4.2-4.0 (m, 3H), 3.82 (s, 3H), 3.7-3.5 (m, 5H), 3.3 (s, 3H), 2.67-2.54 (m, 3H), 2.44 (s, 3H), 2.4(m, 1H), 1.33 (d, J = 6.4 Hz, 6H).

Example 4

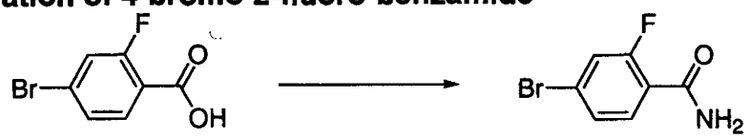
Synthesis of 1-[2-(4-{3-Fluoro-4-[1-(2-methoxy-ethyl)-1H-[1,2,4]triazol-3-yl]-phenyl}-3,6-dihydro-2H-pyridin-1-yl)-2-oxo-ethyl]-3-methoxy-pyrrolidine-3-carboxylic acid [3-(6-isopropoxy-pyridin-3-yl)-1H-indazol-5-yl]-amide



(A16)

Synthesis of (S)-1-[2-(4-{3-fluoro-4-[1-(2-methoxy-ethyl)-1*H*-[1,2,4]triazol-3-yl]-phenyl}-3,6-dihydro-2*H*-pyridin-1-yl)-2-oxo-ethyl]-3-methoxy-pyrrolidine-3-carboxylic acid [3-(6-isopropoxy-pyridin-3-yl)-1*H*-indazol-5-yl]-amide

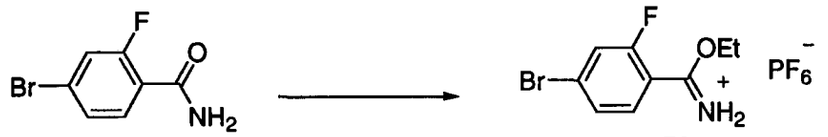
Step 1: Preparation of 4-bromo-2-fluoro-benzamide



1BL **2BL**

At 0 ^{0}C, 1,1'-carbonyldiimidazole (8.8 g, 54.3 mmol) was added in portions to a stirred mixture of 4-bromo-2-fluorobenzoic acid (6 g, 27.3 mmol) in dichloromethane (100 ml). After 20 minutes, a clear solution was obtained. Ammonium hydroxide (28%, 30 ml) was added and the mixture was stirred overnight. Aqueous layer was isolated, extracted with dichloromethane twice. Combined organic extracts were washed with water, 1 N HCl twice, water, brine and dried ($MgSO_4$). Solvent was removed under vacuum, and the solid was washed with hexane to afford 4-bromo-2-fluoro-benzamide **2BL** (5.56 g).

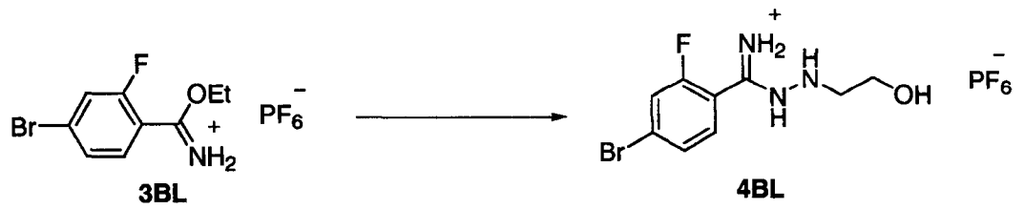
Step 2: Preparation of compound 3BL



2BL **3BL**

A mixture of compound **2BL** (4.66 g, 21.48 mmol), Et_3OPF_6 (6.4 g, 25.77 mmol) in dichloroethane (86 ml) was refluxed for 1 hr. Solvent was removed under reduced pressure. The crude was cooled to 0 ^{0}C, triturated with ether and filtered to give the desired product **3BL** (7.5 g).

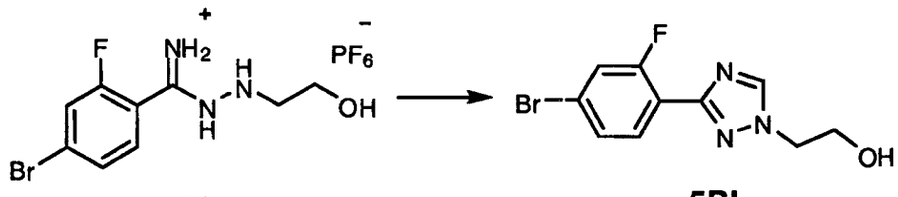
Step 3: Preparation of compound 4BL



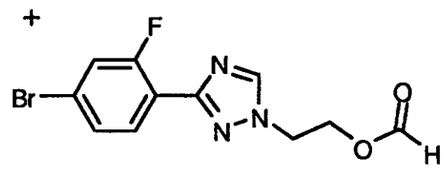
3BL **4BL**

The compound **3BL** (1.96 g) was dissolved in pyridine (10 ml). Hydroxyethylhydrazine (0.51 ml) was added with stirring and the resulting mixture was allowed to stir overnight. The reaction mixture was concentrated under reduced pressure to provide a crude **4BL** as yellow gum which was directly used in next step synthesis without further purification.

Step 4: Preparation of compound 5BL



4BL **5BL**

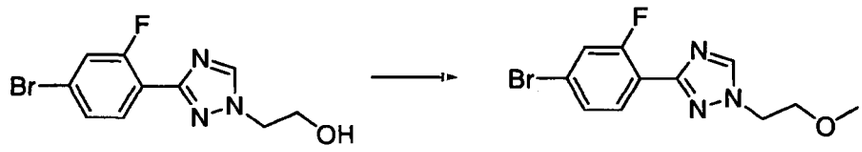


6BL

A mixture of the crude **4BL** from the previous step in formic acid (30 ml) was refluxed overnight and concentrated under reduced pressure. The residue was treated with saturated $NaHCO_3$, and extracted with EtOAc three times. The combined organics were dried over $MgSO_4$. After concentration, compound residue was purified on silica gel. Elution with EtOAc gave compound **6BL** (1.1 g), then **5BL** (183 mg).

Compound **6BL** can be easily converted to **5BL** by aqueous basic hydrolysis.

Step 5: Preparation of compound 7BL

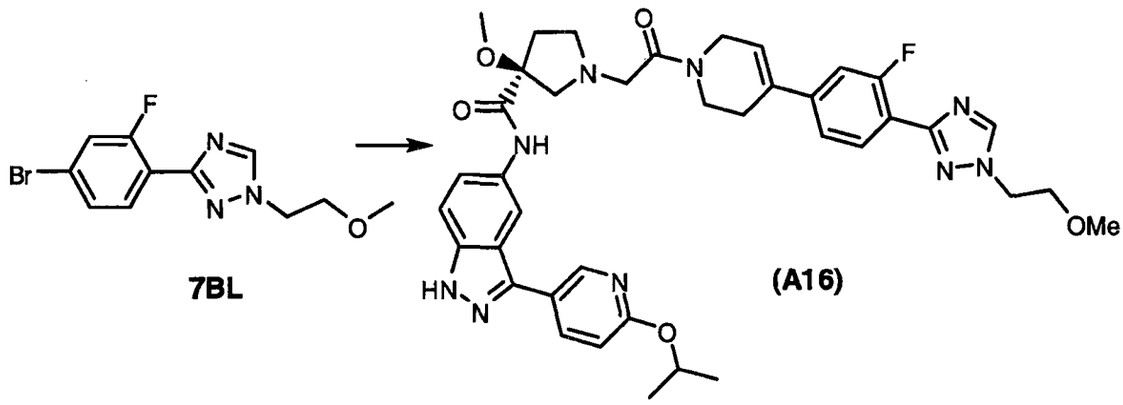


5BL **7BL**

A solution of **5BL** (429 mg, 1.5 mmol) in DMF (3 ml) was added with stirring into a flask containing NaH (60%, 66 mg, 1.65 mmol). After stirring for 30 minutes, MeI (0.103 ml, 1.65 mmol) was added slowly. After 30 minutes, the reaction mixture was diluted with EtOAc, washed with water three times, brine and dried ($MgSO_4$).

After concentration, the residue was purified on silica gel. Elution with 10% MeOH/EtOAc gave compound **7BL** (88 mg).

Step 6: Preparation of compound A16



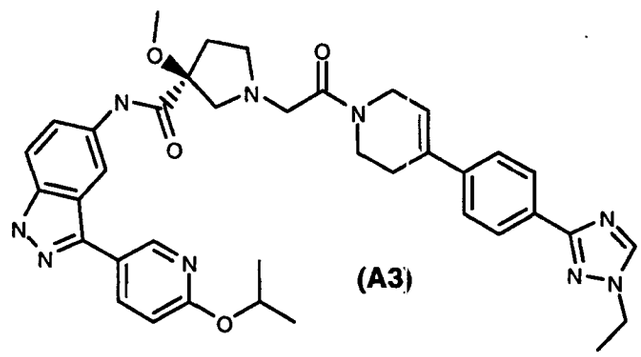
Compound **A16** was prepared from **7BL** following procedures similar to those for the synthesis of (S)-1-(2-(4-(4-(1,5-dimethyl-1*H*-1,2,4-triazol-3-yl)phenyl)-5,6-dihydropyridin-1(2*H*)-yl)-2-oxoethyl)-*N*-(3-(6-isopropoxypyridin-3-yl)-1*H*-indazol-5-yl)-3-methoxypyrrolidine-3-carboxamide (**A14**, Example 3).

Mass spectrum: LCMS M+1= 738, retention time= 4 minutes.

^{1}H NMR of **A16** HCl salt (400 MHz, DMSO-d_6):δ10.45 (br, 1H), 10.23 (d, J = 16.8 Hz, 1H), 8.7 (m, 1H), 8.6 (m, 1H), 8.46 (m, 1H), 8.18 (m, 1H), 8.0 (m, 1H), 7.74 (d, J = 8 Hz, 1H), 7.57 (d, J = 8 Hz, 1H), 7.42 (m, 1H), 6.93 (m, 1H), 6.43 (m, 1H), 5.3 (m, 1H), 4.6-4.5 (m, 2H), 4.41 (m, 2H), 4.21-4.01(m, 4H), 3.8-3.6 (br, 7H), 3.33 (m, 3H), 3.25 (m, 2H), 2.67-2.54 (m, 3H), 2.4(m, 1H), 1.33 (d, J = 6.4 Hz, 6H).

Example 5

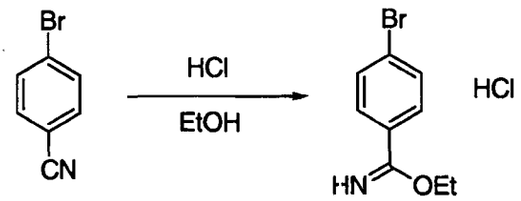
Synthesis of 1-(2-{4-[4-(1-Ethyl-1H-[1,2,4]triazol-3-yl)-phenyl]-3,6-dihydro-2H-pyridin-1-yl}-2-oxo-ethyl)-3-methoxy-pyrrolidine-3-carboxylic acid [3-(6-isopropoxy-pyridin-3-yl)-1H-indazol-5-yl]-amide



(A3)

Synthesis of 4-[4-(1-ethyl-1*H*-[1,2,4]triazol-3-yl)-phenyl]-1,2,3,6-tetrahydro-pyridine hydrochloride

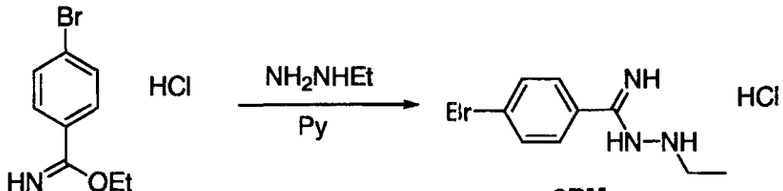
Step 1: Preparation of 4-bromo-benzimidic acid ethyl ester



1BM **2BM**

4-Bromo-benzonitrile (5g) was suspended in absolute EtOH (100 ml) and cooled to 0-5 ^{0} C. HCl gas was bubbled through, initially vigorously for several minutes and later slowly for 5 hours. The resulting solution was allowed to stir overnight. Most of solvent was removed and the precipitate was filtered, washed with EtOH twice and dried to afford compound **2BM** (4.1 g) as white solid.

Step 2: Preparation of Compound 3BM

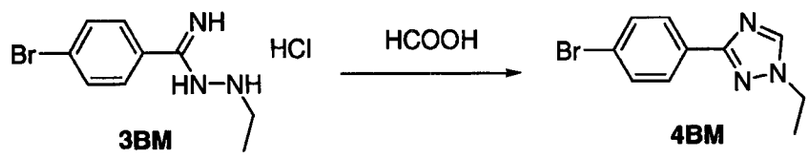


2BM **3BM**

The 4-bromo-benzimidic acid ethyl ester (1 g) was dissolved in pyridine (20 ml). Ethylhydrazine (550 mg) was added with stirring and the resulting mixture was allowed to stir overnight. The reaction mixture was concentrated under reduced

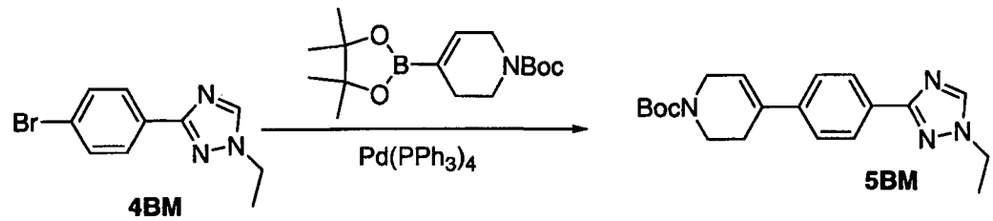
preessure, and added ether, filtered, washed with ether three times and dried to provide the compound **3BM** (1 g).

Step 3: Preparation of 3-(4-bromo-phenyl)-1-ethyl-*1H*-[1, 2, 4]triazole



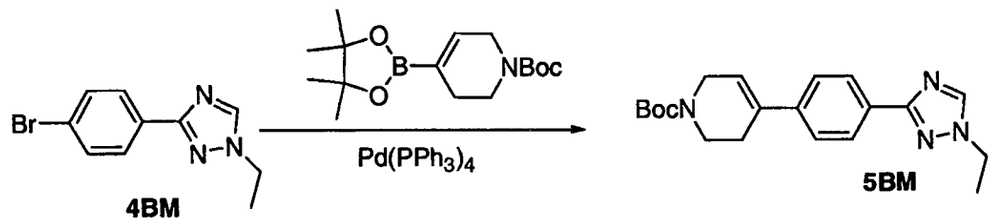
3BM **4BM**

A mixture of compound **3BM** (1 g) in formic acid (10 ml) was refluxed overnight and concentrated. The residue was treated with sat. $NaHCO_3$, and extracted with EtOAc three times. The combined organics were dried over $MgSO_4$. After concentration, compound **4BM** was obtained as colorless crystals (0.9 g).



4BM **5BM**

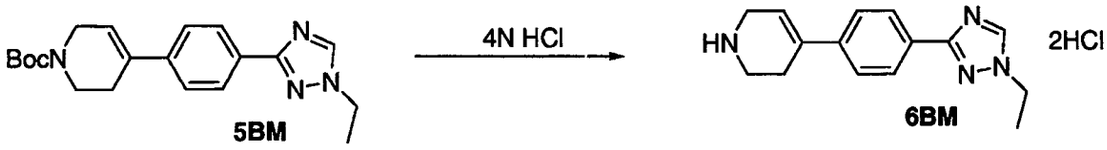
Step 4: Preparation of 4-[4-(1-ethyl-*1H*-[1,2,4]triazol-3-yl)-phenyl]-3,6-dihydro-*2H*-pyridine-1-carboxylic acid *tert*-butyl ester



4BM **5BM**

To a large pressure flask were charged compound **4BM** (400 mg), 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester (540 mg), $Pd(PPh_3)_4$ (180 mg), Na_2CO_3 2N (3 ml) and Dioxane/EtOH/water (7:3:2, 10 ml). The mixture was briefly degassed with Ar for ~0.5 minute, capped and microwaved at 120 °C for 20 mins. After cooling, the reaction mixture was diluted with EtOAc and brine. Organic layer was isolated, and dried ($MgSO_4$). After concentration, the residue was purified on silica gel. Elution with MeOH/EtOAc (0-10%) gave the desired product **5BM** (310 mg).

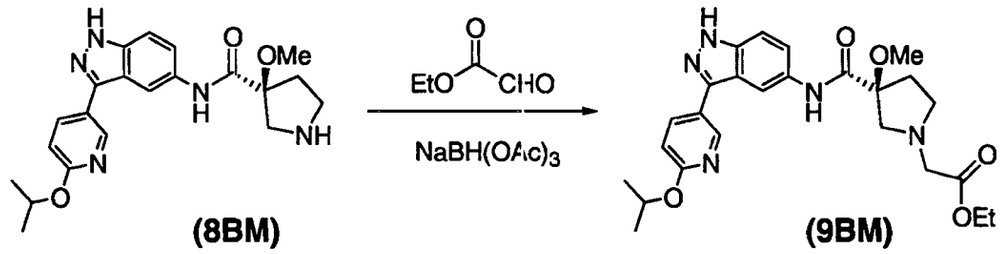
Step 5: Preparation of 4-[4-(1-ethyl-1*H*-[1,2,4]triazol-3-yl)-phenyl]-1,2,3,6-tetrahydro-pyridine hydrochloride



5BM 6BM

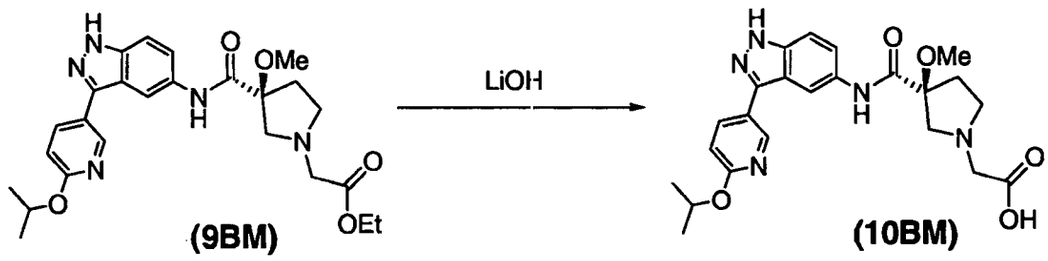
The Boc group can be removed by treating compound **5BM** with 4N HCl in dioxane at rt for two hours. Removal of solvent under vacuum gave compound **6BM**.

Synthesis of 1-(2-{4-[4-(1-Ethyl-1H-[1,2,4]triazol-3-yl)-phenyl]-3,6-dihydro-2H-pyridin-1-yl}-2-oxo-ethyl)-3-methoxy-pyrrolidine-3-carboxylic acid [3-(6-isopropoxy-pyridin-3-yl)-1H-indazol-5-yl]-amide



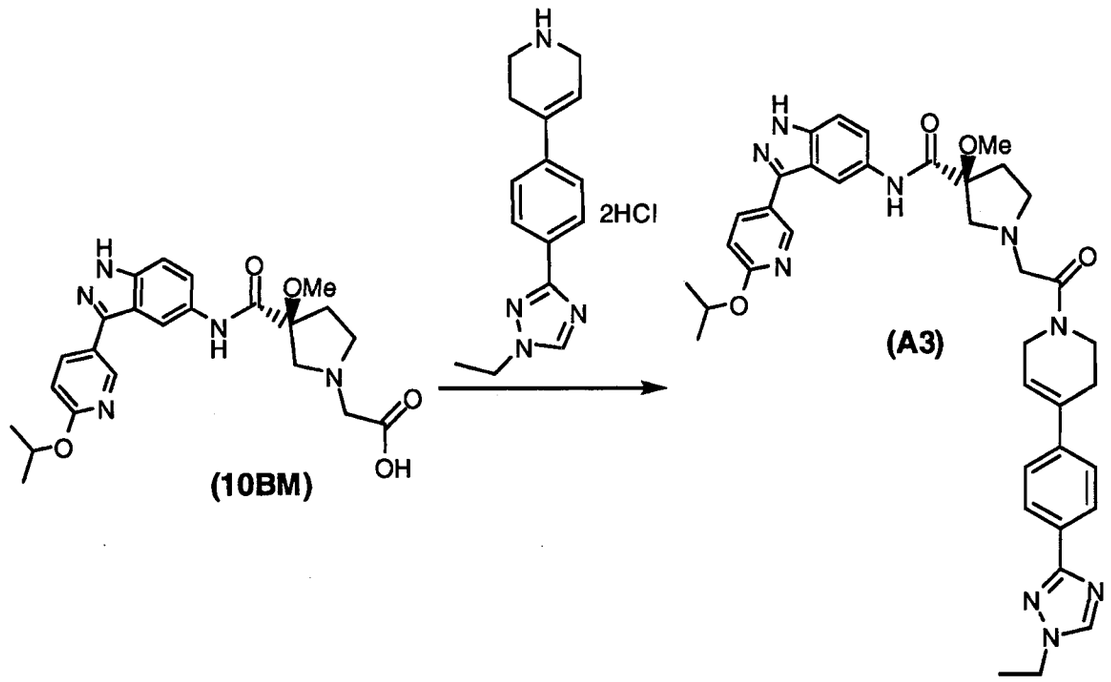
(8BM) (9BM)

The crude **8BM** (5.9 mmol) was stirred in a mixture of dichloromethane/MeOH (1:1, 20 ml), Oxo-acetic acid ethyl ester (10 ml, 50%) and NaBH(OAc)3 (10 ml) at r.t. overnight. The mixture was quenched with saturared aqueous sodium bicarbonate. Solvents were removed in vacuum. Dilute with water and ethyl acetate. Layers were separated and the separated aqueous layer was extracted with ethyl acetate (X3). The combined organic layers were dried ($MgSO_4$), filtered and solvents were removed in vacuum. Column purification gave **8BM** as yellow oil.



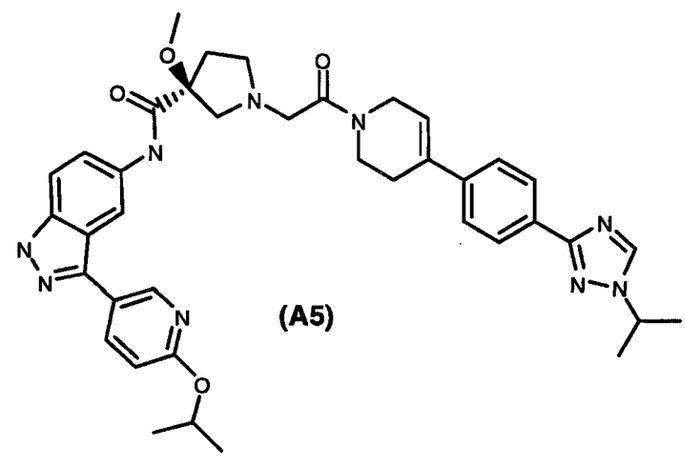
(9BM) (10BM)

The crude **9BM** (2.35 g) was stirred in a solution of LiOH (1M, 10 ml) and THF (10 ml) at r.t. overnight. The mixture was adjusted to pH 3. Solvents were removed in vacuum. The product was used for next step without purification.



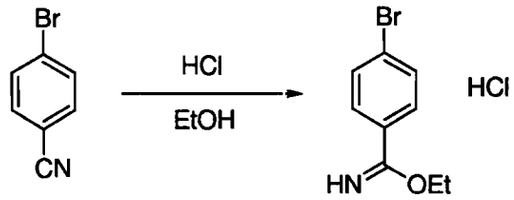
The crude **10BM** (49 mg), 4-[4-(1-Ethyl-1H-[1,2,4]triazol-3-yl)-phenyl]-1,2,3,6-tetrahydro-pyridine (25.4 mg), HATU (45 mg) ang triethyl amine (0.1 ml) was stirred in DMF (1 ml at r.t. overnight. The mixture was purified by HPLC to give **A3** as yellow oil. Mass spectrum: LCMS M+1= 690, retention time= 3.47 minutes

Example 6



Synthesis of 4-[4-(1-isopropyl-1*H*-[1,2,4]triazol-3-yl)-phenyl]-1,2,3,6-tetrahydro-pyridine hydrochloride

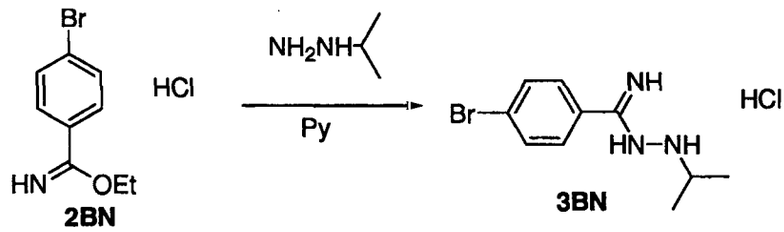
Step 1: Preparation of 4-bromo-benzimidic acid ethyl ester



1BN **2BN**

4-Bromo-benzonitrile (5g) was suspended in absolute EtOH (100 ml) and cooled to 0-5 ^{0} C. HCl gas was bubbled through, initially vigorously for several minutes and later slowly for 5 hours. The resulting solution was allowed to stir overnight. Most of solvent was removed and the precipitate was filtered, washed with EtOH twice and dried to afford compound **2BN** (4.1 g) as white solid. (Note: large scale synthesis may take longer time to get reaction complete. It is better to monitor the disappearance of starting material to get reaction end point.)

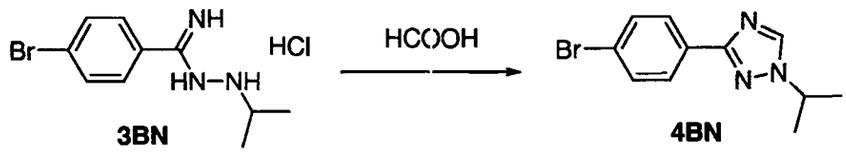
Step 2: Preparation of Compound 3BN



2BN **3BN**

The 4-bromo-benzimidic acid ethyl ester (1 g) was dissolved in pyridine (20 ml). Isopropylhydrazine (550 mg) was added with stirring and the resulting mixture was allowed to stir overnight. The reaction mixture was concentrated under reduced preessure, and added ether, filtered, washed with ether three times and dried to provide the compound **3BN** (0.9 g).

Step 3: Preparation of 3-(4-bromo-phenyl)-1-isopropyl-*1H*-[1, 2, 4]triazole

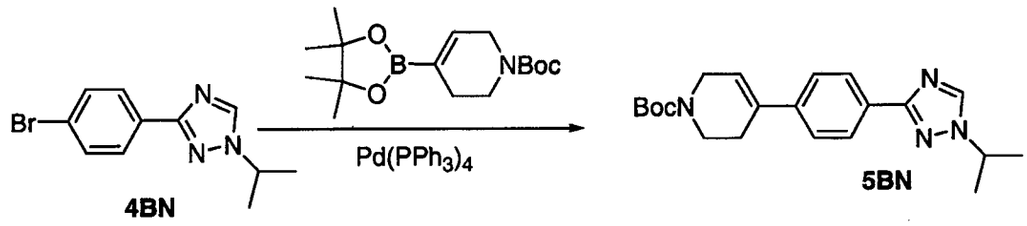


3BN **4BN**

A mixture of compound **3BN** (1 g) in formic acid (10 ml) was refluxed overnight and concentrated. The residue was treated with sat. $NaHCO_3$, and extracted with

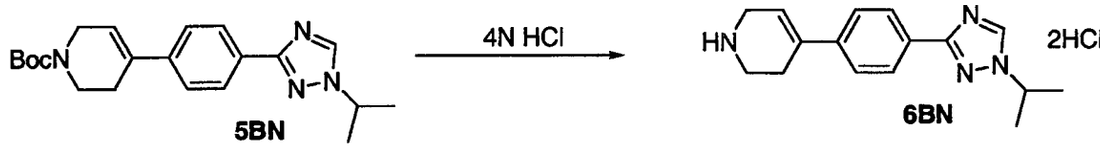
EtOAc three times. The combined organics were dried over $MgSO_4$. After concentration, compound **4BN** was obtained as colorless crystals (0.9 g).

Step 4: Preparation of 4-[4-(1-isopropyl-*1H*-[1,2,4]triazol-3-yl)-phenyl]-3,6-dihydro-*2H*-pyridine-1-carboxylic acid *tert*-butyl ester



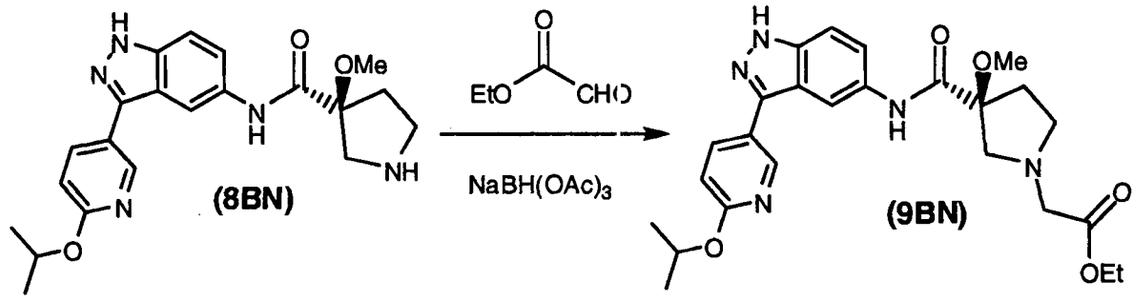
To a pressure flask were charged compound **4BN** (500 mg), 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester (583 mg), $Pd(PPh_3)_4$ (112 mg), Na_2CO_3 2N (3 ml) and Dioxane (10 ml). The mixture was briefly degassed with Ar for ~0.5 minute, capped and stirred at 100C overnight. After cooling, the reaction mixture was diluted with EtOAc and brine. Organic layer was isolated, and dried ($MgSO_4$). After concentration, the residue was purified on silica gel. Elution with MeOH/EtOAc (0-10%) gave the desired product **5BN** (410 mg).

Step 5: Preparation of 4-[4-(1-isopropyl-1*H*-[1,2,4]triazol-3-yl)-phenyl]-1,2,3,6-tetrahydro-pyridine hydrochloride

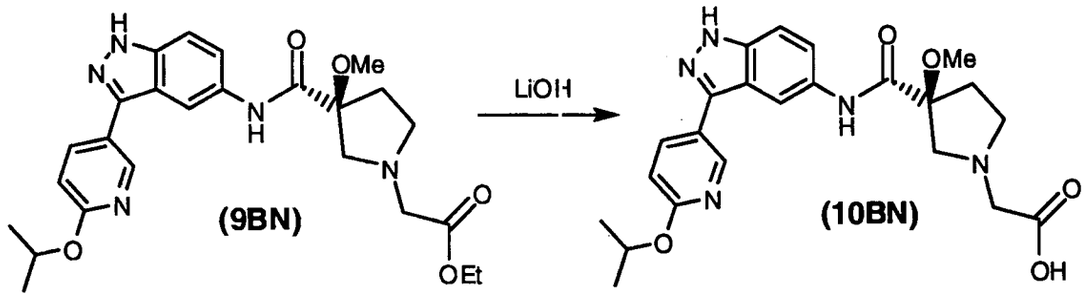


The Boc group can be removed by treating compound **5BN** with 4N HCl in dioxane at rt for two hours. Removal of solvent under vacuum gave compound **6BN**.

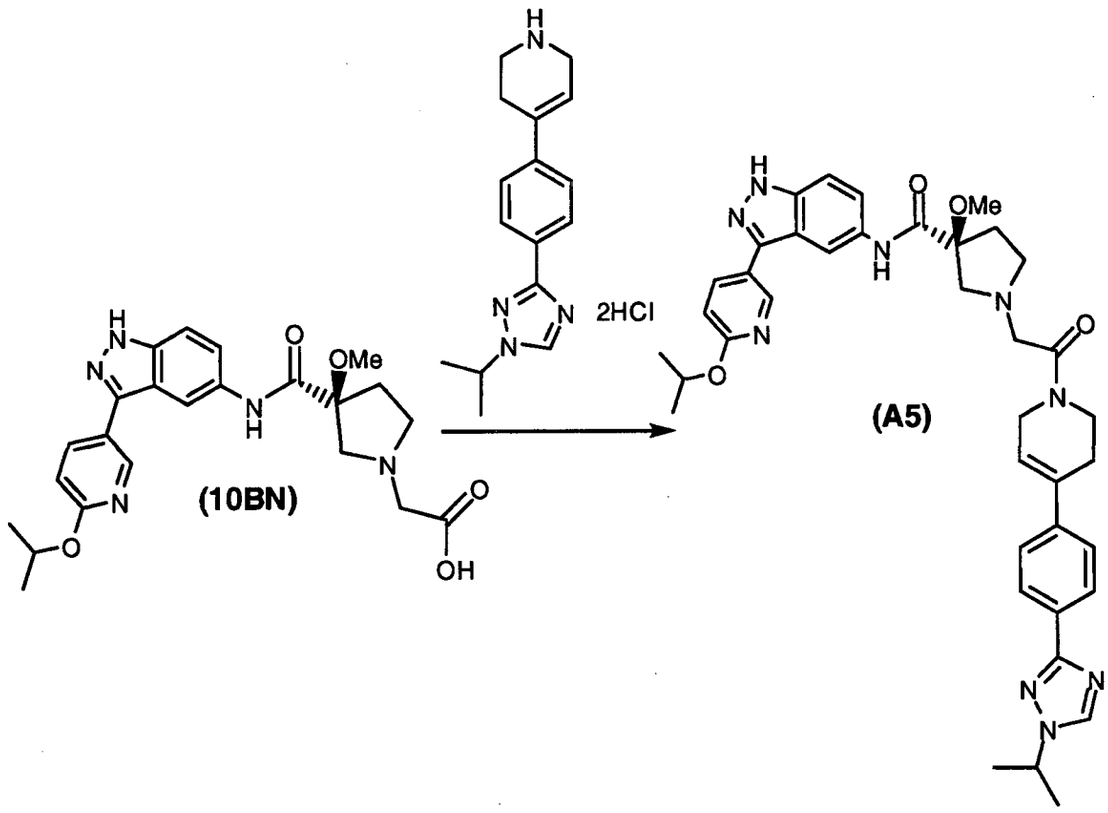
Synthesis of 1-(2-{4-[4-(1-Isopropyl-1H-[1,2,4]triazol-3-yl)-phenyl]-3,6-dihydro-2H-pyridin-1-yl}-2-oxo-ethyl)-3-methoxy-pyrrolidine-3-carboxylic acid [3-(6-isopropoxy-pyridin-3-yl)-1H-indazol-5-yl]-amide



The crude **8BN** (5.9 mmol) was stirred in a mixture of dichloromethane/MeOH (1:1, 20 ml), Oxo-acetic acid ethyl ester (10 ml, 50%) and NaBH(OAc)3 (10 ml) at r.t. overnight. The mixture was quenched with saturared aqueous sodium bicarbonate. Solvents were removed in vacuum. Dilute with water and ethyl acetate. Layers were separated and the separated aqueous layer was extracted with ethyl acetate (X3). The combined organic layers were dried ($MgSO_4$), filtered and solvents were removed in vacuum. Column purification gave **9BN** as yellow oil in 65% yield.



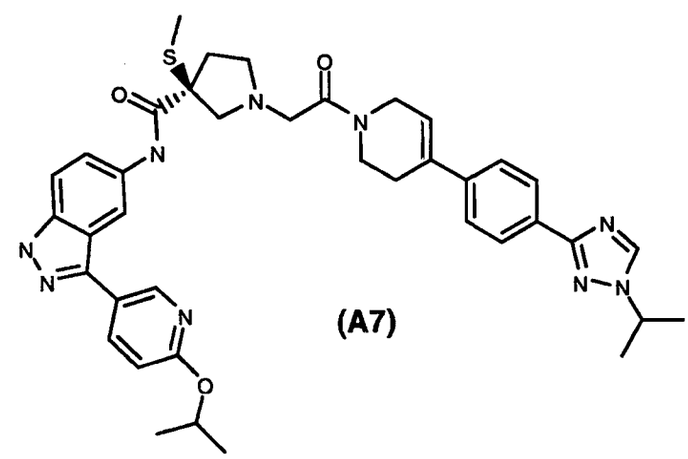
The crude **9 BN** (2.35 g) was stirred in a solution of LiOH (1M, 10 ml) and THF (10 ml) at r.t. overnight. The mixture was adjusted to pH 3. Solvents were removed in vacuum. The product was used for next step without purification, yield was quantitative.



The crude **10BN** (60 mg), 4-[4-(1-Isopropyl-1H-[1,2,4]triazol-3-yl)-phenyl]-1,2,3,6-tetrahydro-pyridine (35 mg), HATU (52 mg) ang triethyl amine (0.1 ml) was stirred in DMF (1 ml at r.t. overnight. The mixture was purified by HPLC to gave **A5** as yellow oil. Mass spectrum: LCMS M+1= 704, retention time= 3.56 minutes

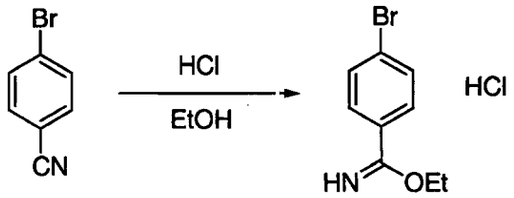
Example 7

Synthesis of 1-(2-{4-[4-(1-Isopropyl-1H-[1,2,4]triazol-3-yl)-phenyl]-3,6-dihydro-2H-pyridin-1-yl}-2-oxo-ethyl)-3-methoxy-pyrrolidine-3-carboxylic acid [3-(6-isopropoxy-pyridin-3-yl)-1H-indazol-5-yl]-amide



Synthesis of 4-[4-(1-isopropyl-1*H*-[1,2,4]triazol-3-yl)-phenyl]-1,2,3,6-tetrahydro-pyridine hydrochloride

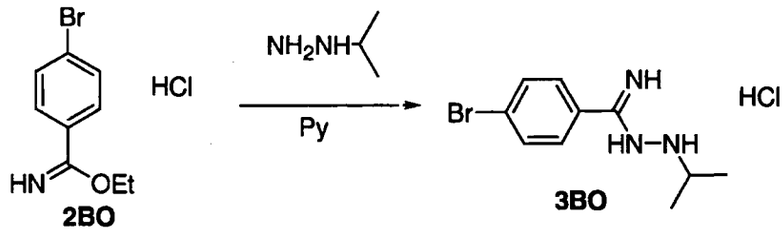
Step 1: Preparation of 4-bromo-benzimidic acid ethyl ester



1BO **2BO**

4-Bromo-benzonitrile (5g) was suspended in absolute EtOH (100 ml) and cooled to 0-5 ^{0} C. HCl gas was bubbled through, initially vigorously for several minutes and later slowly for 5 hours. The resulting solution was allowed to stir overnight. Most of solvent was removed and the precipitate was filtered, washed with EtOH twice and dried to afford compound **2BO** (4.1 g) as white solid.

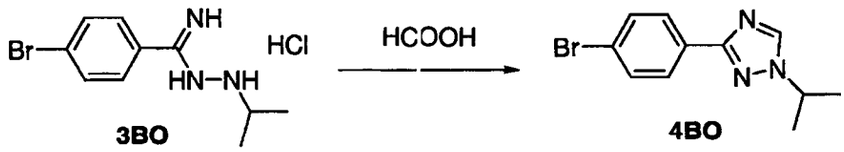
Step 2: Preparation of Compound 3BO



2BO **3BO**

The 4-bromo-benzimidic acid ethyl ester (1 g) was dissolved in pyridine (20 ml). Isopropylhydrazine (550 mg) was added with stirring and the resulting mixture was allowed to stir overnight. The reaction mixture was concentrated under reduced preessure, and added ether, filtered, washed with ether three times and dried to provide the compound **3BO** (0.9 g).

Step 3: Preparation of 3-(4-bromo-phenyl)-1-isopropyl-*1H*-[1, 2, 4]triazole:

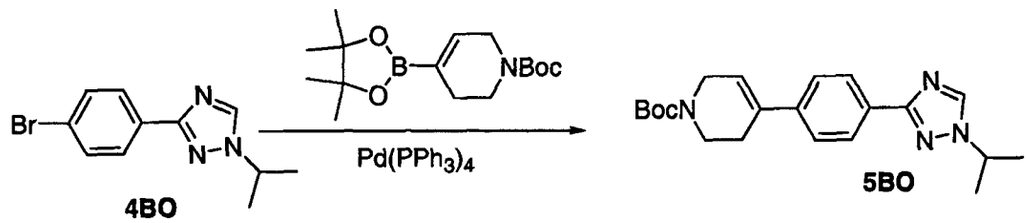


3BO **4BO**

A mixture of compound **3BO** (1 g) in formic acid (10 ml) was refluxed overnight and concentrated. The residue was treated with sat. $NaHCO_3$, and extracted with EtOAc three times. The combined organics were dried over $MgSO_4$. After

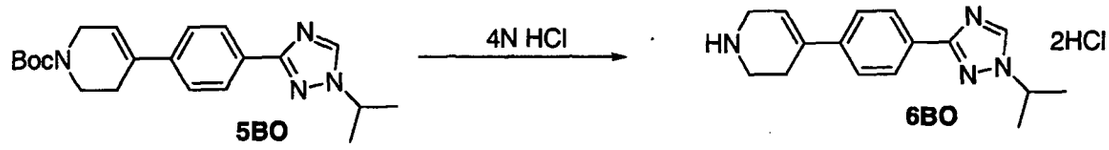
concentration, compound **4BO** was obtained as colorless crystals (0.9 g). (Note: it was found that the reaction can be done in just two hours. In large scale synthesis, use 10% NaOH to replace $NaHCO_3$).

Step 4: Preparation of 4-[4-(1-isopropyl-*1H*-[1,2,4]triazol-3-yl)-phenyl]-3,6-dihydro-*2H*-pyridine-1-carboxylic acid *tert*-butyl ester



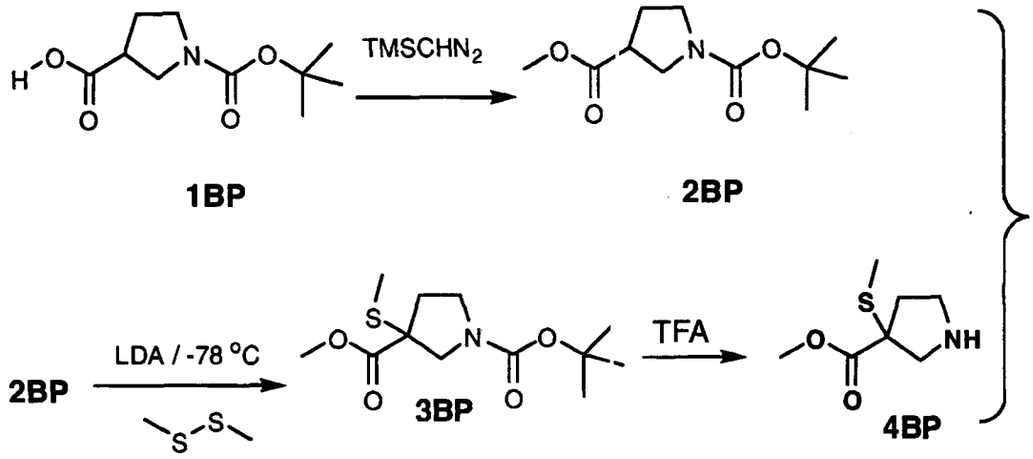
To a large pressure flask were charged compound **4BO** (500 mg), 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester (583 mg), $Pd(PPh_3)_4$ (112 mg), Na_2CO_3 2N (3 ml) and Dioxane (10 ml). The mixture was briefly degassed with Ar for ~0.5 minute, capped and stirred at 100C overnight. After cooling, the reaction mixture was diluted with EtOAc and brine. Organic layer was isolated, and dried ($MgSO_4$). After concentration, the residue was purified on silica gel. Elution with MeOH/EtOAc (0-10%) gave the desired product **5BO** (410 mg).

Step 5: Preparation of 4-[4-(1-isopropyl-1*H*-[1,2,4]triazol-3-yl)-phenyl]-1,2,3,6-tetrahydro-pyridine hydrochloride



The Boc group can be removed by treating compound **5BO** with 4N HCl in dioxane at rt for two hours. Removal of solvent under vacuum gave compound **6BO**.

Preparation and Chiral resolution of of 3-Methylsulfanyl-pyrrolidine-3-carboxylic acid methyl ester 4BP

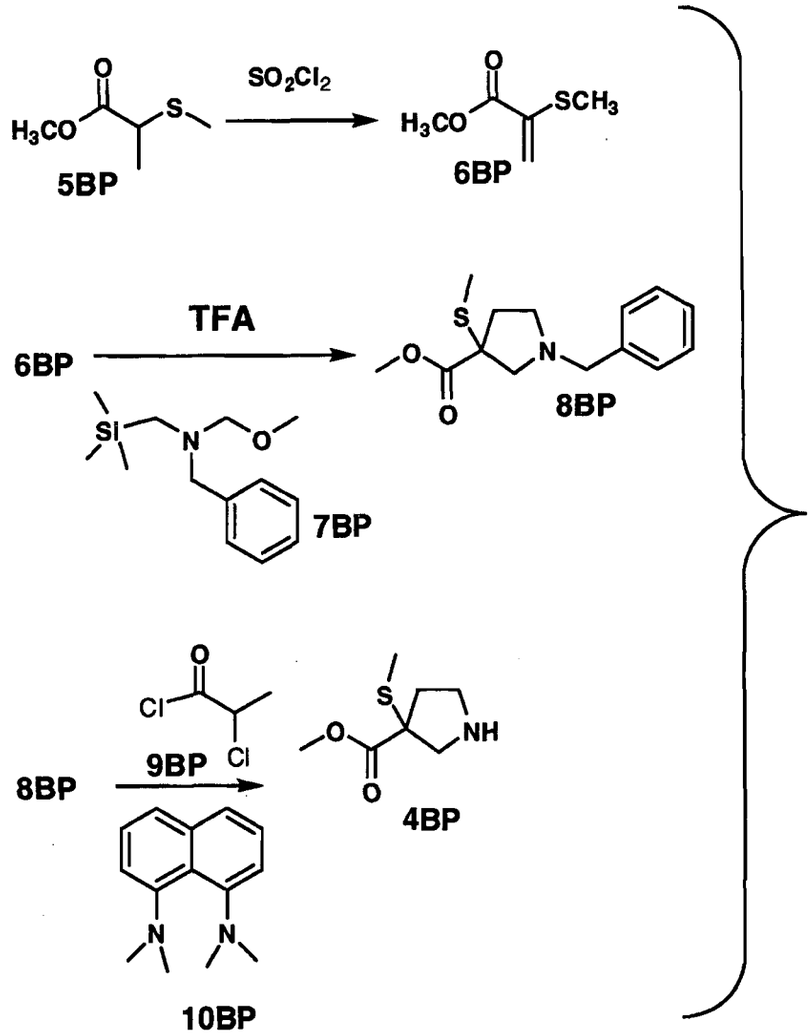


Pyrrolidine-1,3-dicarboxylic acid 1-tert-butyl ester **1BP** (4.3 gm, 20 mmol) was dissolved in 28 mL of toluene and 3.5 ml of methanol. Trimethylsilyldiazomethane 2N solution in hexanes (13 ml, 26 mmol) was added drop wise at 0 C and the reaction mixture stirred for 10 min at ambient temperature. The mixture was evaporated to obtain 4.3 gm of oil.

To the oil **2BP** (0.5 gm, 2.1 mmol) dissolved in tetrahydrofuran (15 ml) 1.2 ml of lithium diisopropylamide 2N solution in hexanes was added drop wise 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 **3BP** after column chromatography.

3-Methylsulfanyl-pyrrolidine-1,3-dicarboxylic acid 1-tert-butyl ester 3-methyl ester (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 give 3.35 g of 3-Methylsulfanyl-pyrrolidine-3-carboxylic acid methyl ester **4BP** as a gummy solid.

Alternatively 4BP can be prepared as follows:



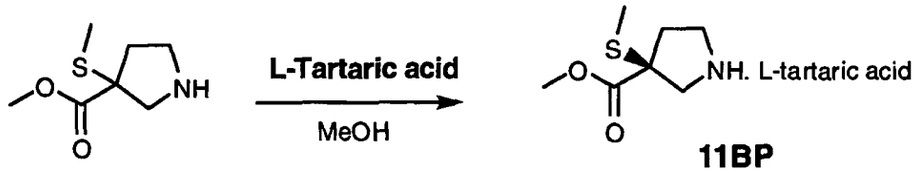
2-Methylsulfanyl-propionic acid methyl ester **5BP** (25 g, 0.1 mol) dissolved in chloroform was added sulfuryl chloride (15.1 mL, 0.1 mol) slowly at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and then refluxed at 65 °C for 30 min. The reaction mixture then concentrated to dryness to give 23.75 g of 2-Methylsulfanyl-acrylic acid methyl ester **6BP** as a liquid.

To a stirred solution of 2-ethoxyacrylate 2-Methylsulfanyl-acrylic acid methyl ester **6BP** (136 g, 1.03 mol) and benzyl-methoxymethyl-trimethylsilanylmethyl-amine **7BP** (290 g, 1.22 mol) in dichloromethane (2.7 L ml) was added at 0 °C a solution of trifluroacetic acid (26 mL, 0.3 mol). The resulting solution was warmed to room temperature and stirred for one overnight. The crude product was purified by column chromatography on silica gel eluting with a solution of ethyl acetate in hexane (1:4) to

give 1-benzyl-3-methylsulfanyl-pyrrolidine-3-carboxylic acid methyl ester **8BP** (131 g, 47%).

To 1-benzyl-3-methylsulfanyl-pyrrolidine-3-carboxylic acid methyl ester **8BP** (131 g, 493.7 mmol) dissolved in dichloroethane (2.6 L) at 0 °C was added N,N,N',N'-Tetramethyl-naphthalene-1,8-diamine **9BP** (31.8 g, 0.144 mmol) and then 2-Chloro-propionyl chloride **10BP** (64 mL, 593.1 mmol) sequentially. The reaction mixture was stirred for one overnight at ambient temperature and then concentrated to dryness. The residue was dissolved in 2.8 L of methanol and refluxed at 65 °C for 3.5 h. The reaction mixture was then concentrated to dryness and the residue was purified by column chromatography on silica gel eluting with a solution of methanol in dichloromethane (1:9) to give 3-Methylsulfanyl-pyrrolidine-3-carboxylic acid methyl ester **4BP** (75 g, 86%).

Chiral resolution of 3-Methylsulfanyl-pyrrolidine-3-carboxylic acid methyl ester 4BP



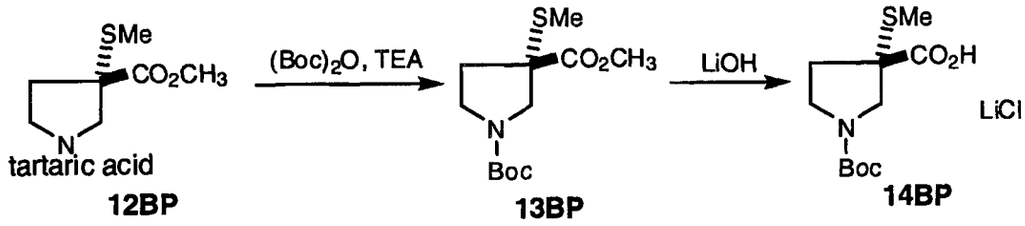
4BP **11BP**

3-Methylsulfanyl-pyrrolidine-3-carboxylic acid methyl ester **4BP** (42.9g, 244.8 mmol) and L-tartaric acid (36.7 g, 244.8 mmol) were placed in a 1L round bottomed flask and dissolved with 250 mL of methanol. The flask was then attached to a rotavapor at 75 °C. The mixture was allowed to gently spin at this temperature for about 20 min. to ensure complete dissolution. After the formation of a clear solution, about 10mg of authentic crystals of 3-Methylsulfanyl-pyrrolidine-3-carboxylic acid methyl ester **11BP** were added (to seed and aid the crystal formation) was allowed to settle gently for crystal formation. After 3 days, 19.4g of crystals were filtered which was then washed with cold methanol (20 -30 mL) to give 18.2g of crystalline 3-Methylsulfanyl-pyrrolidine-3-carboxylic acid methyl ester **11BP**.

The chiral purity of the crystals 3-Methylsulfanyl-pyrrolidine-3-carboxylic acid methyl ester **11BP** was determined by derivatizing with 4-nitrobenzyl chloroformate and subjecting it to analytical HPLC (Chiracel AD column) under the conditions of

20% isopropanol/hexane solvent system with a flow rate of 1mL/min. The purity was found to be >99.9% with a retention time of 16.58 min.

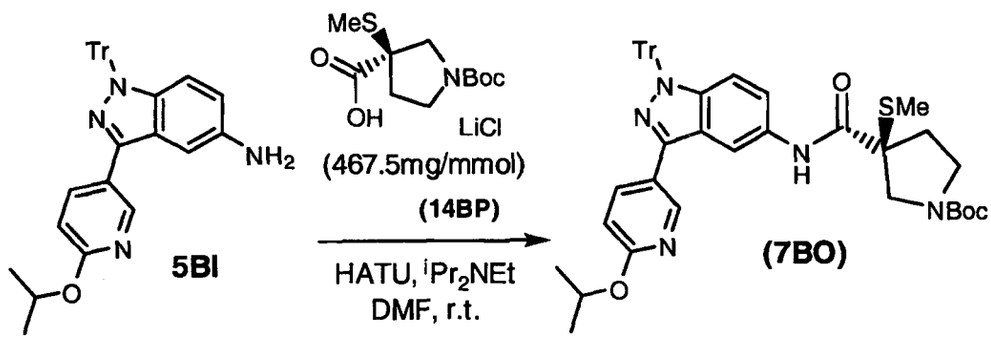
Preparation of 3-Methylsulfanyl-pyrrolidine-1,3-dicarboxylic acid 1-tert-butyl ester



To a cold (0°C) solution of **12BP** (28 g, 90.52 mmol) in dry CH_2Cl_2 (250 mL) was added triethylamine (31.5 mL, 226.32 mmol, 2.5 equiv) followed by $(Boc)_2O$ (25.7 g, 117.68 mmol, 1.3 equiv). The resulting mixture was stirred from 0°C to rt for overnight then diluted with CH_2Cl_2, which was washed with saturated aqueous $NaHCO_3$ solution and brine, dried ($MgSO_4$) and concentrated. Chromatograph on silica gel (hexanes/ethyl acetate, 4:1) gave **13BP** (23.5 mg, 90.52 mmol, 100%) as a colorless oil.

To a stirred solution of **13BP** (23.5 mg, 90.52 mmol) in THF/MeOH (175 mL/175 mL) was added 135 mL of LiOH (1M in H_2O, 135 mmol, 1.5 equiv). The reaction mixture was stirred at rt for overnight, to which 135 mL of 1N HCl was added. The resulting mixture was stirred for additional 15 min and concentrated to give **14BP**.

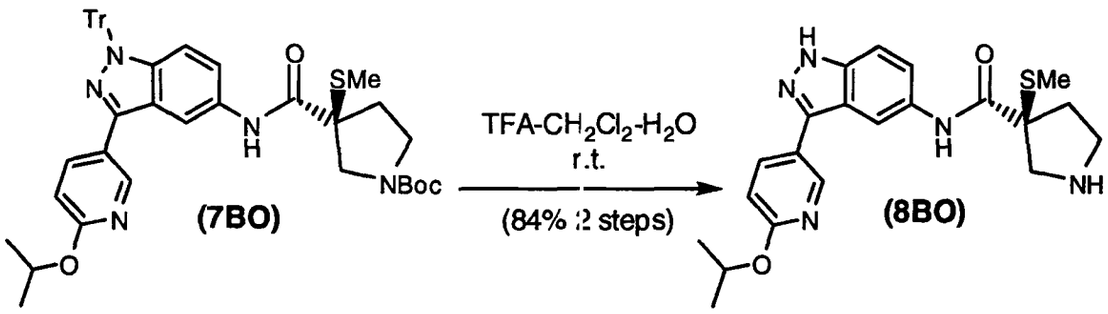
Step 1:



Aminoindazole **5BI** (39g, 0.076mol) and pyrrolidinecarboxylic acid **14BP** (32g, 0.069mol) were dissolved in DMF (300ml) at r.t. HATU (29g, 0.076mol) followed by $^iPr_2NEt$ (14.5ml, 0.083mol) were added. The mixture was stirred at r.t. overnight and

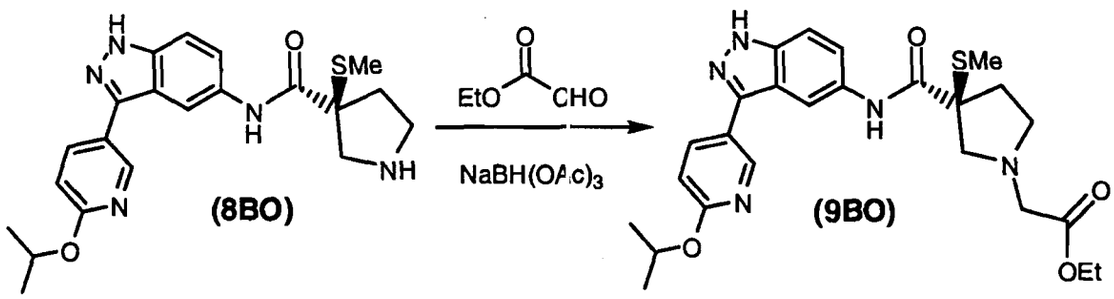
was diluted with ethyl acetate and water. Layers were separated. The separated organic layer was washed with water (X2), dried ($MgSO_4$) and filtered. Concentration in vacuum followed by column purification [hexanes – ethyl acetate = 4:1 (v/v)] gave crude **7BO** as off-white foam.

Step 2:



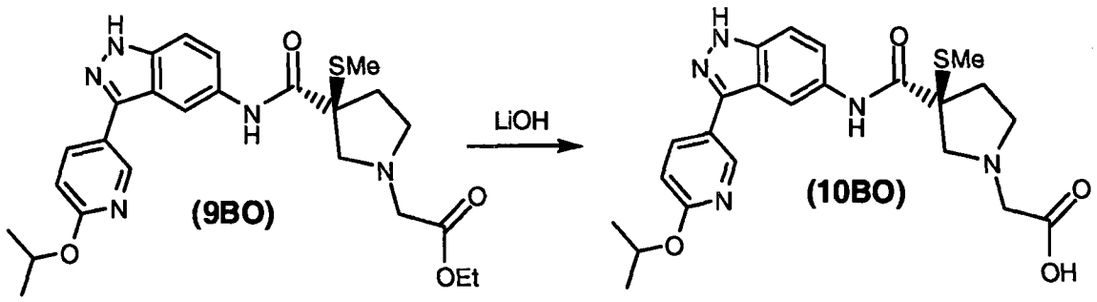
The crude **7BO** was stirred in a mixture of dichloromethane (300ml), trifluoroacetic acid (100ml) and water (50ml) at r.t. overnight. The mixture was cooled at 0 °C and quenched carefully with saturared aqueous sodium bicarbonate. Solvents were removed in vacuum. Dilute with water and ethyl acetate. Layers were separated and the separated aqueous layer was extracted with ethyl acetate (X3). The combined organic layers were dried ($MgSO_4$), filtered and solvents were removed in vacuum. Column purification [5 to 10% MeOH (7N ammonia) in dichloromethane] gave pyrrolidine **8BO** (23g, 84%) as off-white solid.

Synthesis of 1-(2-{4-[4-(1-Isopropyl-1H-[1,2,4]triazol-3-yl)-phenyl]-3,6-dihydro-2H-pyridin-1-yl}-2-oxo-ethyl)-3-methylsulfanyl-pyrrolidine-3-carboxylic acid [3-(6-isopropoxy-pyridin-3-yl)-1H-indazol-5-yl]-amide

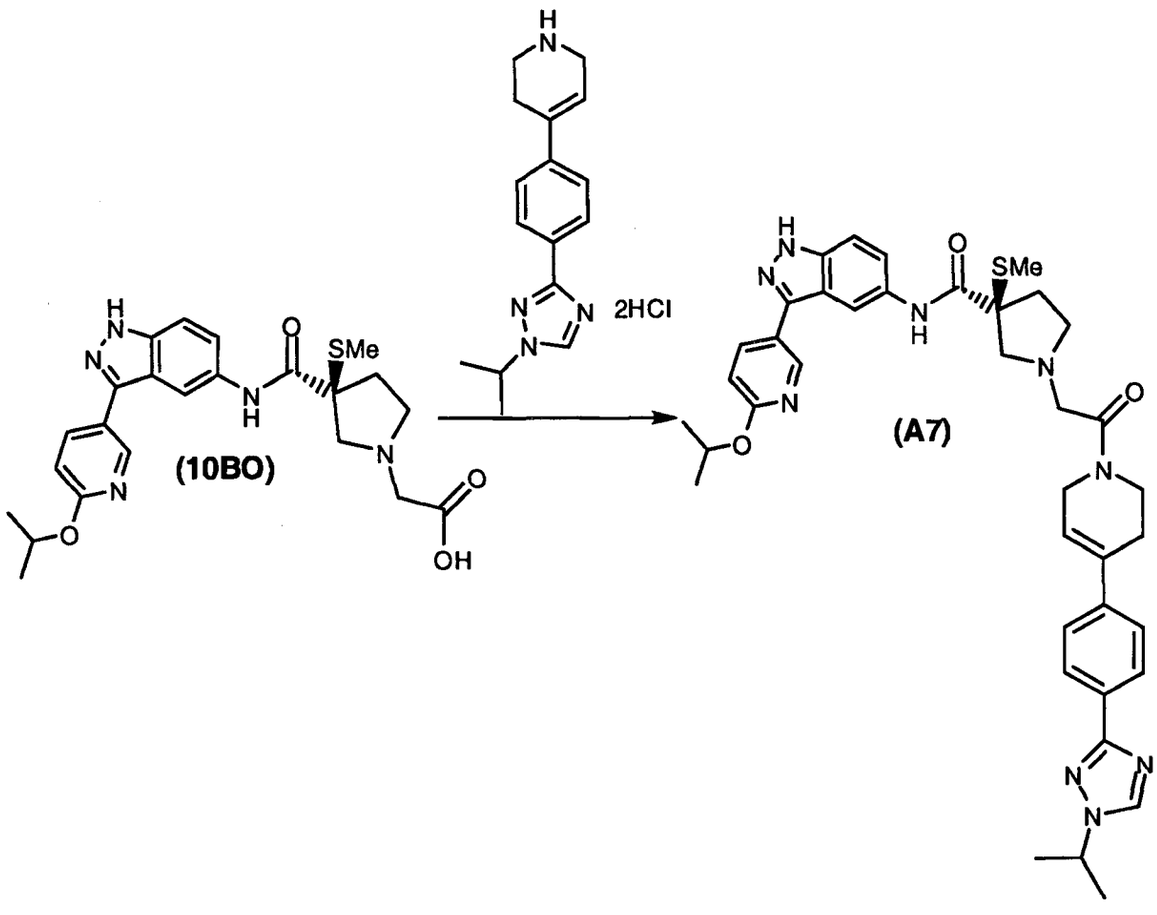


The crude **8BO** (5.9 mmol) was stirred in a mixture of dichloromethane/MeOH (1:1, 20 ml), Oxo-acetic acid ethyl ester (10 ml, 50%) and NaBH(OAc)3 (10 ml) at r.t. overnight. The mixture was quenched with saturared aqueous sodium bicarbonate.

Solvents were removed in vacuum. Dilute with water and ethyl acetate. Layers were separated and the separated aqueous layer was extracted with ethyl acetate (X3). The combined organic layers were dried ($MgSO_4$), filtered and solvents were removed in vacuum. Column purification gave **9BO** as yellow oil.



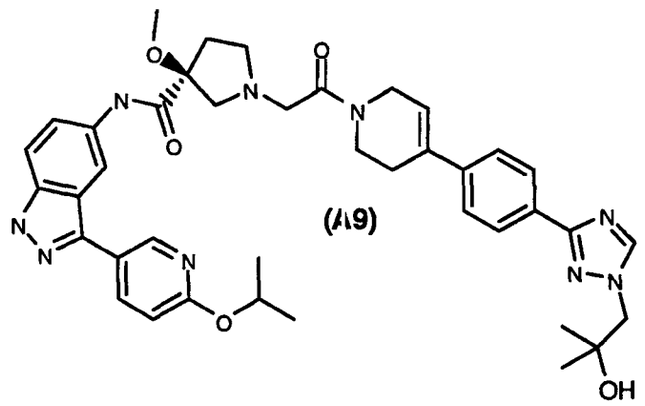
The crude **9BO** (2.35 g) was stirred in a solution of LiOH (1M, 10 ml) and THF (10 ml) at r.t. overnight. The mixture was adjusted to pH 3. Solvents were removed in vacuum. The product was used for next step without purification.



The crude **10BO** (60 mg), 4-[4-(1-Isopropyl-1H-[1,2,4]triazol-3-yl)-phenyl]-1,2,3,6-tetrahydro-pyridine (35 mg), HATU (52 mg) ang triethyl amine (0.1 ml) was stirred in DMF (1 ml at r.t. overnight. The mixture was purified by HPLC to gave **11BO** as yellow oil. Mass spectrum: LCMS M+1= 720, retention time= 3.68 minutes.

Example 8

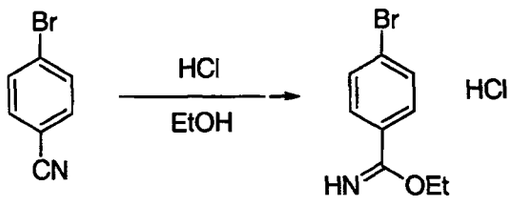
Preparation of 1-[2-(4-{4-[1-(2-Hydroxy-2-methyl-propyl)-1H-[1,2,4]triazol-3-yl]-phenyl}-3,6-dihydro-2H-pyridin-1-yl)-2-oxo-ethyl]-3-methoxy-pyrrolidine-3-carboxylic acid [3-(6-isopropoxy-pyridin-3-yl)-1H-indazol-5-yl]-amide



(A9)

Synthesis of 2-chloro-1-{4-[4-(1-ethyl-1*H*-[1,2,4]triazol-3-yl)-phenyl]-3,6-dihydro-2*H*-pyridin-1-yl}-ethanone

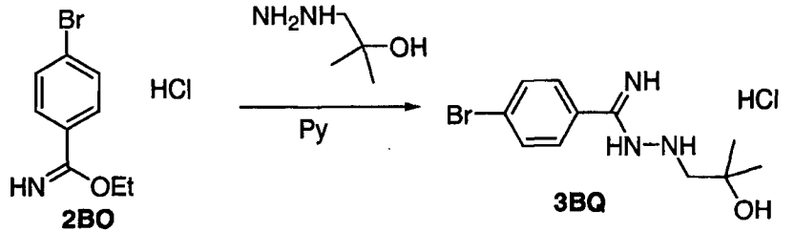
Step 1: Preparation of 4-bromo-benzimidic acid ethyl ester



1BO **2BO**

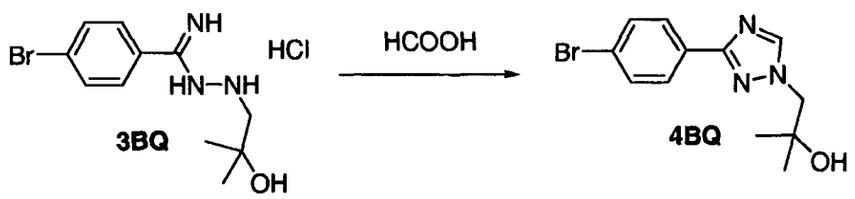
4-Bromo-benzonitrile (5g) was suspended in absolute EtOH (100 ml) and cooled to 0-5 ^{0} C. HCl gas was bubbled through, initially vigorously for several minutes and later slowly for 5 hours. The resulting solution was allowed to stir overnight. Most of solvent was removed and the precipitate was filtered, washed with EtOH twice and dried to afford compound **2BO** (4.1 g) as white solid.

Step 2: Preparation of Compound 3BQ:



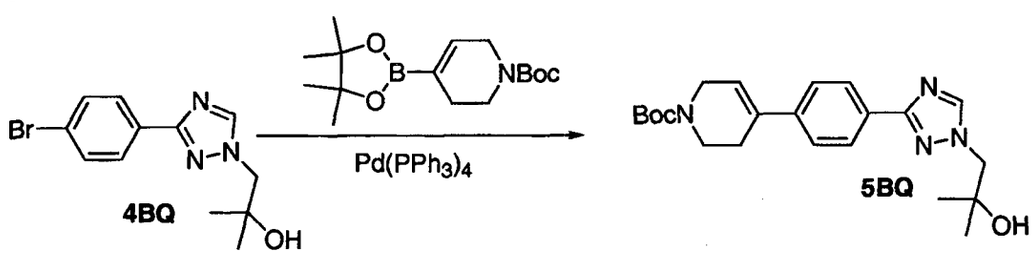
The 4-bromo-benzimidic acid ethyl ester (1.68 g) was dissolved in pyridine (10 ml). 1-Hydrazino-2-methyl-propan-2-ol (1 g) was added with stirring and the resulting mixture was allowed to stir overnight. The reaction mixture was concentrated under reduced pressure, and added ether, filtered, washed with ether three times and dried to provide the compound **3BQ** (1 g).

Step 3: Preparation of 1-[3-(4-Bromo-phenyl)-[1,2,4]triazol-1-yl]-2-methyl-propan-2-ol:



A mixture of compound **3BQ** (1 g) in formic acid (10 ml) was refluxed overnight and concentrated. The residue was treated with sat. $NaHCO_3$, and extracted with EtOAc three times. The combined organics were dried over $MgSO_4$. After concentration, compound **4BQ** was obtained as colorless crystals (0.9 g).

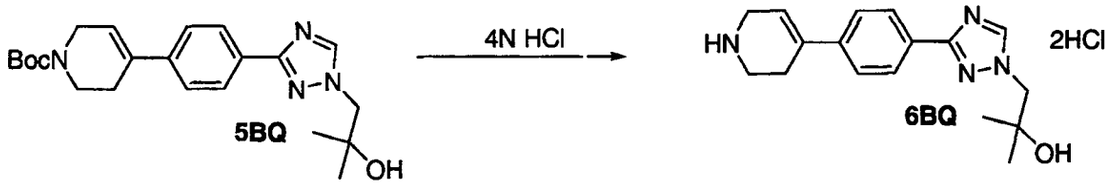
Step 4: Preparation of 4-{4-[1-(2-Hydroxy-2-methyl-propyl)-1H-[1,2,4]triazol-3-yl]-phenyl}-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester



To a large pressure flask were charged compound **4BQ** (400 mg), 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester (540 mg), $Pd(PPh_3)_4$ (180 mg), Na_2CO_3 2N (3 ml) and Dioxane/EtOH/water (7:3:2, 10 ml). The mixture was briefly degassed with Ar for ~0.5 minute, capped

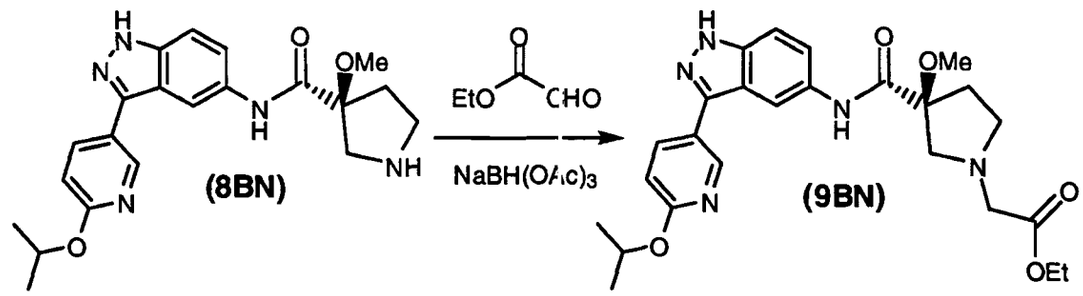
and microwaved at 120C for 20 mins. After cooling, the reaction mixture was diluted with EtOAc and brine. Organic layer was isolated, and dried ($MgSO_4$). After concentration, the residue was purified on silica gel. Elution with MeOH/EtOAc (0-10%) gave the desired product **5BQ** (310 mg).

Step 5: Preparation of 2-Methyl-1-{3-[4-(1,2,3,6-tetrahydro-pyridin-4-yl)-phenyl]-[1,2,4]triazol-1-yl}-propan-2-ol

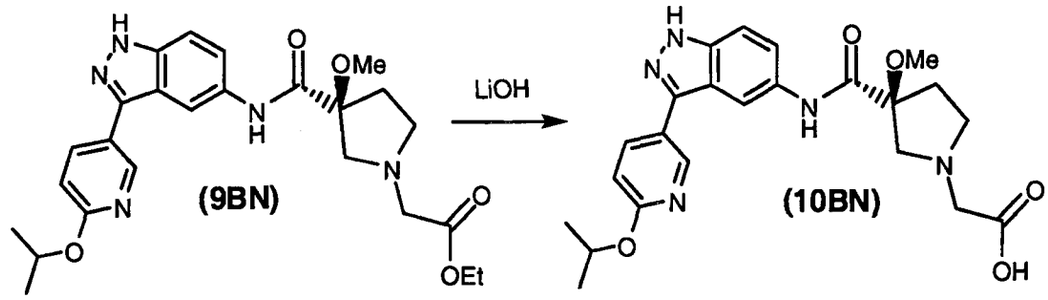


The Boc group can be removed by treating compound **5BQ** with 4N HCl in dioxane at rt for two hours. Removal of solvent under vacuum gave compound **6BQ**.

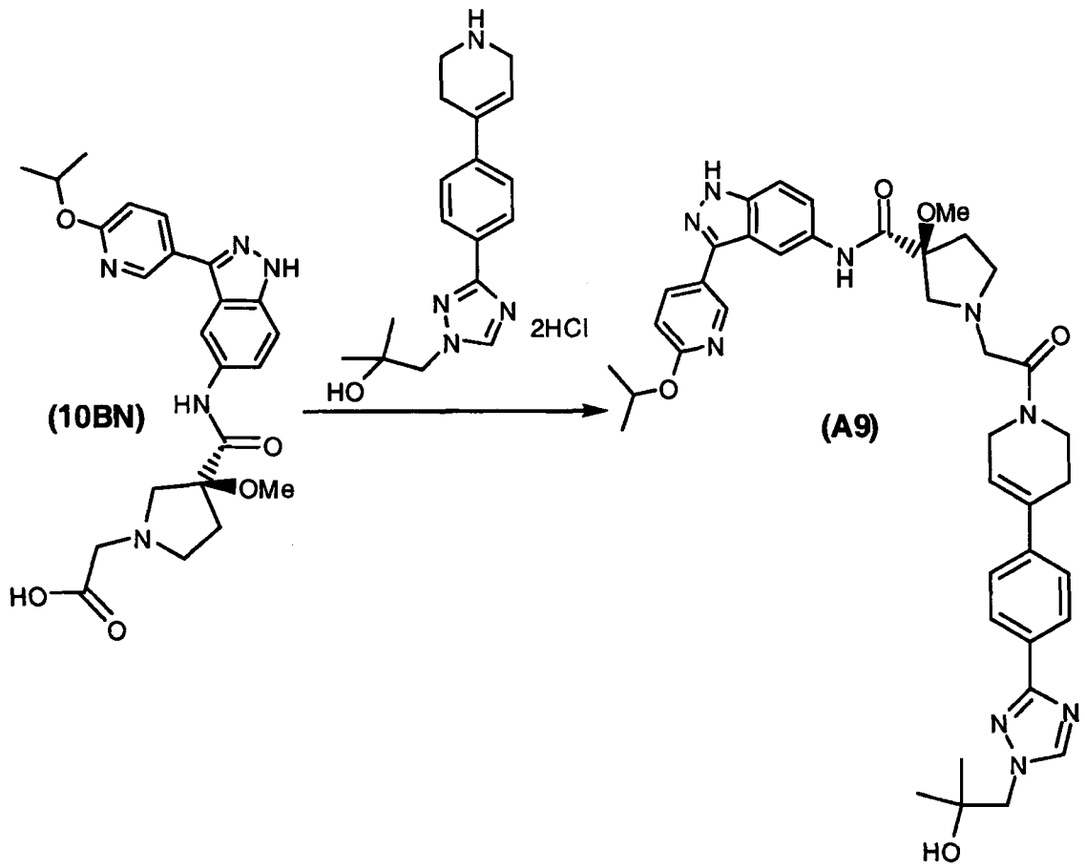
Synthesis of 1-[2-(4-{4-[1-(2-Hydroxy-2-methyl-propyl)-1H-[1,2,4]triazol-3-yl]-phenyl}-3,6-dihydro-2H-pyridin-1-yl)-2-oxo-ethyl]-3-methoxy-pyrrolidine-3-carboxylic acid [3-(6-isopropoxy-pyridin-3-yl)-1H-indazol-5-yl]-amide



The crude **8BN** (5.9 mmol) was stirred in a mixture of dichloromethane/MeOH (1:1, 20 ml), Oxo-acetic acid ethyl ester (10 ml, 50%) and NaBH(OAc)3 (10 ml) at r.t. overnight. The mixture was quenched with saturared aqueous sodium bicarbonate. Solvents were removed in vacuum. Dilute with water and ethyl acetate. Layers were separated and the separated aqueous layer was extracted with ethyl acetate (X3). The combined organic layers were dried ($MgSO_4$), filtered and solvents were removed in vacuum. Column purification gave **9BN** as yellow oil.



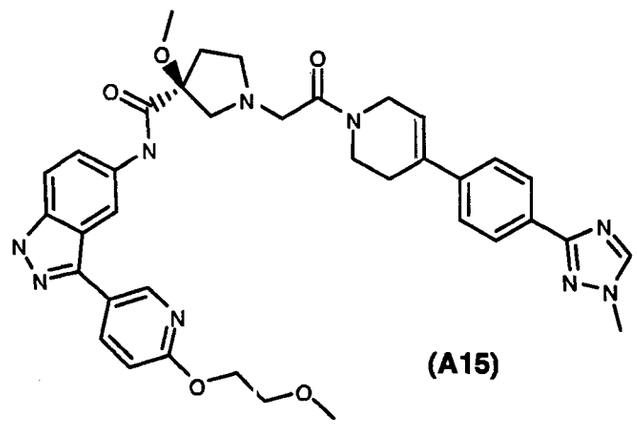
The crude **9BN** (2.35 g) was stirred in a solution of LiOH (1M, 10 ml) and THF (10 ml) at r.t. overnight. The mixture was adjusted to pH 3. Solvents were removed in vacuum. The product was used for next step without purification.



The crude **10BN** (60 mg), 2-Methyl-1-{3-[4-(1,2,3,6-tetrahydro-pyridin-4-yl)-phenyl]-[1,2,4]triazol-1-yl}-propan-2-ol (38 mg), HATU (50 mg) ang triethyl amine (0.1 ml) was stirred in DMF (1 ml at r.t. overnight. The mixture was purified by HPLC to gave **A9** as yellow oil, 50%. Mass spectrum: LCMS M+1= 734, retention time= 3.32 minutes.

Example 9

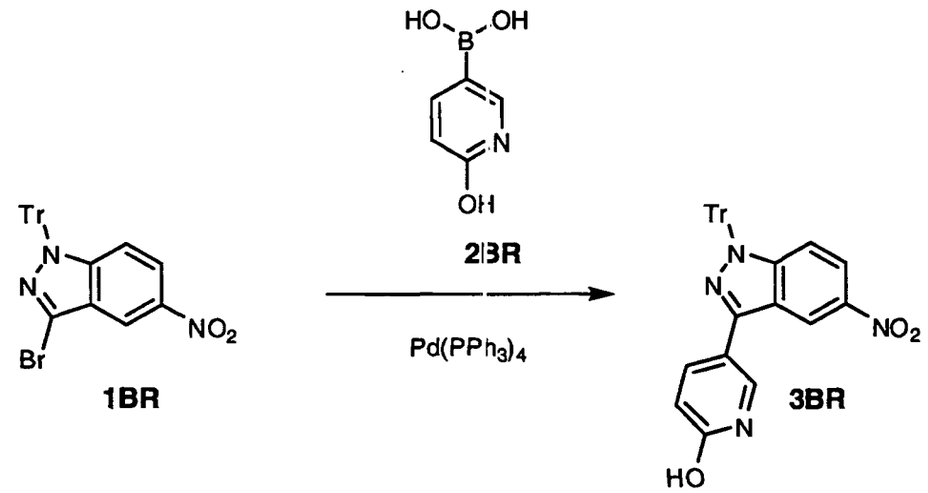
Preparation of 3-Methoxy-1-(2-{4-[4-(1-methyl-1H-[1,2,4]triazol-3-yl)-phenyl]-3,6-dihydro-2H-pyridin-1-yl}-2-oxo-ethyl)-pyrrolidine-3-carboxylic acid {3-[6-(2-methoxy-ethoxy)-pyridin-3-yl]-1H-indazol-5-yl}-amide



(A15)

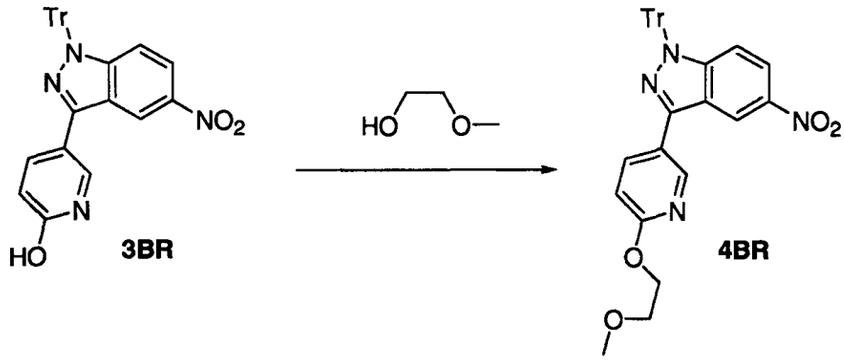
Synthesis of 3-Methoxy-pyrrolidine-3-carboxylic acid {3-[6-(2-methoxy-ethoxy)-pyridin-3-yl]-1H-indazol-5-yl}-amide

Step 1:



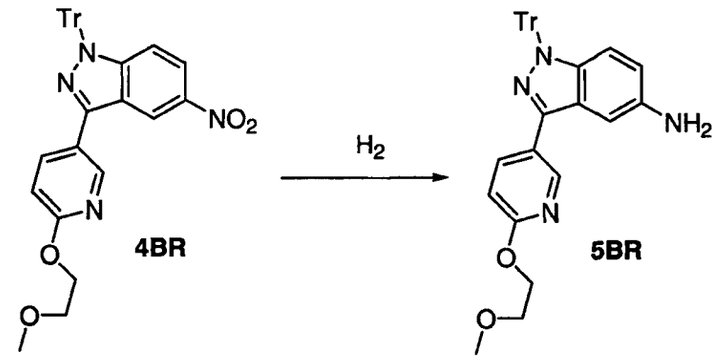
To a pressure flask were charged compound **1BR** (1.75 g), **2BR** (0.5 g), $Pd(PPh_3)_4$ (210 mg), Na_2CO_3 2N (10 ml) and Dioxane (10 ml). The mixture was briefly degassed with Ar for ~0.5 minute, capped and stirred at 100 °C overnight. After cooling, the reaction mixture was diluted with EtOAc and brine. Organic layer was isolated, and dried ($MgSO_4$). After concentration, the residue was purified on silica gel. Elution gave the desired product **3BR** (0.8 g).

Step 2:



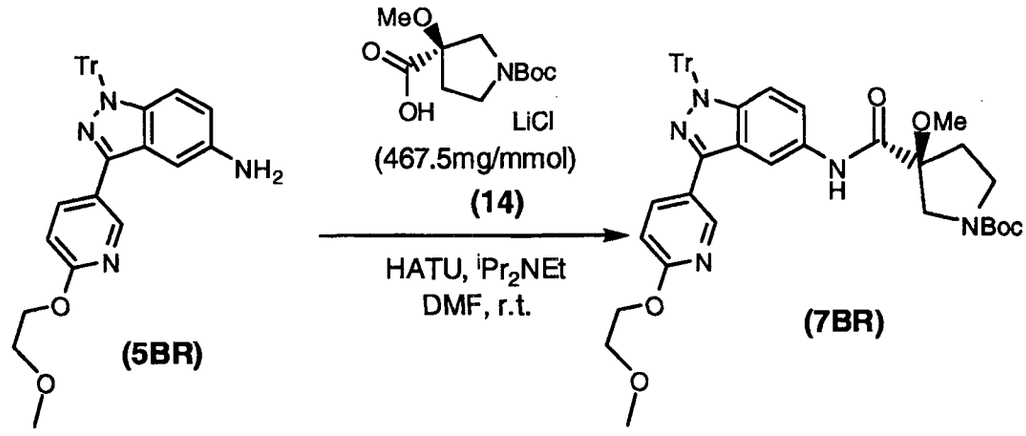
A mixture of compound **3BR** (1.8 g), 2-Methoxy-ethanol (1 g), DEAD (0.8 g) and PPh_3 (1.2 g) in THF (10 ml) was stirred overnight at rt and concentrated. The residue purified by silica gel to gave the desired product **4BR** (0.8 g).

Step 3:



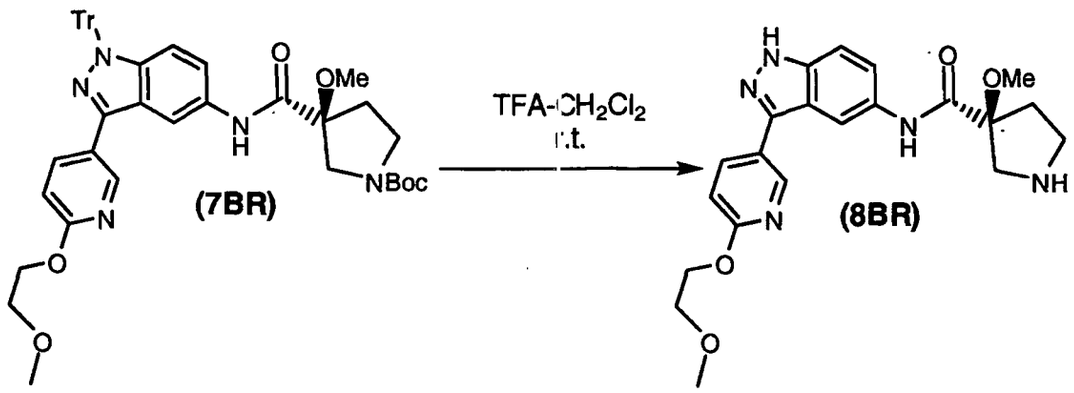
4BR (0.5 g) in MeOH (20 ml) was reduced by H-cube with Pd/C (10%) column.

Step 4:



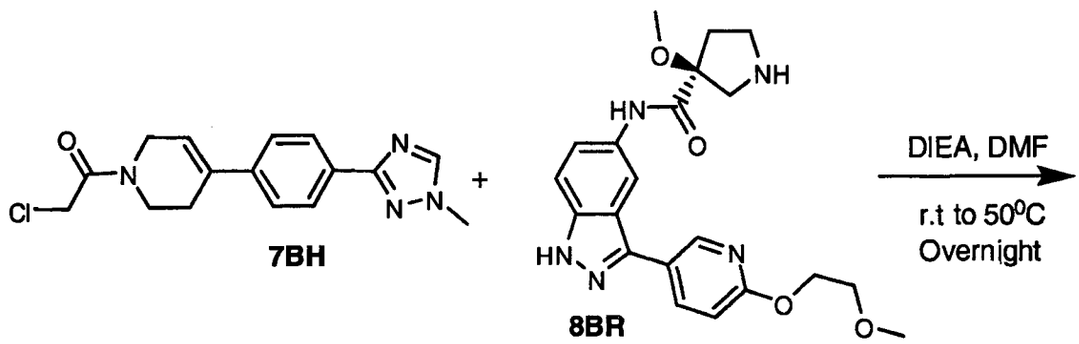
Aminoindazole **5BR** (80 mg) and pyrrolidinecarboxylic acid **14BH** (38 mg) were dissolved in DMF (1 ml) at r.t. HATU (69 mg) followed by $^{i}Pr_2NEt$ (0.1 ml) were added. The mixture was stirred at r.t. overnight and was diluted with ethyl acetate and water. Layers were separated. The separated organic layer was washed with water (X2), dried ($MgSO_4$) and filtered. Concentration in vacuum gave crude **7BR** as off-white foam.

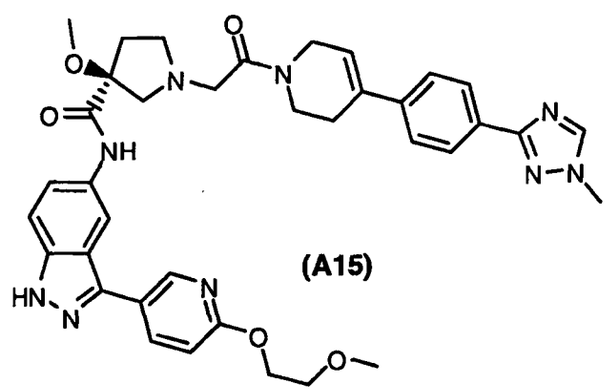
Step 5:



The crude **7BR** was stirred in a mixture of dichloromethane (1 ml), trifluoroacetic acid (1 ml) at r.t. for 1 h. The mixture was cooled at 0 °C and quenched carefully with saturared aqueous sodium bicarbonate. Solvents were removed in vacuum. Dilute with water and ethyl acetate. Layers were separated and the separated aqueous layer was extracted with ethyl acetate (X3). The combined organic layers were dried ($MgSO_4$), filtered and solvents were removed in vacuum and gave pyrrolidine **8BR** as off-white solid.

Synthesis of 3-Methoxy-1-(2-{4-[4-(1-methyl-1H-[1,2,4]triazol-3-yl)-phenyl]-3,6-dihydro-2H-pyridin-1-yl}-2-oxo-ethyl)-pyrrolidine-3-carboxylic acid {3-[6-(2-methoxy-ethoxy)-pyridin-3-yl]-1H-indazol-5-yl}-amide

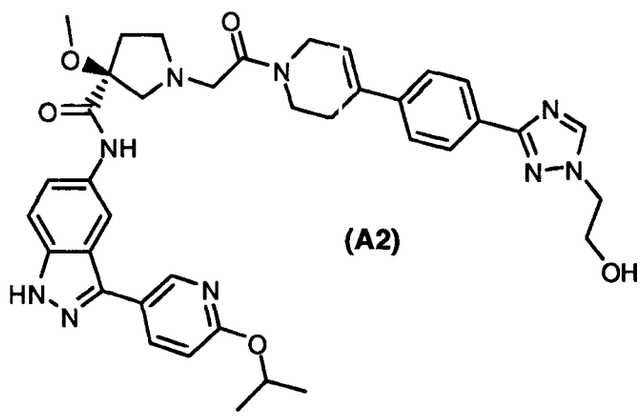




A mixture of compound **7BH** (52 mg), compound **8BR** (62 mg), and DIEA (0.3 ml) in DMF (1.5 ml) was stirred at room temperature overnight. LCMS shows the reaction is complete. DMF was removed under reduced pressure. The crude was purified by HPLC. (LCMS M+1= 692, ret. time= 3.00 min.) 1H NMR (400 MHz, CDCl3):δ11.92 (S, 1H), 11.11 (S, 1H), 9.14 (S, 1H), 8.58 (S, 1H), 8.03 (S, 1H), 7.99 (d, 1H, J= 8.4 Hz), 7.90 (t, 2H, J= 6.8), 7.39 (S, 2H), 7.20 (S, 3H), 6.76 (d, 1H, J=8.0 Hz), 5.85 (d, 1H, J= 20 Hz), 4.4 (S, 4H), 4.05 (q, 4H, J= 7.2 Hz), 3.8 (S, 3H), 3.50-3.56 (m, 6H), 2.34-2.62 (m, 5H), 2.0 (S, 2H), 1.64-1.49 (m, 3H).

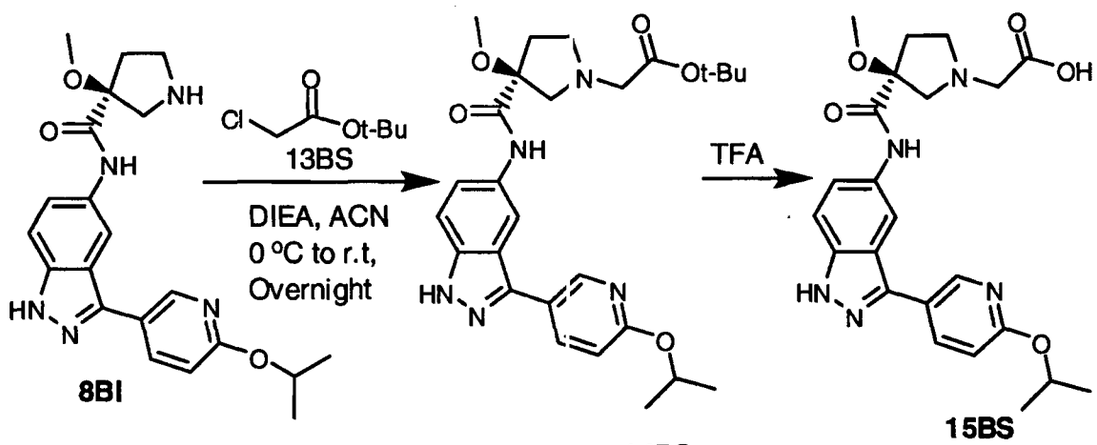
Example 10

Preparation of 1-[2-(4-{4-[1-(2-Hydroxy-ethyl)-1H-[1,2,4]triazol-3-yl]-phenyl}-3,6-dihydro-2H-pyridin-1-yl)-2-oxo-ethyl]-3-methoxy-pyrrolidine-3-carboxylic acid [3-(6-isopropoxy-pyridin-3-yl)-1H-indazol-5-yl]-amide



(A2)

Preparation of {3-[3-(6-Isopropoxy-pyridin-3-yl)-1*H*-inxazol-5-ylcarbamoyl]-3-methoxy-pyrrolidin-1-yl}-acetic acid

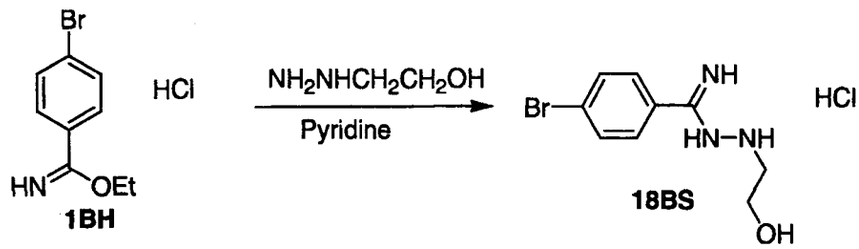


8BI 14BS 15BS

In a solution of compound **8BI** (3.5g, 6.6mmol) in acetonitrile (26ml) was added DIEA (5.7ml, 32.9mmol). It was cooled to 0 °C and 0.47ml (3.29mmol) of compound **13BS** was added dropwise. After stirring for 4hr at 0 °C, 0.47ml (3.29mmol) of compound **13BS** was added again. It was stirred further for 1hr at 0 °C and then warmed up to r.t. After stirring overnight at room temperature, it was dissolved in EtOAc (200ml) and washed with $NaHCO_3$ (1 x 50ml), water (1x 50ml) and brine (1 x 50ml). The organic extracts were dried over $MgSO_4$ and the solvent was removed. The crude was purified by column chromatography using 20%MeOH/EtOAC to get the desired product **14BS** (2.4g).

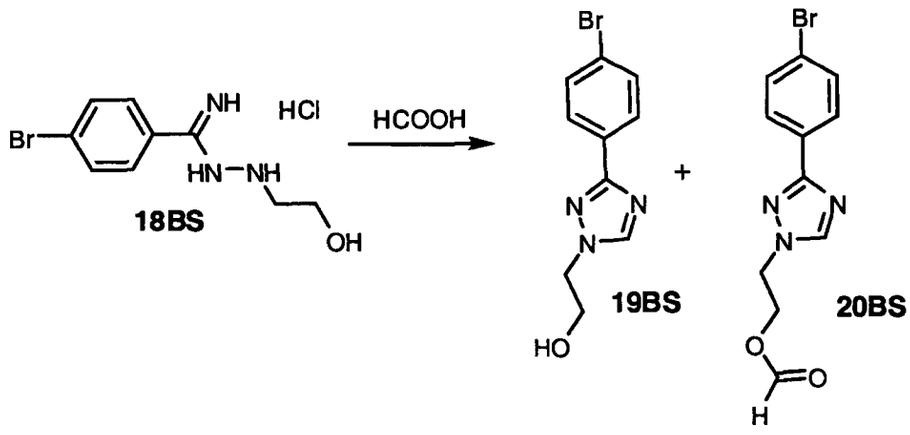
Compound **14BS** (2.4g) was treated with 40ml of TFA for 45 mins at room temperature. TFA was removed under reduced pressure and the solid was washed with ether to get the desired compound **15BS** as a TFA salt (4.4gm, 95%). Compound **15BS** was converted into the HCl salt by adding 4N HCl in water.

Synthesis of Preparation of 2-{3-[[4[(1,2,3,6-Tetrahydro-pyridin-4-yl)-phenyl]-[1,2,4]triazol-1-yl}-ethanol hydrochloride



Preparation of 4-bromo-*N*'-(2-hydroxyethyl)benzimidohydrazide hydrochloride

The 4-bromo-benzimidic acid ethyl ester **1BH** (5g) was dissolved in pyridine (100ml). Hydroxyethylhydrazine (1.92ml) was added with stirring and the resulting mixture was allowed to stir overnight. The precipitate was collected by filtration and mother liquor was concentrated to almost dryness and ether was added. Solid was collected by filtration. Combined solid was washed with ether twice and dried to afford **18BS** (5.1g).



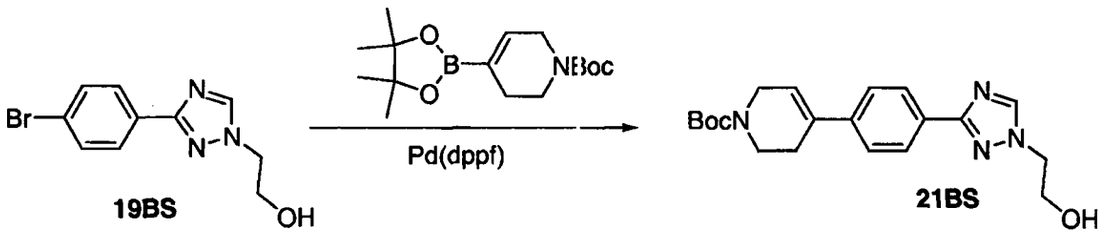
Preparation of 2-(3-(4-bromophenyl)-1*H*-1,2,4-triazol-1-yl)ethanol

A mixture of compound **18BS** (3g) in formic acid (50ml) was stirred at room temperature for 30 minutes, at 100 ^{0}C for 1.5 hours and concentrated. The residue was treated with saturated $NaHCO_3$, and extracted with EtOAc three times. The

combined organic extracts were dried over $MgSO_4$. After concentration, the crude was purified on silica gel. Elution with EtOAc gave compound **20BS** (2g), and compound **19BS** (262mg).

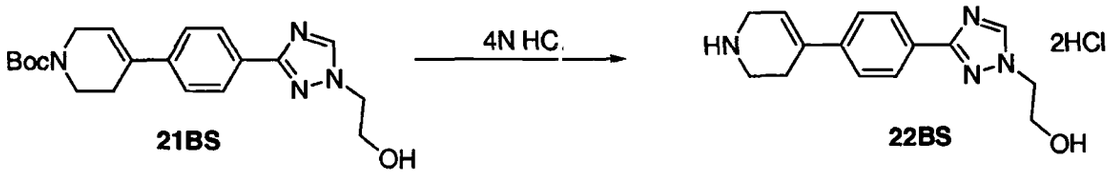
Compound **20BS** can be easily converted to **19BS** by aqueous hydrolysis

Preparation of 4-[4-(1-(2-Hydroxy-ethyl)-*1H*-[1,2,4]triazol-3-yl)-phenyl]-3,6-dihydro-*2H*-pyridine-1-carboxylic acid *tert*-butyl ester



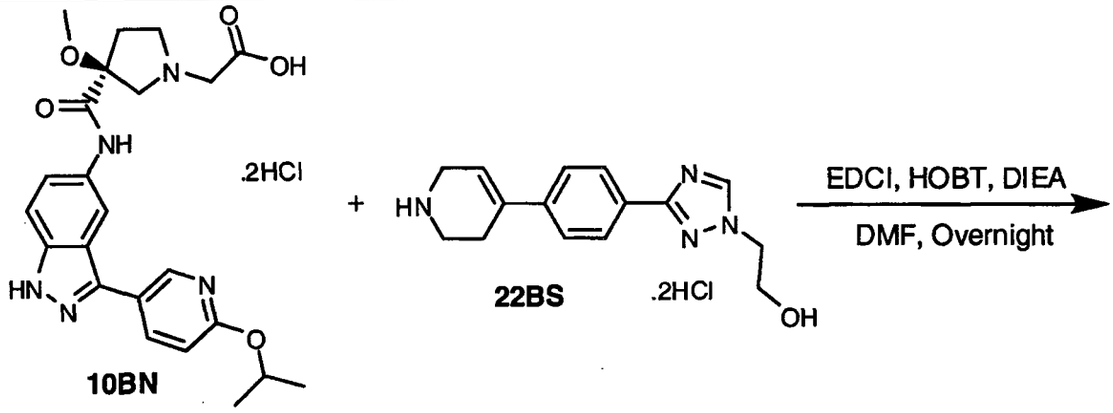
To a large pressure flask were charged compound **19BS** (1.5 g, 5.6 mmols), 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester (1.9g, 6.2mmols), [1,1'-bis(diphenylphosphino)-ferrocene]dichloropalladium(II), complex with dichloromethane(1:1) (0.22g, 0.28 mmols), K_2CO_3 (2.32g, 16.8mmols) and DME/water (5:1, 12ml). The mixture was briefly degassed with Ar for ~0.5 minute, capped and stirred at 80°C overnight. After cooling, the reaction mixture was diluted with EtOAc and washed with water (1X) and brine (1x). Organic layer was isolated, and dried over $MgSO_4$. After concentration, the residue was purified on silica gel. Elution with MeOH/EtOAc (0-10%) gave the desired product **21BS** (1.4g, 73%).

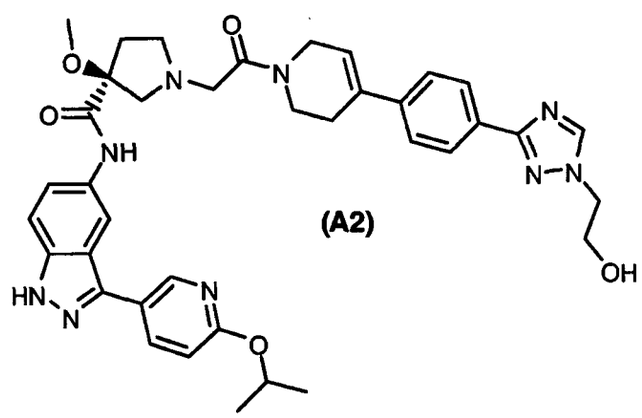
Preparation of 2-{3-[[4[(1,2,3,6-Tetrahydro-pyridin-4-yl)-phenyl]-[1,2,4]triazol-1-yl}-ethanol hydrochloride



The Boc group can be removed by treating compound **21BS** with 4N HCl in dioxane at rt for two hours. Removal of solvent under vacuum gave compound **22BS**.

Preparation of 1-[2-(4-{4-[1-(2-Hydroxy-ethyl)-1*H*-[1,2,4]triazol-3-yl]-phenyl}-3,6-dihydro-2*H*-pyridin-1-yl)-2-oxo-ethyl]-3-methoxy-pyrrolidine-3-carboxylic acid [3-(6-isopropoxy-pyrididn-3-yl)-1*H*-inxazol-5-yl]-amide

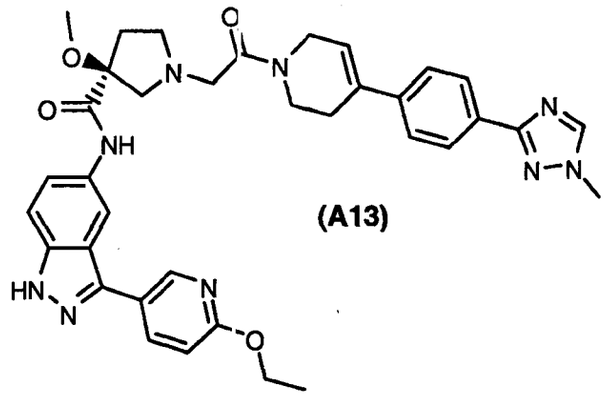




A mixture of compound **10BN** (0.49g, 1mmol), 1-(3-Dimethyl-aminopropyl)-3-ethylcarboxiimide hydrochloride (0.38g, 2mmol), and 1-hydroxybenzotriazole (0.14g, 1mmol) was dissolved in DMF (3ml). After stirring for 20 min at room temperature, compound **16BS** (0.34g, 1mmol) and DIEA (0.7ml, 4mmol) were added. After stirring for overnight at room temperature, it was diluted with DCM (45ml) and washed with $NaHCO_3$ (1 X 7ml), water (3 x 7ml) and brine (1X10ml). The organic layer was dried over $MgSO_4$. After concentration, the residue was purified on silica gel. Elution with 2% NH_3 in 20 %MeOH/EtOAc gave the desired product **A2** (0.3g). This compound was converted to HCl salt by adding 4N HCl in 1,4-dixoane. (LCMS: M+1= 706, ret. time = 3.13 min.), ^1H NMR (400 MHz, DMSO-*d*6): δ = 10.5 – 10.8(m, 1H), 10.25 (d, 1H, J = 19.2Hz), 8.60 - 8.75 (m, 2H), 8.43 (m, 1H), 8.18 (m, 1H), 7.98 (m, 2H), 7.78 (d, 2H, J = 20Hz), 7.5 - 7.6 (m, 4H), 6.9 (m, 2H), 6.3 (m, 1H), 5.3 (m, 1H), 4.5 - 4.6 (m, 2H), 4.15 - 4.3 (m, 4H), 4.0 - 4.15 (m, 2H), 3.75 (t, 4H, 5.2 Hz), 3.5 - 3.6 (m, 2H), 3.4 - 3.3 (m, 1H), 3.29 (s, 2H), 2.5 - 2.7 (m, 3H), 2.3 - 2.4 (m, 1H), 1.3 (d, 6H, J = 6.4Hz).

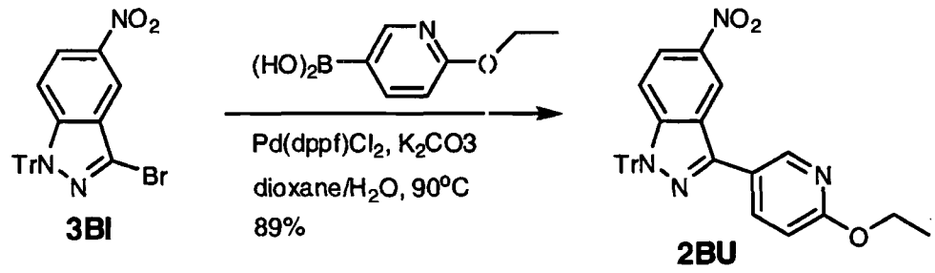
Example 11

Synthesis of 3-Methoxy-1-(2-{4-[4-(1-methyl-1H-[1,2,4]triazol-3-yl)-phenyl]-3,6-dihydro-2H-pyridin-1-yl}-2-oxo-ethyl)-pyrrolidine-3-carboxylic acid [3-(6-ethoxy-pyridin-3-yl)-1H-indazol-5-yl]-amide (Example 1)



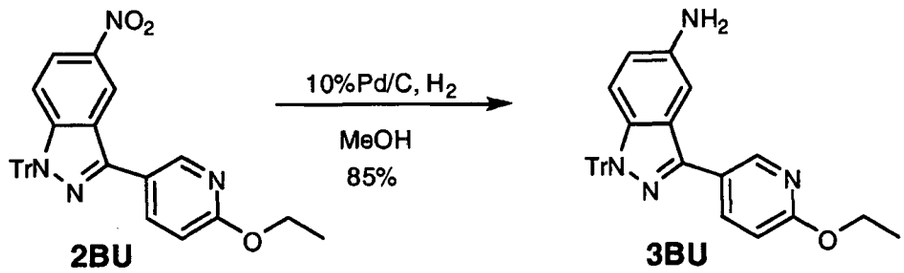
(A13)

Step 1:



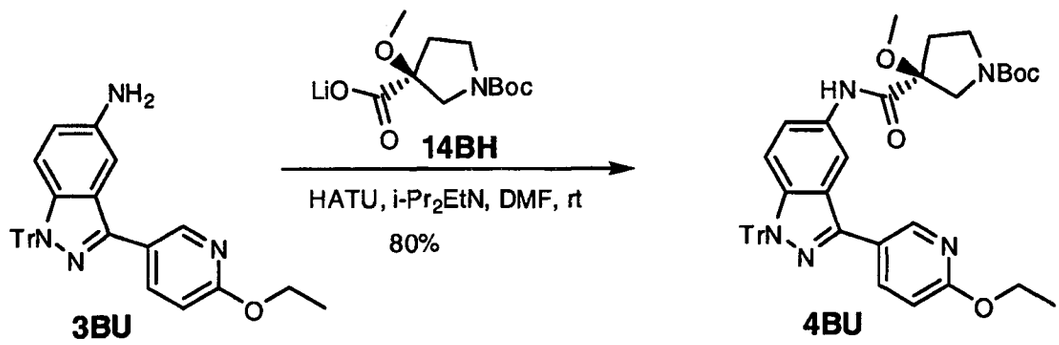
A mixture of 6-ethoxypyridine-3-boronic acid (2.5 g, 14.97 mmol), bromoindazole **3BI** (7.25 g, 14.97 mmol), potassium carbonate (6.2 g, 44.91 mmol), $PdCl_2(dppf)_2.CH_2Cl_2$ (1.22 g, 1.497 mmol), 1,4-dioxane (40 mL) and water (10 mL), was purged with nitrogen for 15 min at r.t. and then heated at 90 °C for 18 hrs and cooled to r.t. Water (100 mL) and ethyl acetate (300 mL) were added. Solids were filtered through Celite. Layers were separated and the separated organic layer was washed with water (100 mL). The combined organic layers were dried (Na_2SO_4), filtered and solvents were removed in vacuum. Column purification [Hexanes-ethyl acetate = 9:1 (v/v)] gave Compound **2BU** (7 g, 89%).

Step 2:



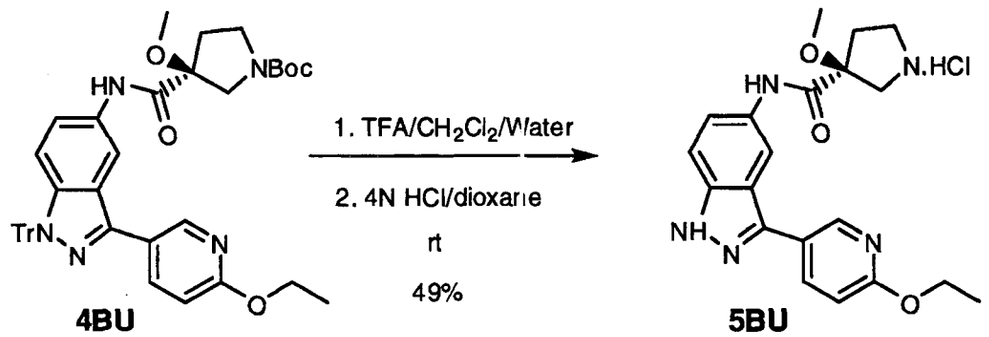
Compound **2BU** (2 g, 3.8 mmol) and Pd/C (10%, 50% wet, 0.7 g) were stirred in toluene (30 mL) and MeOH (15 mL) under H_2 (balloon) at r.t. for 18 hrs. The solid catalyst was filtered through Celite and solvents were removed in vacuum. Column purification using 4%MeOH/CH_2Cl_2 gave Compound **3BU** (1.6 g, 85%).

Step 3:



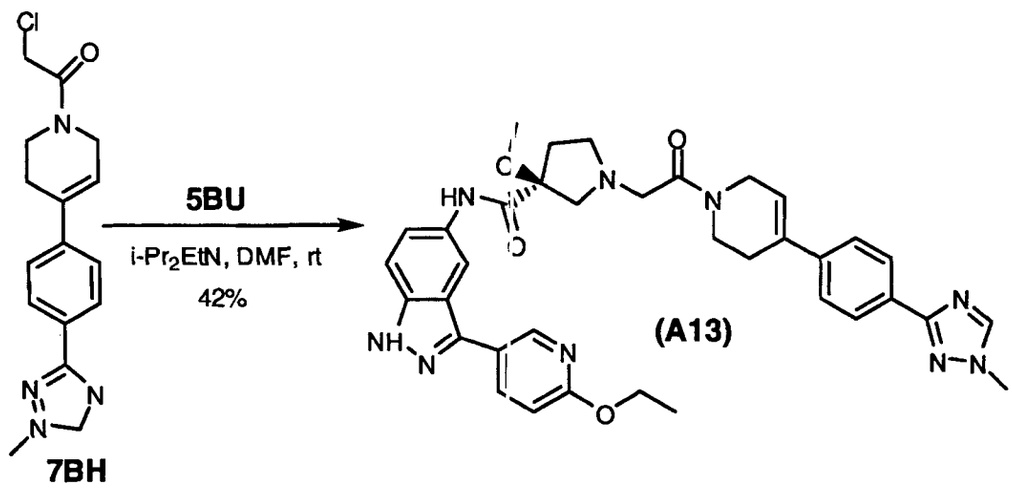
Compound **3BU** (1.46 g, 3.22 mmol) and pyrrolidinecarboxylic acid **14BH** (0.56 g, 3.22 mmol) were dissolved in DMF (300ml) at r.t. HATU (1.68 g, 4.83 mmol) followed by $^{i}Pr_2NEt$ (0.78 mL, 4.83 mmol) were added. The mixture was stirred at r.t. overnight and was diluted with ethyl acetate (200 mL) and water (100 mL). Layers were separated. The separated organic layer was washed with water (100 mL), dried (Na_2SO_4) and filtered. Concentration in vacuum followed by column purification [hexanes – ethyl acetate = 9:1 (v/v)] gave product **4BU**.

Step 4:



Compound **4BU** (1.6 g) was stirred in a mixture of dichloromethane (30 mL), trifluoroacetic acid (4 mL) and few drops of water at r.t. overnight. The mixture was cooled at 0 °C and quenched carefully with 7% MeOH (NH_3)/CH_2Cl_2. Solvents were removed in vacuum. Dilute with water (100 mL) and ethyl acetate (200 mL). Layers were separated. The organic layer was dried (Na_2SO_4), filtered and solvents were removed in vacuum. Column purification [7% MeOH (7N ammonia) in dichloromethane] gave Compound **5BU** (0.44 g, 49%) which was converted to mono HCl salt by treating with 4 N HCl/dioxane and evaporating the solution to dryness.

Step 5:



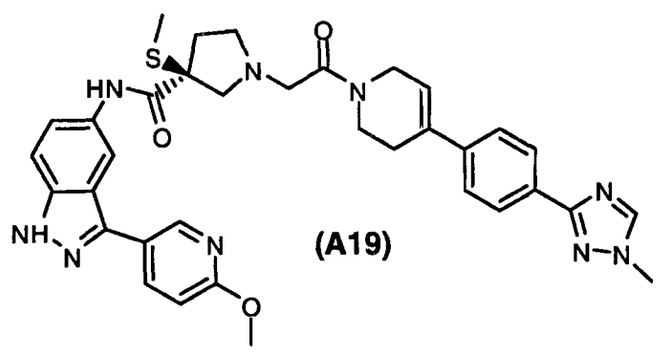
A mixture of Compound **7BH** (46 mg, 0.144 mmol), Compound **5BU** (60 mg, 0.144 mmol), DMF (2 mL) and N,N-diisopropylethylamine (0.076 mL, 0.432 mmol) was stirred at room temperature for 18 hours. Diluted with EtOAc (100 mL) and washed with water (2 x 100 mL). The organic layer was dried over Na_2SO_4, filtered

and concentrated. The residue was purified on silica gel eluting with 4% MeOH (NH_3)/ CH_2Cl_2 to give the desired product **6BU** (40 mg, 42%).

LCMass Spec M+1 @ ret. time = 662 @ 2.57 min

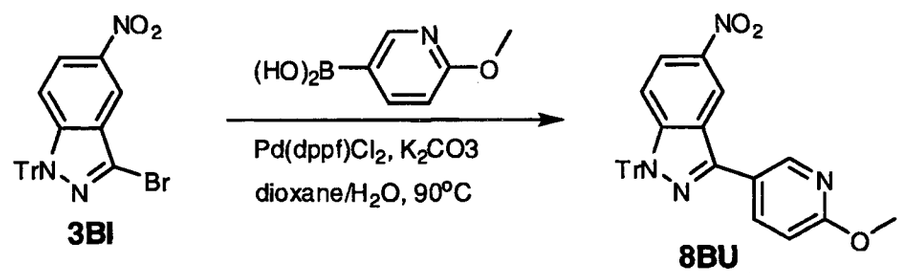
Example 12

Synthesis of 3-Methylsulfanyl-1-(2-{4-[4-(1-methyl-1H-[1,2,4]triazol-3-yl)-phenyl]-3,6-dihydro-2H-pyridin-1-yl}-2-oxo-ethyl)-pyrrolidine-3-carboxylic acid [3-(6-methoxy-pyridin-3-yl)-1H-indazol-5-yl]-amide



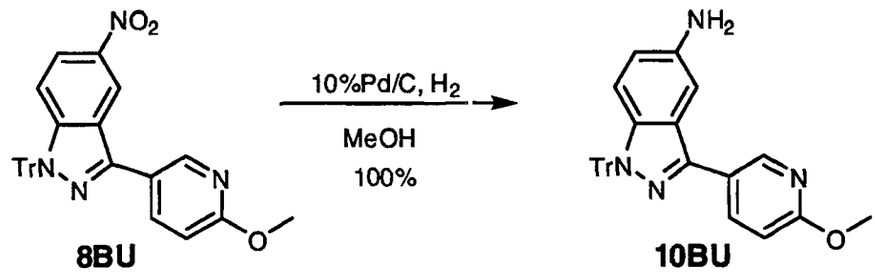
(A19)

Step 1:



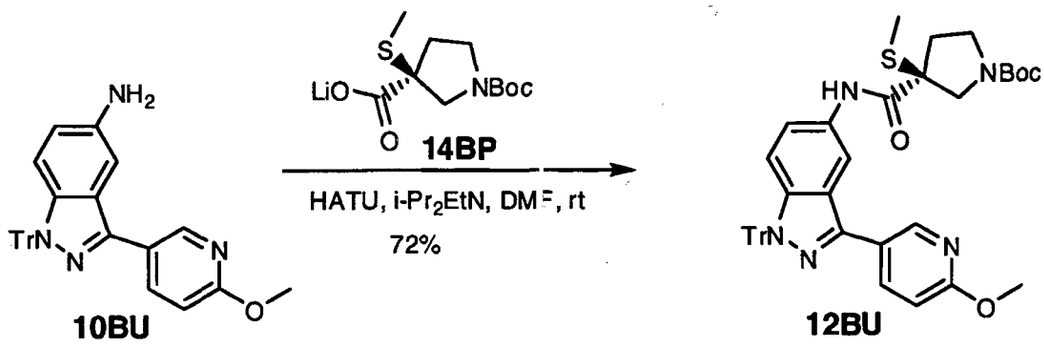
Compound **8BU** was prepared from Compound **3BI** using essentially the same procedure as described for the preparation of Compound **2BU** from Compound **3BI** (Example 11, Step 1), using 6-methoxypyridine-3-boronic acid in place of 6-ethoxypyridine-3-boronic acid.

Step 2:



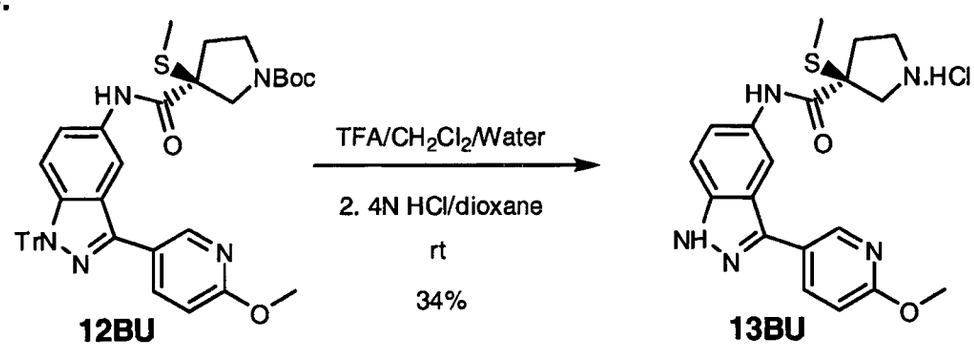
Compound **8BU** (3 g, 3.8 mmol) and Pd/C (10%, 50% wet, 1.2g) were stirred in toluene (30 mL) and MeOH (15 mL) under H_2 (balloon) at r.t. for 18 hrs. The solid catalyst was filtered through Celite and solvents were removed in vacuum to give Compound **10BU** (2.8 g, 100%).

Step 3:



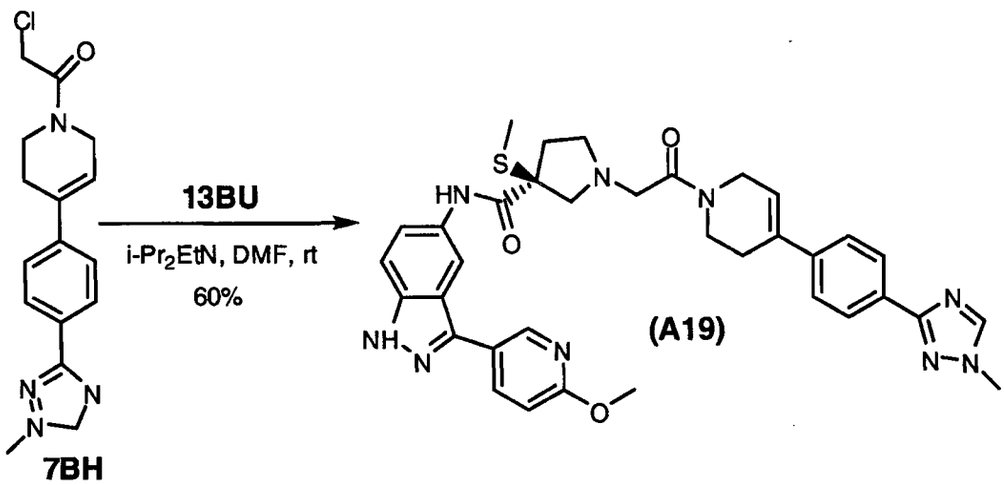
Compound **10BU** (0.6 g, 1.24 mmol) and pyrrolidinecarboxylic acid **14BP** (0.33 g, 1.24 mmol) were dissolved in DMF (5 mL) at r.t. HATU (0.71 g, 1.86 mmol) followed by $^{i}Pr_2NEt$ (00.66 mL, 3.72 mmol) were added. The mixture was stirred at r.t. overnight and was diluted with ethyl acetate (200 mL) and water (100 mL). Layers were separated. The separated organic layer was washed with water (100 mL), dried (Na_2SO_4) and filtered. Concentration in vacuum followed by column purification [hexanes – ethyl acetate = 9:1 (v/v)] gave product **12BU** (0.65 g, 72%).

Step 4:



Compound **12BU** (0.65 g) was stirred in a mixture of dichloromethane (30 mL), trifluoroacetic acid (4 mL) and few drops of water at r.t. overnight. The mixture was cooled at 0 °C and quenched carefully with 7% MeOH (NH_3)/CH_2Cl_2. Solvents were removed in vacuum. Dilute with water (100 mL) and ethyl acetate (200 mL). Layers were separated. The organic layer was dried (Na_2SO_4), filtered and solvents were removed in vacuum. Column purification [15% MeOH (7N ammonia) in dichloromethane] gave Compound **13BU** (0.22 g, 34%).

Step 5:



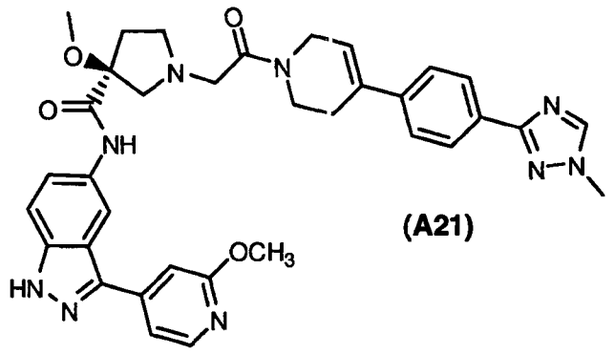
A mixture of Compound **7BH** (40 mg, 0.126 mmol), Compound **13BU** (50 mg, 0.126 mmol), DMF (2 mL) and N,N-diisopropylethylamine (0.045 mL, 0.25 mmol) was stirred at room temperature for 18 hours. Diluted with EtOAc (100 mL) and washed with water (2 x 100 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified on silica gel eluting with 3% MeOH (NH_3)/ CH_2Cl_2 to give the desired product **A19** (50 mg, 60%).

LCMass Spec M+1 @ ret. time = 664 @ 2.88 min

143

Example 13

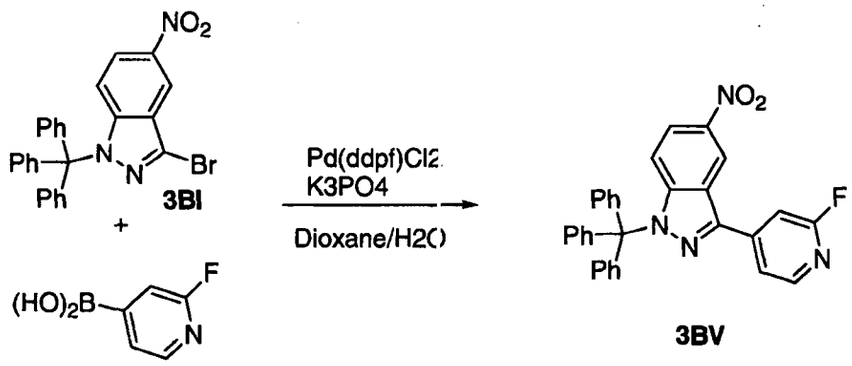
Synthesis of 3-Methoxy-1-(2-{4-[4-(1-methyl-1H-[1,2,4]triazol-3-yl)-phenyl]-3,6-dihydro-2H-pyridin-1-yl}-2-oxo-ethyl)-pyrrolidine-3-carboxylic acid [3-(2-methoxy-pyridin-4-yl)-1H-indazol-5-yl]-amide



(A21)

Step 1:

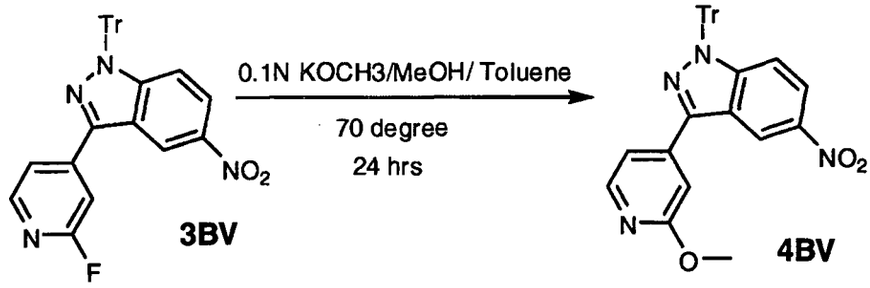
Synthesis of 3-(2-Fluoro-pyridin-4-yl)-5-nitro-1-trityl-1H-indazole



3-Bromo-5-nitro-1-trityl-1H-indazole **3BI** (15.64g, 32.3 mmol), 2-fluoro-4-pyridine boronic acid **2BV** (5.0g, 35.5 mmol), K_3PO_4 (17.1g, 80.7 mmol) and $Pd(dppf)Cl_2$ (2.64g, 3.23 mmol) was mixed in dioxane/H_2O (240 mL/60 mL) at rt and heated at 80 °C overnight. The reaction mixture was cooled to rt and concentrated to a small volume. The residue was partitioned between ethyl acetate (200 mL) and brine (150 mL). The organic layer was washed with brine, dried ($MgSO_4$) and filtered. The resulting filtrate was concentrated and the residue was purified on silica gel column eluting with hexanes, 5% ethyl acetate in hexanes, 10% ethyl acetate in hexanes sequentially to yield a yellow solid **3BV** (3.33g, 64%).

Step 2:

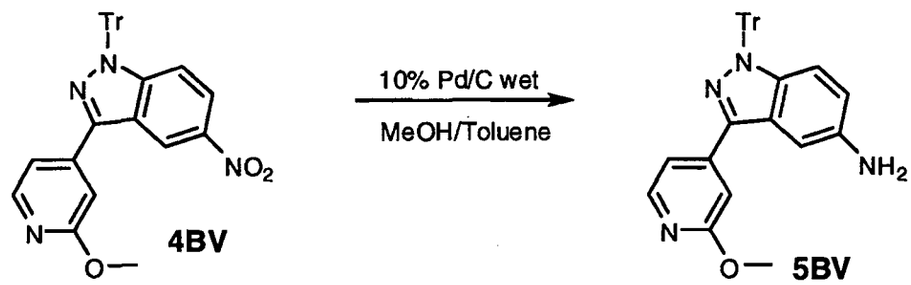
Preparation of 3-(2-Methoxy-pyridin-4-yl)-5-nitro-1-trityl-1H-indazole



In a 250 ml pressure vessel, 3-(2-Fluoro-pyridin-4-yl)-5-nitro-1-trityl-1H-indazole **3BV** (5.005 g, 10.0 mmole) was dissolved in 0.1N $KOCH_3$/MeOH/Toluene(Acros, 150 mL, 15.0 mmole) under dry N_2 gas. The pressure vessel was tightly sealed and heated under stirring at 70 °C for 24 hours. The pressure vessel was cooled to 0 °C in ice-bath before opening. The contents of the pressure vessel were transferred to 500 ml RBF and evaporated to dryness. The resulting solid was dissolved in CH_2Cl_2 and washed with saturated NaCl solution and dried over $MgSO_4$. The solvent was evaporated to dryness and dried under high vacuum to yield **4BV** as a brown solid (5.12 g, 100%).

Step 3:

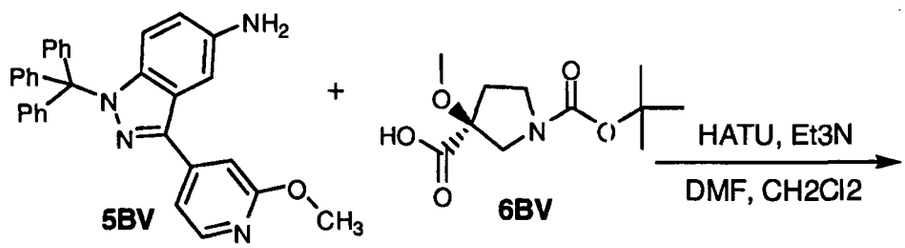
Preparation of 3-(2-methoxy-pyridin-4-yl)-1-trityl-1H-indazol-5-ylamine

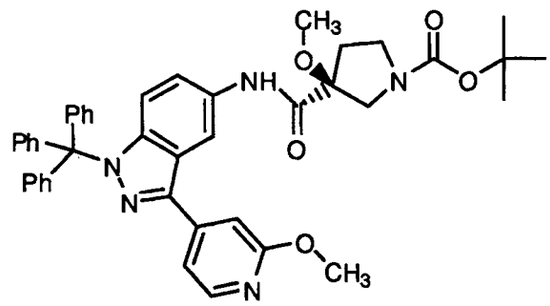


To the stirred suspension of 3-(2-Methoxy-pyridin-4-yl)-5-nitro-1-trityl-1H-indazole **4BV** (5.125 g ,10.0 mmole) in MeOH/toluene (50 mL/50 mL) was added 10% Pd/C (Degussa type, 0.5g) at r.t. under dry N_2 gas. The mixture was degassed and was stirred under a balloon inflated with H_2 gas overnight. The catalyst was filtered through microfiber filter and was washed with MeOH and CH_2Cl_2. The filtrate was evaporated to dryness and a brown solid **5BV** was obtained (5.0 g).

Step 4

Preparation 3-Methoxy-3-[3-(2-methoxy-pyridin-4-yl)-1-trityl-1H-indazol-5-ylcarbamoyl]-pyrrolidine-1-carboxylic acid tert-butyl ester



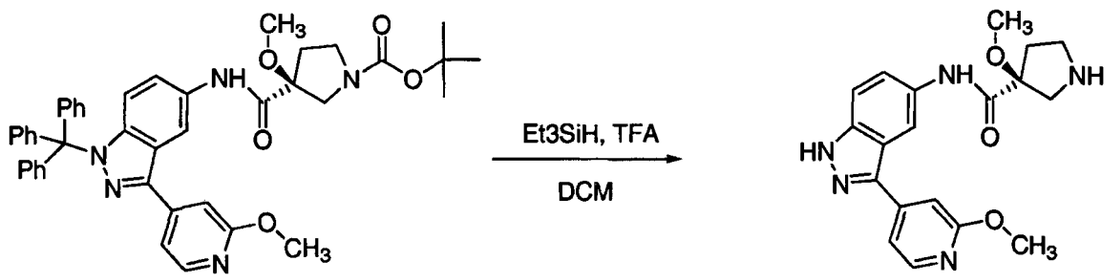


7BV

To the stirred suspension of 3-methoxy-pyrrolidine-1,3-dicarboxylic acid 1-tert-butyl ester **6BV** (4.16 mmole, crude) in DMF/DCM (25 mL/25 mL), 3-(2-methoxy-pyridin-4-yl)-1-trityl-1H-indazol-5-ylamine **5BV** (2.008 g, 4.16 mmole) and Et_3N (2.9 mL,21 mmole) were added at r. t. under dry N_2 gas followed by HATU (3.16 g, 8.32 mmole). The mixture was stirred at r.t. under dry N_2 gas overnight. The mixture was partitioned between 1:1 EtOAc and sat. $NaHCO_3$ solution. The organic phase was separated, washed with brine, dried over MgSO4 and evaporated to dryness. The crude solid was purified on RediSep 120g cartridge eluting with 10-25% EtOAc/Hexanes to yield a brown solid **7BV** (2.95 g, 100%).

Step 5

Preparation 3-Methoxy-pyrrolidine-3-carboxylic acid [3-(2-methoxy-pyridin-4-yl)-1H-indazol-5-yl]-amide

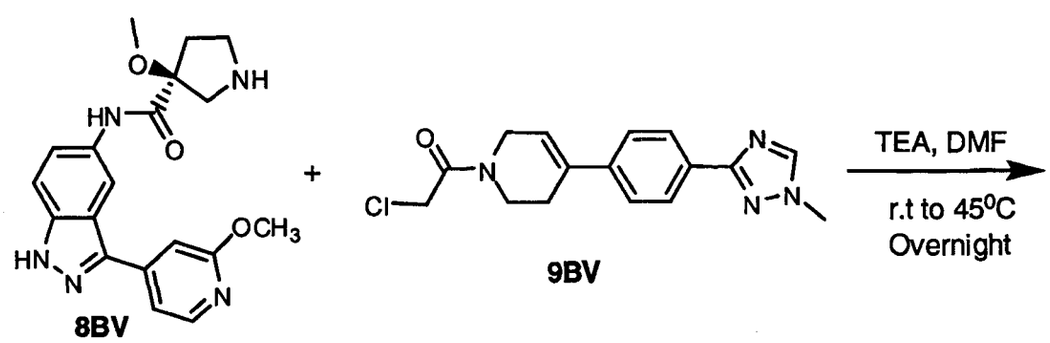


7BV **8BV**

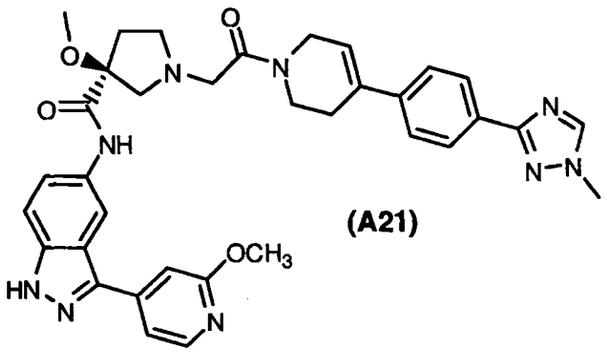
To the stirred solution 3-Methoxy-3-[3-(2-methoxy-pyridin-4-yl)-1-trityl-1H-indazol-5-ylcarbamoyl]-pyrrolidine-1-carboxylic acid tert-butyl ester **7BV** (2.95 g, 4.16 mmole) in DCM (50 mL) at r.t. was added triethylsilane (1.00 ml, 6.24 mmole) followed by TFA (10 mL). The mixture was stirred at r.t. under dry N_2 gas for 4-5 hours. The mixture was evaporated to dryness and co-evaporated with dry toluene (2x75 mL). The resulting crude solid was purified on RediSep 120 g cartridge eluting with 2.5%-6% 2M NH_3-MeOH/CH_2Cl_2 to yield an off-white solid **8BV** (1.23 g, 80%).

Step 6

Synthesis of 3-Methoxy-1-(2-{4-[4-(1-methyl-1H-[1,2,4]triazol-3-yl)-phenyl]-3,6-dihydro-2H-pyridin-1-yl}-2-oxo-ethyl)-pyrrolidine-3-carboxylic acid [3-(2-methoxy-pyridin-4-yl)-1H-indazol-5-yl]-amide



8BV **9BV**

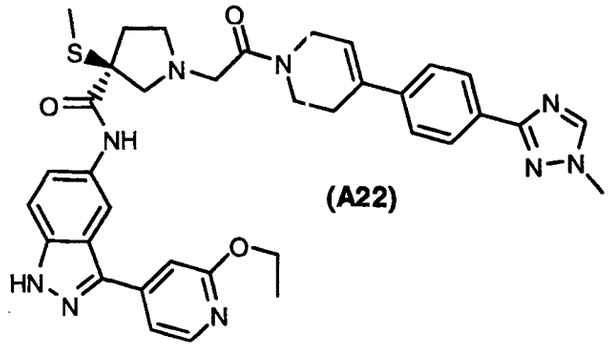


(A21)

A mixture of compound **8BV** (40 mg, 0.11 mmol), compound **9BV** (41.6 mg, 0.13 mmol) and triethylamine (0.1 mL) in DMF (3 mL) was heated at 45 °C with stirring overnight. The reaction mixture was then concentrated *in vacuo* and the resulting crude was purified on silica gel column eluting with 2% and 4% 2N NH_3/MeOH in CH_2Cl_2 to isolate a yellow solid **A21** (39.6 mg, 55%). (LCMS M+1 = 648, ret. time = 2.34 min.) ^{1}H-NMR (400 MHz, $CDCl_3$): δ 10.54 (br, 1H), 9.51 & 9.44 (s, s, 1H), 8.46 (dd, 1H, J=8.2 Hz & 1.4 Hz), 8.27 (d, 1H, J=5.3 Hz), 8.07 (s, 1H), 8.05 (m, 2H), 7.76 (m, 1H), 7.54 (m, 1H), 7.44 (m, 3H), 7.37 (br, 1H), 6.20 & 6.11 (t, t, 1H, J=2.5 Hz), 4.27 (m, 2H), 4.00 & 3.98 (s, s, 6H), 3.96 & 3.86 (m, m, 1H), 3.74 (m, 1H), 3.47-3.60 (m, 2H), 3.453 & 3.446 (s, s, 3H), 3.32 (d, 1H, 9.9 Hz), 3.02 (m, 1H), 2.97 (dd, 1H, J=10.1 Hz & 1.0 Hz), 2.91 (m, 1H), 2.64 (m, 2H), 2.47 (m, 1H), 2.19 (m, 1H).

Example 14

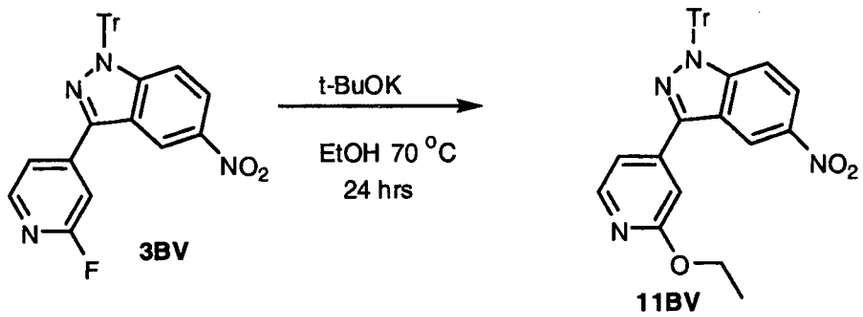
Synthesis of 3-Methylsulfanyl-1-(2-{4-[4-(1-methyl-1H-[1,2,4]triazol-3-yl)-phenyl]-3,6-dihydro-2H-pyridin-1-yl}-2-oxo-ethyl)-pyrrolidine-3-carboxylic acid [3-(2-ethoxy-pyridin-4-yl)-1H-indazol-5-yl]-amide



(A22)

Step 1:

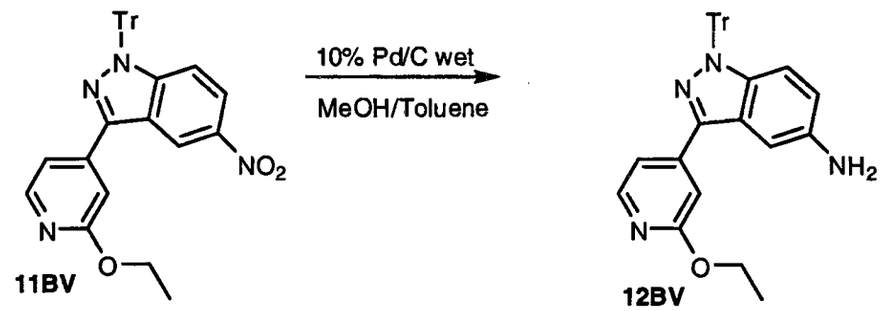
Preparation of 3-(2-Ethoxy-pyridin-4-yl)-5-nitro-1-trityl-1H-indazole



In a 150 mL pressure vessel, to the stirred solution of 3-(2-Fluoro-pyridin-4-yl)-5-nitro-1-trityl-1H-indazole **3BV** (2.0 g, 4.0 mmole) in anhydrous EtOH (40 mL), solid potassium tert-butoxide (12 g, 10.0 mmole) was added under dry N_2 gas. The pressure vessel was tightly sealed and heated at 80 °C for 24 hours. The pressure vessel was cooled to 0 °C in ice-bath before opening. The contents of the pressure vessel were transferred to 250 mL RBF and concentrated to a small volume. The resulting mixture was partitioned between EtOAc and H_2O. The organic phase was separated, washed with saturated NaCl solution and dried over $MgSO_4$. The solvent was evaporated to dryness to give a crude solid **11BV** (1.5 g, 71%).

Step 2:

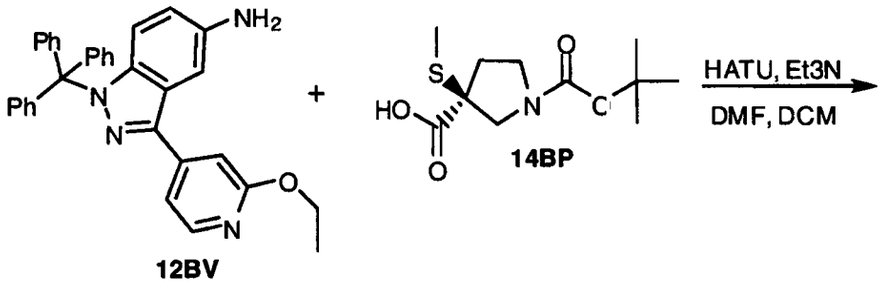
Preparation of 3-(2-ethoxy-pyridin-4-yl)-1-trityl-1H-indazol-5-ylamine



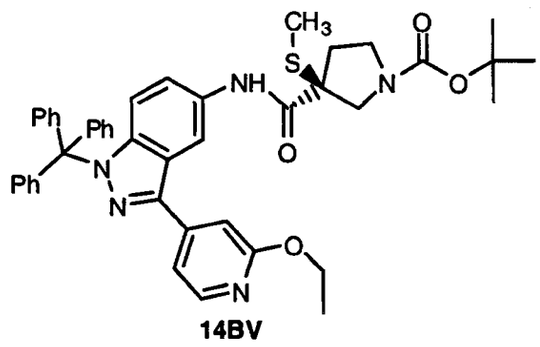
12BV was prepared by using essentially the same procedure as in Example 13, Step 3, except using **11BV** instead of **4BV.**

Step 3:

Preparation of 3-[3-(2-Ethoxy-pyridin-4-yl)-1-trityl-1H-indazol-5-ylcarbamoyl]-3-methylsulfanyl-pyrrolidine-1-carboxylic acid tert-butyl ester



12BV

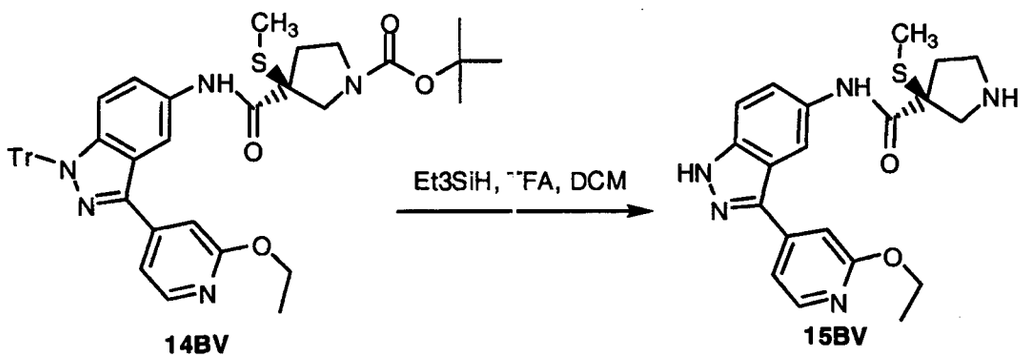


14BV

14BV, with a yield of 88%, was prepared using essentially the same procedure as in Example 13, Step 4, except using **12BV** and **14BP** instead of **5BV** and **6BV**.

Step 4:

Preparation of 3-Methylsulfanyl-pyrrolidine-3-carboxylic acid [3-(2-ethoxy-pyridin-4-yl)-1H-indazol-5-yl]-amide

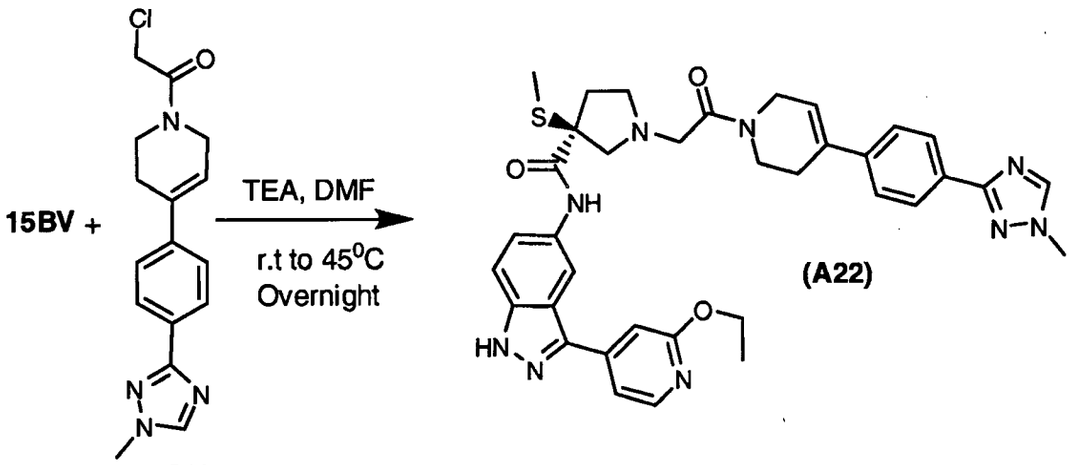


14BV 15BV

15BV, with a yield of 80%, was prepared using essentially the same procedure as in Example 13, Step 5, except using **14BV** instead of **7BV**.

Step 5:

Preparation of 3-Methylsulfanyl-1-(2-{4-[4-(1-methyl-1H-[1,2,4]triazol-3-yl)-phenyl]-3,6-dihydro-2H-pyridin-1-yl}-2-oxo-ethyl)-pyrrolidine-3-carboxylic acid [3-(2-ethoxy-pyridin-4-yl)-1H-indazol-5-yl]-amide

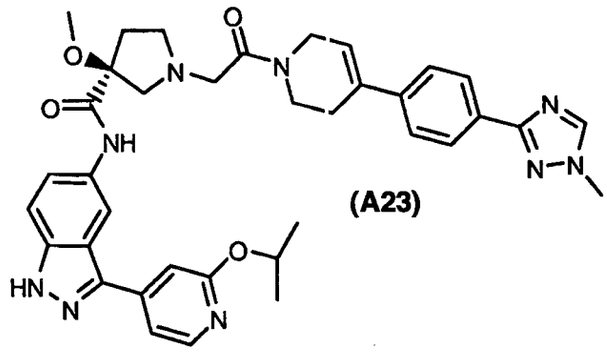


7BH

A mixture of compound **15BV** (40 mg, 0.10 mmol), compound **7BH** (41.6 mg, 0.13 mmol) and triethylamine (0.1 mL) in DMF (3 mL) was heated at 45 °C with stirring overnight. The reaction mixture was then concentrated *in vacuo* and the resulting crude was purified on silica gel column eluting with 2% and 4% 2N NH_3/MeOH in CH_2Cl_2 to isolate a yellow solid **A22** (36.0 mg, 53%). (LCMS M+1 = 678, ret. time = 2.41 min.) ^{1}H-NMR (400 MHz), $CDCl_3$): δ 10.55 (br, 1H), 10.01 & 9.84 (s, s, 1H), 8.50 & 8.44 (d, d, 1H, J=1 Hz), 8.25 (d, 1H, J=5.2 Hz), 8.08 (s, 1H), 8.04 (d, 1H, J=8.2 Hz), 8.00 (d, 1H, J=8.2 Hz), 7.75 (m, 1H), 7.53 (m, 1H), 7.43 (d, 1H, J=8.2 Hz), 7.39 (m, 2H), 7.34 (d, 1H, J=5.2 Hz), 6.18 & 6.11 (t, t, 1H, J=2.5 Hz), 4.42 (q, 2H, J=7.0 Hz), 4.35 & 4.30 (m, m, 1H), 4.22 (m, 1H), 3.99 (s, 3H), 3.92 (t, 1H, J=5.6 Hz), 3.72 (m, 3H), 3.42 (m, 1H), 3.12 (m, 1H), 2.84 (q, 1H, J=7.9 Hz), 2.76 (d, 1H, J=9.9 Hz), 2.70 (m, 1H), 2.63 (m, 2H), 2.15 (s, 3H), 2.11 (m, 1H), 1.44 (t, 3H, J=7.0 Hz).

Example 15

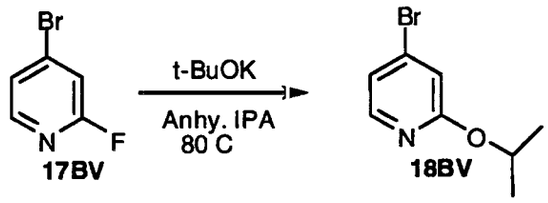
Synthesis of 3-Methoxy-1-(2-{4-[4-(1-methyl-1H-[1,2,4]triazol-3-yl)-phenyl]-3,6-dihydro-2H-pyridin-1-yl}-2-oxo-ethyl)-pyrrolidine-3-carboxylic acid [3-(2-isopropoxy-pyridin-4-yl)-1H-indazol-5-yl]-amide



(A23)

Step 1:

Preparation of 4-Bromo-2-Isopropoxy-pyridine

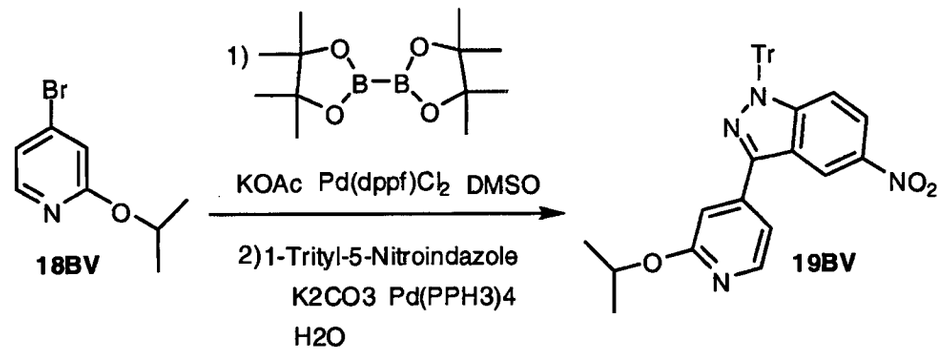


17BV 18BV

To the stirred solution of 4-bromo-2-fluoro-pyridine **17BV** (4.12 g, 23.41 mmole) in 50 mL anhydrous IPA in a 150 mL pressure vessel was added 2.627 g (23.41 mmole) of solid potassium tert-butoxide under dry N_2 gas. The pressure vessel was tightly sealed and heated at 80 °C for 3 hours. The pressure vessel was cooled to 0 °C in ice-bath before opening. The contents of the pressure vessel were transferred to 250 mL RBF and concentrated to a small volume. The resulting mixture was partitioned between EtOAc and H_2O. The organic phase was separated, washed with saturated NaCl solution and dried over $MgSO_4$. The solvent was evaporated and resulting clear oil was purified on RediSep 80 g cartridge eluting with 20:1 Hexanes/EtOAc to give clear oil **18BV** (4.2 g, 83%).

Step 2

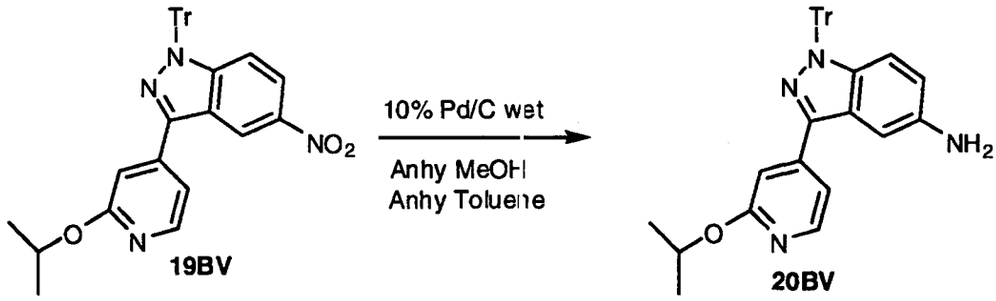
Preparation of 3-(2-Isopropoxy-pyridin-4-yl)-5-nitro-1-trityl-1H-indazole



To the stirred solution of 4.20 g (19.4 mmole) 4-bromo-2-isopropoxy-pyridine **18BV** in 150 mL anhydrous DMSO, 7.39 g (29.1 mmole) of bis(pinacolato)diboron, 5.704 g (58.2 mmole) of potassium acetate, and 1.584 g (1.94 mmole) of $Pd(dppf)Cl_2$ were added at r.t. under dry N_2 gas. The mixture was degassed couple of times with dry N_2 gas. The dark orange mixture was heated at 100 °C for 2 hours. The dark colored mixture was allowed to cool to r.t. 75 mL of H_2O was added followed by 9.396 g (19.4 mmole) of 1-Trityl-5-Nitroindazole, 13.401 g (96.96 mmole) of potassium carbonate, and 2.246 g (1.94 mmole) of PdTetrakis(Triphenylphosphine) were added at r.t. under dry N_2 gas. The mixture was degassed couple of times with dry N_2 gas. The dark colored mixture was heated at 100 °C overnight. The mixture was allowed to cool to r.t. and diluted with 1:1 mixture of H_2O/EtOAc.The diluted mixture was filtered through the pad of Celite and Celite pad was liberally washed with EtOAc. The contents were transferred to a separation funnel and shaken well. The organic phase was separated and washed couple of times with saturated NaCl solution, dried over $MgSO_4$ and evaporated to dryness. The dark colored gum was purified on RediSep 330 g cartridge eluting with Hexanes, 5% EtOAc/Hexane and 10% EtOAc/Hexanes, gave 3.24 g (31%) pale yellow solid **19BV**.

Step 3

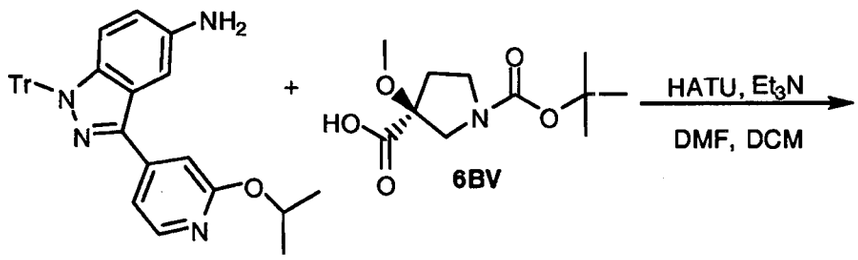
Preparation of 3-(2-Isopropoxy-pyridin-4-yl)-1-trityl-1H-indazol-5-ylamine

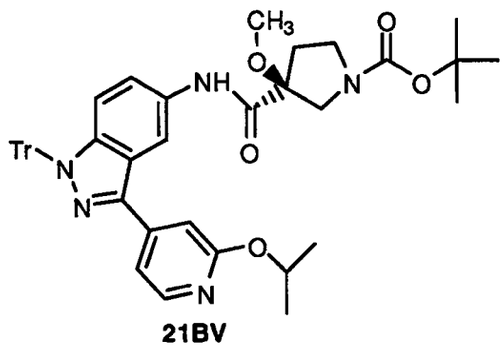


20BV was prepared, with a crude yield of 100%, using essentially the same procedure as in Example 13, Step 3, except using **19BV** instead of **4BV**.

Step 4:

Preparation of 3-[3-(2-Isopropoxy-pyridin-4-yl)-1-trityl-1H-indazol-5-ylcarbamoyl]-3-methoxy-pyrrolidine-1-carboxylic acid tert-butyl ester

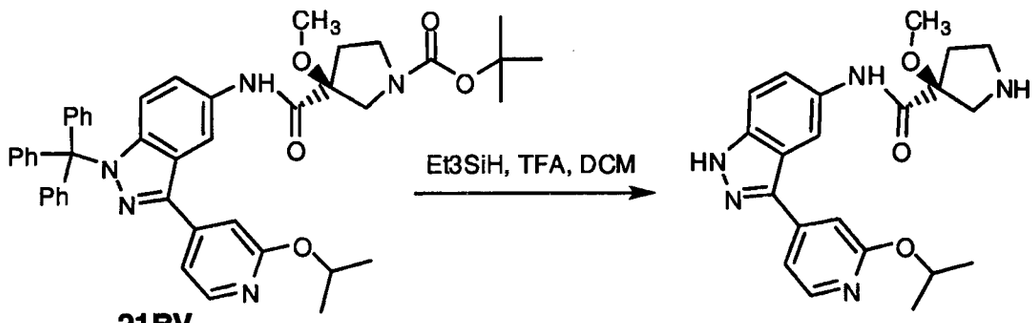




21BV was prepared using essentially the same procedure as in Example 13, Step 4, starting with **20BV** instead of **5BV**.

Step 5:

Preparation of 3-Methoxy-pyrrolidine-3-carboxylic acid [3-(2-isopropoxy-pyridin-4-yl)-1H-indazol-5-yl]-amide

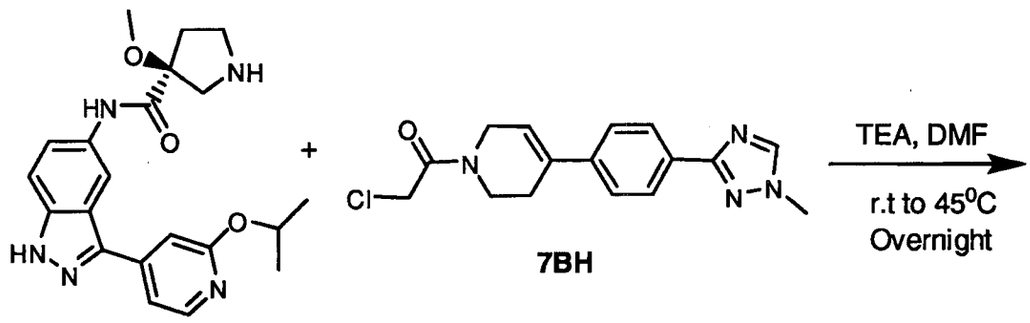


21BV **22BV**

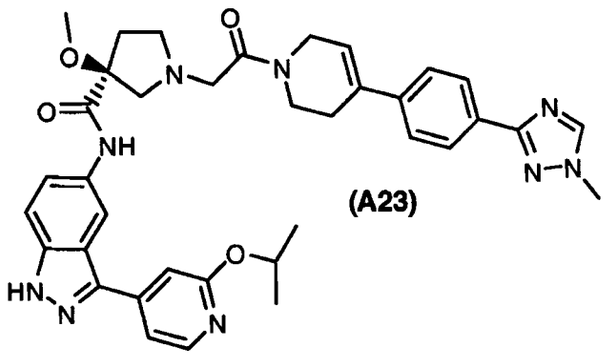
22BV was prepared using essentially the same procedure as in Example 13, Step 5, using **21BV** instead of **7BV**.

Step 6:

Preparation of 3-Methoxy-1-(2-{4-[4-(1-methyl-1H-[1,2,4]triazol-3-yl)-phenyl]-3,6-dihydro-2H-pyridin-1-yl}-2-oxo-ethyl)-pyrrolidine-3-carboxylic acid [3-(2-isopropoxy-pyridin-4-yl)-1H-indazol-5-yl]-amide



22BV **7BH**

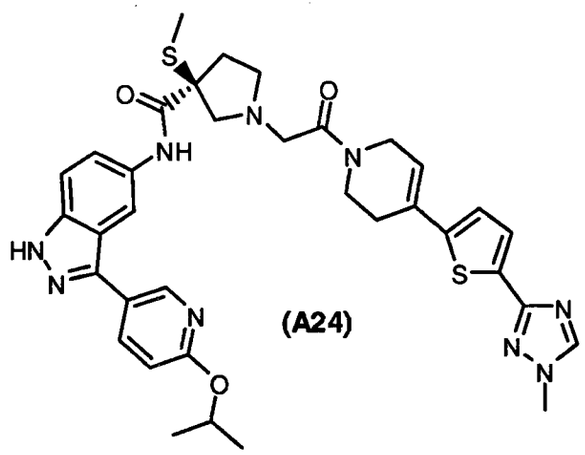


(A23)

A mixture of compound **22BV** (40 mg, 0.10 mmol), compound **7BH** (41.6 mg, 0.13 mmol) and triethylamine (0.1 mL) in DMF (3 mL) was heated at 45 °C with stirring overnight. The reaction mixture was then concentrated *in vacuo* and the resulting crude was purified on silica gel column eluting with 2% and 4% 2N NH_3/MeOH in CH_2Cl_2 to isolate a yellow solid **23BV** (35.0 mg, 52%). LCMS M+1 = 676, ret. time = 2.45 min. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 10.42 (br, 1H), 9.41 & 9.34 (s, s,1H), 8.43 (dd, 1H, J=10.7 Hz & 1.2 Hz), 8.25 (d, 1H, J=5.2 Hz), 8.07 (s, 1H), 8.05 (m, 2H), 7.74 (m, 1H), 7.49 (m,1H), 7.44 (m, 3H), 7.29 (br, 1H), 6.20 & 6.11 (t, t, 1H, J=2.5 Hz), 5.37 (m, 1H), 4.27 (m, 2H), 3.98 (s, 3H), 3.80-3.98 (m, 1H), 3.74 (m, 1H), 3.53 (d, 1H, J=6.6 Hz), 3.49 (br, 1H), 3.47 & 3.46 (s, s, 3H), 3.28 (d, 1H, J=10 Hz), 3.02 (m, 2H), 2.88 (m, 1H), 2.64 (m, 2H), 2.47 (m, 1H), 2.19 (m, 1H), 1.40 (d, 6H, J=6.1 Hz).

Example 16

Synthesis of 3-Methylsulfanyl-1-(2-{4-[5-(1-methyl-1H-[1,2,4]triazol-3-yl)-thiophen-2-yl]-3,6-dihydro-2H-pyridin-1-yl}-2-oxo-ethyl)-pyrrolidine-3-carboxylic acid [3-(6-isopropoxy-pyridin-3-yl)-1H-indazol-5-yl]-amide

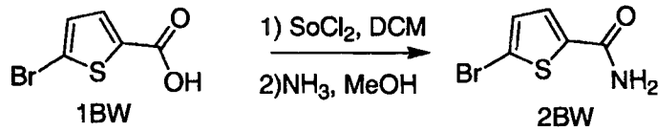


(A24)

Synthesis of 2-Chloro-1-{4-[5-(1-methyl-1*H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-3,6-dihydro-2*H*-pyridin-1-yl}-ethanone

Step 1:

Preparation of 5-bromo-thiophene-2-carboxylic acid amide

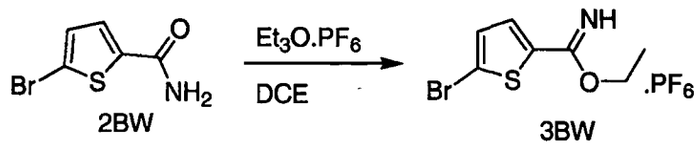


1BW 2BW

5-Bromo-thiophene 2-carboxylic acid (**1BW)** (6g) was suspended in dichloromethane (30 ml) and thionyl chloride (30ml). The resulting solution was allowed to reflux for overnight at 80 ^{0}C. Solvent was removed under reduced pressure and the precipitate was dissolved in dichloromethane which was added dropwise to the cooled solution of ammonia in methanol (100 mL) reaction was monitored by TLC and LC-MS. Solvent was removed under reduced pressure to yield 5-bromo-thiophene2-carboxylic acid amide (**2BW).**

Step 2:

Preparation of 5-bromo-thiophene 2- carboximidic acid ethyl ester

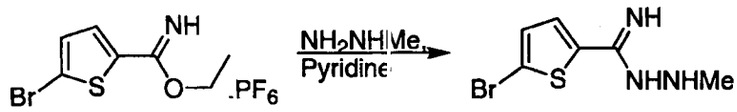


2BW 3BW

The 5-bromo-thiophene2-carboxylic acid amide **(2BW)** (7g, 34.1 mmols) was dissolved in dichloroethane (170 ml). Triethyloxonium hexaflourophosphate (10.16g, 40.97 mmols) was added and the resulting mixture was refluxed for 1hr at 90 ^{0}C. The reaction mixture was concentrated under reduced pressure, and was taken directly to next step.

Step 3:

Preparation of 5-bromo-thiophene 2-carboximidic-N'-methyl-hydrazide

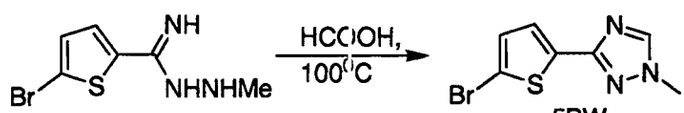


3BW 4BW

The 5-bromo-thiophene 2- carboximidic acid ethyl ester **(3BW)** (13g, 34.3 mmols) was dissolved in pyridine (100 ml). Methylhydrazine (2.7, 51.45 mmols) was added with stirring and the resulted mixture was allowed to stir overnight. The reaction mixture was concentrated under reduced pressure, and added ether, filtered, washed with ether three times and dried to provide the titled compound **(4BW)** (13 g).

Step 4:

Preparation of 3-(5-bromo-thiophen-2-yl)-1-methyl-*1H*-[1,2, 4]triazole

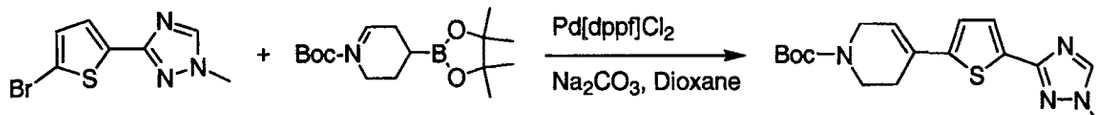


4BW 5BW

A mixture of compound 5-bromo-thiophene 2-carboximidic-N'-methyl-hydrazide **(4BW)** (13 g) in formic acid (100 ml) was refluxed overnight and concentrated. The residue was treated with sat. $NaHCO_3$, and extracted with EtOAc three times. The combined organics were dried over $MgSO_4$. After concentration, compound **5BW** was purified by column using 80% EtoAc/hexane to yield light yellow colored solid.

Step 5:

Preparation of 4-[5-(1-methyl-*1H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-3,6-dihydro-*2H*-pyridine-1-carboxylic acid *tert*-butyl ester

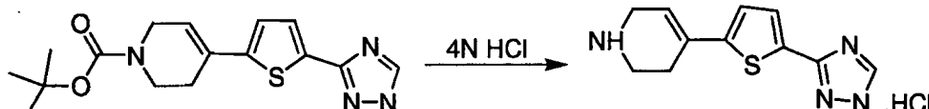


5BW 6BW

To a large pressure flask were charged compound 3-(5-bromo-thiophen-2-yl)-1-methyl-1H-[1,2, 4]triazole (3.1 g, 12.8 mmols) **(5BW)**, 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester (3.6g, 11.65 mmols), [1,1'-bis(diphenylphosphino)-ferrocene]dichloro-palladium (II), complex with dichloromethane(1:1) (0.475 g, 0.89 mmols), Na_2CO_3 (8.5ml) and dioxane (40ml). The mixture was briefly degassed with Ar for ~0.5 minute, capped and stirred at 80^{0}C overnight. After cooling, the reaction mixture was diluted with EtOAc and brine. Organic layer was isolated, and dried $MgSO_4$. After concentration, the residue was purified on silica gel. Elution with EtOAc (100%) gave the desired product **(6BW)** (3.5 g).

Step 6:

Preparation of 4-[5-(1-methyl-1*H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-1,2,3,6-tetrahydro-pyridine hydrochloride

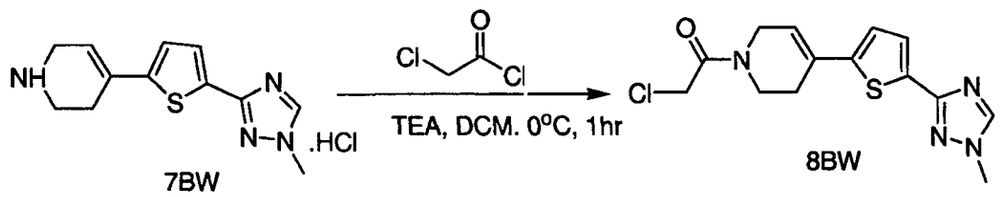


6BW 7BW

The Boc group on **6BW** can be removed by treating compound 4-[5-(1-methyl-1H-[1,2,4]triazol-3-yl)-thiophen-2-yl]-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester with 4N HCl in dioxane at room temperature for two hours. Removal of solvent under vacuum followed by ether wash yielded the desired compound **(7BW)**.

Step 7:

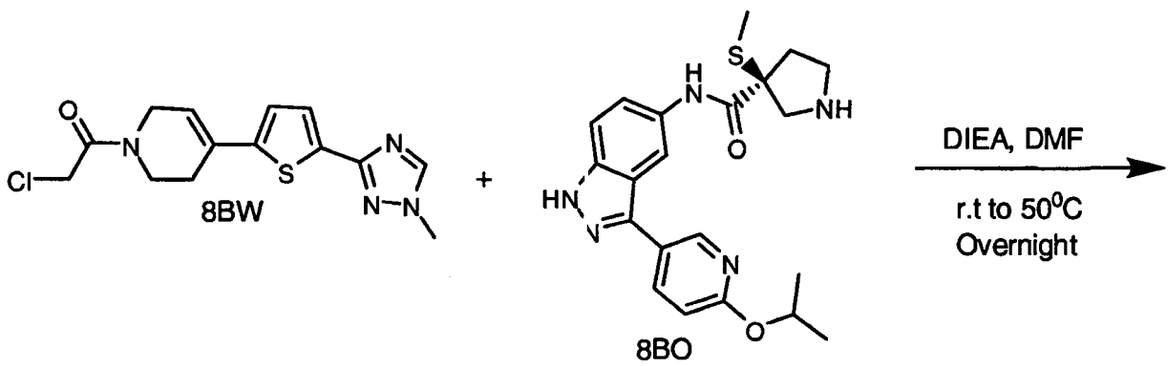
Preparation of 2-chloro-1-{4-[5-(1-methyl-1*H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-3,6-dihydro-2*H*-pyridin-1-yl}-ethanone

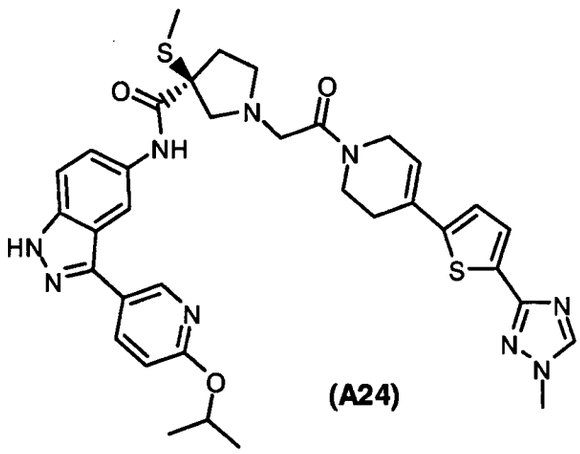


To a cold (0 °C) solution of 4-[5-(1-methyl-1*H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-1,2,3,6-tetrahydro-pyridine **(7BW)** (1.5g, 4.72mmol) in dichloromethane (50ml) was added TEA (4.5ml, 28.32mmol) dropwise. After stirred at 0 °C for 10min, chloroacetyl chloride (1.12 ml, 14.2 mmol) was added to the reaction mixture. The resulting mixture was stirred at 0 °C for 1hr., and quenched with water (15.6ml). The reaction mixture was diluted with dichloromethane (200ml). The organic layer was separated and washed with brine, dried over $MgSO_4$. Reaction mixture was concentrated to ~50ml, ether was added and the solid was filtered out to get the desired product **(8BW)**.

Step 8:

Synthesis of 3-Methoxy-1-(2-{4-[4-(1-methyl-1H-[1,2,4]triazol-3-yl)-phenyl]-3,6-dihydro-2H-pyridin-1-yl}-2-oxo-ethyl)-pyrrolidine-3-carboxylic acid [3-(6-isopropoxy-pyridin-3-yl)-1H-indazol-5-yl]-amide





(A24)

A mixture of 2-chloro-1-{4-[5-(1-methyl-1H-[1,2,4]triazol-3-yl)-thiophen-2-yl]-3,6-dihydro-2H-pyridin-1-yl}-ethanone **(8BW)** (0.522gm, 0.863mmol), 3-Methylsulfanyl-pyrrolidine-3-carboxylic acid [3-(6-isopropoxy-pyridin-3-yl)-1H-indazol-5-yl]-amide **(8BO)** (0.463gm, 0.95 mmol), and DIEA (0.9ml, 5.2mmol) in DMF (10ml) was stirred at room temperature for overnight. DMF was removed under reduced pressure. The crude reaction mixture was precipitated in 30ml ice cold water, filtered, dried, and purified by column chromatography using 10% MeOH/EtOAc to get desired product **A24** as a yellow solid (70%). (LCMS M+1= 698, ret. time= 3.6 min.) 1H NMR (400 MHz, DMSO):□8.67 (S, 1H), 8.64(S,1H), 8.36 (S, 1H), 8.15 (S, 1H), 7.64(d, 1H, J= 8.8Hz), 7.52 (S, 1H), 7.49 (d, 1H J= 5.2Hz), 7.40(d, 1H J=8.8Hz), 7.02 (m, 1H), 6.18 (d, 1H, J= 18.8 Hz), 5.08 (m, 1H), 4.41 (d, 2H, J=7.6Hz), 4.34 (d, 1H, J=6.4Hz)), 4.12(S, 1H), 3.96 (s, 2H), 3.84 (S, 3H), 3.76 (S, 2H), 3.52(S, 2H), 2.76 (S, 1H), 2.58 (d, 2H J = 20.4Hz), 2.13 (S, 3H), 1.94 (t, 2H J= 2.8Hz), 1.39 (d, 6H, J=4.8 Hz).

Examples 17 to 25

Compounds A4, A6, A8, A10-A12, A18, A25 and A26 were prepared following the procedures indicated in the Table 1 below.

Table 1

Ex.	Compound Prepared	Procedure Followed
17	A4	Essentially the same procedure as in Example 4 except substituting hydrazine for hydroxyethylhydrazine in the preparation of 4BL
18	A6	Essentially the same procedure as in Example 1 except substituting 11BP for 14BH
19	A8	Essentially the same procedure as in Example 10 except substituting 8BO for 8BN in the preparation of 10BN
20	A10	Essentially the same procedure as in Example 8 except substituting 8BO for 8BN in the preparation of 10BN
21	A11	Essentially the same procedure as in Example 4 except substituting hydroxyethylhydrazine for methoxyethylhydrazine
22	A12	Essentially the same procedure as in Example 21 except substituting except substituting 8BO for 8BN in the preparation of 10BN
23	A18	Essentially the same procedure as in Example 7 using commercially available 5-(4-Bromo-phenyl)-2H-[1,2,4]triazol-3-ylamine for 4BN.
24	A25	Essentially the same procedure as in Example 14 except substituting 4BV for 11BV
25	A26	Essentially the same procedure as in Example 14 except substituting 20BV for 11BV

The LCMS data for compounds in Table 1 are given in Table 2 below.

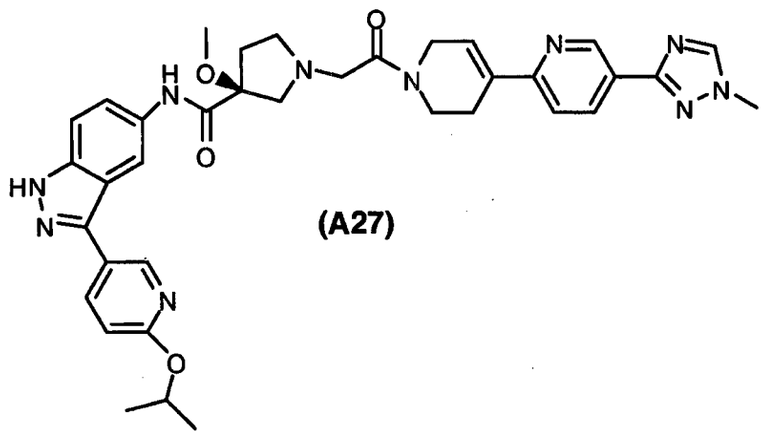
Table 2

Compound	LCMS Retention Time (Minutes)	LCMS M + 1
A4	3.08	680
A6	3.36	692
A8	3.16	722
A10	3.41	750
A11	3.23	724
A12	3.19	740

A18	3.21	693
A25	2.24	664
A26	2.49	692

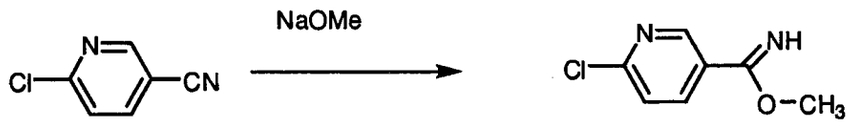
EXAMPLE 26

Preparation of (S)-N-(3-(6-isopropoxypyridin-3-yl)-1H-indazol-5-yl)-3-methoxy-1-(2-(4-(5-(1-methyl-1H-1,2,4-triazol-3-yl)pyridin-2-yl)-5,6-dihydropyridin-1(2H)-yl)-2-oxoethyl)pyrrolidine-3-carboxamide:



(A27)

Step 1: Methyl 6-chloronicotinimidate (1BX)

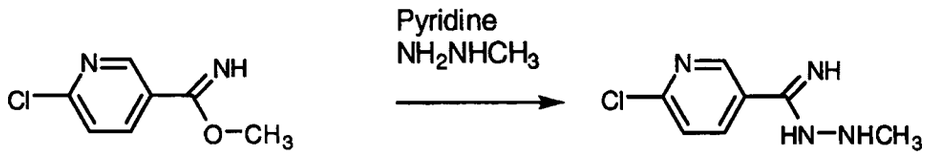


6-chloronicotinonitrile methyl 6-chloronicotinimidate

1BX

Sodium methoxide (725mg, 13.42mmol) was added to a solution of 2-Chloro pyridine-5-carbonitrile (1.8g,13.04mmol) in MeOH:dioxane (40ml,1:1) at 0^0C, then stirred for 30 minutes at 0^0C, and 1 hour at room temperature.The reaction was diluted with EtOAc (200ml) and H_2O (100ml), organic layer separated,dried over Na_2SO_4, filtered and solvent evaporated to yield title compound **1BX** as a white solid (2.6g,100%) MS (MH 171)

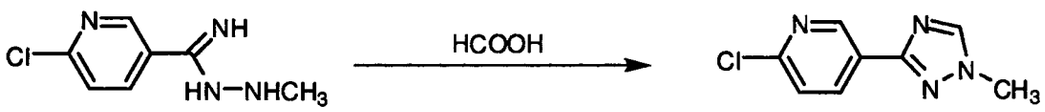
Step 2: 6-chloro-N'-methylnicotinimidohydrazide (2BX)



1BX 2BX

Methyl hydrazine (750mg, 16.30mmol) was added to a solution of Methyl 6-chloronicotinimidate (**1BX**) (2.6g, 15.29mmol) in Pyridine (10ml) at room temperature, then stirred for 1 hour. The solvent was evaporated, and residual solid triturated with cold Ether (2x10ml) yielding title product **2BX** as a yellow powder (2.4g, 85%) MS (MH, 185)

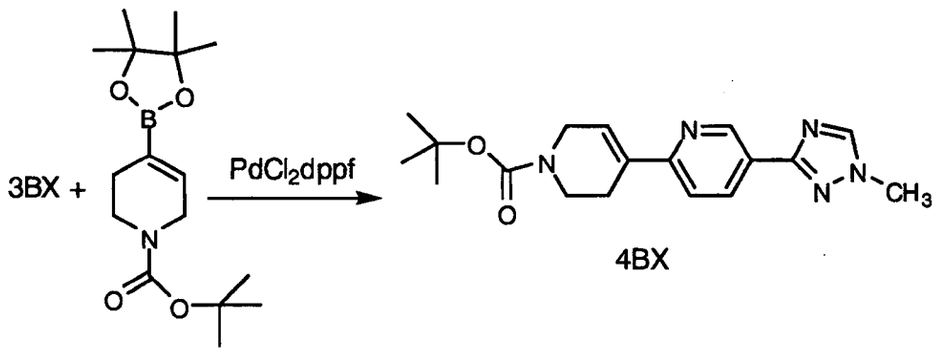
Step 3: 2-chloro-5-(1-methyl-1H-1,2,4-triazol-3-yl)pyridine (3BX)



2BX 3BX

A solution of 6-chloro-N'-methylnicotinimidohydrazide (**2BX**) (2.4g, 13mmol) in Formic Acid (99%,10ml) was stirred at reflux temperature for 1 hour. Reaction was cooled and solvent evaporated. The residue was extracted with EtOAc (100ml) and Aqueous $NaHCO_3$ (50ml), organic layer was separated,dried over Na_2SO_4, filtered and solvent evaporated.The residue chromatographed on silica gel eluting with 10% MeOH:CH_2Cl_2 yielding title product as a solid (1.8g, 72%) MS (MH, 195)

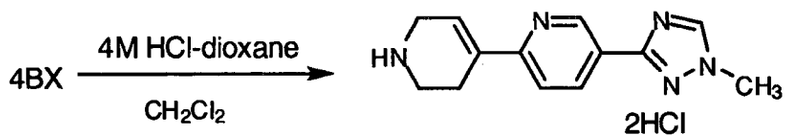
Step 4: Tert-butyl 4-(5-(1-methyl-1H-1,2,4-triazol-3-yl)pyridin-2-yl)-5,6-dihydropyridine-1(2H)-carboxylate (4BX)



4BX

A mixture of 2-chloro-5-(1-methyl-1H-1,2,4-triazol-3-yl)pyridine (**3BX**) (400mg, 2.06mmol); N-Tert-Butoxycarbonyl-1,2,3,6-tetrahydropyridine-4-boronic acid,pinacol ester (1.4g, 4.53mmol); Cesium carbonate (2.3g,7.07mmol) and $PdCl_2$dppf (100mg) in dioxane/H_2O (v/v10:1, 20ml) was stirred at 100°C for 2 hours.The reaction was cooled,diluted with CH_2Cl_2 (300ml) and H_2O (100ml), organic layer separated,dried over Na_2SO_4, filtered and solvent evaporated yielding a residue which chromatographed on silica gel eluting with EtOAc yielding title product **4BX** as a solid (400mg,57%) MS (MH,342).

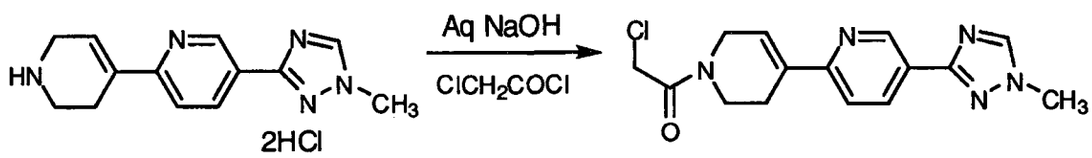
Step 5: 5-(1-methyl-1H-1,2,4-triazol-3-yl)-2-(1,2,3,6-tetrahydropyridin-4-yl)pyridine dihydrochloride (5BX)



5BX

4M HCl in dioxane (20ml) was added to a solution of Tert-butyl 4-(5-(1-methyl-1H-1,2,4-triazol-3-yl)pyridin-2-yl)-5,6-dihydropyridine-1(2H)-carboxylate (**4BX**) (4g, 11.67mmol) in CH_2Cl_2 (50ml) at room temperature. The mixture was stirred for 3 hours then solvent was evaporated yielding title product as a white solid (3.8g).

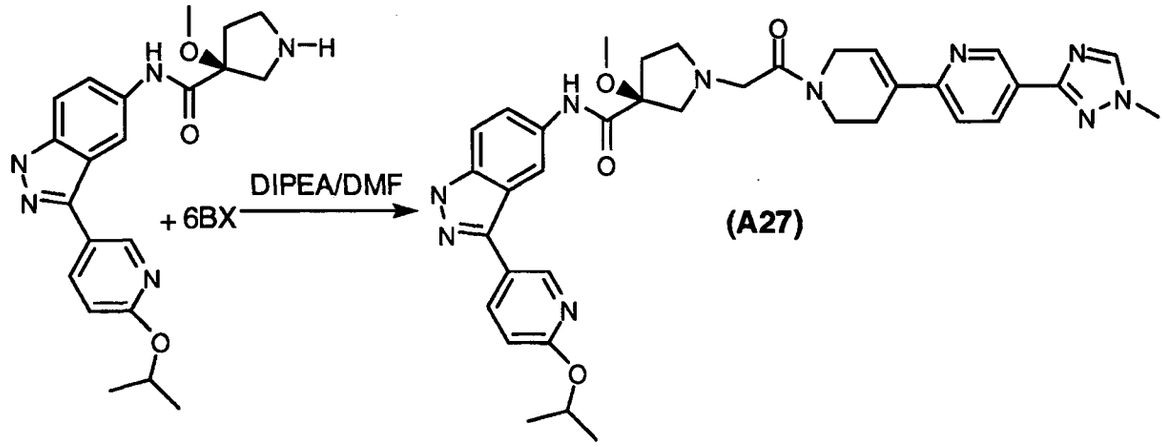
Step 6: 2-chloro-1-(4-(5-(1-methyl-1H-1,2,4-triazol-3-yl)pyridin-2-yl)-5,6-dihydropyridin-1(2H)-yl)ethanone (6BX)



5BX 6BX

Added 1N NaOH (50ml,50mmol) and Chloroacetyl chloride (3ml, 37.7mmol) in CH_2Cl_2 (50ml) dropwise to a solution of 5-(1-methyl-1H-1,2,4-triazol-3-yl)-2-(1,2,3,6-tetrahydropyridin-4-yl)pyridine dihydrochloride (**5BX**) (1g, 3.60mmol) in CH_2Cl_2(50ml at 0°C, maintaining pH at >12. Mixture was stirred for 2 hours at 0°C, then reaction was diluted with CH_2Cl_2 (200ml) and H_2O (100ml). The organic layer was separated, washed with H_2O (50ml), dried (Na_2SO_4), filtered and solvent evaporated yielding title product as a white solid (1.1g, 100%) MS (MH, 318)

Step 7

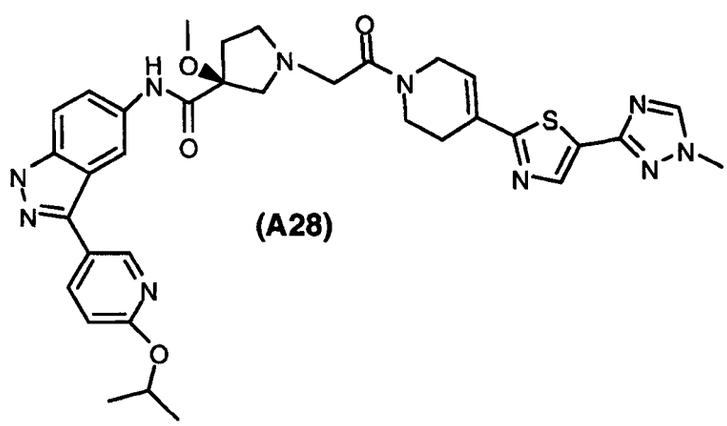


Added a solution of 2-chloro-1-(4-(5-(1-methyl-1H-1,2,4-triazol-3-yl)pyridin-2-yl)-5,6-dihydropyridin-1(2H)-yl)ethanone (**6BX**) (0.85g,2.68mmol) in CH_2Cl_2 (10ml) to a solution of the Indazole (1g,2.53mmol) in DMF (10ml) at room temperature, then stirred at 50°C for 3 hours. The reaction was diluted with EtOAc (300ml) and H_20 (100ml), then the organic layer was separated,dried over Na_2SO_4, filtered and evaporated solvent. The residue chromatographed on silica gel eluting with 10% v/v MeOH/CH_2Cl_2/NH_4OH yielding product **A27** as a white solid (1.3g,76%) MS (MH,677)

LCMS Elution time = 2.61minutes

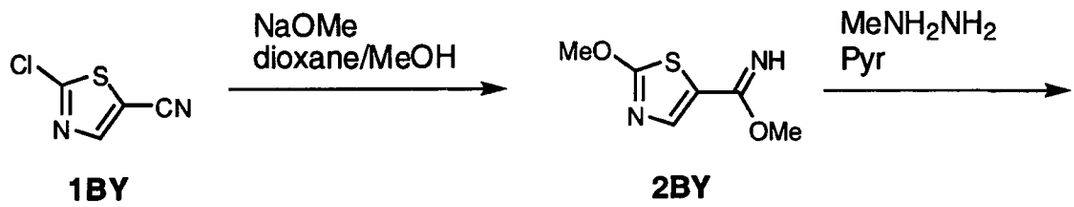
EXAMPLE 27

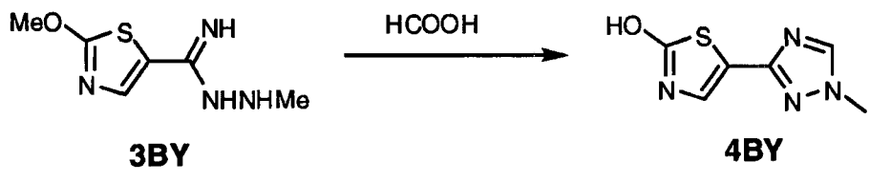
Preparation of (S)-N-(3-(6-isopropoxypyridin-3-yl)-1H-indazol-5-yl)-3-methoxy-1-(2-(4-(5-(1-methyl-1H-1,2,4-triazol-3-yl)thiazol-2-yl)-5,6-dihydropyridin-1(2H)-yl)-2-oxoethyl)pyrrolidine-3-carboxamide:



(A28)

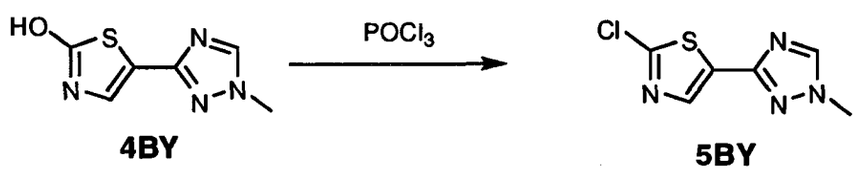
Step 1





To a stirred mixture of 2-chlorothiazole-carbonitrile (1 g, 6.92 mmol) in MeOH was added NaOMe (745 mg, 13.8 mmol, 2 equiv.) and the the reaction mixture was stirred at 0 ºC for 15 min and warmed to rt for another 15 min, quenched with water, extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated to give crude **2BY** (1.2 g) as a yellow oil. To the stirred solution of crude **2BY** in pyridine (1 ml) was added methyl hydrazine (363 µL, 6.9 mmol, 1 equiv.), the resulting mixture was stirred at 0 ºC for 15 min and quenched with HCOOH (5 ml). The resulting mixture was then transferred to a sealed tube and stirred at 110 ºC for overnight, cooled to rt, to which water was added. The resulting mixture was extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried and concentrated to give a yellow solid, which was filtered and washed with CH_2Cl_2. The resulting yellow solid (375 mg) is desired product **4BY**. The filtrate was concentrated and could be further purified on column to provide more product.

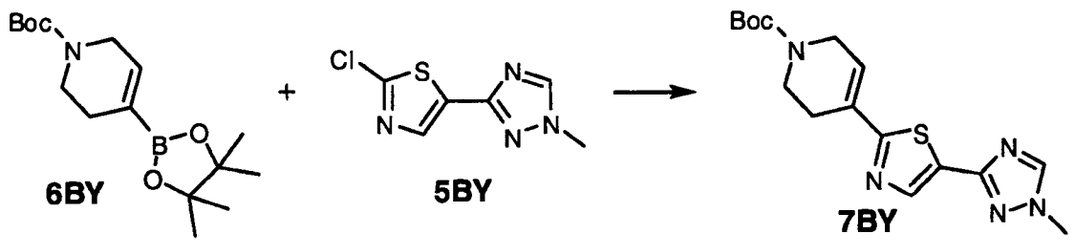
Step 2



A mixture of **4BY** (130 mg) in $POCl_3$ was stirred under N_2 at 120 ºC for 2 d. The initial heterogeneous mixture became a cleaer brown solution, which was concentrated and purified on silica gel (CH_2Cl_2/MeOH, 50/1) to give **5BY** (143 mg) as

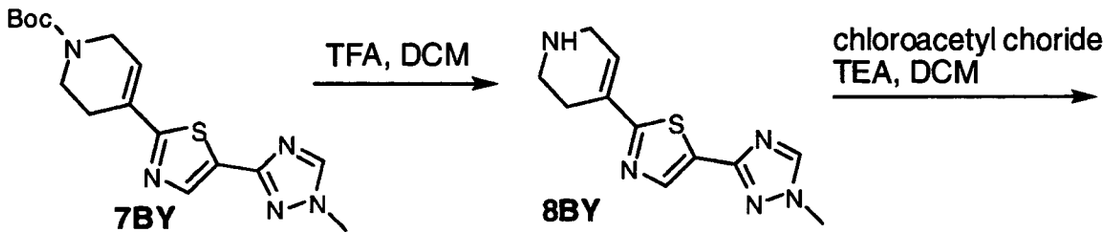
a yellow solid.

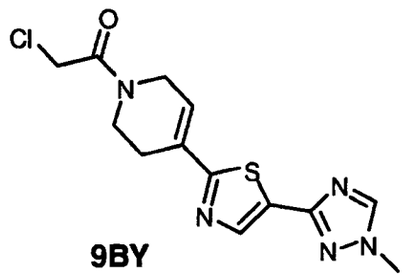
Step 3



A mixture of **5BY** (118 mg, 0.59 mmol), **6BY** (274 mg, 0.89 mmol, 1.5 equiv.), 2 M Na_2CO_3 (590 µL, 1.18 mmol, 2 equiv.) and $Pd(PPh_3)_4$ (34 mg, 0.05 equiv.) in benzene/MeOH (5 mL, 4/1) was degassed and stirred under N_2 at 80 ºC for overnight. The reaction mixture was then concentrated and purified on silica gel (CH_2Cl_2/MeOH, 30/1) to give **7BY** (150 mg) as a yellow solid.

Step 4

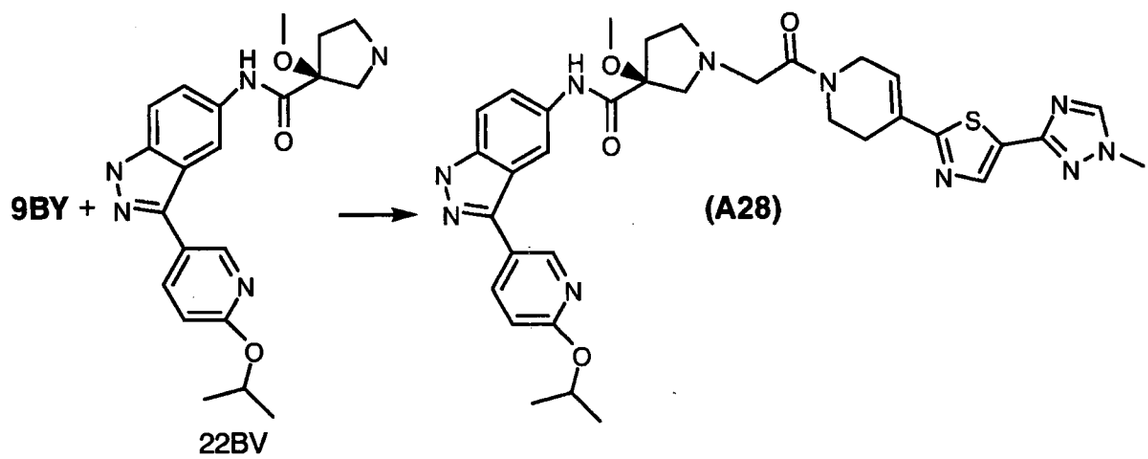




A mixture of **7BY** (150 mg, 0.43 mmol) and TFA (1.5 mL) was stirred at rt for 1 h and concentrated. Chromatograph on silica gel (CH_2Cl_2/MeOH, 15/1) gave the **8BY** (98 mg). To a stirred mixture of **8BY** (98 mg, 0.4 mmol) and triethylamine (335 µL, 2.4 mmol, 6 equiv.) in CH_2Cl_2/MeOH (6 mL, 2/1) at 0 ºC was added chloroacetyl chloride (126 µL, 1.6 mmol, 4 equiv.). The reaction mixture was stirred at 0 ºC for 1 h and concentrated. Chromatograph on silica gel (CH_2Cl_2/MeOH, 25/1) gave the **9BY**

(103 mg) as a white solid.

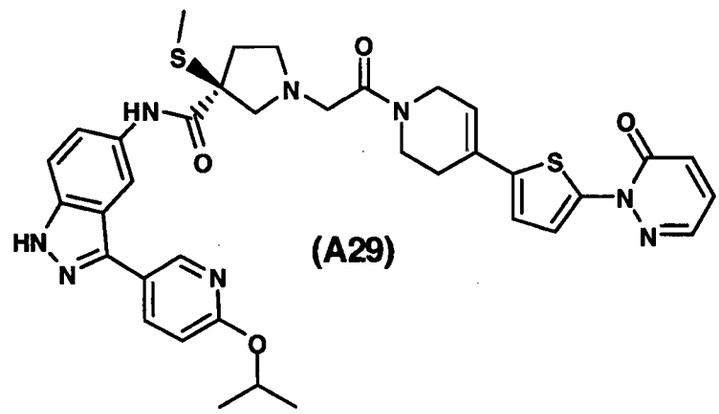
Step 5



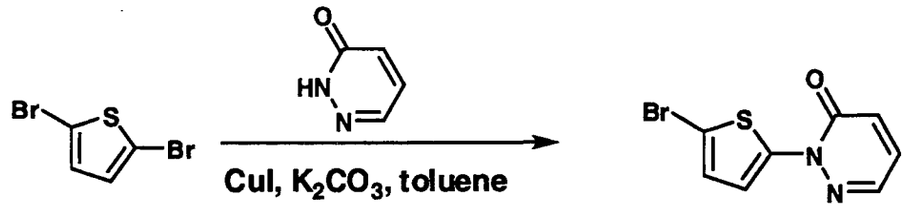
Compound **9BY** was substituted for compound **7BH** in Example 15 step 6 to obtain **A28**. LCMS MH = 683.4, Retention time = 2.77 minutes

EXAMPLE 28

Preparation of (*S*)-N-(3-(6-isopropoxypyridin-3-yl)-1H-indaol-5-yl)-3-(methylthio)-1-(2-oxo-2-(4-(5-(6-oxopyridazin-1(6H)-yl)-5,6-dihydropyridin-1(2H)-yl)ethyl)pyrrolidine-3-carboxamide) (A29)



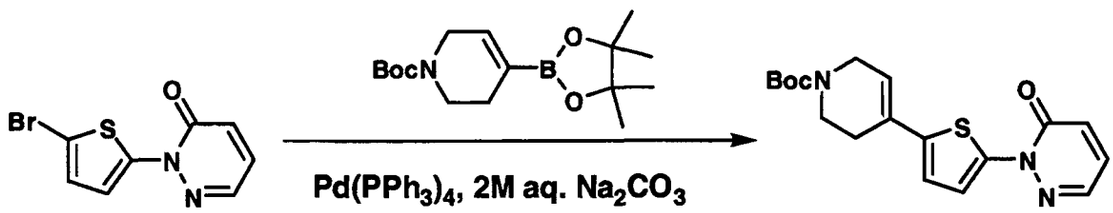
Step 1: Preparation of 2-(5-bromothiophen-2-yl)pyridazin-3(2*H*)-one



1BZ **2BZ**

A mixture of 2,5-dibromothiophene (1.5 g, 6.2 mmol), pyridazin-3(2*H*)-one (0.4 g, 4.1 mmol), copper(I) iodide (0.24 g, 1.2 mmol), potassium carbonate (1.7 g, 12.4 mmol), trans-N,N'-dimethylcyclohexane-1,2-diamine (0.2 mL, 1.2 mmol) and toluene (15 mL) was degassed for 15 minutes and then heated in a sealed tube at 110 °C for 18 hours. Cooled to room temperature, filtered through celite and washed with EtOAc. The filterate was washed with water (100 mL x 2). The organic layer was dried over Na_2SO_4, filtered and concentrated give the desired product **2BZ** (0.9 g, 90%). The residue was purified on silica gel eluting with 80% EtOAc/ hexane to give the desired product **2BZ** (0.7 g, 67%).

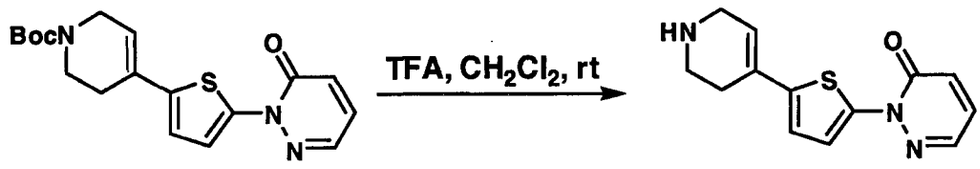
Step 2: Preparation of tert-butyl 4-(5-(6-oxopyridazin-1(6H)-yl)thiophen-2-yl)-5,6-dihydropyridine-1(2*H*)-carboxylate



2BZ **3BZ**

A mixture of Compound **2BZ** (0.7 g, 2.7 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 (0.84 g, 2.7 mmol), 2M aq. sodium carbonate solution (6.8 mL, 13.6 mmol), $Pd(PPh_3)_4$ (0.31g, 0.27 mmol) and 1/1 /toluene/ethanol (20 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 eluting with 60% EtOAc/hexane to give the desired product **3BZ** (0.63 g, 65%).

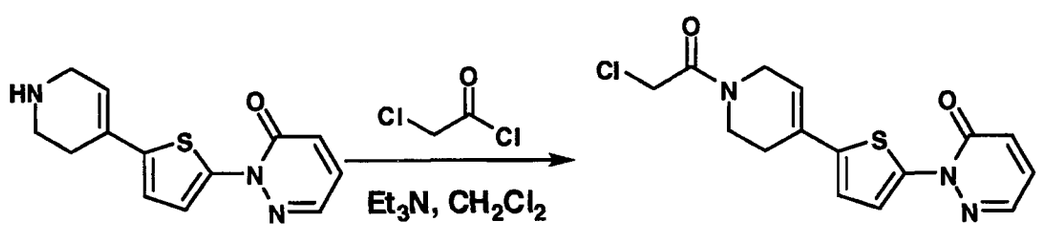
Step 4: Preparation of 2-(5-(1,2,3,6-tetrahydropyridin-4-yl)thiophen-2-yl)pyridazin-3(2*H*)-one



3BZ **4BZ**

A mixture of Compound **3BZ** (0.63 g, 1.75 mmol), CH_2Cl_2 (20 mL) and TFA (23mL) 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 **4BZ** (0.4 g, 89%).

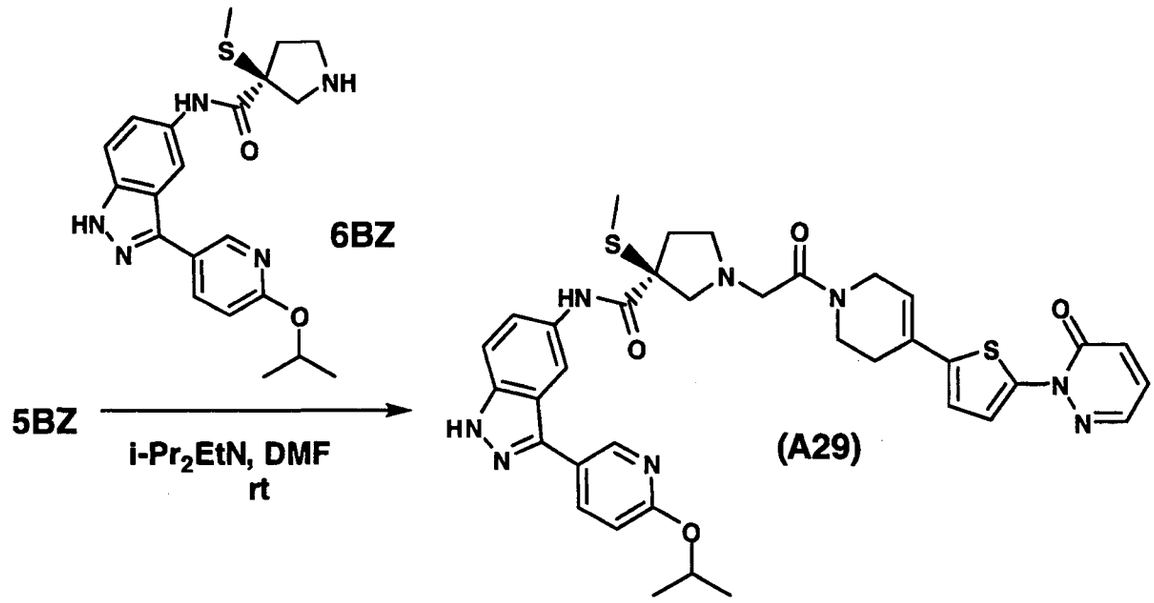
Step 5: Preparation of 2-(5-(1-(2-chloroacetyl)-1,2,3,6-tetrahydropyridin-4-yl)thiophen-2-yl)pyridazin-3(2*H*)-one



4BZ **5BZ**

To a mixture of Compound **4BZ** (0.62 g, 2.39 mmol), CH_2Cl_2 (10 mL), MeOH (3 mL) and triethyl amine (0.67 mL, 4.78 mmol) at -78 °C was added chloroacetyl chloride (0.19 mL, 2.39 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 taken in CH_2Cl_2 and added ether. Resulting solid was filtered and washed with ether and dried to give the desired product **5BZ** (0.56 g, 70%).

Step 6

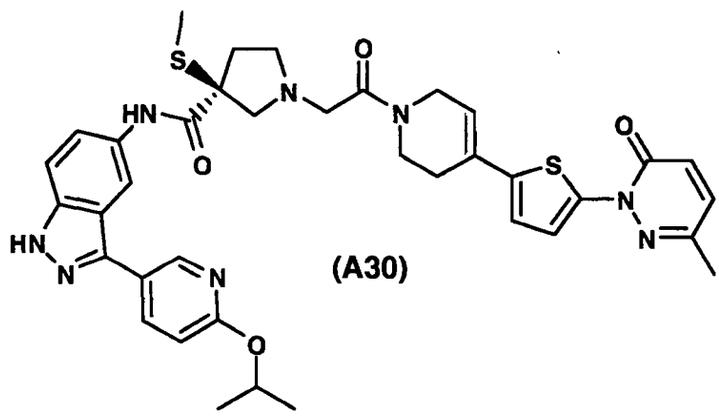


A mixture of Compound **5BZ** (0.04 g, 0.12 mmol), compound **6BZ** (0.05 g, 0.12 mmol), DMF (2 mL) and N,N-diisopropylethylamine (0.042 mL, 0.24 mmol) was stirred at room temperature for 18 hours. Diluted with EtOAc (100 mL) and washed with water (2 x 100 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified on silica gel eluting with 3% MeOH (NH_3)/ CH_2Cl_2 to give the desired product **A29** (0.083 g, 97%).

LCMS MH = 711, Retention time = 3.26 minutes.

EXAMPLE 29

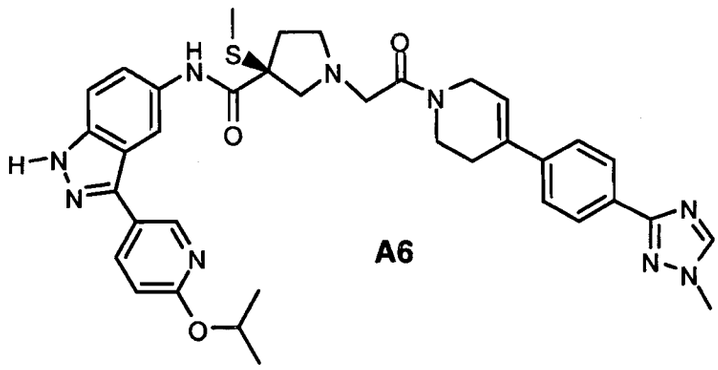
Preparation of (*S*)-N-(3-(6-isopropoxypyridin-3-yl)-1*H*-indaol-5-yl)-1-(2-(4-(5-(3-methyl-6-oxopyridazin-1(6*H*)-yl)thiophen-2-yl)-5,6-dihydropyridin-1(2*H*)-yl)-2-oxoethyl)-3-(methylthio)pyrrolidine-3-carboxamide (A30)



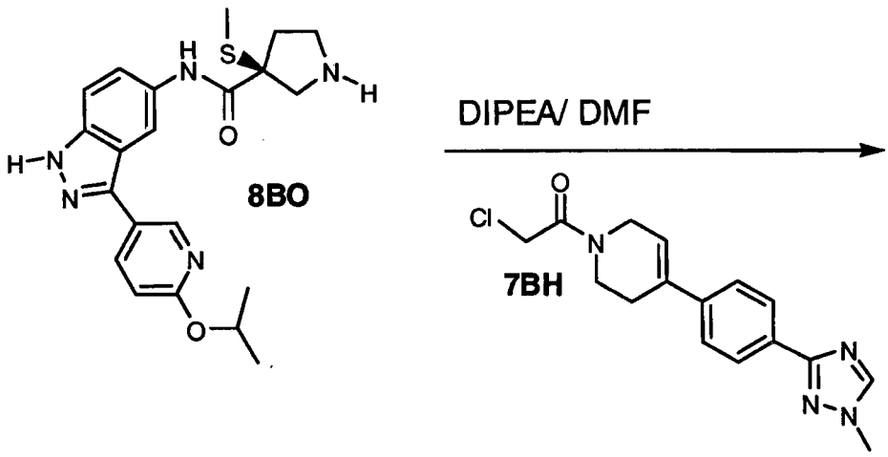
Compound **A30** was prepared using a procedure similar to that in Example 28 except that 6-methylpyridazin-3(2*H*)-one was used in place of pyridazin-3(2*H*)-one in Step 1.

LCMS MH = 725, Retention time = 3.21 minutes.

EXAMPLE 30

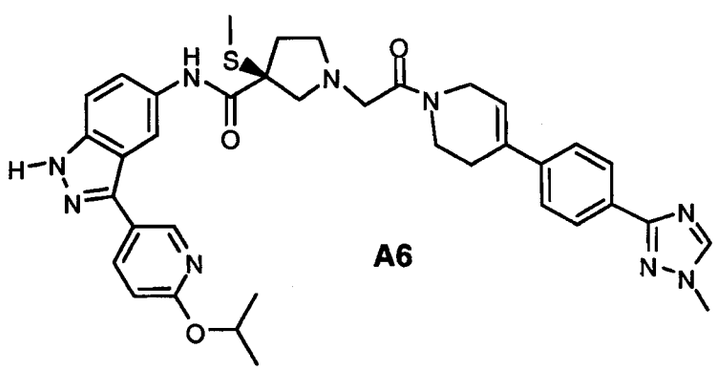


A6



8BO

7BH

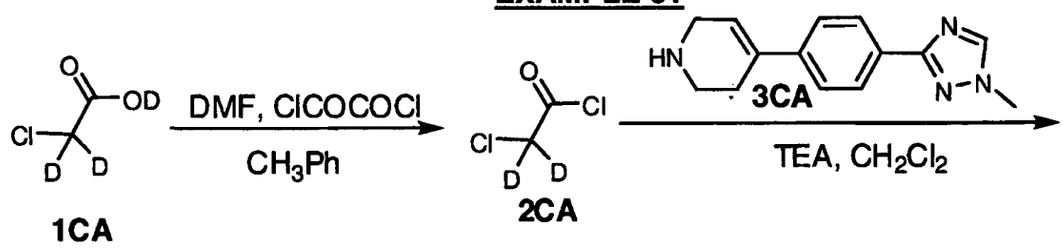


A6

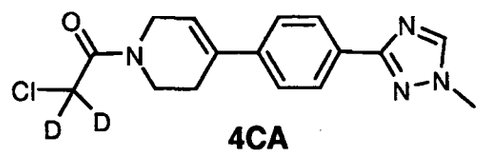
8BO (4.25g, 10.33 mmol) was dissolved in N,N-dimethylformamide (40 ml) at room temperature. Diisopropylethylamine (5.1 mL, 30.99 mmol) was added followed

by **7BH** (3.27g, 10.33 mmol). The reaction mixture was stirred for 1hr. overnite at ambient temperature. Brine was added to the reaction mixture which was then extracted with ethylacetate (3X100 mL). The ethylacetate extracts were dried over magnesium sulfate, filtered and evaporated to obtain crude title product. The crude product was chromatographed to obtain 4.95g (69%) of title product (**A6**)(10% 2*N* NH_3 in MeOH:CH_2Cl_2).

EXAMPLE 31



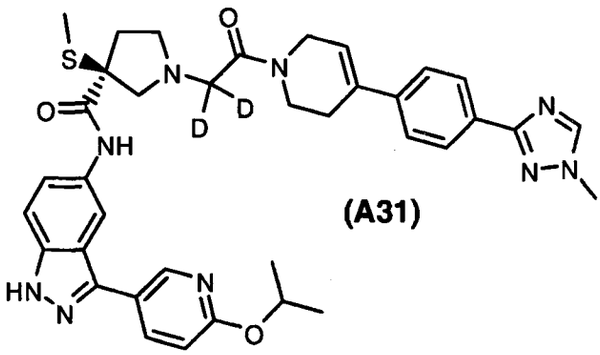
1CA **2CA**



4CA

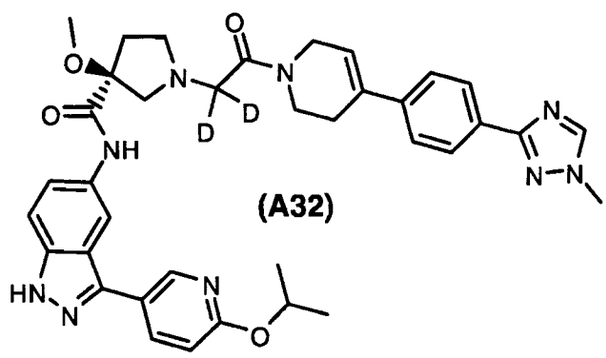
To CH_3Ph (3 mL) solution of **1CA** (140 mg, 1.4 mmol) was added a drop of DMF followed by addition of oxalyl chloride (0.14 mL, 1.6 mmol) at r.t. After 30 mins, the resulting clear solution was added to a CH_2Cl_2 solution of **3CA** (240 mg, 1 mmol) and triethyl amine (0.5 mL). After stirring at r.t. for 30 mins, it was quenched with sat. $NaHCO_3$, extracted with CH_2Cl_2 and conc. to get an off white solid as a crude **4CA** (312 mg) which was used directly in next reactions. In **1CA**, **2CA**, and **4CA** "D" represents deuterium.

Compounds **A31** and **A32,** were prepared by a method similar to the method for preparing Compound **A1** and **A6** substituting **4CA** for **7BH**. Compounds **A45** and **A48** were prepared by a method similar to the method for preparing **A23** and **A25** substituting **4CA** for **7BH**. In **A31**, **A32**, **A45** and **A48** "D" represents deuterium.



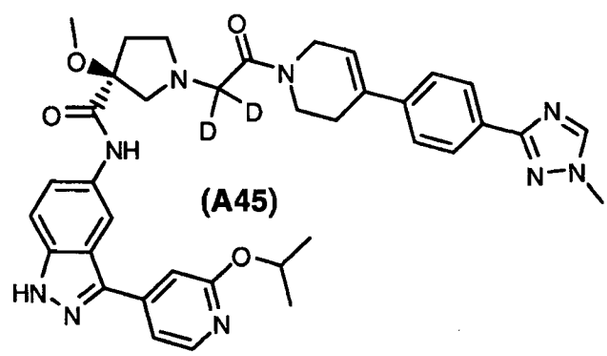
(A31)

LCMS 3.95 min M+1 = 694.4



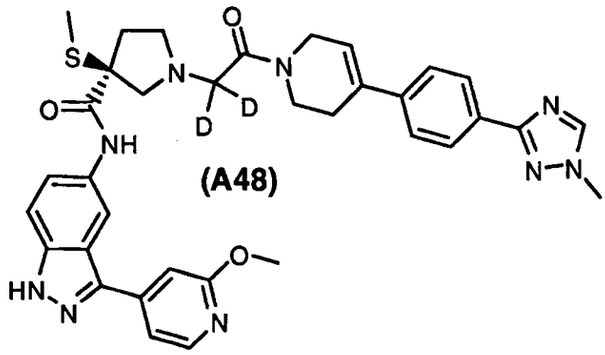
(A32)

LCMS 4.24 min M+1 = 678.4



(A45)

LCMS 3.94 min M+1 = 674

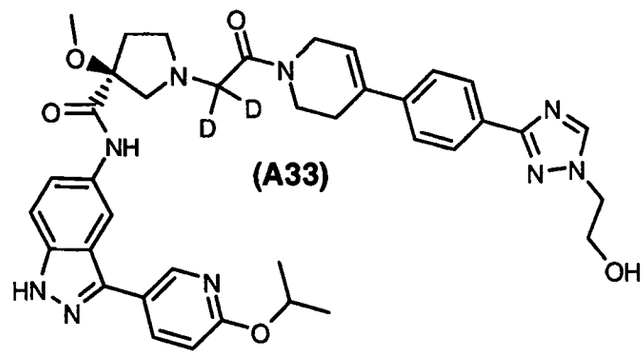


(A48)

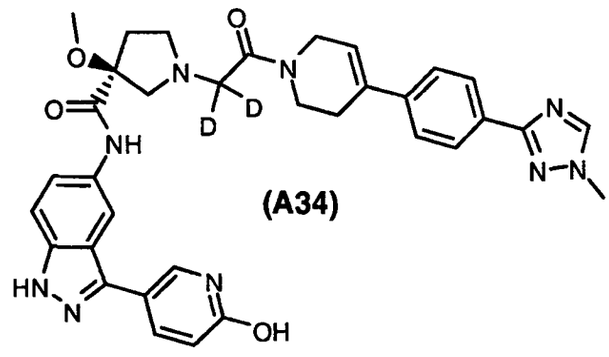
LCMS 3.61 min M+1 = 664

EXAMPLE 32

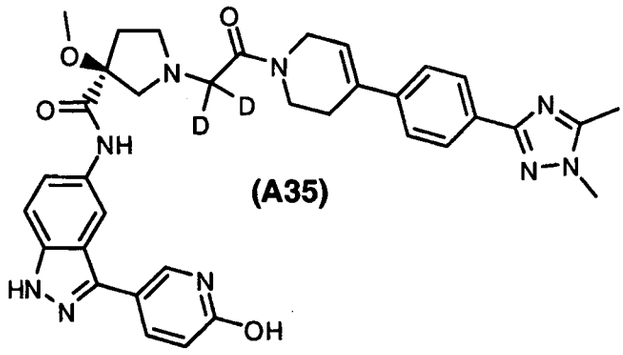
If one were to follow a procedure similar to the procedure in Example 31, Compounds **A33** to **A44**, **A46**, and **A47** below would be obtained. In **A33** to **A44**, **A46**, and **A47** "D" represents deuterium.



(A33)

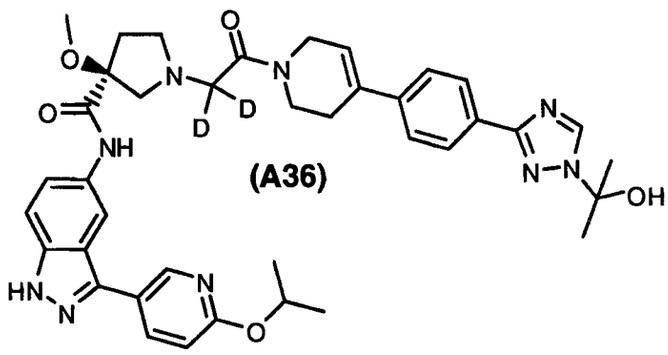


(A34)



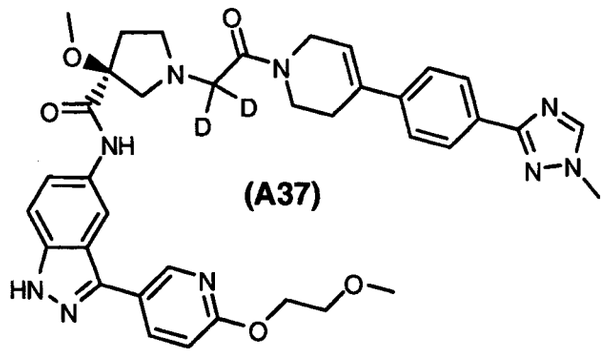
(A35)

,



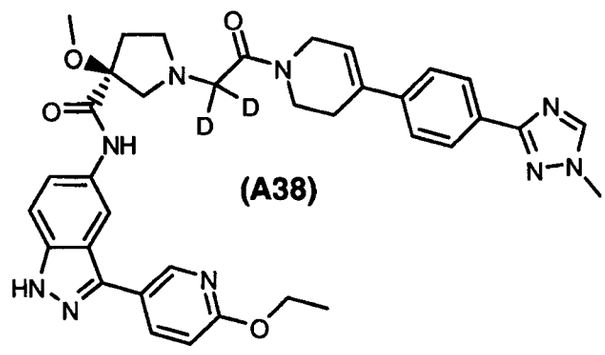
(A36)

,



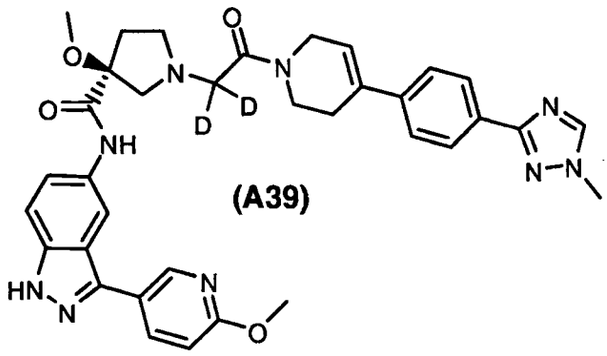
(A37)

5 ,

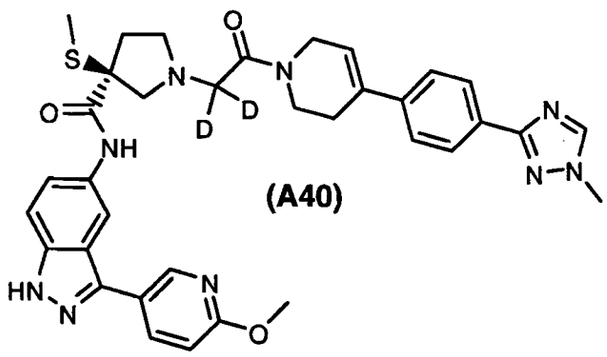


(A38)

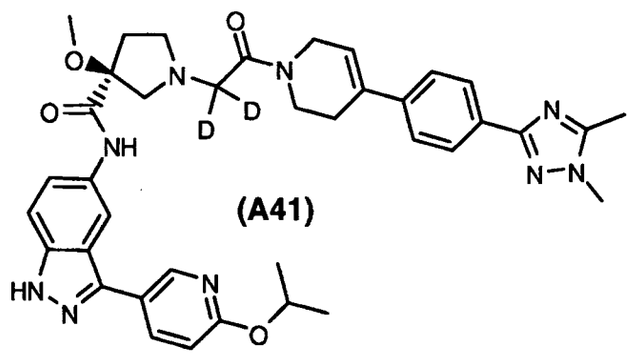
,



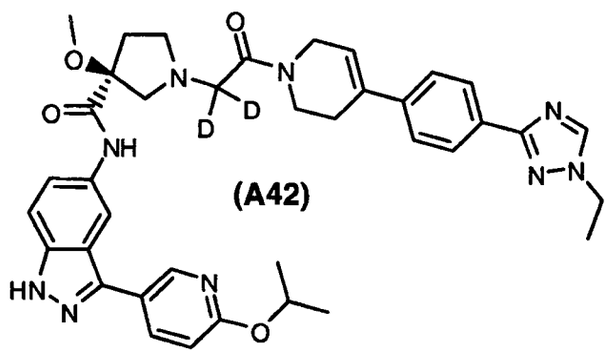
(A39),



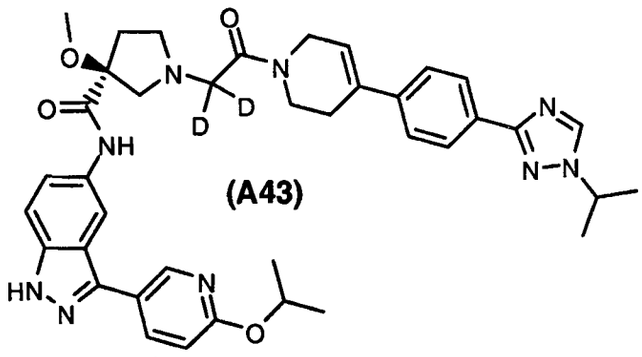
(A40),



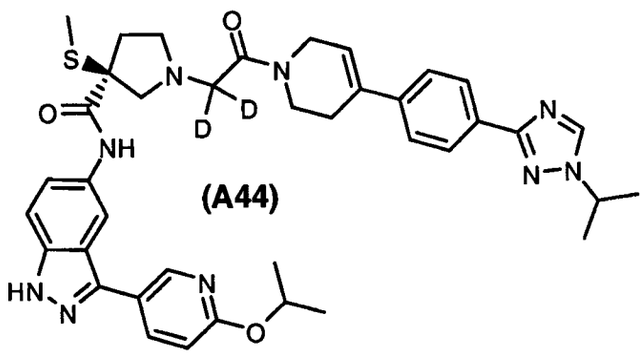
(A41),



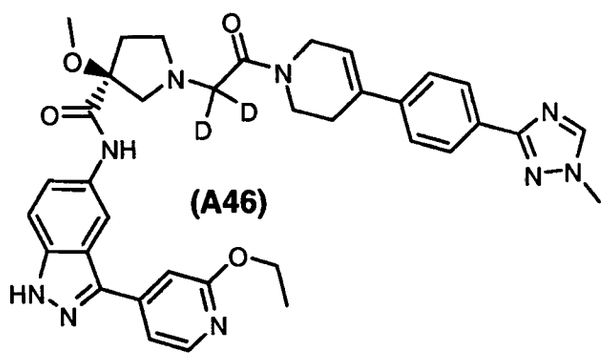
(A42),



(A43),

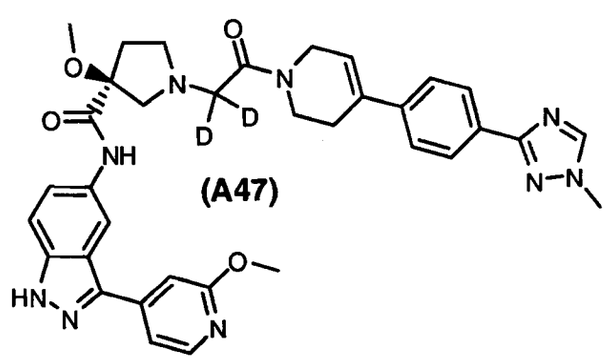


(A44),

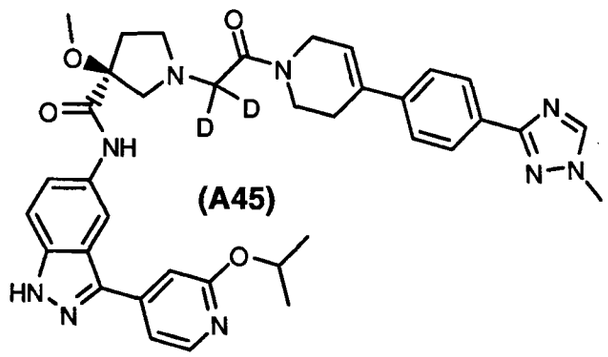


(A46)

and

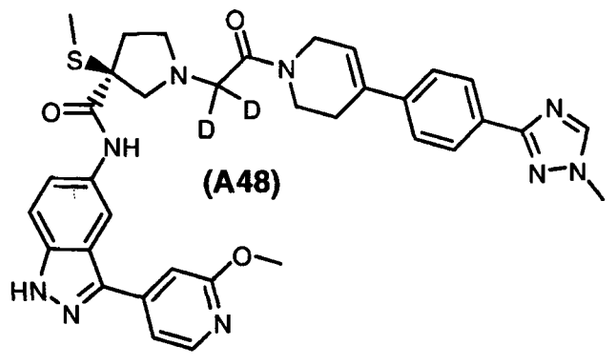


(A47).



(A45)

and



(A48)

In **A33** to **A44**, **A46**, and **A47** "D" represents deuterium.

ASSAYS

Coupled ERK2 Assay:

Activity of compounds against inactive ERK2 can be tested in a coupled MEK1/ERK2 IMAP assay as follows: Compounds can be 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 can be added to each well of a black 384-well assay plate. 1µl of 25x compound can be 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 can be determined to be insensitive to DMSO concentrations up to 20%. ERK2 can then be activated and it's kinase activity can be 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 can be 4%. After one hour, reactions can be terminated by addition of 60µl IMAP detections beads in binding buffer (Molecular Devices). Binding can be allowed to equilibrate for 30 minutes before reading the plate on an LJL Analyst Fluorescence Polarization plate reader. Compound inhibition can be calculated relative to DMSO and fully inhibited standards. Active compounds can be 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}) 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.

Compounds A1 to A16, A18, A20, A21, A23, A25, A26, and A27 to A30 had an AERK2 IC50 in the range of 1.2 to 50 nM.

Compounds A1-A3, A6, A8-A11, A13-A16, A20-A24, A26 and A27 to A30 had an AUC in the range of 36 to 50,999nM.hr in the CARRS assay.

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.

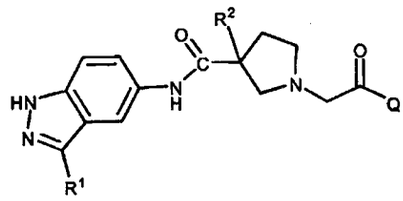
The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage regimen for a particular situation is within the skill in the art. For convenience, the total daily dosage may be divided and administered 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:

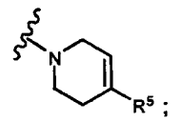
1. A compound of formula 1.0:



(1.0)

or a pharmaceutically acceptable salt or solvate thereof, wherein R^1, R^2 and Q are independently selected, and wherein:

Q is:



R^1 is selected from the group consisting of: heteroaryl and substituted heteroaryl, wherein said substituted heteroaryl is substituted with 1 to 3 substituents independently selected from the group consisting of: -OH, alkoxy, and –O-alkylene-O-alkyl;

R^2 is selected from the group consisting of: -O-alkyl and -S-alkyl; and

R^5 is selected from the group consisting of:

(a) triazolyl-phenyl-,

(b) triazolyl-phenyl- wherein said phenyl is optionally substituted with 1 to 3 substituents independently selected from the group consisting of: halo and alkoxy,

(c) substituted triazolyl-phenyl- wherein said phenyl is optionally substituted with 1 to 3 substituents independently selected from the group consisting of: halo and alkoxy, and said triazolyl group is substituted with one or two substitutents independently selected from the group consisting of: alkyl, hydroxy substituted alkyl, -alkylene-O-alkyl, and amino,

(d) triazolyl-thienyl-,

(e) triazolyl-thienyl- wherein said thienyl is optionally substituted with 1 to 2 substituents independently selected from the group consisting of: halo and alkoxy,

(f) substituted triazolyl-thienyl- wherein said thienyl is optionally substituted with 1 to 2 substituents independently selected from the group consisting of: halo and

alkoxy, and said triazolyl group is substituted with one or two substitutents independently selected from the group consisting of: alkyl, hydroxy substituted alkyl, -alkylene-O-alkyl, and amino,

(g) triazolyl-pyridyl-,

(h) triazolyl-pyridyl- wherein said pyridyl is optionally substituted with 1 to 3 substituents independently selected from the group consisting of: halo, alkyl, and alkoxy, provided that the carbon atoms adjacent to the nitrogen atom in said pyridyl are not substituted with halo, and

(i) substituted triazolyl-pyridyl- wherein: (1) said pyridyl is optionally substituted with 1 to 3 substituents independently selected from the group consisting of: halo, alkyl, and alkoxy, provided that the carbon atoms adjacent to the nitrogen atom in said pyridyl are not substituted with halo, and (2) said triazolyl group is substituted with one or two substitutents independently selected from the group consisting of: alkyl, hydroxy substituted alkyl, -alkylene-O-alkyl, and amino,

(j) triazolyl-thiazolyl-,

(k) triazolyl-thiazolyl- wherein said thiazolyl is optionally substituted with 1 substituent independently selected from the group consisting of: halo, alkyl, and alkoxy, amino, alkylamino, and dialkylamino wherein each alkyl is independently selected, and

(l) substituted triazolyl-thiazolyl- wherein (1) said thiazolyl is optionally substituted with 1 substituent independently selected from the group consisting of: halo, alkyl, and alkoxy, amino, alkylamino, and dialkylamino wherein each alkyl is independently selected, and (2) said triazolyl group is substituted with one or two substitutents independently selected from the group consisting of: alkyl, hydroxy substituted alkyl, -alkylene-O-alkyl, and amino,

(m) pyridazinyl-thienyl-,

(n) pyridazinyl-thienyl- wherein said thienyl is optionally substituted with 1 to 2 substituents independently selected from the group consisting of: halo and alkoxy, and

(o) substituted pyridazinyl-thienyl- wherein (1) said thienyl is optionally substituted with 1 to 2 substituents independently selected from the group consisting of: halo and alkoxy, and (2) said pyridazinyl group is substituted with 1 to 3 substitutents independently selected from the group consisting of: =O, alkyl, amino, alkylamino, dialkylamino wherein each alkyl is independently selected, and halo,

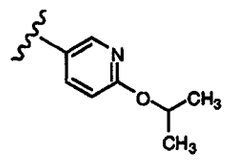
provided that the carbon atoms adjacent to the nitrogen atoms in said pyridazinyl are not substituted with halo, and

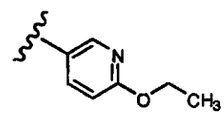
provided that when said -alkylene-O-alkyl group is bound to the nitrogen of said triazolyl in (c), (f), (i) and (l) of R^5 the alkylene moiety of said -alkylene-O-alkyl group is not $-CH_2-$.

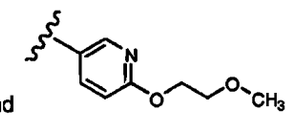
2. The compound of Claim 1 wherein R^1 is a pyridyl substituted with a substituent selected from the group consisting of: -OH, alkoxy, and –O-alkylene-O-alkyl.

3. The compound of Claim 2 wherein said substituent is selected from the group consisting of: $-O-CH_3$, $-O-C_2H_5$, $-O-CH(CH_3)_2$, and $-O-(CH_2)_2-O-CH_3$.

4. The compound of Claim 1 wherein R^1 is selected from the group consisting of:



,


, and


.

5. The compound of Claim 1 wherein R^2 is selected from the group consisting of: $-OCH_3$ and $-SCH_3$.

6. The compound of Claim 1 wherein R^5 is selected from the group consisting of:

(a) a substituted triazolyl-phenyl- wherein the triazolyl moiety is substituted with one or two alkyl groups selected from the group consisting of: $-C_1-C_6$alkyl, $-C_1-C_4$alkyl, $-C_1-C_2$alkyl, and $-CH_3$;

(b) a substituted triazolyl-phenyl- wherein the triazolyl moiety is substituted with one or two alkyl groups selected from the group consisting of: $-C_1-C_4$alkyl, $-C_1-C_2$alkyl, and $-CH_3$;

(c) a substituted triazolyl-phenyl- wherein the triazolyl moiety is substituted on the nitrogen with an alkyl group selected from the group consisting of: -C_1-C_4alkyl, -C_1-C_2alkyl, and –CH_3;

(d) a substituted triazolyl-phenyl- wherein the triazolyl moiety is substituted on the nitrogen with an -alkylene-O-alkyl group selected from the group consisting of: -C_2-C_4alkylene-O-C_1-C_6alkyl, -C_2alkylene-O-C_1-C_2alkyl, -C_2-C_4alkylene-O-CH_3, and –$CH_2CH_2OCH_3$;

(e) a substituted triazolyl-phenyl- wherein the triazolyl moiety is substituted on the nitrogen with an -alkylene-O-alkyl group selected from the group consisting of: -C_2alkylene-O-C_1-C_2alkyl, and –$CH_2CH_2OCH_3$;

(f) a substituted triazolyl-phenyl- wherein the triazolyl moiety is substituted on the nitrogen with a hydroxy substituted alkyl group selected from the group consisting of: hydroxy substituted -C_1-C_4alkyl, hydroxy substituted -C_1-C_2alkyl, and hydroxy substituted -CH_3; and

(g) a substituted triazolyl-phenyl- wherein the triazolyl moiety is substituted on the nitrogen with a hydroxy substituted alkyl group selected from the group consisting of: $CH_2COH(CH_3)_2$, and -CH_2CH_2OH.

7. The compound of Claim 1 wherein the optional halo substituents for the phenyl moiety of R^5 are F.

8. The compound of Claim 1 wherein R^5 is a substituted triazolyl-phenyl- group wherein:

(1)

(a) said triazolyl moiety is optionally substituted on the nitrogen with a substituent selected from the group consisting of: –$CH_2COH(CH_3)_2$, and -CH_2CH_2OH, (b) said triazolyl moiety is optionally substituted on the nitrogen with an alkyl group, (c) said triazolyl moiety is optionally substituted on the nitrogen with an alkyl group, and on the carbon with an alkyl group, (d) said triazolyl moiety is optionally substituted on the nitrogen with a –CH_3 group, (e) said triazolyl moiety is optionally substituted on the nitrogen with one –CH_3 group, and on the carbon with one –CH_3 group, (f) said triazolyl moiety is optionally substituted on the carbon with a –NH_2 group, or (g) said triazolyl moiety is optionally substituted on the nitrogen with a –$CH_2CH_2OCH_3$ group; and wherein said phenyl moiety is optionally substituted with halo; or

(2)

(a) said triazolyl moiety is optionally substituted on the nitrogen with a substituent selected from the group consisting of: $-CH_2COH(CH_3)_2$, and $-CH_2CH_2OH$, (b) said triazolyl moiety is optionally substituted on the nitrogen with an alkyl group, (c) said triazolyl moiety is optionally substituted on the nitrogen with an alkyl group, and on the carbon with an alkyl group, (d) said triazolyl moiety is optionally substituted on the nitrogen with a $-CH_3$ group, (e) said triazolyl moiety is optionally substituted on the nitrogen with one $-CH_3$ group, and on the carbon with one $-CH_3$ group, (f) said triazolyl moiety is optionally substituted on the carbon with a $-NH_2$ group, or (g) said triazolyl moiety is optionally substituted on the nitrogen with a $-CH_2CH_2OCH_3$ group; and wherein said phenyl moiety is optionally substituted with alkoxy; or

(3)

(a) said triazolyl moiety is optionally substituted on the nitrogen with a substituent selected from the group consisting of: $-CH_2COH(CH_3)_2$, and $-CH_2CH_2OH$, (b) said triazolyl moiety is optionally substituted on the nitrogen with an alkyl group, (c) said triazolyl moiety is optionally substituted on the nitrogen with an alkyl group, and on the carbon with an alkyl group, (d) said triazolyl moiety is optionally substituted on the nitrogen with a $-CH_3$ group, (e) said triazolyl moiety is optionally substituted on the nitrogen with one $-CH_3$ group, and on the carbon with one $-CH_3$ group, (f) said triazolyl moiety is optionally substituted on the carbon with a $-NH_2$ group, or (g) said triazolyl moiety is optionally substituted on the nitrogen with a $-CH_2CH_2OCH_3$ group; and wherein said phenyl moiety is substituted with halo; or

(4)

(a) said triazolyl moiety is optionally substituted on the nitrogen with a substituent selected from the group consisting of: $-CH_2COH(CH_3)_2$, and $-CH_2CH_2OH$, (b) said triazolyl moiety is optionally substituted on the nitrogen with an alkyl group, (c) said triazolyl moiety is optionally substituted on the nitrogen with an alkyl group, and on the carbon with an alkyl group, (d) said triazolyl moiety is optionally substituted on the nitrogen with a $-CH_3$ group, (e) said triazolyl moiety is optionally substituted on the nitrogen with one $-CH_3$ group, and on the carbon with one $-CH_3$ group, (f) said triazolyl moiety is optionally substituted on the carbon with a $-NH_2$ group, or (g) said

triazolyl moiety is optionally substituted on the nitrogen with a $-CH_2CH_2OCH_3$ group; and wherein said phenyl moiety is substituted with alkoxy; or

(5)

(a) said triazolyl moiety is substituted on the nitrogen with a substituent selected from the group consisting of: $-CH_2COH(CH_3)_2$, and $-CH_2CH_2OH$, (b) said triazolyl moiety is substituted on the nitrogen with an alkyl group, (c) said triazolyl moiety is substituted on the nitrogen with an alkyl group, and on the carbon with an alkyl group, (d) said triazolyl moiety is substituted on the nitrogen with a $-CH_3$ group, (e) said triazolyl moiety is substituted on the nitrogen with one $-CH_3$ group, and on the carbon with one $-CH_3$ group, (f) said triazolyl moiety is substituted on the carbon with a $-NH_2$ group, or (g) said triazolyl moiety is substituted on the nitrogen with a $-CH_2CH_2OCH_3$ group; and wherein said phenyl moiety is optionally substituted with halo; or

(6)

(a) said triazolyl moiety is substituted on the nitrogen with a substituent selected from the group consisting of: $-CH_2COH(CH_3)_2$, and $-CH_2CH_2OH$, (b) said triazolyl moiety is substituted on the nitrogen with an alkyl group, (c) said triazolyl moiety is substituted on the nitrogen with an alkyl group, and on the carbon with an alkyl group, (d) said triazolyl moiety is substituted on the nitrogen with a $-CH_3$ group, (e) said triazolyl moiety is substituted on the nitrogen with one $-CH_3$ group, and on the carbon with one $-CH_3$ group, (f) said triazolyl moiety is substituted on the carbon with a $-NH_2$ group, or (g) said triazolyl moiety is substituted on the nitrogen with a $-CH_2CH_2OCH_3$ group; and wherein said phenyl moiety is optionally substituted with alkoxy; or

(7)

(a) said triazolyl moiety is substituted on the nitrogen with a substituent selected from the group consisting of: $-CH_2COH(CH_3)_2$, and $-CH_2CH_2OH$, (b) said triazolyl moiety is substituted on the nitrogen with an alkyl group, (c) said triazolyl moiety is substituted on the nitrogen with an alkyl group, and on the carbon with an alkyl group, (d) said triazolyl moiety is substituted on the nitrogen with a $-CH_3$ group, (e) said triazolyl moiety is substituted on the nitrogen with one $-CH_3$ group, and on the

carbon with one $-CH_3$ group, (f) said triazolyl moiety is substituted on the carbon with a $-NH_2$ group, or (g) said triazolyl moiety is substituted on the nitrogen with a $-CH_2CH_2OCH_3$ group; and wherein said phenyl moiety is substituted with halo; or

(8)

(a) said triazolyl moiety is substituted on the nitrogen with a substituent selected from the group consisting of: $-CH_2COH(CH_3)_2$, and $-CH_2CH_2OH$, (b) said triazolyl moiety is substituted on the nitrogen with an alkyl group, (c) said triazolyl moiety is substituted on the nitrogen with an alkyl group, and on the carbon with an alkyl group, (d) said triazolyl moiety is substituted on the nitrogen with a $-CH_3$ group, (e) said triazolyl moiety is substituted on the nitrogen with one $-CH_3$ group, and on the carbon with one $-CH_3$ group, (f) said triazolyl moiety is substituted on the carbon with a $-NH_2$ group, or (g) said triazolyl moiety is substituted on the nitrogen with a $-CH_2CH_2OCH_3$ group; and wherein said phenyl moiety is substituted with alkoxy; or

(9)

(a) said triazolyl moiety is substituted on the nitrogen with a substituent selected from the group consisting of: $-CH_2COH(CH_3)_2$, and $-CH_2CH_2OH$, (b) said triazolyl moiety is substituted on the nitrogen with an alkyl group, (c) said triazolyl moiety is substituted on the nitrogen with an alkyl group, and on the carbon with an alkyl group, (d) said triazolyl moiety is substituted on the nitrogen with a $-CH_3$ group, (e) said triazolyl moiety is substituted on the nitrogen with one $-CH_3$ group, and on the carbon with one $-CH_3$ group, (f) said triazolyl moiety is substituted on the carbon with a $-NH_2$ group, or (g) said triazolyl moiety is substituted on the nitrogen with a $-CH_2CH_2OCH_3$ group; and wherein said phenyl moiety is unsubstituted.

9. The compound of Claim 1 wherein R^5 is a substituted triazolyl-phenyl group wherein said triazolyl moiety is substituted with: (a) one substituent selected from the group consisting of: $-CH_2COH(CH_3)_2$, and $-CH_2CH_2OH$, (b) one alkyl group, (c) two alkyl groups, (d) one $-CH_3$ group, (e) two $-CH_3$ groups, (f) one $-NH_2$ group, or (g) one $-CH_2CH_2OCH_3$ group.

10. The compound of Claim 1 wherein the optional alkoxy substituents for the phenyl moiety of R^5 are $-OCH_3$.

11. The compound of Claim 1 wherein R^5 is selected from the group consisting of:

(a) a substituted triazolyl-thienyl- wherein the triazolyl moiety is substituted with one or two alkyl groups selected from the group consisting of: -C_1-C_6alkyl, -C_1-C_4alkyl, -C_1-C_2alkyl, and –CH_3;

(b) a substituted triazolyl-thienyl- wherein the triazolyl moiety is substituted with one or two alkyl groups selected from the group consisting of: -C_1-C_4alkyl, -C_1-C_2alkyl, and –CH_3;

(c) a substituted triazolyl-thienyl- wherein the triazolyl moiety is substituted on the nitrogen with an alkyl group selected from the group consisting of: -C_1-C_4alkyl, -C_1-C_2alkyl, and –CH_3;

(d) a substituted triazolyl-thienyl- wherein the triazolyl moiety is substituted on the nitrogen with an -alkylene-O-alkyl group selected from the group consisting of: -C_2-C_4alkylene-O-C_1-C_6alkyl, -C_2alkylene-O-C_1-C_2alkyl, -C_2-C_4alkylene-O-CH_3, and –$CH_2CH_2OCH_3$;

(e) a substituted triazolyl-thienyl- wherein the triazolyl moiety is substituted on the nitrogen with an -alkylene-O-alkyl group selected from the group consisting of: -C_2alkylene-O-C_1-C_2alkyl, and –$CH_2CH_2OCH_3$;

(f) a substituted triazolyl-thienyl- wherein the triazolyl moiety is substituted on the nitrogen with a hydroxy substituted alkyl group selected from the group consisting of: hydroxy substituted -C_1-C_4alkyl, hydroxy substituted -C_1-C_2alkyl, and hydroxy substituted -CH_3; and

(g) a substituted triazolyl-thienyl- wherein the triazolyl moiety is substituted on the nitrogen with a hydroxy substituted alkyl group selected from the group consisting of: $CH_2COH(CH_3)_2$, and -CH_2CH_2OH.

12. The compound of Claim 1 wherein R^5 is a substituted triazolyl-thienyl- group wherein:

(A)

(a) said triazolyl moiety is optionally substituted on the nitrogen with a substituent selected from the group consisting of: –$CH_2COH(CH_3)_2$, and -CH_2CH_2OH, (b) said triazolyl moiety is optionally substituted on the nitrogen with an alkyl group, (c) said triazolyl moiety is optionally substituted on the nitrogen with an alkyl group, and

on the carbon with an alkyl group, (d) said triazolyl moiety is optionally substituted on the nitrogen with a $-CH_3$ group, (e) said triazolyl moiety is optionally substituted on the nitrogen with one $-CH_3$ group, and on the carbon with one $-CH_3$ group, (f) said triazolyl moiety is optionally substituted on the carbon with a $-NH_2$ group, or (g) said triazolyl moiety is optionally substituted on the nitrogen with a $-CH_2CH_2OCH_3$ group; and wherein said thienyl moiety is optionally substituted with halo; or

(B)

(a) said triazolyl moiety is optionally substituted on the nitrogen with a substituent selected from the group consisting of: $-CH_2COH(CH_3)_2$, and $-CH_2CH_2OH$, (b) said triazolyl moiety is optionally substituted on the nitrogen with an alkyl group, (c) said triazolyl moiety is optionally substituted on the nitrogen with an alkyl group, and on the carbon with an alkyl group, (d) said triazolyl moiety is optionally substituted on the nitrogen with a $-CH_3$ group, (e) said triazolyl moiety is optionally substituted on the nitrogen with one $-CH_3$ group, and on the carbon with one $-CH_3$ group, (f) said triazolyl moiety is optionally substituted on the carbon with a $-NH_2$ group, or (g) said triazolyl moiety is optionally substituted on the nitrogen with a $-CH_2CH_2OCH_3$ group; and wherein said thienyl moiety is optionally substituted with alkoxy; or

(C)

(a) said triazolyl moiety is optionally substituted on the nitrogen with a substituent selected from the group consisting of: $-CH_2COH(CH_3)_2$, and $-CH_2CH_2OH$, (b) said triazolyl moiety is optionally substituted on the nitrogen with an alkyl group, (c) said triazolyl moiety is optionally substituted on the nitrogen with an alkyl group, and on the carbon with an alkyl group, (d) said triazolyl moiety is optionally substituted on the nitrogen with a $-CH_3$ group, (e) said triazolyl moiety is optionally substituted on the nitrogen with one $-CH_3$ group, and on the carbon with one $-CH_3$ group, (f) said triazolyl moiety is optionally substituted on the carbon with a $-NH_2$ group, or (g) said triazolyl moiety is optionally substituted on the nitrogen with a $-CH_2CH_2OCH_3$ group; and wherein said thienyl moiety is substituted with halo; or

(D)

(a) said triazolyl moiety is optionally substituted on the nitrogen with a substituent selected from the group consisting of: $-CH_2COH(CH_3)_2$, and $-CH_2CH_2OH$,

(b) said triazolyl moiety is optionally substituted on the nitrogen with an alkyl group, (c) said triazolyl moiety is optionally substituted on the nitrogen with an alkyl group, and on the carbon with an alkyl group, (d) said triazolyl moiety is optionally substituted on the nitrogen with a $-CH_3$ group, (e) said triazolyl moiety is optionally substituted on the nitrogen with one $-CH_3$ group, and on the carbon with one $-CH_3$ group, (f) said triazolyl moiety is optionally substituted on the carbon with a $-NH_2$ group, or (g) said triazolyl moiety is optionally substituted on the nitrogen with a $-CH_2CH_2OCH_3$ group; and wherein said thienyl moiety is substituted with alkoxy; or

(E)

(a) said triazolyl moiety is substituted on the nitrogen with a substituent selected from the group consisting of: $-CH_2COH(CH_3)_2$, and $-CH_2CH_2OH$, (b) said triazolyl moiety is substituted on the nitrogen with an alkyl group, (c) said triazolyl moiety is substituted on the nitrogen with an alkyl group, and on the carbon with an alkyl group, (d) said triazolyl moiety is substituted on the nitrogen with a $-CH_3$ group, (e) said triazolyl moiety is substituted on the nitrogen with one $-CH_3$ group, and on the carbon with one $-CH_3$ group, (f) said triazolyl moiety is substituted on the carbon with a $-NH_2$ group, or (g) said triazolyl moiety is substituted on the nitrogen with a $-CH_2CH_2OCH_3$ group; and wherein said thienyl moiety is optionally substituted with halo; or

(F)

(a) said triazolyl moiety is substituted on the nitrogen with a substituent selected from the group consisting of: $-CH_2COH(CH_3)_2$, and $-CH_2CH_2OH$, (b) said triazolyl moiety is substituted on the nitrogen with an alkyl group, (c) said triazolyl moiety is substituted on the nitrogen with an alkyl group, and on the carbon with an alkyl group, (d) said triazolyl moiety is substituted on the nitrogen with a $-CH_3$ group, (e) said triazolyl moiety is substituted on the nitrogen with one $-CH_3$ group, and on the carbon with one $-CH_3$ group, (f) said triazolyl moiety is substituted on the carbon with a $-NH_2$ group, or (g) said triazolyl moiety is substituted on the nitrogen with a $-CH_2CH_2OCH_3$ group; and wherein said thienyl moiety is optionally substituted with alkoxy; or

(G)

(a) said triazolyl moiety is substituted on the nitrogen with a substituent selected from the group consisting of: $-CH_2COH(CH_3)_2$, and $-CH_2CH_2OH$, (b) said triazolyl moiety is substituted on the nitrogen with an alkyl group, (c) said triazolyl moiety is substituted on the nitrogen with an alkyl group, and on the carbon with an alkyl group, (d) said triazolyl moiety is substituted on the nitrogen with a $-CH_3$ group, (e) said triazolyl moiety is substituted on the nitrogen with one $-CH_3$ group, and on the carbon with one $-CH_3$ group, (f) said triazolyl moiety is substituted on the carbon with a $-NH_2$ group, or (g) said triazolyl moiety is substituted on the nitrogen with a $-CH_2CH_2OCH_3$ group; and wherein said thienyl moiety is substituted with halo; or

(H)

(a) said triazolyl moiety is substituted on the nitrogen with a substituent selected from the group consisting of: $-CH_2COH(CH_3)_2$, and $-CH_2CH_2OH$, (b) said triazolyl moiety is substituted on the nitrogen with an alkyl group, (c) said triazolyl moiety is substituted on the nitrogen with an alkyl group, and on the carbon with an alkyl group, (d) said triazolyl moiety is substituted on the nitrogen with a $-CH_3$ group, (e) said triazolyl moiety is substituted on the nitrogen with one $-CH_3$ group, and on the carbon with one $-CH_3$ group, (f) said triazolyl moiety is substituted on the carbon with a $-NH_2$ group, or (g) said triazolyl moiety is substituted on the nitrogen with a $-CH_2CH_2OCH_3$ group; and wherein said thienyl moiety is substituted with alkoxy; or

(I)

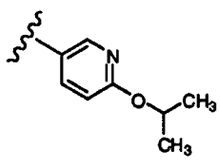
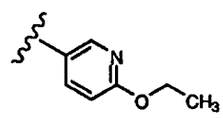
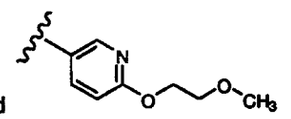
(a) said triazolyl moiety is substituted on the nitrogen with a substituent selected from the group consisting of: $-CH_2COH(CH_3)_2$, and $-CH_2CH_2OH$, (b) said triazolyl moiety is substituted on the nitrogen with an alkyl group, (c) said triazolyl moiety is substituted on the nitrogen with an alkyl group, and on the carbon with an alkyl group, (d) said triazolyl moiety is substituted on the nitrogen with a $-CH_3$ group, (e) said triazolyl moiety is substituted on the nitrogen with one $-CH_3$ group, and on the carbon with one $-CH_3$ group, (f) said triazolyl moiety is substituted on the carbon with a $-NH_2$ group, or (g) said triazolyl moiety is substituted on the nitrogen with a $-CH_2CH_2OCH_3$ group; and wherein said thienyl moiety is unsubstituted.

13. The compound of Claim 1 wherein R^5 is a substituted triazolyl-thienyl group wherein said triazolyl moiety is substituted with: (a) one substituent selected from the group consisting of:–$CH_2COH(CH_3)_2$ and -CH_2CH_2OH, (b) one alkyl group, (c) two alkyl groups, (d) one –CH_3 group, (e) two –CH_3 groups, (f) one –NH_2 group, or (g) one –$CH_2CH_2OCH_3$ group.

14. The compound of Claim 1 wherein the optional alkoxy substituents for the phenyl moiety of R^5 are –OCH_3.

15. The compound of Claim 8 wherein R^1 is a pyridyl substituted with a substituent selected from the group consisting of: -O-CH_3, -O-C_2H_5, –O-$CH(CH_3)_2$, and –O-$(CH_2)_2$-O-CH_3, and R^2 is selected from the group consisting of: -OCH_3 and –SCH_3.

16. The compound of Claim 8 wherein R^1 is selected from the group consisting of:



, and

,

and R^2 is selected from the group consisting of: -OCH_3 and –SCH_3.

17. The compound of Claim 1 wherein:

(a) R^5 is a substituted triazolyl-pyridyl- wherein said triazolyl is substituted and said pyridyl is substituted; or

(b) R^5 is a substituted triazolyl-pyridyl- wherein said triazolyl is substituted on the nitrogen and said pyridyl is substituted; or

(c) R^5 is a substituted triazolyl-pyridyl- wherein said triazolyl is substituted on the carbon and said pyridyl is substituted; or

(d) R^5 is a substituted triazolyl-pyridyl- wherein said triazolyl is substituted on the nitrogen and on the carbon, and said pyridyl is substituted; or

(e) R^5 is a substituted triazolyl-pyridyl- wherein said triazolyl is unsubstituted and said pyridyl is substituted.

18. The compound of Claim 1 wherein:

(a) R^5 is a substituted triazolyl-pyridyl- wherein the triazolyl is substituted on the nitrogen with an alkyl group, and the pyridyl is unsubstituted; or

(b) R^5 is a substituted triazolyl-pyridyl- wherein the triazolyl is substituted on the nitrogen with an alkyl group and substituted on the carbon with an alkyl group, wherein each alkyl group is independently selected, and the pyridyl is unsubstituted; or

(c) R^5 is a substituted triazolyl-pyridyl- wherein the triazolyl is substituted on the nitrogen with a $-CH_3$ group, and the pyridyl is unsubstituted; or

(d) R^5 is a substituted triazolyl-pyridyl- wherein the triazolyl is substituted on the nitrogen with a $-CH_3$ group and on the carbon with a $-CH_3$ group, and the pyridyl is unsubstituted.

19. The compound of Claim 1 wherein:

(a) R^5 is a substituted triazolyl-thiazolyl- wherein said triazolyl is substituted and said thiazolyl is unsubstituted; or

(b) R^5 is a substituted triazolyl-thiazolyl- wherein said triazolyl is substituted on the nitrogen and said thiazolyl is unsubstituted; or

(c) R^5 is a substituted triazolyl-thiazolyl- wherein said triazolyl is substituted on the carbon and said thiazolyl is unsubstituted; or

(d) R^5 is a substituted triazolyl-thiazolyl- wherein said triazolyl is substituted on the nitrogen and on the carbon, and said thiazolyl is unsubstituted; or

(e) R^5 is a substituted triazolyl-thiazolyl- wherein said triazolyl is substituted and said thiazolyl is substituted; or

(f) R^5 is a substituted triazolyl-thiazolyl- wherein said triazolyl is substituted on the nitrogen and said thiazolyl is substituted; or

(g) R^5 is a substituted triazolyl-thiazolyl- wherein said triazolyl is substituted on the carbon and said thiazolyl is substituted; or

(f) R^5 is a substituted triazolyl-thiazolyl- wherein said triazolyl is substituted on the nitrogen and on the carbon, and said thiazolyl is substituted; or

(h) R^5 is a substituted triazolyl-thiazolyl- wherein said triazolyl is unsubstituted and said thiazolyl is substituted.

20. The compound of Claim 1 wherein:

(a) R^5 is a substituted triazolyl-thiazolyl- wherein the triazolyl is substituted on the nitrogen with alkyl, and said thiazolyl is unsubstituted; or

(b) R^5 is a substituted triazolyl-thiazolyl- wherein the triazolyl is substituted on the nitrogen with an alkyl group and substituted on the carbon with an alkyl group, wherein each alkyl group is independently selected, and said thiazolyl is unsubstituted; or

(c) R^5 is a substituted triazolyl-thiazolyl- wherein the triazolyl is substituted on the nitrogen with a $-CH_3$ group, and said thiazolyl is unsubstituted; or

(d) R^5 is a substituted triazolyl-thiazolyl- wherein the triazolyl is substituted on the nitrogen with a $-CH_3$ group and on the carbon with a $-CH_3$ group, and said thiazolyl is unsubstituted.

21. The compound of Claim 1 wherein R^5 is a substituted pyridazinyl-thienyl- wherein said pyridazinyl is substituted and said thienyl is unsubstituted; or R^5 is a substituted pyridazinyl-thienyl- wherein said pyridazinyl is unsubstituted and said thienyl is substituted; or R^5 is a substituted pyridazinyl-thienyl- wherein said pyridazinyl is substituted and said thienyl is substituted.

22. The compound of Claim 1 wherein:

(a) R^5 is a substituted pyridazinyl-thienyl-wherein said pyridazinyl is substituted with a =O group, and said thienyl is unsubstituted; or

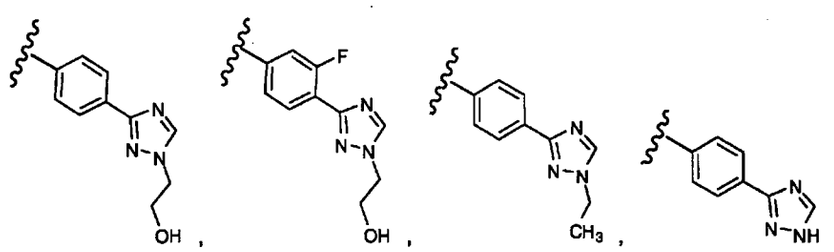
(b) R^5 is a substituted pyridazinyl-thienyl-wherein said pyridazinyl is substituted with an alkyl group, and said thienyl is unsubstituted; or

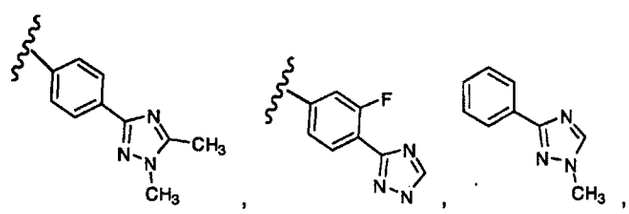
(c) R^5 is a substituted pyridazinyl-thienyl-wherein said pyridazinyl is substituted with a methyl group, and said thienyl is unsubstituted; or

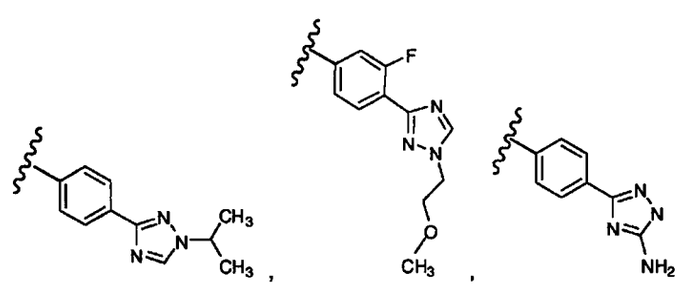
In another embodiment of this invention R^5 is a substituted pyridazinyl-thienyl-wherein said pyridazinyl is substituted with a =O group, and with an alkyl group, and said thienyl is unsubstituted.

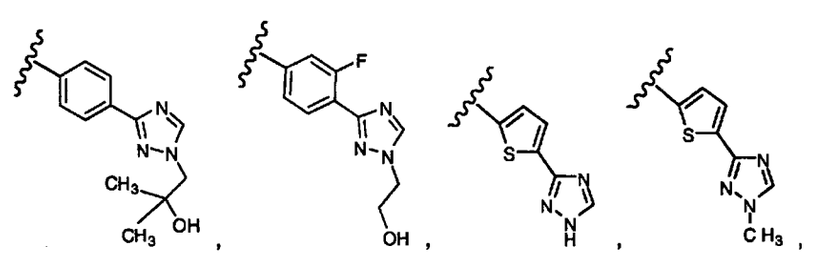
(d) R^5 is a substituted pyridazinyl-thienyl-wherein said pyridazinyl is substituted with a =O group, and with a methyl group, and said thienyl is unsubstituted.

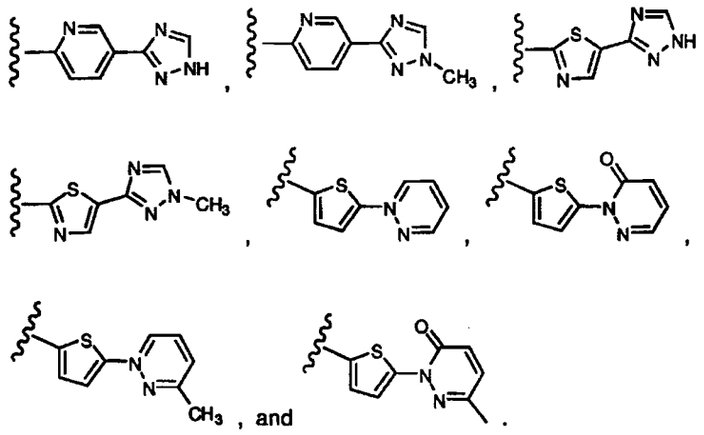
23. The compound of Claim 1 wherein:





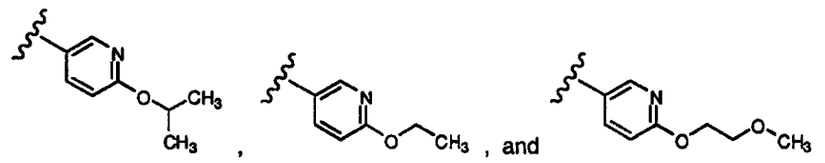






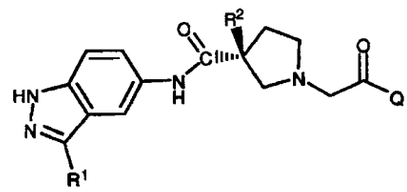
24. The compound of Claim 23 wherein R^1 is a pyridyl substituted with a substituent selected from the group consisting of: -O-CH_3, -O-C_2H_5, –O-$CH(CH_3)_2$, and –O-$(CH_2)_2$-O-CH_3, and R^2 is selected from the group consisting of: -OCH_3 and –SCH_3.

25. The compound of Claim 24 wherein R^1 is selected from the group consisting of:



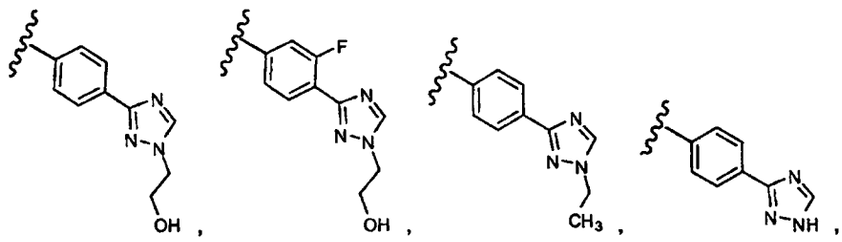
and R^2 is selected from the group consisting of: -OCH_3 and –SCH_3.

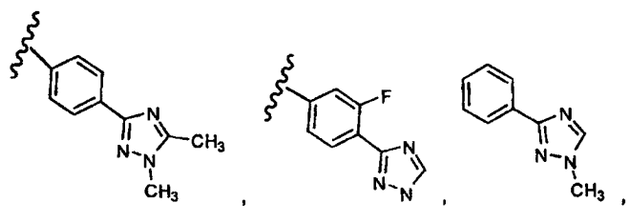
26. The compound of Claim 11 wherein the compound of formula 1.0 is a compound of formula 1.1:

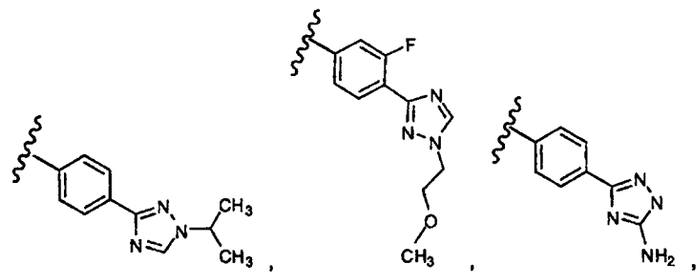


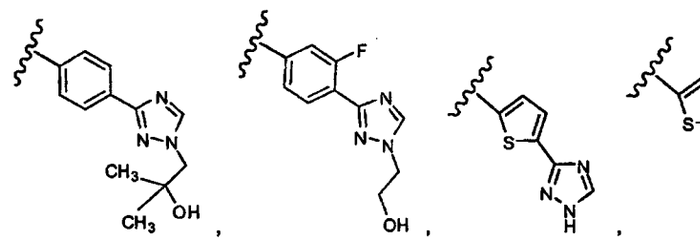
(1.1)

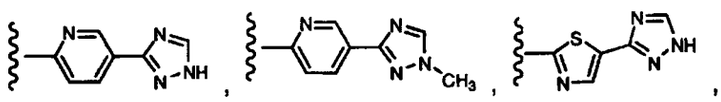
27. The compound of Claim 26 wherein R^5 is selected from the group consisting of:

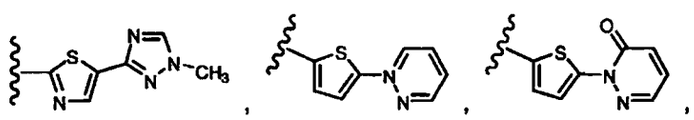


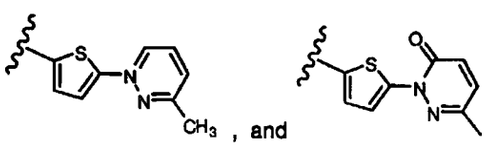






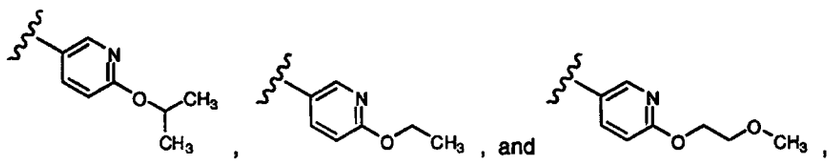




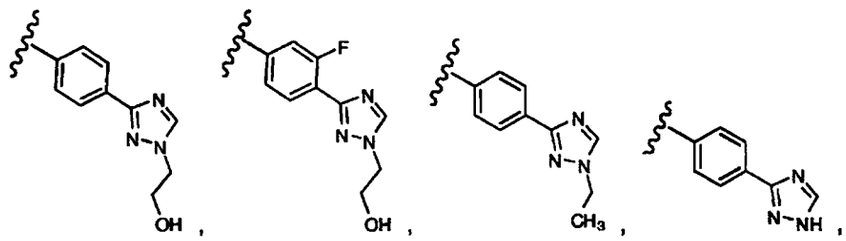


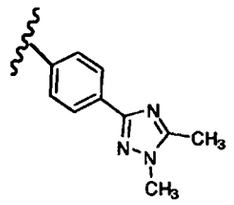
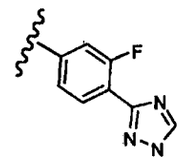
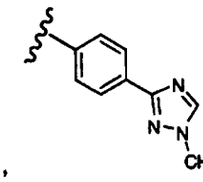
28. The compound of Claim 27 wherein R^1 is a pyridyl substituted with a substituent selected from the group consisting of: -O-CH_3, -O-C_2H_5, –O-$CH(CH_3)_2$, and –O-$(CH_2)_2$-O-CH_3, and R^2 is selected from the group consisting of: -OCH_3 and –SCH_3.

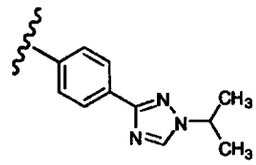
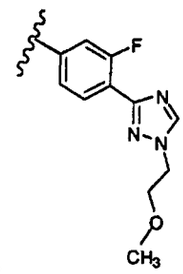
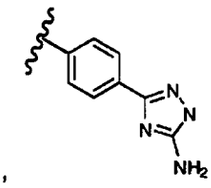
29. The compound of Claim 28 wherein R^1 is selected from the group consisting of:



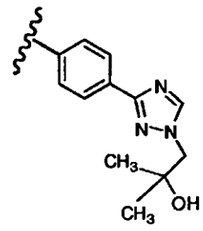
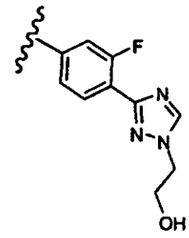
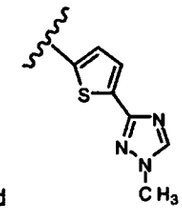
30. The compound of Claim 1 wherein R^5 is selected from the group consisting of:



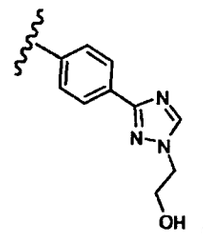
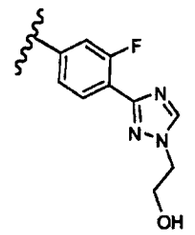
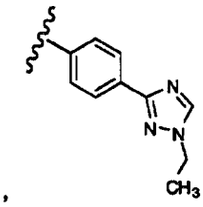

,

,

,


,

,

,

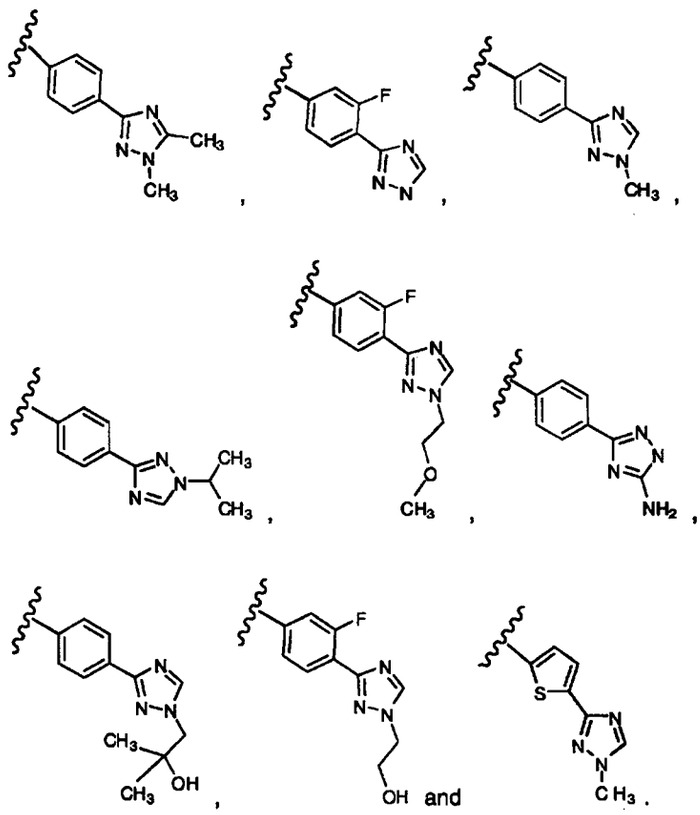
5


,

and

.

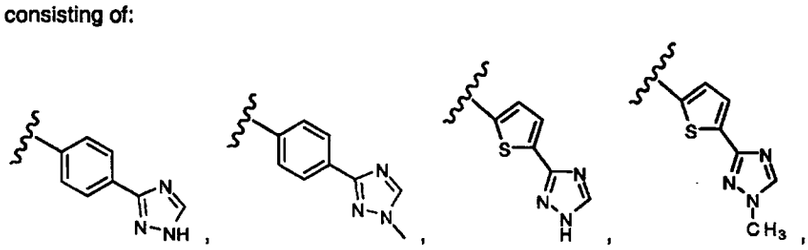
31. The compound of Claim 29 wherein R^5 is selected from the group consisting of:

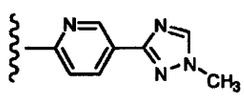
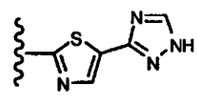
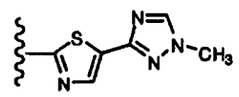

,

,

,

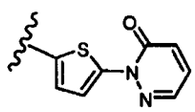
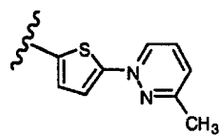
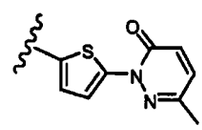
10

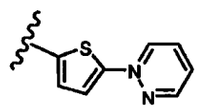


32. The compound of Claim 1 wherein R^5 is selected from the group consisting of:

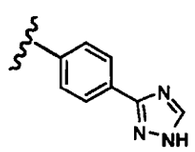
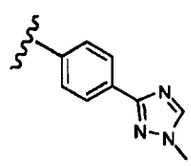
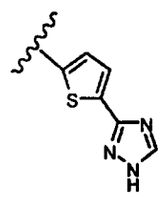
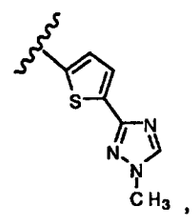


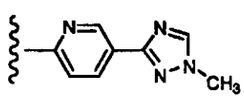
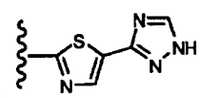
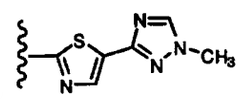

,

,

,

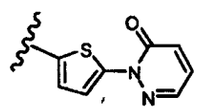
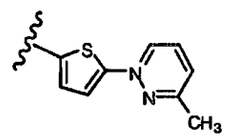
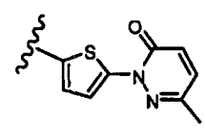

,

,

, and

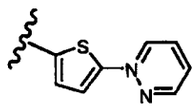

.

33. The compound of Claim 29 wherein R^5 is selected from the group consisting of:


,

,

,

,


,

,

,

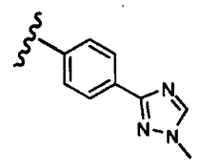

,

,

, and



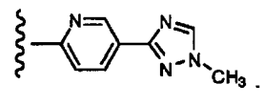
34. The compound of Claim 1 wherein R^5 is triazolyl-phenyl-.

35. The compound of Claim 1 wherein R^5 is triazolyl-thienyl-.

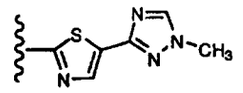
36. The compound of Claim 1 wherein R^5 is



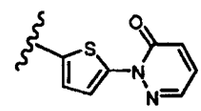
37. The compound of Claim 1 wherein R^5 is:



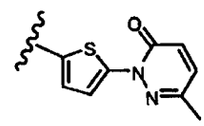
38. The compound of Claim 1 wherein R^5 is



39. The compound of Claim 1 wherein R^5 is



40. The compound of Claim 1 wherein R^6 is



41. A compound selected from the group consisting of compounds A1 to A16 and A18 to A30.

42. A compound selected from the group consisting of compounds A31 to A48.

43. The compound of Claim 41 wherein said compound is compound A1.

44. The compound of Claim 41 wherein said compound is compound A2.

45. The compound of Claim 41 wherein said compound is compound A3.

46. The compound of Claim 41 wherein said compound is compound A6.

47. The compound of Claim 41 wherein said compound is compound A7.

48. The compound of Claim 41 wherein said compound is compound A13.

49. The compound of Claim 41 wherein said compound is compound A19.

50. The compound of Claim 41 wherein said compound is compound A22.

51. The compound of Claim 41 wherein said compound is compound A24.

52. The compound of Claim 41 wherein said compound is compound A25.

53. The compound of Claim 41 wherein said compound is compound A27.

54. The compound of Claim 41 wherein said compound is compound A28.

55. The compound of Claim 41 wherein said compound is compound A29.

56. The compound of Claim 41 wherein said compound is compound A30.

57. A solvate, or a pharmaceutically acceptable salt, of a compound selected from the group consisting of compounds A1 to A16 and A18 to A48.

58. A pharmaceutically acceptable salt of a compound of Claim 41.

59. A solvate of a compound of Claim 41.

60. A solvate, or a pharmaceutically acceptable salt, of a compound of Claim 42.

61. The compound of Claim 1 in pure and isolated form.

62. The compound of Claim 41 in pure and isolated form.

63. The compound of Claim 42 in pure and isolated form.

64. A pharmaceutically acceptable salt of a compound of Claim 42.

65. A pharmaceutical composition comprising at least one compound of Claim 1 and a pharmaceutically acceptable carrier.

66. A pharmaceutical composition comprising at least one compound of Claim 41 and a pharmaceutically acceptable carrier.

67. A pharmaceutical composition comprising at least one compound of Claim 42 and a pharmaceutically acceptable carrier.

68. 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 compound of Claim 1.

69. 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

compound of Claim 1 in combination with an effective amount of at least one chemotherapeutic agent.

70. 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 Claim 1 in combination with an effective amount of at least one chemotherapeutic agent, and an effective amount of radiation therapy.

71. 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 compound of Claim 1, and therapeutically effective amounts of 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.

72. 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) at least one compound of Claim 1 in combination with at least one signal transduction inhibitor;

(b) at least one compound of Claim 1, 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;

(c) at least one compound of Claim 1, wherein said cancer is selected from the group consisting of: melanoma, pancreatic cancer, thryroid cancer, colorectal cancer, lung cancer, breast cancer, and ovarian cancer;

(d) at least one compound of Claim 1, 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 cancer, lung cancer, breast cancer, and ovarian cancer;

(e) at least one compound of Claim 1, and said cancer is melanoma;

(f) at least one compound of Claim 1, in combination with an effective amount of at least one chemotherapeutic agent, and said cancer is melanoma;

(g) at least one compound of Claim 1, and said cancer is pancreatic cancer;

(h) at least one compound of Claim 1, in combination with an effective amount of at least one chemotherapeutic agent, and said cancer is pancreatic cancer;

(i) at least one compound of Claim 1, and said cancer is thyroid cancer;

(j) at least one compound of Claim 1, in combination with an effective amount of at least one chemotherapeutic agent, and said cancer is thyroid cancer;

(k) at least one compound of Claim 1, and said cancer is colorectal cancer;

(l) at least one compound of Claim 1, in combination with an effective amount of at least one chemotherapeutic agent, and said cancer is colorectal cancer;

(m) at least one compound of Claim 1, and said cancer is lung cancer;

(n) at least one compound of Claim 1, in combination with an effective amount of at least one chemotherapeutic agent, wherein said cancer is lung cancer;

(o) at least one compound of Claim 1, and said cancer is breast cancer;

(p) at least one compound of Claim 1, in combination with an effective amount of at least one chemotherapeutic agent, and said cancer is breast cancer;

(q) at least one compound of Claim 1, and said cancer is ovarian cancer;

(r) at least one compound of Claim 1, in combination with an effective amount of at least one chemotherapeutic agent, and said cancer is ovarian cancer;

(s) at least one compound of Claim 1, in combination with antihormonal agents, wherein said cancer is hormone-dependent breast cancer;

(t) at least one compound of Claim 1, in combination with antihormonal agents, and in combination with an effective amount of at least one chemotherapeutic agent wherein said cancer is hormone-dependent breast cancer;

(u) at least one compound of Claim 1, and said cancer is brain cancer;

(v) at least one compound of Claim 1, in combination with an effective amount of at least one chemotherapeutic agent, and said cancer is brain cancer;

(w) at least one compound of Claim 1, in combination with an effective amount of at least one chemotherapeutic agent, and said chemotherapeutic agent is temozolomide, and wherein said cancer is brain cancer;

(x) at least one compound of Claim 1, and said cancer is prostate cancer;

(y) at least one compound of Claim 1, in combination with an effective amount of at least one chemotherapeutic agent, and said cancer is prostate cancer;

(z) at least one compound of Claim 1, and said cancer is myelodysplastic syndrome;

(aa) at least one compound of Claim 1, in combination with an effective amount of at least one chemotherapeutic agent, and said cancer is myelodysplastic syndrome cancer;

(ab) at least one compound of Claim 1, and said cancer is a myeloid leukemia;

(ac) at least one compound of Claim 1, in combination with an effective amount of at least one chemotherapeutic agent, and said cancer is a myeloid leukemia;

(ad) at least one compound of Claim 1, and said cancer is acute myelogenous leukemia;

(ae) at least one compound of Claim 1, in combination with an effective amount of at least one chemotherapeutic agent, and said cancer is acute myelogenous leukemia;

(af) at least one compound of Claim 1, and said cancer is chronic myelomonocytic leukemia;

(ag) at least one compound of Claim 1, in combination with an effective amount of at least one chemotherapeutic agent, and said cancer is chronic myelomonocytic leukemia;

(ah) at least one compound of Claim 1, and said cancer is chronic myelogenous leukemia;

(ai) at least one compound of Claim 1, in combination with an effective amount of at least one chemotherapeutic agent, and said cancer is chronic myelogenous leukemia;

(aj) at least one compound of Claim 1, and said cancer is bladder cancer;

(ak) at least one compound of Claim 1, in combination with an effective amount of at least one chemotherapeutic agent, and said cancer is bladder cancer;

(al) at least one compound of Claim 1, and said cancer is non-Hodgkin's lymphoma;

(am) at least one compound of Claim 1, in combination with an effective amount of at least one chemotherapeutic agent, and said cancer is non-Hodgkin's lymphoma;

(an) at least one compound of Claim 1, and said cancer is multiple myeloma; or

(ao) at least one compound of Claim 1, in combination with an effective amount of at least one chemotherapeutic agent, and said cancer is multiple myeloma;

73. A method of preventing hormone-dependent breast cancer in a patient in need of such treatment, said treatment comprising the administration of an effective amount of:

(a) at least one compound of Claim 1 in combination with antihormonal agents; or

(b) at least one compound of Claim 1 in combination with antihormonal agents, and in combination with an effective amount of at least one chemotherapeutic agent.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/034447

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D403/14 A61K31/435

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 A61K

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2008/153858 A (SCHERING CORP [US]; COOPER ALAN [US]; DENG YONGQI [US]; SHIPPS GERALD) 18 December 2008 (2008-12-18) the whole document	1-73
X	WO 2007/070398 A (SCHERING CORP [US]; COOPER ALAN [US]; DENG YONGQI [US]; SHIPPS GERALD) 21 June 2007 (2007-06-21) the whole document. page 41; compounds 2.11-2.13	1-73

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 May 2009	10/06/2009

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, Fax: (+31-70) 340-3016	Bader, Karl Günther

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2009/034447

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2008153858 A	18-12-2008	NONE	
WO 2007070398 A	21-06-2007	AR 056891 A1	31-10-2007
		AU 2006326616 A1	21-06-2007
		CA 2633023 A1	21-06-2007
		CN 101370784 A	18-02-2009
		EC SP088550 A	30-07-2008
		EP 1966151 A1	10-09-2008
		KR 20080085018 A	22-09-2008
		US 2007191604 A1	16-08-2007

COMPUESTOS NOVEDOSOS QUE SON INHIBIDORES DE ERK

REFERENCIA A UNA SOLICITUD RELACIONADA

Esta Solicitud reivindica el beneficio de la Solicitud Provisional de los Estados Unidos con Número de Serie 61/030407, presentada el 21 de febrero de 2008.

ANTECEDENTES DE LA INVENCIÓN

Los procesos involucrados en el crecimiento, progresión y metástasis de tumores son mediados por vías de señalización que están activadas en células cancerosas. La vía ERK desempeña un rol central en la regulación del crecimiento de células mamíferas mediante la transmisión de señales extracelulares de receptores de la superficie celular de tirosina quinasa unidos a ligandos tal como receptores de la tirosina quinasa PDGF, FGF, y VEGF de la familia erbB. La activación de la vía ERK se produce mediante una cascada de eventos de fosforilación que comienza con la activación de Ras. La activación de Ras da lugar al reclutamiento y activación de Raf, una serina-treonina quinasa. Luego, la Raf activada fosforila y activa la MEK1/2, que fosforila y activa la ERK1/2. Una vez activada, la ERK1/2 fosforila numerosos blancos corriente abajo involucrados en una multitud de eventos celulares que incluyen cambios citoesqueléticos y activación transcripcional. La vía ERK/MAPK es una de las más importantes para la proliferación celular, y se presume que la misma se encuentra frecuentemente activada en numerosos tumores. Los genes Ras, que se encuentran corriente arriba de ERK1/2, son mutados en diversos cánceres que incluyen cáncer colorectal, melanoma, cáncer de mama y tumores pancreáticos. La elevada actividad de Ras es acompañada por una elevada actividad de ERK en numerosos tumores humanos. Además, las mutaciones de BRAF, una serina-treonina quinasa de la familia Raf, se asocian con un aumento de la actividad de la quinasa. Se

han identificado mutaciones de BRAF en melanomas (60%), cánceres de tiroides (más del 40%) y cánceres colorectales. Estas observaciones indican que la vía de señalización ERK1/2 es una vía atractiva para las terapias anticáncer en un amplio espectro de tumores humanos.

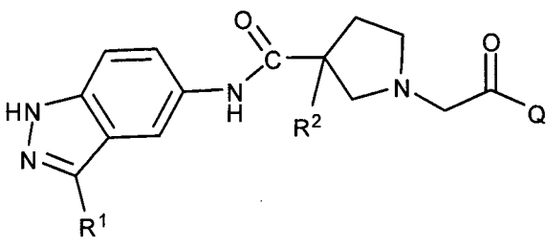
Por lo tanto, moléculas pequeñas (es decir, compuestos) que inhiban la actividad de ERK (es decir, la actividad de ERK1 y ERK2) comprenderían una contribución bienvenida a la técnica, dichas moléculas pequeñas serían útiles para tratar un amplio espectro de cánceres, tal como, por ejemplo, melanoma, cáncer pancreático, cáncer de tiroides, cáncer colorectal, cáncer de pulmón, cáncer de mama y cáncer de ovarios. Una contribución tal es provista por 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 también inhiben 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 siendo de la fórmula 1.0:



(1.0)

o las sales aceptables para uso farmacéutico, y solvatos de los mismos, donde: Q es un tetrahidropiridinilo (por ej., 1,2,3,6-tetrahidopiridinilo), o un tetrahidropiridinilo sustituido (por ej., un 1,2,3,6-tetrahidro-piridinilo sustituido); y R^1 y R^2 son lo definido a continuación.

Esta invención provee compuestos de fórmula 1.0.

Esta invención provee compuestos de fórmula 1.0 en forma pura o aislada.

Esta invención provee sales aceptables para uso farmacéutico de los compuestos de formula 1.0.

Esta invención provee solvatos de los compuestos de fórmula 1.0.

Esta invención provee compuestos de fórmula 1.0 donde de uno hasta el número total de hidrógenos son deuterio.

Esta invención provee compuestos de fórmula 1.0 donde al menos un H es deuterio.

Esta invención provee compuestos de fórmula 1.0 donde 1 a 5 H son deuterio.

Esta invención provee compuestos de fórmula 1.0 donde un H es deuterio.

Esta invención provee compuestos A1 a A16 y A18 a A48.

Esta invención provee compuestos A1 a A16 y A18 a A30.

Esta invención provee compuestos A1 a A16 y A18 a A26.

Esta invención provee compuestos A31 a A48.

Esta invención también provee una composición farmacéutica que comprende una cantidad efectiva de al menos un compuesto de fórmula 1.0 y un vehículo aceptable para uso farmacéutico.

Esta invención también provee una composición farmacéutica que comprende una cantidad efectiva de al menos un compuesto de fórmula 1.0 y una cantidad efectiva de al menos uno de otro componente farmacéuticamente activo (tal como, por ejemplo, un agente quimioterapéutico), y un vehículo aceptable para uso farmacéutico.

Esta invención también provee un método para inhibir ERK (es decir, inhibir la actividad de ERK) en un paciente necesitado de dicho tratamiento que

comprende administrar a dicho paciente una cantidad efectiva de al menos un compuesto de fórmula 1.0.

Esta invención también provee un método para inhibir ERK1 (es decir, inhibir la actividad de ERK1) en un paciente necesitado de dicho tratamiento que comprende administrar a dicho paciente una cantidad efectiva de al menos un compuesto de fórmula 1.0.

Esta invención también provee un método para inhibir ERK2 (es decir, inhibir la actividad de ERK2) en un paciente necesitado de dicho tratamiento que comprende administrar a dicho paciente una cantidad efectiva de al menos un compuesto de fórmula 1.0.

Esta invención también provee un método para inhibir ERK1 y ERK2 (es decir, inhibir la actividad de ERK1 y ERK2) en un paciente necesitado de dicho tratamiento que comprende administrar a dicho paciente una cantidad efectiva de al menos un compuesto de fórmula 1.0.

Esta invención también provee un método para tratar el cáncer en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de al menos un compuesto de fórmula 1.0.

Esta invención también provee un método para tratar el cáncer en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprenda una cantidad efectiva de al menos un compuesto de fórmula 1.0.

Esta invención también provee un método para tratar el cáncer en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de al menos un compuesto de fórmula 1.0, en combinación con una cantidad efectiva de al menos un agente quimioterapéutico.

Esta invención también provee un método para tratar el cáncer en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprenda una cantidad efectiva de al menos un compuesto de fórmula 1.0, en combinación con una cantidad efectiva de al menos un agente quimioterapéutico.

Esta invención también provee un método para tratar el cáncer en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de al menos un compuesto de formula 1.0 en combinación con al menos un inhibidor de la transducción de señales.

Esta invención también provee un método para tratar el cáncer en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprenda una cantidad efectiva de al menos un compuesto de fórmula 1.0 en combinación con al menos un inhibidor de la transducción de señales.

En los métodos de esta invención, los compuestos de esta invención pueden administrarse en forma concurrente o secuencial (es decir, consecutiva) con los agentes quimioterapéuticos o el inhibidor de la transducción de señales.

Los métodos para tratar el cáncer descriptos en la presente pueden incluir en forma opcional la administración de una cantidad efectiva de radiación (es decir, los métodos para tratar el cáncer descriptos en la presente pueden incluir en forma opcional la administración de terapia de radiación).

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

Según lo descripto en la presente, a menos que se indique lo contrario, el uso de una droga o compuesto en un período especificado es por ciclo de tratamiento. Por ejemplo, una vez al día significa una vez al día de cada día del

ciclo de tratamiento. Una vez a la semana significa una vez a la 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 a menos que se defina lo contrario:

ACN	Acetonitrilo
AcOH	Ácido acético
Anhy	Anhidro
DAST	trifluoruro de (dietilamino)azufre
DCC	Diciclohexilcarbodiimida
DCU	Diciclohexilurea
DCM	Diclorometano
DI	Agua desionizada
DIAD	Diisopropilazodicarboxilato
DIEA	Diisopropiletilamina
DMAP	4-Dimetilaminopiridina
DME	Dimetoxietano
DMF	Dimetilformamida
DMFDMA	Dimetilacetal de N,N-dimetilformamida
DMSO	Dimetil sulfóxido
DTT	Ditiotreitol
EDCI	Clorhidrato de 1-(3-dimetilamino-propil)-3-etilcarbodiimida
Et	Etilo
EtOAc	Acetato de etilo
EtOH	Etanol
HATU	Hexafluorsfosfato de N,N,N',N'-tetrametil-O-(7-azabenzotriazol-1-il)uronio

Hex	Hexanos
HOBt	1-Hidroxilbenzotriazol
HPLC	Cromatografía líquida de alta presión
LCMS	Cromatografía líquida-Espectrometría de masas
LDA	Diisopropilamida de litio
mCPBA	Ácido *meta*-cloroperoxibenzoico
MeOH	Metanol
MTT	bromuro de (3-[4,5-dimetil-tiazol-2-il]-2,5-difeniltetrazolio, azul de Tiazolilo)
RMN	Resonancia magnética nuclear
PFP	Pentafluorfenol
PMB	p-metoxibencilo
Py	Piridina
Pyr	Piridina
Rb	Matraz de fondo redondo
Rbt	Matraz de fondo redondo
TA (ta)	Temperatura ambiente
SEMCl	2-cloruro de 2-(trimetilsililo)etoximetilo
TEA	Trietilamina
Tr	Trifenil metano
Trt	Trifenil metano
TrCl	Cloruro de trifenil metano
TFA	Ácido trifluoracético
THF	Tetrahidrofurano
TLC	Cromatografía en capa delgada
TMS	Trimetilsililo

Según lo utilizado en la presente, a menos que se especifique lo contrario, los siguientes términos tienen los siguientes significados:

"agente anti-cáncer" significa una droga (medicamento o componente farmacéuticamente activo) para tratar el cáncer;

"agente antineoplásico" significa una droga (medicamento o componente farmacéuticamente activo) para tratar el cáncer (es decir, un agente quimioterapéutico);

"al menos uno", utilizado en referencia al número de compuestos de esta invención significa, por ejemplo, 1-6, en general 1-4, más en general 1, 2 o 3, y a menudo uno o dos, y más a menudo uno; así, en un ejemplo "al menos uno" significa uno, en otro ejemplo "al menos uno" significa dos, y en otro ejemplo "al menos uno" significa tres;

"al menos uno", utilizado en referencia al número de agentes quimioterapéuticos utilizados significa, por ejemplo, 1-6, en general 1-4, más en general 1, 2 o 3, y a menudo uno o dos, o uno; así, en un ejemplo "al menos uno" significa uno, en otro ejemplo "al menos uno" significa dos, y en otro ejemplo "al menos uno" significa tres;

"agente quimioterapéutico" significa una droga (medicamento o componente farmacéuticamente activo) para tratar el cáncer (es decir, y agente antineoplásico);

"compuesto" con referencia a los agentes antineoplásicos, incluye los agentes que son anticuerpos;

"en forma concurrente" significa (1) en forma simultánea en el tiempo (por ej., al mismo tiempo); o (2) en momentos diferentes durante el curso de un programa de tratamiento ordinario;

"en forma consecutiva" significa uno tras otro;

"diferente" utilizado en la frase "agentes antineoplásicos diferentes" significa que los agentes no son el mismo compuesto o estructura; preferentemente, "diferente" utilizado en la frase "agentes antineoplásicos diferentes" significa no de la misma clase de agentes antineoplásicos; por ejemplo, un agente antineoplásico es un taxano, y otro agente antineoplásico es un compuesto coordinador de platino;

"cantidad efectiva" o "cantidad efectiva para uso terapéutico" se utiliza para describir una cantidad de compuesto o una composición de la presente invención, o una cantidad de radiación, efectiva para tratar o inhibir las enfermedades o afecciones descriptas en la presente, y así producir el efecto terapéutico, aliviante, inhibitorio o preventivo deseado; así, por ejemplo, en los métodos para tratar el cáncer descriptos en la presente "cantidad efectiva" (o "cantidad efectiva para uso terapéutico") significa, por ejemplo, la cantidad del compuesto (o droga), o radiación, que da lugar a: (a) la reducción, mejora o desaparición de uno o más síntomas causados por el cáncer, (b) la reducción del tamaño del tumor, (c) el retiro del tumor, y/o (d) estabilización de la enfermedad a largo plazo (interrupción del crecimiento) del tumor; por ejemplo, en el tratamiento de cáncer de pulmón (por ej., cáncer de pulmón de células no pequeñas) una cantidad efectiva para uso terapéutico es aquella cantidad que palia o elimina la tos, falta de aliento y/o dolor; también, por ejemplo, una cantidad efectiva, o una cantidad efectiva para uso terapéutico del inhibidor de ERK (es decir, un compuesto de esta invención) es aquella cantidad que da lugar a la reducción de la actividad y fosforilación de ERK (ERK1 y/o ERK2); la reducción de la actividad de ERK puede determinarse por el análisis de marcadores farmacodinámicos tal como RSK1,2 fosforilida y ERK1,2 fosforilada, utilizando técnicas bien conocidas en la técnica;

"Ej." en las tablas representa "Ejemplo";

"uno o más" tiene el mismo significado que "al menos uno";

"paciente" significa un animal, tal como un mamífero (por ej., un ser humano, y preferentemente un ser humano);

"prodroga" significa compuestos que son rápidamente transformados, por ejemplo, por hidrólisis en sangre, in vivo al compuesto principal, es decir, a los compuestos de fórmula 1.0 o a una sal y/o a un solvato del mismo; se provee una discusión detallada en T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems, Vol. 14 de la 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 en la presente como referencia; el alcance de esta invención incluye Prodrogas de los compuestos novedosos de esta invención;

"en forma secuencial" representa (1) la administración de un componente del método ((a) compuesto de la invención, o (b) agente quimioterapéutico, inhibidor de la transducción de señales y/o terapia de radiación) seguida por la administración del otro componente o componentes; luego de la administración de un componente, el componente siguiente puede administrarse sustancialmente inmediatamente después del primer componente, o el componente siguiente puede administrarse luego de un período de tiempo efectivo posterior a la administración del primer componente; el período de tiempo efectivo es la cantidad de tiempo dada para la realización del máximo beneficio de 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 involucra grados variables de unión iónica y covalente, que incluye unión de hidrógenos; en ciertos casos, el solvato será capaz de aislamiento, por ejemplo cuando se incorporen una o más moléculas de solvente en el entramado de

cristal del sólido cristalino; "solvato" abarca ambos solvatos, solvatos de fase en solución y solvatos aislables; los ejemplos no limitantes de solvatos adecuados incluyen etanolatos, metanolatos, y similares; "hidrato" es un solvato donde la molécula de solvente es H_2O.

Según lo utilizado en la presente, a menos que se espefique lo contrario, los siguientes términos tienen los siguientes significados, y a menos que se especifique lo contrario, las definiciones de cada término (es decir, resto o sustituyente) se aplican cuando dicho término se utilice en forma individual o como un componente de otro término (por ej., la definición de arilo es la misma para arilo y para la porción de arilo de 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)- donde los varios grupos son como definido a continuación (y según lo definido a continuación, los restos de alquilo, alquenilo, alquinilo, cicloalquilo, cicloalquenilo y cicloalquinilo pueden sustituirse); el enlace al resto principal es a través del carbonilo; acilos preferidos contienen un alquilo inferior; los ejemplos no limitantes de grupos acilo apropiados incluyen formilo, acetilo, propanoilo, 2-metilpropanoilo, butanoilo y ciclohexanoilo;

"alquenilo" significa un grupo hidrocarbonado alifático (cadena) que comprende al menos un doble enlace carbono-carbono, donde la cadena puede ser recta o ramificada, y donde dicho grupo comprende aproximadamente 2 a aproximadamente 15 átomos de carbono; grupos alquenilo preferidos comprenden aproximadamente 2 a aproximadamente 12 átomos de carbono en la cadena; y con más preferencia, aproximadamente 2 a aproximadamente 6 átomos de carbono en la cadena; ramificado significa que uno o más grupos alquilo inferiores, tal como grupos metilo, etilo o propilo, o

alquenilo están unidos a un cadena lineal de alquenilo; "alquenilo inferior" significa un grupo alquenilo que comprende aproximadamente 2 a 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 se sustituye con 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(alquil); ejemplos no limitantes de grupos alquenilo adecuados incluyen etenilo, propenilo, n-butenilo, 3-metilbut-2-enilo, n-pentenilo, octenilo y decenilo;

"alcoxi" significa un grupo alquil-O- (es decir, el enlace al resto principal es a través del oxígeno éter) donde el grupo alquilo no está sustituido o se sustituye según lo descripto a continuación; ejemplos no limitantes de grupos alcoxi adecuados incluyen metoxi, etoxi, n-propoxi, isopropoxi, n-butoxi y heptoxi;

"alcoxicarbonilo" significa un grupo alquil-O-CO- (es decir, el enlace al resto principal es a través del carbonilo) donde el grupo alquilo no está sustituido o se sustituye según lo previamente definido; ejemplos no limitantes de grupos alcoxicarbonilo adecuados incluyen metoxicarbonilo y etoxicarbonilo;

"alquilo" (que incluye las porciones de alquilo de otros restos, tal como trifluoralquilo y alquiloxi) significa un grupo hidrocarbonado alifático (cadena) que puede ser recto o ramificado donde dicho grupo comprende aproximadamente 1 a aproximadamente 20 átomos de carbono en la cadena; grupos alquilo preferidos comprenden aproximadamente 1 a aproximadamente 12 átomos de carbono en la cadena; grupos alquilo más preferidos comprenden aproximadamente 1 a aproximadamente 6 átomos de carbono en la cadena; ramificado significa que uno o más grupos alquilo inferiores, tal como metilo, etilo o propilo, están unidos a una cadena lineal de alquilo;

"alquilo inferior" significa un grupo que comprende aproximadamente 1 a 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 se sustituye con 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 limitantes de grupos alquilo adecuados incluyen metilo, etilo, n-propilo, isopropilo, n-butilo, t-butilo, n-pentilo, heptilo, nonilo, decilo, fluormetilo, trifluormetilo y ciclopropilmetilo;

"alquilarilo" (o alcarilo) significa un grupo alquil-aril- (es decir, el enlace al resto principal es a través del grupo arilo) donde el grupo alquilo no está sustituido o se sustituye según lo definido con anterioridad, y el grupo arilo no está sustituido o se sustituye según lo definido a continuación; alquilarilos preferidos comprenden un grupo alquilo inferior; ejemplos no limitantes de grupos alquilarilos adecuados incluyen o-tolilo, p-tolilo y xililo;

"alquilheteroarilo" significa un grupo alquil-heteroaril- (es decir, el enlace al resto principal es a través del grupo heteroarilo) donde el alquilo no está sustituido o se sustituye según lo definido con anterioridad y el grupo heteroarilo no está sustituido o se sustituye según lo definido a continuación;

"alquilsulfinilo" significa un grupo alquil-S(O)- (es decir, el enlace al resto principal es a través del sulfinilo) donde el grupo alquilo no está sustituido o se sustituye según lo previamente definido; son grupos preferidos aquellos donde el grupo alquilo es alquilo inferior;

"alquilsulfonilo" significa un grupo alquil-S(O_2)- (es decir, el enlace al resto principal es a través del sulfonilo) donde el grupo alquilo no está

sustituido o se sustituye según lo previamente definido; son grupos preferidos aquellos donde el grupo alquilo es alquilo inferior;

"alquiltio" significa un grupo alquil-S- (es decir, el enlace al resto principal es a través del azufre) donde el grupo alquilo no está sustituido o se sustituye según lo previamente descripto; ejemplos no limitantes de grupos alquiltio adecuados incluyen metiltio, etiltio, i-propiltio y heptiltio;

"alquinilo" significa un grupo hidrocarbonado alifático (cadena) que comprende al menos un enlace triple carbono a carbono, donde la cadena puede ser recta o ramificada, y donde el grupo comprende aproximadamente 2 a aproximadamente 15 átomos de carbono en la cadena; grupos alquinilo preferidos comprenden aproximadamente 2 a aproximadamente 12 átomos de carbono en la cadena; y con más preferencia, aproximadamente 2 a aproximadamente 4 átomos de carbono en la cadena; ramificado significa que uno o más grupos alquilo inferiores, tal como metilo, etilo o propilo, están unidos a una cadena lineal de alquilo; "alquinilo inferior" significa un grupo alquinilo que comprende aproximadamente 2 a aproximadamente 6 átomos de carbono en la cadena, y la cadena puede ser recta o ramificada; ejemplos no limitantes de grupos alquinilo adecuados incluyen etinilo, propinilo, 2-butinilo, 3-metilbutinilo, n-pentinilo, y decinilo; el término "alquinilo sustituido" significa que el grupo alquinilo se sustituye con 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 grupo $-NH_2$;

"aralquenilo" (o arilalquenilo) significa un grupo aril-alquenil- (es decir, el enlace al resto principal es a través del grupo alquenilo) donde el grupo arilo no está sustituido o se sustituye según lo definido a continuación, y el grupo alquenilo no está sustituido o se sustituye según lo definido con anterioridad;

aralquenilos preferidos contienen un grupo alquenilo inferior; ejemplos no limitantes de grupos alquenilo adecuados incluyen 2-fenetenilo y 2-naftiletenilo;

"aralquilo" (o arilalquilo) significa un grupo aril-alquil- (es decir, el enlace al resto principal es a través del grupo alquilo) donde el arilo no está sustituido o se sustituye según lo definido a continuación y el alquilo no está sustituido o se sustituye según lo definido con anterioridad; aralquilos preferidos comprenden un grupo alquilo inferior; ejemplos no limitantes de grupos aralquilo adecuados incluyen bencilo, 2-fenetilo y naftalenilmetilo;

"aralquiloxi" (o arilalquiloxi) significa un grupo aralquil-O- (es decir, el enlace al resto principal es a través del éter oxígeno) donde el grupo aralquilo no está sustituido o se sustituye según lo previamente descripto; ejemplos no limitantes de grupos aralquiloxi adecuados incluyen benciloxi y 1- o 2-naftalenmetoxi;

"aralcoxicarbonilo" significa un grupo aralquil-O-C(O)- (es decir, el enlace al resto principal es a través del carbonilo) donde el grupo aralquilo no está sustituido o se sustituye según lo previamente definido; un ejemplo no limitativo de un grupo aralcoxicarbonilo adecuado es benciloxicarbonilo;

"aralquiltio" significa un grupo aralquil-S- (es decir, el enlace al resto principal es a través del azufre) donde el grupo aralquilo no está sustituido o se sustituye según lo previamente descripto; un ejemplo no limitativo de un grupo aralquiltio adecuado es benciltio;

"aroilo" significa un grupo aril-C(O)- (es decir, el enlace al resto principal es a través del carbonilo) donde el grupo arilo no está sustituido o se sustituye según lo definido a continuación; ejemplos no limitantes de grupos aroilo adecuados incluyen benzoilo y 1- y 2-naftoilo;

"arilo" (a menudo abreviado "ar") significa un sistema anular aromático monocíclico o multicíclico que comprende aproximadamente 6 a

aproximadadamente 14 átomos de carbono, con preferencia aproximadamente 6 a aproximadamente 10 átomos de carbono; el grupo arilo puede sustituirse en forma opcional con uno o más "sustituyentes de sistema anular" seleccionados en forma independiente (definidos a continuación). Ejemplos no limitantes de grupos arilo adecuados incluyen fenilo y naftilo;

"arilalquinilo" significa un grupo aril-alquinil- (es decir, el enlace al resto principal es a través del grupo alquinilo) donde grupo el arilo no está sustituido o se sustituye según lo definido con anterioridad, y el grupo alquinilo no está sustituido o se sustituye según lo definido con anterioridad;

"arilaminoheteroarilo" significa un grupo aril-amino-heteroarilo (es decir, el enlace al resto principal es a través del grupo heteroarilo) donde el grupo arilo no está sustituido o se sustituye según lo definido con anterioridad, el grupo amino es lo definido con anterioridad (es decir, un –NH- de la presente), y el grupo heteroarilo no está sustituido o se sustituye según lo definido a continuación;

"arilheteroaril" significa un grupo aril-heteroaril- (es decir, el enlace al resto principal es a través del grupo heteroarilo) donde el arilo grupo no está sustituido o se sustituye según lo definido con anterioridad, y el grupo heteroarilo no está sustituido o se sustituye según lo definido a continuación;

"ariloxi" significa un grupo aril-O- (es decir, el enlace al resto principal es a través del éter oxígeno) donde el grupo arilo no está sustituido o se sustituye según lo definido con anterioridad; ejemplos no limitantes de grupos ariloxi adecuados incluyen fenoxi y naftoxi;

"ariloxicarbonil" significa un grupo aril-O-C(O)- (es decir, el enlace al resto principal es a través del carbonilo) donde el grupo arilo no está sustituido o se sustituye según lo previamente definido; ejemplos no limitantes de grupos ariloxicarbonilo adecuados incluyen fenoxicarbonilo y naftoxicarbonilo;

"arilsulfinilo" significa un grupo aril-S(O)- (es decir, el enlace al resto principal es a través del sulfinilo) donde arilo no está sustituido o se sustituye según lo previamente definido;

"arilsulfonilo" significa un grupo aril-$S(O_2)$- (es decir, el enlace al resto principal es a través del sulfonilo) donde arilo no está sustituido o se sustituye según lo previamente definido;

"ariltio" significa un grupo aril-S- (es decir, el enlace al resto principal es a través del azufre) donde el grupo arilo no está sustituido o se sustituye según lo previamente descripto; ejemplos no limitantes de grupos ariltio adecuados incluyen feniltio y naftiltio;

"cicloalquenilo" significa un sistema anular no aromático mono o multicíclico que comprende aproximadamente 3 a aproximadamente 10 átomos de carbono, con preferencia aproximadamente 5 a aproximadamente 10 átomos de carbono que contiene al menos un enlace doble carbono-carbono; anillos cicloalquenilo preferidos contienen aproximadamente 5 a aproximadamente 7 átomos de carbono; el cicloalquenilo puede sustituirse en forma opcional con uno o más "sustituyentes de sistema anular" seleccionados en forma independiente (definidos a continuación); Ejemplos no limitantes de cicloalquenilos monocíclicos incluyen ciclopentenilo, ciclohexenilo, cicloheptenil, y similares; un ejemplo no limitativo de un cicloalquenilo multicíclico es norbornilenilo;

"cicloalquilo" significa un sistema anular no aromático mono o multicíclico que comprende aproximadamente 3 a aproximadamente 7 átomos de carbono, con preferencia aproximadamente 3 a aproximadamente 6 átomos de carbono; el cicloalquilo puede sustituirse en forma opcional con uno o más "sustituyentes de sistema anular" seleccionados en forma independiente (definidos a continuación); ejemplos no limitantes de cicloalquilos monocíclicos

adecuados incluyen ciclopropilo, ciclopentilo, ciclohexilo, cicloheptilo y similares; ejemplos no limitantes de cicloalquilos multicíclicos adecuados incluyen 1-decalina, norbornilo, adamantilo y similares;

"cicloalquilalquilo" significa un grupo cicloalquil-alquil- (es decir, el enlace al resto principal es a través del grupo alquilo) donde el resto cicloalquilo no está sustituido o se sustituye según lo definido con anterioridad, y el resto alquilo no está sustituido o se sustituye según lo definido con anterioridad;

"halo" significa grupos flúor, cloro, bromo, o yodo; son grupos halo preferidos flúor, cloro o bromo, y son más preferidos flúor y cloro;

"halógeno" significa flúor, cloro, bromo, o yodo; son halógenos preferidos flúor, cloro y bromo;

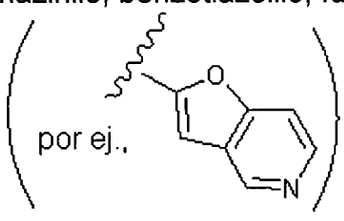
"haloalquilo" significa un alquilo, según lo definido con anterioridad, donde uno o más átomos de hidrógeno sobre el alquilo se reemplazan con un grupo halo, según lo definido con anterioridad;

"heteroaralquenilo" significa un grupo heteroaril-alquenil- (es decir, el enlace al resto principal es a través del grupo alquenilo) donde el grupo heteroarilo no está sustituido o se sustituye según lo definido a continuación, y el grupo alquenilo no está sustituido o se sustituye según lo definido con anterioridad;

"heteroaralquilo" (o heteroarilalquilo) significa un grupo heteroaril-alquil- (es decir, el enlace al resto principal es a través del grupo alquilo) donde el heteroarilo no está sustituido o se sustituye según lo definido a continuación, y el grupo alquilo no está sustituido o se sustituye según lo definido con anterioridad; heteroaralquilos preferidos comprenden un grupo alquilo que es un grupo alquilo inferior; ejemplos no limitantes de grupos aralquilo adecuados incluyen piridilmetilo, 2-(furan-3-il)etilo y quinolin-3-ilmetilo;

"heteroaralquiltio" significa un grupo heteroaralquil-S- donde el grupo heteroaralquilo no está sustituido o se sustituye según lo definido con anterioridad;

"heteroarilo" significa un sistema anular aromático monocíclico o multicíclico que comprende aproximadamente 5 a aproximadamente 14 átomos de carbono, con preferencia aproximadamente 5 a aproximadamente 10 átomos de carbono, donde uno o más de los átomos de carbono es un elemento diferente a carbono, por ejemplo nitrógeno, oxígeno o azufre, solo o en combinación; heteroarilos preferidos comprenden aproximadamente 5 a aproximadamente 6 átomos de carbono; el "heteroarilo" puede sustituirse en forma opcional con uno o más "sustituyentes de sistema anular" seleccionados en forma independiente (definidos a continuación); el prefijo aza, oxa o tia antes de la raíz de heteroarilo significa que al menos un átomo de nitrógeno, oxígeno o azufre, respectivamente, está presente como un átomo anular; un átomo de nitrógeno de un heteroarilo puede oxidarse en forma opcional al N-óxido correspondiente; ejemplos no limitantes de heteroarilos adecuados incluyen piridilo, pirazinilo, furanilo, tienilo, pirimidinilo, isoxazolilo, isotiazolilo, oxazolilo, tiazolilo, pirazolilo, furazanilo, pirrolilo, pirazolilo, triazolilo, 1,2,4-tiadiazolilo, pirazinilo, piridazinilo, quinoxalinilo, phtalazinilo, 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 al resto principal es a través del grupo alquinilo) donde el grupo heteroarilo no está sustituido o se sustituye según lo definido con anterioridad, y el grupo alquinilo no está sustituido o se sustituye según lo definido con anterioridad;

"heteroarilarilo" (o heteroararilo) significa un grupo heteroaril-aril- (es decir, el enlace al resto principal es a través del grupo arilo) donde el grupo heteroarilo no está sustituido o se sustituye según lo definido con anterioridad, y el grupo arilo no está sustituido o se sustituye según lo definido con anterioridad;

"heteroarilheteroarilarilo" significa un grupo heteroaril-heteroaril- (es decir, el enlace al resto principal es a través del ultimo grupo heteroarilo) donde cada grupo heteroarilo está independiente no sustituido o sustituido según lo definido con anterioridad;

"heteroarilsulfinilo" significa un grupo heteroaril-SO- donde el grupo heteroarilo no está sustituido o se sustituye según lo definido con anterioridad;

"heteroarilsulfonilo" significa un grupo heteroaril-SO_2- donde el grupo heteroarilo no está sustituido o se sustituye según lo definido con anterioridad;

"heteroariltio" significa un grupo heteroaril-S- donde el grupo heteroarilo no está sustituido o se sustituye según lo definido con anterioridad;

"heterociclenilo" (o heterocicloalquenilo) significa un sistema anular no aromático monocíclico o multicíclico que comprende aproximadamente 3 a aproximadamente 10 átomos de carbono, con preferencia aproximadamente 5 a aproximadamente 10 átomos de carbono, donde uno o más de los átomos en el sistema anular es un elemento diferente a carbono (por ejemplo uno o más heteroátomos seleccionados en forma independiente del grupo que consiste en átomo de nitrógeno, oxígeno y azufre), y que contiene al menos un enlace

doble carbono-carbono o un enlace doble carbono-nitrógeno; no hay átomos adyacentes de oxígeno y/o azufre presentes en el sistema anular; anillos heterociclenilos preferidos contienen aproximadamente 5 a aproximadamente 6 átomos de carbono; el prefijo aza, oxa o tia antes de la raíz de heterociclenilo significa que al menos un átomo de nitrógeno, oxígeno o azufre, respectivamente, está presente como un átomo anular; el heterociclenilo puede sustituirse en forma opcional con uno o más "sustituyentes de sistema anular" seleccionados en forma independiente (definidos a continuación); el átomo de nitrógeno o azufre del heterociclenilo puede oxidarse en forma opcional al N-óxido, S-óxido o S,S-dióxido correspondiente; ejemplos no limitantes de grupos azaheterociclenilos monocíclicos incluyen 1,2,3,4-tetrahidropiridina, 1,2-dihidropiridil, 1,4-dihidropiridil, 1,2,3,6-tetrahidropiridina, 1,4,5,6-tetrahidropirimidina, 2-pirrolinil, 3-pirrolinil, 2-imidazolinil, 2-pirazolinil, y similares; Ejemplos no limitantes de grupos oxaheterociclenilo adecuados incluyen 3,4-dihidro-2H-piran, dihidrofuranil, fluordihidrofuranil, y similares; Un ejemplo no limitativo de un grupo oxaheterociclenilo multicíclico apropiado es 7-oxabiciclo[2.2.1]heptenilo; ejemplos no limitantes de anillos tiaheterociclenilo monocíclicos adecuados incluyen dihidrotiofenilo, dihidrotiopiranilo, y similares;

"heterocicloalquilalquilo" (o heterociclilalquilo) significa un grupo heterocicloalquil-alquil- (es decir, el enlace al resto principal es a través del grupo alquilo) donde el grupo heterocicloalquilo (es decir, el grupo heterociclilo) no está sustituido o se sustituye según lo definido a continuación, y el grupo alquilo no está sustituido o se sustituye según lo definido con anterioridad;

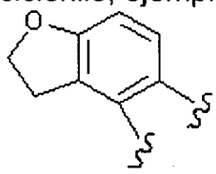
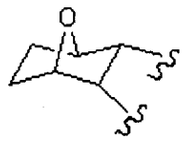
"heterociclilo" (o heterocicloalquilo) significa un sistema anular no aromático saturado monocíclico o multicíclico que comprende aproximadamente 3 a aproximadamente 10 átomos de carbono, con preferencia aproximadamente 5 a aproximadamente 10 átomos de carbono,

donde uno o más de los átomos en el sistema anular es un elemento diferente a carbono, por ejemplo nitrógeno, oxígeno o azufre, solo o en combinación; no hay átomos adyacentes de oxígeno y/o azufre presentes en el sistema anular; heterociclilos preferidos contienen aproximadamente 5 a aproximadamente 6 átomos de carbono; el prefijo aza, oxa o tia antes de la raíz de heterociclilo significa que al menos un átomo de nitrógeno, oxígeno o azufre, respectivamente, está presente como un átomo anular; el heterocicliclo puede sustituirse en forma opcional con uno o más "sustituyentes de sistema anular" seleccionados en forma independiente (definidos a continuación); el átomo de nitrógeno o azufre del heterocicliclo puede oxidarse en forma opcional al N-óxido, S-óxido o S,S-dióxido correspondiente; ejemplos no limitantes de anillos de heterociclilo monocíclicos adecuados incluyen piperidilo, pirrolidinilo, piperazinilo, morpholinilo, tiomorpholinilo, tiazolidinilo, 1,3-dioxolanilo, 1,4-dioxanilo, tetrahidrofuranilo, tetrahidrotiofenilo, tetrahidrotiopiranil, y similares;

"hidroxialquilo" significa un grupo HO-alquil- donde el grupo alquilo está sustituido o no sustituido según lo definido con anterioridad; hidroxialquilos preferidos comprenden un alquilo inferior; Ejemplos no limitantes de grupos hidroxialquilo adecuados incluyen hidroximetilo y 2-hidroxietilo; y

"sustituyente de sistema anular" significa un sustituyente unido a un sistema anular aromático o no aromático que, por ejempo, reemplaza un hidrógeno disponible sobre el sistema anular; los sustituyentes de sistema anular se seleccionan 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 $R^{60}R^{65}NSO_2$-, donde R^{60} y R^{65} se seleccionan cada uno en forma independiente del grupo que consiste en: hidrógeno, alquilo, arilo, y aralquilo; "Sustituyente de sistema anular" también significa un anillo cíclico de 3 a 7 átomos de carbono, donde 1-2 átomos de carbono pueden ser heteroátomos, unidos a un anillo arilo, heteroarilo, heterociclilo o heterociclenilo mediante la sustitución simultánea de dos átomos de hidrógeno anulares sobre dicho anillo arilo, heteroarilo, heterociclilo o heterociclenilo; ejemplos no limitantes incluyen:

y similares

Las líneas trazadas en un anillo significan que el enlace indicado puede unirse a cualquiera de los átomos de carbono anulares sustituibles.

Cualquier carbono o heteroátomo con valencias no satisfechas en el texto, esquemas, ejemplos, fórmulas estructurales, y cualquier Tabla de la presente, se asume que tiene el átomo o átomos de hidrógeno para satisfacer las valencias. Uno cualquiera o más de estos átomos de hidrógeno puede ser deuterio.

Uno o más compuestos de la invención pueden también existir como, u opcionalmente convertirse a, un solvato. La preparación de solvatos es en general conocido. Así, por ejemplo, M. Caira *et al*, *J. Pharmaceutical Sci.*, 93(3), 601-611 (2004) describen la preparación de los solvatos del antihongos fluconazol en acetato de etilo así como en agua. Se describen preparaciones similares de solvatos, hemisolvato, hidratos y similares en E. C. van Tonder *et al*, *AAPS PharmSciTech.*, 5(1), art. 12 (2004); y A. L. Bingham *et al*, *Chem. Commun.*, 603-604 (2001). Un proceso típico, no limitante, incluye disolver el

compuesto inventivo en cantidades deseadas del solvente deseado (orgánico o agua o mezclas de los mismos) a una temperatura superior a la de ambiente, y enfriar la solución lo suficiente para formar cistrales que luego se aíslan mediante métodos estándar. Técnicas analíticas tal como, por ejemplo, espectroscopía I. R., muestran la presencia del solvente (o agua) en los cristales como un solvato (o hidrato).

El término "composición farmacéutica" también pretende abarcar la composición bruta y unidades individuales de dosificación compuestas por más de un (por ej., dos) agente farmacéuticamente activo tal como, por ejemplo, un compuesto de la presente invención y un agente adicional seleccionado de las listas de los agentes adicionales descriptos en la presente, junto con cualquier agente farmacéuticamente inactivo. La composición bruta y cada unidad individual de dosificación puede contener cantidades fijas de los "más de un agente farmacéuticamente activo" mencionados con anterioridad. La composición bruta es material que no ha sido aún formado en unidades individuales de dosificación. Una unidad de dosificación ilustrativa es una unidad de dosificación oral tal como comprimidos, cápsulas, píldoras y similares. En forma similar, los métodos descriptos en la presente para tratar a un paciente mediante la administración de una composición farmacéutica de la presente invención también pretenden abarcar la administración de las composiciones brutas y unidades individuales de dosificación mencionadas con anterioridad.

También se contemplan en la presente prodrogas de los compuestos de la invención. El término "prodrga", empleado en la presente, denota un compuesto que es un precursor de droga que, tras la administración a un sujeto, experimenta una conversión química mediante procesos metabólicos o químicos para dar un compuesto de fórmula 1.0 o una sal y/o solvato del

191

mismo. Se provee una discusión sobre prodrogas en T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems* (1987) 14 de la 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 en la presente como referencia.

Por ejemplo, si un compuesto de fórmula 1.0, o una sal aceptable para uso farmacéutico, hidrato o solvato del compuesto, contiene un grupo funcional de 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-metilo (C_2-C_{12}), 1-(alcanoiloxi)etilo que tiene de 4 a 9 átomos de carbono, 1-metil-1-(alcanoiloxi)etilo que tiene de 5 a 10 átomos de carbono, alcoxicarboniloximetilo que tiene de 3 a 6 átomos de carbono, 1-(alcoxicarboniloxi)etilo que tiene de 4 a 7 átomos de carbono, 1-metil-1-(alcoxicarboniloxi)etilo que tiene de 5 a 8 átomos de carbono, N-(alcoxicarbonyl)aminometilo que tiene de 3 a 9 átomos de carbono, 1-(N-(alcoxi-carbonil)amino)etilo que tiene de 4 a 10 átomos de carbono, 3-ftalidil, 4-crotonolactonil, gamma-butirolacton-4-il, di-N,N-alquilamino (C_1-C_2) alquilo (C_2-C_3) (tal como β-dimetilaminoetilo), carbamoil-alquilo (C_1-C_2), N,N-di alquilcarbamoil (C_1-C_2) alquilo (C_1-C_2) y piperidino-, pirrolidino- o morfolino alquilo (C_2-C_3), y similares.

En forma similar, si un compuesto de fórmula 1.0 contiene un grupo funcional de alcohol, puede formarse una prodroga mediante el reemplazo del átomo de hidrógeno del grupo alcohol con un grupo tal como, por ejemplo, alcanoiloximetilo (C_1-C_6), 1-(alcanoil-oxi (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-aminoalcanilo (C_1-C_4), arilacilo y α-aminoacilo, o un α-aminoacil- α-aminoacilo, donde cada grupo α-aminoacilo se selecciona en

forma independiente de L-amino ácidos naturales, $P(O)(OH)_2$, -P(O)(Oalquil $(C_1\text{-}C_6))_2$ o glicosilo (el radical resultante de la eliminación de un grupo hidroxilo de la forma hemiacetal de un carbohidrato), y similares.

Si un compuesto de fórmula 1.0 incorpora un grupo funcional de amina, puede formarse una prodroga mediante 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 ($C_1\text{-}C_{10}$), cicloalquilo ($C_3\text{-}C_7$), 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 ($C_1\text{-}C_6$) o bencilo, —$C(OY^{82})Y^{84}$ donde Y^{82} es alquilo ($C_1\text{-}C_4$) e Y^{84} es alquilo ($C_1\text{-}C_6$), carboxi alquilo ($C_1\text{-}C_6$), aminoalquilo ($C_1\text{-}C_4$) o mono-N—o di-N,N-alquilaminoalquilo ($C_1\text{-}C_6$), —$C(Y^{86})Y^{88}$ donde Y^{86} es H o metilo e Y^{88} es mono-N— o di-N,N-alquilamino morfolino ($C_1\text{-}C_6$), piperidin-1-ilo o pirrolidin-1-ilo, y similares.

Esta invención también incluye los compuestos de esta invención en forma aislada y purificada.

También se pretende incluir en la presente invención, formas polimórficas de los compuestos de fórmula 1.0, y de las sales, solvatos y prodrogas de los compuestos de fórmula 1.0.

Ciertos compuestos de la invención pueden existir en diferentes formas isoméricas (por ej., enantiómeros, diastereoisómeros, atropisómeros). La invención contempla todas las tales formas de isómeros puras y en mezcla, que incluyen mezclas racémicas. También se incluyen formas de enol.

Se contemplan dentro del alcance de esta invención, todos los estereoisómeros (por ejemplo, isómeros geométricos, isómeros ópticos y similares) de los compuestos de la presente (que incluyen aquellos de las sales, solvatos y prodrogas de los compuestos así como las sales y solvatos de

las prodrogas), tal como aquellos que pueden existir debido a la presencia de carbonos asimétricos sobre varios sustituyentes, que incluyen formas enantioméricas (que pueden existir incluso en la ausencia de carbonos asimétricos), formas rotaméricas, atropisómeros, y formas diastereoméricas. Estereoisómeros individuales de los compuestos de la invención pueden, por ejemplo, estar sustancialmente libres de otros isómeros, o pueden mezclarse, por ejemplo, como racematos o con todos los otros estereoisómeros o estereoisómeros seleccionados. Los centros quirales de la presente invención pueden tener la configuración S o R definidas por las Recomendaciones de *IUPAC* 1974. El uso de los términos "sal", "solvato" "prodroga" y similares, se pretenda aplicar de igual forma a la sal, solvato y prodroga de los enantiómeros, estereoisómeros, rotámeros, tautómeros, racematos o prodrogas de los compuestos inventivos.

Pueden separarse mezclas diasteroméricas en sus diastereómeros individuales sobre la base de sus diferencias físico-químicas mediante métodos bien conocidos por aquellos con experiencia en la técnica, tal como, por ejemplo, mediante cromatografía y/o cristalización fraccional. Pueden separarse enantiómeros mediante la conversión de la mezcla enantiomérica en una mezcla diastereomérica mediante la reacción con compuesto ópticamente activo adecuado (por ej., auxiliar quiral tal como alcohol quiral o cloruro de ácido Mosher), separación de los diastereómeros y conversión (por ej., hidrolizado) de los diastereómeros individuales en los enantiómeros puros correspondientes. También, algunos de los compuestos de fórmula (I) pueden ser atropisómeros (por ej., biarilos sustituidos) y se consideran parte de esta invención. Pueden también separarse enantiómeros mediante el uso de una columna quiral de HPLC.

Los compuestos de fórmula 1.0 forman sales que también se encuentran dentro del alcance de esta invención. En la presente, la referencia a un compuesto de fórmula 1.0 se comprende como incluyendo referencia a las sales del mismo, a menos que se indique lo contrario. El término "sales", según lo empleado en la presente, denota sales acídicas formadas con ácidos inorgánicos y/u orgánicos, así como sales básicas formadas con bases inorgánicas y/u orgánicas. Además, cuando un compuesto de fórmula 1.0 contiene un resto básico, tal como, pero sin limitación, piridina o imidazol, y un resto acídico, tal como, pero sin limitación un ácido carboxílico, pueden formarse iones dipolares ("sales internas") y se incluyen dentro del término "sales" utilizado en la presente. Se prefieren sales aceptables para uso farmacéutico (es decir, sales no tóxicas, aceptables para uso fisiológico). Pueden formarse sales de los compuestos de la fórmula 1.0, por ejemplo, haciendo reaccionar un compuesto de fórmula 1.0 con una cantidad de ácido o base, tal como una cantidad equivalente, en un medio tal como uno donde la sal precipite o en un medio acuoso seguido por liofilización. Se discuten ácidos (y bases) que generalmente se consideran adecuadas para la formación de sales útiles para uso farmacéutico a partir de compuestos farmacéuticos básicos (o acídicos), por ejemplo, en 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. Estos descubrimiento se incorporan en la presente como referencia.

193

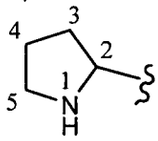
Las sales con adición de ácido representativas incluyen acetatos, adipatos, alginatos, ascorbatos, aspartatos, benzoatos, bencensulfonatos, bisulfatos, boratos, butiratos, citratos, canforatos, canforsulfonatos, ciclopentanpropionatos, digluconatos, dodecilsulfatos, etansulfonatos, fumaratos, glucoheptanoatos, glicerofosfatos, hemisulfatos, heptanoatos, hexanoatos, clorhidrato, 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 (tal como los mencionados en la presente), tartaratos, tiocianatos, toluensulfonatos (también denominados tosilatos,) undecanoatos, y similares.

Las sales básicas representativas incluyen sales de amonio, sales de metal alcalino tal como sales de sodio, litio, y potasio, sales de metal térreo-alcalino tal como sales de calcio y magnesio, sales de aluminio, sales de zinc, sales con bases orgánicas (por ejemplo, aminas orgánicas) tal 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 tal como arginina, lisina y similares. Pueden cuaternizarse grupos básicos que contienen nitrógeno con agentes tal como haluros de alquilo inferior (por ej., cloruros, bromuros, yoduros de metilo, etilo, propilo, y butilo), dialquil sulfatos (por ej., dimetil, dietil, dibutil, y diamil sulfatos), haluros de cadenas largas (por ej., cloruros, bromuros, yoduros de decilo, laurilo, miristilo y estearilo), aralquil haluros (por ej., bromuros de bencilo y fenetilo), y otros.

Se pretende que todas las sales con ácido y base sean sales aceptables para uso farmacéutico dentro del alcance de la invención y todas las sales con ácido y base se consideran, para los propósitos de la invención, equivalentes a las formas libres de los compuestos correspondientes.

Compuestos de fórmula 1.0, y sales, solvatos y prodrogas de los mismos, pueden existir en sus formas tautoméricas (por ejemplo, como una amida o imino éter). Todas las dichas formas tautoméricas se contemplan en la presente como parte de la presente invención.

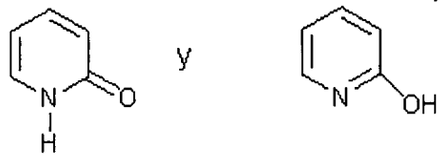
En sistemas anulares que contienen heteroátomo de esta invención, no existen grupos hidroxilo sobre átomos de carbono adyacentes a N, O o S, y no existen grupos N o S sobre carbono adyacente a otro heteroátomo. Así, por ejemplo, en el anillo:



no hay -OH directamente unido a los carbonos marcados 2 y 5.

Los compuestos de fórmula 1.0 pueden existir en diferentes formas tautoméricas, y todas las tales formas se incluyen dentro del alcance de la invención. También, por ejemplo, se incluyen dentro de la invención todas las formas ceto-enol e imina-enamina de los compuestos.

Formas tautoméricas tal como, por ejemplo, los restos:



se consideran equivalentes en ciertas realizaciones de esta invención.

El término "sustituido" significa que uno o más hidrógenos sobre el átomo designado se reemplazan con una selección del grupo indicado, con la condición que no se exceda la valencia normal del átomo designado bajo las

circunstancias existentes, y que la sustitución de lugar a un compuesto estable. Combinaciones de sustituyentes y/o variables son permisibles sólo si tales combinaciones dan lugar a compuestos estables. "Compuesto estable" o "estructura estable" significa un compuesto lo suficientemente robusto para sobrevivir un aislamiento a un grado de pureza útil de una mezcla de reacción, y formulación en un agente terapéutico eficaz.

El término "sustituido en forma opcional" significa sustitución opcional con los grupos, radicales o restos especificados.

El término "purificado", "en forma purificada" o "en forma aislada y purificada" para un compuesto hace referencia al estado físico de dicho compuesto luego de ser aislado mediante un proceso sintético o fuente natural o combinación de los mismos. Así, el término "purificado", "en forma purificada" o "en forma aislada y purificada" para un compuesto hace referencia al estado físico de dicho compuesto luego de ser obtenido mediante un proceso o procesos de purificación descriptos en la presente o bien conocidos por aquellos con experiencia en la técnica, con una pureza suficiente para ser caracterizable mediante técnicas analíticas estándar descriptas en la presente o bien conocidas por aquellos con experiencia en la técnica.

Cuando se afirma que un grupo funcional en un compuesto se encuentra "protegido", esto significa que el grupo está en forma modificada para descartar reacciones colaterales no deseadas en el sitio protegido cuando el compuesto se somete a una reacción. Aquellos con experiencia en la técnica reconocerán grupos de protección adecuados, o puede remitirse a manuales de texto estándar tal como, por ejemplo, T. W. Greene *et al*, *Protective Groups in organic Synthesis* (1991), Wiley, New York.

Cuando cualquier variable (por ej., arilo, heterociclo, R^3, etc.) aparece más de una vez en cualquier resto o compuesto de fórmula 1.0, su definición en cada aparación es independiente de su definición en las otras.

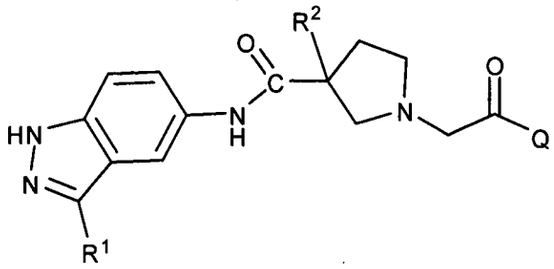
Según lo utilizado en la presente, el término "composición" pretende abarca un producto que comprende los componentes especificados en las cantidades especificadas, así como cualquier producto que resulta, directa o indirectamente, de la combinación de los componentes especificados en las cantidades especificadas.

La presente invención también abarca compuestos isotópicamente marcados de la presente invención que son idénticos a los referidos en la presente, salvo por el hecho de que se reemplazan uno o más átomos por un átomo que cuente con una masa atómica o número de masa diferente de la masa atómica o número de masa normalmente hallado en la naturaleza. Los ejemplos de isótopos que pueden incorporarse en compuestos de la invención incluyen isótopos de hidrógeno, carbono, nitrógeno, oxígeno, fósforo, flúor, cloro, e yodo, tal como ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, ^{36}Cl, e ^{123}I, respectivamente.

Ciertos compuestos isotópicamente marcados de fórmula 1.0 (por ej., aquellos marcados con ^{3}H y ^{14}C) son útiles en ensayos de distribución del tejido en compuestos y/o sustratos. En particular, se prefieren isótopos tritiados (es decir, ^{3}H) y de carbono-14 (es decir, ^{14}C) por su facilidad de preparación y detectabilidad. Ciertos compuestos isotópicamente marcados de Fórmula (I) pueden ser útiles por propósitos medicinales de obtención de imágenes. Por ej., aquellos marcados con isótopos emisores de positrones como ^{11}C o ^{18}F pueden ser útiles para aplicación en Tomografía por Emisión de Positrones (PET) y aquellos marcadois con isótopos emisores de rayos gamma como ^{123}I pueden ser útiles para aplicación en Tomografía Computada por Emisión de

Fotones Simples (SPECT). Más aún, la sustitución con isótopos más pesados tal como deuterio (es decir, ^{2}H) puede provocar ciertas ventajas terapéuticas que resultan de la mayor estabilidad metabólica (por ej., aumento in-vivo de la vida útil o reducción de los requerimientos de dosificación) y, por lo tanto, preferirse en ciertas circunstancias. Los compuestos isotópicamente marcados de Fórmula (I), en particular aquellos que contienen isótopos con mayor vida útil (T1/2 >1 día), pueden en general prepararse siguiendo procedimientos análogos a los descriptos en los Esquemas y/o Ejemplos a continuación, mediante la sustitución de un reactivo isotópidamente marcado adecuado por un reactivo isotópidamente no marcado.

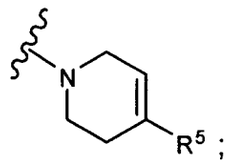
Esta invención provee compuestos de fórmula 1.0:



(1.0)

o las sales aceptables para uso farmacéutico, o solvatos de los mismos, donde R^1, R^2 y Q se seleccionan independientemente, y donde:

Q es:



;

R^1 se selecciona del grupo que consiste en: heteroarilo y heteroarilo sustituido, donde dicho heteroarilo sustituido se sustituye con 1 a 3 (preferentemente 1) sustituyentes seleccionados en forma independiente del grupo que consiste en: -OH, alcoxi, y –O-alquilen-O-alquilo;

R^2 se selecciona del grupo que consiste en: -O-alquilo y -S-alquilo; y

R^5 se selecciona del grupo que consiste en:

(a) triazolil-fenil-,

(b) triazolil-fenil- donde dicho fenilo se sustituye en forma opcional con 1 a 3 sustituyentes seleccionados en forma independiente del grupo que consiste en: halo (por ej., Br, Cl, F, y en un ejemplo F) y alcoxi (por ej., alcoxi C_1-C_6, y en un ejemplo, alcoxi C_1-C_2, y en otro ejemplo $-OCH_3$),

(c) triazolil-fenil- sustituido donde dicho fenilo se sustituye en forma opcional con 1 a 3 sustituyentes seleccionados en forma independiente del grupo que consiste en: halo (por ej., Br, Cl, F, y en un ejemplo F) y alcoxi (por ej., alcoxi C_1-C_6, y en un ejemplo, alcoxi C_1-C_2, y en otro ejemplo $-OCH_3$), y dicho grupo triazolilo se sustituye con uno o dos sustituyentes seleccionados en forma independiente del grupo que consiste en: alquilo, alquilo sustituido con hidroxi,-alquilen-O-alquilo, y amino (es decir, $-NH_2$),

(d) triazolil-tienil-,

(e) triazolil-tienil- donde dicho tienilo se sustituye en forma opcional con 1 a 2 sustituyentes seleccionados en forma independiente del grupo que consiste en: halo (por ej., Br, Cl, F, y en un ejemplo F) y alcoxi (por ej., alcoxi C_1-C_6, y en un ejemplo, alcoxi C_1-C_2, y en otro ejemplo $-OCH_3$),

(f) triazolil-tienil- sustituido donde dicho tienilo se sustituye en forma opcional con 1 a 2 sustituyentes seleccionados en forma independiente del grupo que consiste en: halo (por ej., Br, Cl, F, y en un ejemplo F) y alcoxi (por ej., alcoxi C_1-C_6, y en un ejemplo, alcoxi C_1-C_2, y en otro ejemplo $-OCH_3$), y dicho grupo triazolilo se sustituye con uno o dos sustituyentes seleccionados en forma independiente del grupo que consiste en: alquilo, alquilo sustituido con hidroxi,-alquilen-O-alquilo, y amino (es decir, $-NH_2$),

(g) triazolil-piridil-,

(h) triazolil-piridil- donde dicho piridilo se sustituye en forma opcional con 1 a 3 sustituyentes seleccionados en forma independiente del grupo que consiste en: halo (por ej., Br, Cl, F, y en un ejemplo F), alquilo, y alcoxi (por ej., alcoxi C_1-C_6, y en un ejemplo, alcoxi C_1-C_2, y en otro ejemplo $-OCH_3$), con la condición de que los átomos de carbono adyacentes al átomo de nitrógeno en dicho piridilo no estén sustituidos con halo, y

(i) triazolil-piridil- sustituido donde: (1) dicho piridilo se sustituye en forma opcional con 1 a 3 sustituyentes seleccionados en forma independiente del grupo que consiste en: halo (por ej., Br, Cl, F, y en un ejemplo F), alquilo, y alcoxi (por ej., alcoxi C_1-C_6, y en un ejemplo, alcoxi C_1-C_2, y en otro ejemplo $-OCH_3$), con la condición de que los átomos de carbono adyacentes al átomo de nitrógeno en dicho piridilo no estén sustituidos con halo, y (2) dicho triazolilo se sustituye con uno o dos sustituyentes seleccionados en forma independiente del grupo que consiste en: alquilo, alquilo sustituido con hidroxi, -alquilen-O-alquilo, y amino (es decir, $-NH_2$),

(j) triazolil-tiazolil-,

(k) triazolil-tiazolil- donde dicho tiazolilo se sustituye en forma opcional con 1 sustituyente seleccionado en forma independiente del grupo que consiste en: halo (por ej., Br, Cl, F, y en un ejemplo F), alquilo, y alcoxi (por ej., alcoxi C_1-C_6, y en un ejemplo, alcoxi C_1-C_2, y en otro ejemplo $-OCH_3$), amino (es decir, NH_2), alquilamino, y dialquilamino donde cada alquilo se selecciona en forma independiente, y

(l) triazolil-tiazolil- sustituido donde (1) dicho tiazolilo se sustituye en forma opcional con 1 sustituyente seleccionado en forma independiente del grupo que consiste en: halo (por ej., Br, Cl, F, y en un ejemplo F), alquilo, y alcoxi (por ej., alcoxi C_1-C_6, y en un ejemplo, alcoxi C_1-C_2, y en otro ejemplo $-OCH_3$), amino (es decir, NH_2), alquilamino, y dialquilamino donde cada alquilo

se selecciona en forma independiente, y (2) dicho triazolilo se sustituye con uno o dos sustituyentes seleccionados en forma independiente del grupo que consiste en: alquilo, alquilo sustituido con hidroxi,-alquilen-O-alquilo, y amino (es decir, $-NH_2$),

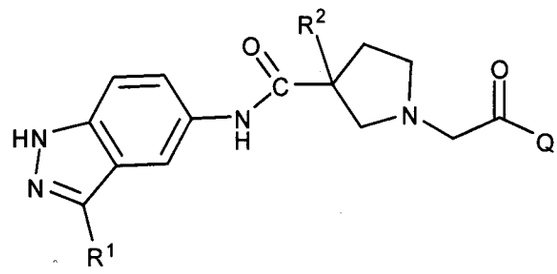
(m) piridazinil-tienil-,

(n) piridazinil-tienil- donde dicho tienilo se sustituye en forma opcional con 1 a 2 sustituyentes seleccionados en forma independiente del grupo que consiste en: halo (por ej., Br, Cl, F, y en un ejemplo F) y alcoxi (por ej., alcoxi C_1-C_6, y en un ejemplo, alcoxi C_1-C_2, y en otro ejemplo $-OCH_3$), y

(o) piridazinil-tienil- sustituido donde (1) dicho tienilo se sustituye en forma opcional con 1 a 2 sustituyentes seleccionados en forma independiente del grupo que consiste en: halo (por ej., Br, Cl, F, y en un ejemplo F) y alcoxi (por ej., alcoxi C_1-C_6, y en un ejemplo, alcoxi C_1-C_2, y en otro ejemplo $-OCH_3$), y (2) dicho grupo piridazinilo se sustituye con 1 a 3 sustituyentes seleccionados en forma independiente del grupo que consiste en: =O, alquilo, amino (es decir, $-NH_2$), alquilamino, dialquilamino donde cada alquilo se selecciona en forma independiente, y halo (por ej., Br, Cl, F, y en un ejemplo F), con la condición de que los átomos de carbono adyacentes al átomo de nitrógeno en dicho piridazinilo no estén sustituidos con halo, y

con la condición de que cuando dicho grupo -alquilen-O-alquilo esté unido al nitrógeno de dicho triazolilo en (c), (f), (i) y (l) de R^5 el resto alquileno de dicho grupo -alquilen-O-alquilo no sea $-CH_2-$ (es decir, que el resto alquileno tenga una longitud de 2 o más carbonos).

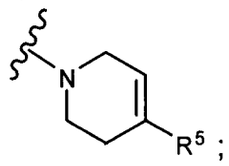
Esta invención provee compuestos de fórmula 1.0:



(1.0)

o las sales aceptables para uso farmacéutico, o solvatos de los mismos, donde:

Q es:



R^1 se selecciona del grupo que consiste en: heteroarilo y heteroarilo sustituido, donde dicho heteroarilo sustituido se sustituye con 1 a 3 (preferentemente 1) sustituyentes seleccionados en forma independiente del grupo que consiste en: -OH, alcoxi, y –O-alquilen-O-alquilo;

R^2 se selecciona del grupo que consiste en: -O-alquilo y -S-alquilo; y

R^5 se selecciona del grupo que consiste en:

(a) triazolil-fenil-,

(b) triazolil-fenil- donde dicho fenilo se sustituye en forma opcional con 1 a 3 sustituyentes seleccionados en forma independiente del grupo que consiste en: halo (por ej., Br, Cl, F, y en un ejemplo F) y alcoxi (por ej., alcoxi C_1-C_6, y en un ejemplo, alcoxi C_1-C_2, y en otro ejemplo –OCH_3),

(c) triazolil-fenil- sustituido donde dicho fenilo se sustituye en forma opcional con 1 a 3 sustituyentes seleccionados en forma independiente del grupo que consiste en: halo (por ej., Br, Cl, F, y en un ejemplo F) y alcoxi (por ej., alcoxi C_1-C_6, y en un ejemplo, alcoxi C_1-C_2, y en otro ejemplo –OCH_3), y dicho grupo triazolilo se sustituye con uno o dos sustituyentes seleccionados en

forma independiente del grupo que consiste en: alquilo, alquilo sustituido con hidroxi,-alquilen-O-alquilo, y amino (es decir, $-NH_2$);

(d) triazolil-tienil-,

(e) triazolil-tienil- donde dicho tienilo se sustituye en forma opcional con 1 a 2 sustituyentes seleccionados en forma independiente del grupo que consiste en: halo (por ej., Br, Cl, F, y en un ejemplo F) y alcoxi (por ej., alcoxi C_1-C_6, y en un ejemplo, alcoxi C_1-C_2, y en otro ejemplo $-OCH_3$), y

(f) triazolil-tienil- sustituido donde dicho tienilo se sustituye en forma opcional con 1 a 2 sustituyentes seleccionados en forma independiente del grupo que consiste en: halo (por ej., Br, Cl, F, y en un ejemplo F) y alcoxi (por ej., alcoxi C_1-C_6, y en un ejemplo, alcoxi C_1-C_2, y en otro ejemplo $-OCH_3$), y dicho grupo triazolilo se sustituye con uno o dos sustituyentes seleccionados en forma independiente del grupo que consiste en: alquilo, alquilo sustituido con hidroxi,-alquilen-O-alquilo, y amino (es decir, $-NH_2$), y

con la condición de que cuando dicho grupo -alquilen-O-alquilo esté unido al nitrógeno de dicho triazolilo en (c) y (f) de R^5 el resto alquileno de dicho grupo -alquilen-O-alquilo no sea $-CH_2-$ (es decir, que el resto alquileno tenga una longitud de 2 o más carbonos).

Aquellos con experiencia en la técnica apreciarán que el término "alquileno", utilizado en los sustituyentes -O-alquilen-O-alquilo y -alquilen-O-alquilo, significa un grupo hidrocarbonado divalente saturado. Así, un ejemplo de un resto alquileno es $-CH_2-CH_2-$, y un ejemplo de un resto -O-alquilen-O-alquilo es $-O-(CH_2)_2-O-CH_3$, y un ejemplo de un resto -alquilen-O-alquilo es $-(CH_2)_2-O-CH_3$.

Aquellos con experiencia en la técnica también apreciarán que el término alquileno también incluye el resto $-CH_2-$.

Los ejemplos del grupo heteroarilo R^1 incluyen, pero sin limitación, piridilo, pirrolilo, pirazolilo, imidazolilo, furanilo, tienilo, tiazolilo, piridil N-O, y pirimidinilo.

Los ejemplos del grupo heteroarilo sustituido con R^1 incluyen, pero sin limitación, piridilo sustituido, pirrolilo sustituido, pirazolilo sustituido, imidazolilo sustituido, furanilo sustituido, tienilo sustituido, tiazolilo sustituido, piridil N-O sustituido, y pirimidinilo sustituido.

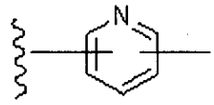
En una realización de esta invención R^1 es piridilo.

En otra realización de esta invención R^1 es piridilo sustituido.

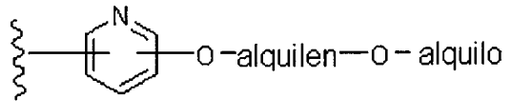
En otra realización de esta invención R^1 es piridilo sustituido con un sustituyente.

Los sustitutyentes sobre los grupos R^1 sustituidos (por ej., el piridilo sustituido) se seleccionan en forma independiente del grupo que consiste en: -OH, alcoxi, y –O-alquilen-O-alquilo. Los ejemplos del grupo alcoxi incluyen, por ejemplo, alcoxi C_1 a C_6 (tal como, por ejemplo, $-O-CH_3$, $-O-C_2H_5$, y $-O-CH(CH_3)_2$). Los ejemplos del grupo –O-alquilen-O-alquilo incluyen, por ejemplo, –O-alquilen (C_1-C_4)-O-alquilo (C_1-C_6), –O-alquilen (C_1-C_2)-O-(alquil C_1-C_3), y $-O-(CH_2)_2-O-CH_3$).

Los ejemplos de R^1 incluyen, por ejemplo,



alcoxi y

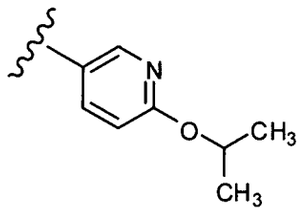


En una realización de esta invención R^1 es piridilo sustituido con alcoxi.

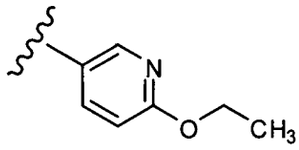
En otra realización de esta invención R^1 se sustituye con $-OCH(CH_3)_2$.

En otra realización de esta invención R^1 se sustituye con $-OC_2H_5$.

En otra realización de esta invención R^1 es:



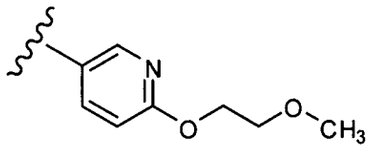
En otra realización de esta invención R^1 es:



En otra realización de esta invención R^1 se sustituye con –O-alquilen-O-alquilo.

En otra realización de esta invención R^1 se sustituye con $-OCH_2CH_2OCH_3$.

En otra realización de esta invención R^1 es:



Los ejemplos del grupo –O-alquilo R^2 incluyen, por ejemplo, –O-alquilo (C_1-C_6), –O-alquilo (C_1-C_2), y $-OCH_3$.

Los ejemplos del grupo –S-alquilo R^2 incluyen, por ejemplo, –S-alquilo (C_1-C_6), –S-alquilo (C_1-C_2), y $-SCH_3$.

En una realización de esta invención R^2 es un grupo –O-alquilo (C_1-C_2).

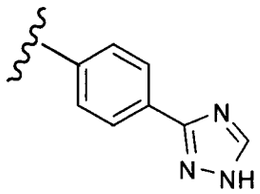
En otra realización de esta invención R^2 es $-OCH_3$.

En otra realización de esta invención R^2 es un grupo –S-alquilo (C_1-C_2).

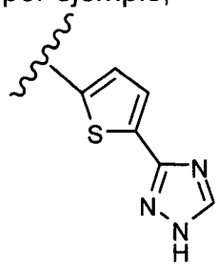
En otra realización de esta invención R^2 es $-SCH_3$.

En una realización de esta invención R^5 es un resto triazolil-fenilo donde el resto triazolilo se une al resto fenlo mediante un carbono anular del resto triazolilo

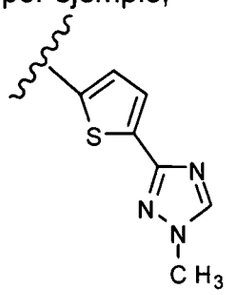
En una realización de esta invención R^5 es un resto triazolil-fenil-, tal como, por ejemplo,



En otra realización de esta invención R^5 es un resto triazolil-tienil-, tal como, por ejemplo,



En otra realización de esta invención R^5 es un resto triazolil-tienil-, tal como, por ejemplo,



En otra realización de esta invención el resto triazolilo sustituido de dicho grupo R^5 se sustituye sobre el nitrógeno anular.

Cuando el resto triazolilo de R^5 se sustituye con alquilo, los ejemplos de los grupos alquilo incluyen, por ejemplo, alquilo-C_1-C_6, alquilo-C_1-C_4, alquilo-C_1-C_2, y -CH_3. Y en una realización, se produce una sustitución de alquilo sobre el resto triazolilo de R^5 y dicho alquilo es –CH_3.

Cuando el resto triazolilo de R^5 se sustituye con grupos -alquilen-O-alquilo, los ejemplos de los grupos -alquilen-O-alquilo incluyen, por ejemplo, -alquilen C_1-C_4-O-alquilo C_1-C_6, -alquilen C_1-C_2 O-alquilo C_1-C_2, -alquilen C_1-C_4-O-CH_3, y –$CH_2CH_2OCH_3$. Y en una realización, se produce una sustitución de -

alquilen-O-alquilo sobre el resto triazolilo de R^5 y dicho -alquilen-O-alquilo es –$CH_2CH_2OCH_3$.

Cuando el nitrógeno del resto triazolilo de R^5 se sustituye con un grupo -alquilen-O-alquilo, los ejemplos del grupo -alquilen-O-alquilo incluyen, por ejemplo, -alquilen C_2-C_4-O-alquilo C_1-C_6, -alquilen C_2-O-alquilo C_1-C_2, -alquilen C_2-C_4-O-CH_3, y –$CH_2CH_2OCH_3$. Y en una realización, se produce una sustitución de -alquilen-O-alquilo sobre el nitrógeno del resto triazolilo de R^5 y dicho

-alquilen-O-alquilo es –$CH_2CH_2OCH_3$.

Cuando el resto triazolilo de R^5 se sustituye con grupos alquilo sustituidos con hidroxi, los ejemplos de los grupos alquilo sustituidos con hidroxi incluyen, por ejemplo, alquilo-C_1-C_4 sustituido con hidroxi, alquilo-C_1-C_2 sustituido con hidroxi, y -CH_3 sustituido con hidroxi. Los ejemplos también incluyen, por ejemplo, –$CH_2COH(CH_3)_2$, y -CH_2CH_2OH.

Cuando el resto fenilo de R^5 se sustituye con átomos de halo, los ejemplos de los átomos de halo incluyen, por ejemplo, Cl, F y Br. En una realización de esta invención el halo sobre el fenilo es F. En otra realización de esta invención el fenilo se sustituye con un F.

En una realización de esta invención R^5 es un triazolil-fenil- sustituido donde dicho triazolilo está sustituido y dicho fenilo no está sustituido.

En otra realización de esta invención R^5 es un triazolil-fenil- sustituido donde dicho triazolilo se sustituye sobre el nitrógeno y dicho fenilo no está sustituido.

En otra realización de esta invención R^5 es un triazolil-fenil- sustituido donde dicho triazolilo se sustituye sobre el carbono y dicho fenilo no está sustituido.

En otra realización de esta invención R^5 es un triazolil-fenil- sustituido donde dicho triazolilo se sustituye sobre el nitrógeno y sobre el carbono, y dicho fenilo no está sustituido.

En otra realización de esta invención R^5 es un triazolil-fenil- sustituido donde dicho triazolilo está sustituido y dicho fenilo está sustituido.

En otra realización de esta invención R^5 es un triazolil-fenil- sustituido donde dicho triazolilo se sustituye sobre el nitrógeno y dicho fenilo está sustituido.

En otra realización de esta invención R^5 es un triazolil-fenil- sustituido donde dicho triazolilo se sustituye sobre el carbono y dicho fenilo está sustituido.

En otra realización de esta invención R^5 es un triazolil-fenil- sustituido donde dicho triazolilo se sustituye sobre el nitrógeno y sobre el carbono, y dicho fenilo está sustituido.

En otra realización de esta invención R^5 es un triazolil-fenil- sustituido donde dicho triazolilo no está sustituido y dicho fenilo está sustituido.

En otra realización de esta invención R^5 es un untriazolil-fenil- sustituido.

En otra realización de esta invención R^5 es un triazolil-fenil- sustituido donde el triazolilo se sustituye sobre el nitrógeno con $-CH_2COH(CH_3)_2$.

En otra realización de esta invención R^5 es un triazolil-fenil- sustituido donde el triazolilo se sustituye sobre el nitrógeno con $-CH_2CH_2OH$.

En otra realización de esta invención R^5 es un triazolil-fenil- sustituido donde el triazolilo se sustituye sobre el nitrógeno con un grupo alquilo.

En otra realización de esta invención R^5 es un triazolil-fenil- sustituido donde el triazolilo se sustituye sobre el nitrógeno con un grupo alquilo y se sustituye sobre el carbono con un grupo alquilo, donde cada grupo alquilo se selecciona en forma independiente.

En otra realización de esta invención R^5 es un triazolil-fenil- sustituido donde el triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_3$.

En otra realización de esta invención R^5 es un triazolil-fenil- sustituido donde el triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_3$ y sobre el carbono con un grupo $-CH_3$.

En otra realización de esta invención el resto R^5 es un triazolil-fenil-sustituido donde el triazolilo se sustituye sobre el carbono con un grupo $-NH_2$.

En otra realización de esta invención R^5 es un triazolil-fenil- sustituido donde el triazolilo se sustituye sobre el nitrógeno con un grupo -alquilen-O-alquilo.

En otra realización de esta invención R^5 es un triazolil-fenil- sustituido donde el triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_2CH_2OCH_3$.

En otra realización de esta invención el resto R^5 es un triazolil-fenil-sustituido donde dicho resto fenilo se sustituye con halo, y dicho resto triazolilo se sustituye según lo descripto en cualquiera de las realizaciones anteriores.

En otra realización de esta invención R^5 es un triazolil-fenil- sustituido donde dicho resto fenilo se sustituye con un halo, y dicho resto triazolilo se sustituye según lo descripto en cualquiera de las realizaciones anteriores.

En otra realización de esta invención R^5 es un triazolil-fenil- sustituido donde dicho resto fenilo se sustituye con F, y dicho resto triazolilo se sustituye según lo descripto en cualquiera de las realizaciones anteriores.

En otra realización de esta invención R^5 es un triazolil-fenil- sustituido donde dicho resto fenilo se sustituye con un F, y dicho resto triazolilo se sustituye según lo descripto en cualquiera de las realizaciones anteriores.

En otra realización de esta invención R^5 es un grupo triazolil-fenil-sustituido donde dicho resto fenilo se sustituye con un F, y dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo sustituido con hidroxilo.

En otra realización de esta invención R^5 es un triazolil-fenil- sustituido donde dicho resto fenilo se sustituye con un F, y dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_2CH_2OH$.

En otra realización de esta invención R^5 es un triazolil-fenil- sustituido donde dicho resto fenilo se sustituye con un F, y dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo -alquilen-O-alquilo.

En otra realización de esta invención R^5 es un triazolil-fenil- sustituido donde dicho resto fenilo se sustituye con un F, y dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_2CH_2OCH_3$.

En otra realización de esta invención R^5 es un triazolil-fenil- sustituido donde dicho resto fenilo se sustituye con halo, y dicho resto triazolilo no está sustituido.

En otra realización de esta invención R^5 es un triazolil-fenil- sustituido donde dicho resto fenilo se sustituye con un halo, y dicho resto triazolilo no está sustituido.

En otra realización de esta invención R^5 es un triazolil-fenil- sustituido donde dicho resto fenilo se sustituye con F, y dicho resto triazolilo no está sustituido.

En otra realización de esta invención R^5 es un triazolil-fenil- sustituido donde dicho resto fenilo se sustituye con un F, y dicho resto triazolilo no está sustituido.

En otra realización de esta invención el resto R^5 es un triazolil-fenil-sustituido donde dicho resto fenilo se sustituye con alcoxi, y dicho resto triazolilo se sustituye según lo descripto en cualquiera de las realizaciones anteriores.

En otra realización de esta invención R^5 es un triazolil-fenil- sustituido donde dicho resto fenilo se sustituye con un alcoxi, y dicho resto triazolilo se sustituye según lo descripto en cualquiera de las realizaciones anteriores.

En otra realización de esta invención R^5 es un triazolil-fenil- sustituido donde dicho resto fenilo se sustituye con $-OCH_3$, y dicho resto triazolilo se sustituye según lo descripto en cualquiera de las realizaciones anteriores.

En otra realización de esta invención R^5 es un triazolil-fenil- sustituido donde dicho resto fenilo se sustituye con un $-OCH_3$, y dicho resto triazolilo se sustituye según lo descripto en cualquiera de las realizaciones anteriores.

En otra realización de esta invención R^5 es un grupo triazolil-fenil-sustituido donde dicho resto fenilo se sustituye con un $-OCH_3$, y dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo sustituido con hidroxilo.

En otra realización de esta invención R^5 es un triazolil-fenil- sustituido donde dicho resto fenilo se sustituye con un $-OCH_3$, y dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_2CH_2OH$.

En otra realización de esta invención R^5 es un triazolil-fenil- sustituido donde dicho resto fenilo se sustituye con un $-OCH_3$, y dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo -alquilen-O-alquilo.

En otra realización de esta invención R^5 es un triazolil-fenil- sustituido donde dicho resto fenilo se sustituye con un $-OCH_3$, y dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_2CH_2OCH_3$.

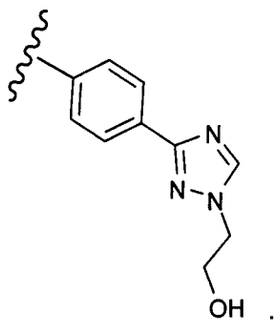
En otra realización de esta invención R^5 es un triazolil-fenil- sustituido donde dicho resto fenilo se sustituye con alcoxi, y dicho resto triazolilo no está sustituido.

En otra realización de esta invención R^5 es un triazolil-fenil- sustituido donde dicho resto fenilo se sustituye con un alcoxi, y dicho resto triazolilo no está sustituido.

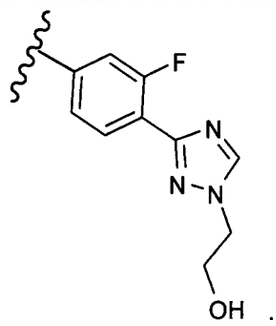
En otra realización de esta invención R^5 es un triazolil-fenil- sustituido donde dicho resto fenilo se sustituye con–OCH_3, y dicho resto triazolilo no está sustituido.

En otra realización de esta invención R^5 es un triazolil-fenil- sustituido donde dicho resto fenilo se sustituye con un –OCH_3, y dicho resto triazolilo no está sustituido.

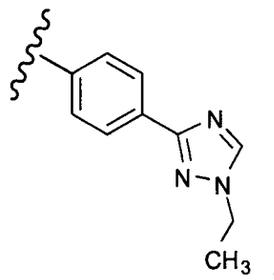
En otra realización de esta invención R^5 es:



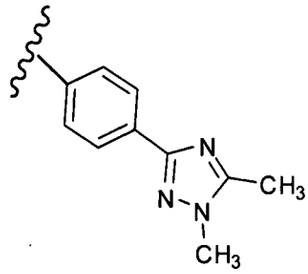
En otra realización de esta invención R^5 es:



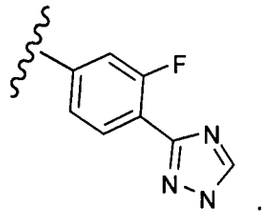
En otra realización de esta invención R^5 es:



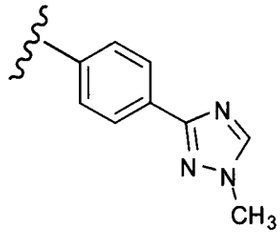
En otra realización de esta invención R^5 ss:



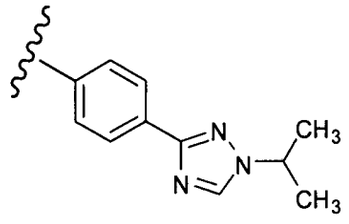
En otra realización de esta invención R^5 es:



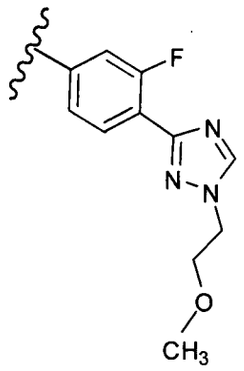
En otra realización de esta invención R^5 es:



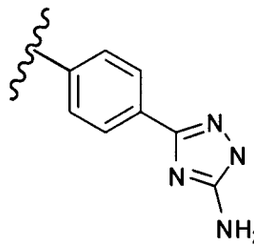
En otra realización de esta invención R^5 es:



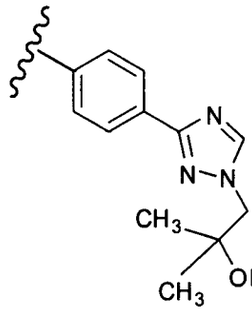
En otra realización de esta invención R^5 es:



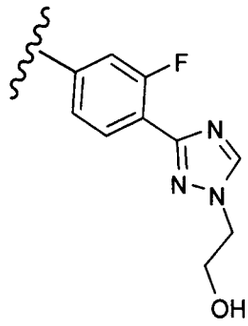
En otra realización de esta invención R^5 es:



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 un triazolil-tienil- sustituido donde dicho triazolilo está sustituido y dicho tienilo no está sustituido.

En otra realización de esta invención R^5 es un triazolil-tienil- sustituido donde dicho triazolilo se sustituye sobre el nitrógeno y dicho tienilo no está sustituido.

En otra realización de esta invención R^5 es un triazolil-tienil- sustituido donde dicho triazolilo se sustituye sobre el carbono y dicho tienilo no está sustituido.

En otra realización de esta invención R^5 es un triazolil-tienil- sustituido donde dicho triazolilo se sustituye sobre el nitrógeno y sobre el carbono, y dicho tienilo no está sustituido.

En otra realización de esta invención R^5 es un triazolil-tienil- sustituido donde dicho triazolilo está sustituido y dicho tienilo está sustituido.

En otra realización de esta invención R^5 es un triazolil-tienil- sustituido donde dicho triazolilo se sustituye sobre el nitrógeno y dicho tienilo está sustituido.

En otra realización de esta invención R^5 es un triazolil-tienil- sustituido donde dicho triazolilo se sustituye sobre el carbono y dicho tienilo está sustituido.

En otra realización de esta invención R^5 es un triazolil-tienil- sustituido donde dicho triazolilo se sustituye sobre el nitrógeno y sobre el carbono, y dicho tienilo está sustituido.

En otra realización de esta invención R^5 es un triazolil-tienil- sustituido donde dicho triazolilo no está sustituido y dicho tienilo está sustituido.

En otra realización de esta invención R^5 es un triazolil-tienil- no sustituido.

En otra realización de esta invención R^5 es un triazolil-tienil- sustituido donde el triazolilo se sustituye sobre el nitrógeno con $-CH_2COH(CH_3)_2$.

En otra realización de esta invención R^5 es un triazolil-tienil- sustituido donde el triazolilo se sustituye sobre el nitrógeno con $-CH_2CH_2OH$.

En otra realización de esta invención R^5 es un triazolil-tienil- sustituido donde el triazolilo se sustituye sobre el nitrógeno con un grupo alquilo.

En otra realización de esta invención R^5 es un triazolil-tienil- sustituido donde el triazolilo se sustituye sobre el nitrógeno con un grupo alquilo y se sustituye sobre el carbono con un grupo alquilo, donde cada grupo alquilo se selecciona en forma independiente.

En otra realización de esta invención R^5 es un triazolil-tienil- sustituido donde el triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_3$.

En otra realización de esta invención R^5 es un triazolil-tienil- sustituido donde el triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_3$ y sobre el carbono con un grupo $-CH_3$.

En otra realización de esta invención el resto R^5 es un triazolil-tienil-sustituido donde el triazolilo se sustituye sobre el carbono con un grupo $-NH_2$.

En otra realización de esta invención R^5 es un triazolil-tienil- sustituido donde el triazolilo se sustituye sobre el nitrógeno con un grupo -alquilen-O-alquilo.

En otra realización de esta invención R^5 es un triazolil-tienil- sustituido donde el triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_2CH_2OCH_3$.

En otra realización de esta invención el resto R^5 es un triazolil-tienil-sustituido donde dicho resto tienilo se sustituye con halo, y dicho resto triazolilo se sustituye según lo descripto en cualquiera de las realizaciones anteriores.

En otra realización de esta invención R^5 es un triazolil-tienil- sustituido donde dicho resto tienilo se sustituye con un halo, y dicho resto triazolilo se sustituye según lo descripto en cualquiera de las realizaciones anteriores.

En otra realización de esta invención R^5 es un triazolil-tienil- sustituido donde dicho resto tienilo se sustituye con F, y dicho resto triazolilo se sustituye según lo descripto en cualquiera de las realizaciones anteriores.

En otra realización de esta invención R^5 es un triazolil-tienil- sustituido donde dicho resto tienilo se sustituye con un F, y dicho resto triazolilo se sustituye según lo descripto en cualquiera de las realizaciones anteriores.

En otra realización de esta invención R^5 es un grupo triazolil-tienil-sustituido donde dicho resto tienilo se sustituye con un F, y dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo sustituido con hidroxilo.

En otra realización de esta invención R^5 es un triazolil-tienil- sustituido donde dicho resto tienilo se sustituye con un F, y dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_2CH_2OH$.

En otra realización de esta invención R^5 es un triazolil-tienil- sustituido donde dicho resto tienilo se sustituye con un F, y dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo -alquilen-O-alquilo.

En otra realización de esta invención R^5 es un triazolil-tienil- sustituido donde dicho resto tienilo se sustituye con un F, y dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_2CH_2OCH_3$.

En otra realización de esta invención R^5 es un triazolil-tienil- sustituido donde dicho resto tienilo se sustituye con halo, y dicho resto triazolilo no está sustituido.

En otra realización de esta invención R^5 es un triazolil-tienil- sustituido donde dicho resto tienilo se sustituye con un halo, y dicho resto triazolilo no está sustituido.

En otra realización de esta invención R^5 es un triazolil-tienil- sustituido donde dicho resto tienilo se sustituye con F, y dicho resto triazolilo no está sustituido.

En otra realización de esta invención R^5 es un triazolil-tienil- sustituido donde dicho resto tienilo se sustituye con un F, y dicho resto triazolilo no está sustituido.

En otra realización de esta invención el resto R^5 es un triazolil-tienil-sustituido donde dicho resto tienilo se sustituye con alcoxi, y dicho resto triazolilo se sustituye según lo descripto en cualquiera de las realizaciones anteriores.

En otra realización de esta invención R^5 es un triazolil-tienil- sustituido donde dicho resto tienilo se sustituye con un alcoxi, y dicho resto triazolilo se sustituye según lo descripto en cualquiera de las realizaciones anteriores.

En otra realización de esta invención R^5 es un triazolil-tienil- sustituido donde dicho resto tienilo se sustituye con $-OCH_3$, y dicho resto triazolilo se sustituye según lo descripto en cualquiera de las realizaciones anteriores.

En otra realización de esta invención R^5 es un triazolil-tienil- sustituido donde dicho resto tienilo se sustituye con un $-OCH_3$, y dicho resto triazolilo se sustituye según lo descripto en cualquiera de las realizaciones anteriores.

En otra realización de esta invención R^5 es un grupo triazolil-tienil-sustituido donde dicho resto tienilo se sustituye con un $-OCH_3$, y dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo sustituido con hidroxilo.

En otra realización de esta invención R^5 es un triazolil-tienil- sustituido donde dicho resto tienilo se sustituye con un $-OCH_3$, y dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_2CH_2OH$.

En otra realización de esta invención R^5 es un triazolil-tienil- sustituido donde dicho resto tienilo se sustituye con un $-OCH_3$, y dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo -alquilen-O-alquilo.

En otra realización de esta invención R^5 es un triazolil-tienil- sustituido donde dicho resto tienilo se sustituye con un $-OCH_3$, y dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_2CH_2OCH_3$.

En otra realización de esta invención R^5 es un triazolil-tienil- sustituido donde dicho resto tienilo se sustituye con alcoxi, y dicho resto triazolilo no está sustituido.

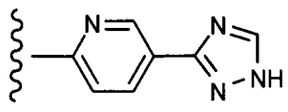
En otra realización de esta invención R^5 es un triazolil-tienil- sustituido donde dicho resto tienilo se sustituye con un alcoxi, y dicho resto triazolilo no está sustituido.

En otra realización de esta invención R^5 es un triazolil-tienil- sustituido donde dicho resto tienilo se sustituye con $-OCH_3$, y dicho resto triazolilo no está sustituido.

En otra realización de esta invención R^5 es un triazolil-tienil- sustituido donde dicho resto tienilo se sustituye con un $-OCH_3$, y dicho resto triazolilo no está sustituido.

En otra realización de esta invención R^5 es riazolil-piridil-.

En otra realización de esta invención R^5 es



En otra realización de esta invención R^5 es un triazolil-piridil- sustituido donde dicho triazolilo está sustituido y dicho piridilo no está sustituido.

En otra realización de esta invención R^5 es un triazolil-piridil- sustituido donde dicho triazolilo se sustituye sobre el nitrógeno y dicho piridilo no está sustituido.

En otra realización de esta invención R^5 es un triazolil-piridil- sustituido donde dicho triazolilo se sustituye sobre el carbono y dicho piridilo no está sustituido.

En otra realización de esta invención R^5 es un triazolil-piridil- sustituido donde dicho triazolilo se sustituye sobre el nitrógeno y sobre el carbono, y dicho piridilo no está sustituido.

En otra realización de esta invención R^5 es un triazolil-piridil- sustituido donde dicho triazolilo está sustituido y dicho piridilo está sustituido.

En otra realización de esta invención R^5 es un triazolil-piridil- sustituido donde dicho triazolilo se sustituye sobre el nitrógeno y dicho piridilo está sustituido.

En otra realización de esta invención R^5 es un triazolil-piridil- sustituido donde dicho triazolilo se sustituye sobre el carbono y dicho piridilo está sustituido.

En otra realización de esta invención R^5 es un triazolil-piridil- sustituido donde dicho triazolilo se sustituye sobre el nitrógeno y sobre el carbono y dicho piridilo está sustituido.

En otra realización de esta invención R^5 es un triazolil-piridil- sustituido donde dicho triazolilo no está sustituido y dicho piridilo está sustituido.

En otra realización de esta invención R^5 es un triazolil-piridil- sustituido donde el triazolilo se sustituye sobre el nitrógeno con alquilo.

Cuando el resto piridilo de R^5 se sustituye con alquilo, los ejemplos de los grupos alquilo incluyen, por ejemplo, alquilo-C_1-C_6, alquilo-C_1-C_4, alquilo-C_1-C_2, y -CH_3.

Cuando el resto piridilo de R^5 se sustituye con átomos de halo, los ejemplos de los átomos de halo incluyen, por ejemplo, Cl, F y Br, con la condición de que los átomos de carbono adyacentes al átomo de nitrógeno en dicho piridilo no estén sustituidos con halo. En una realización de esta invención el halo sobre el piridilo es F. En otra realización de esta invención el piridilo se sustituye con un F.

En otra realización de esta invención R^5 es un triazolil-piridil- sustituido donde el triazolilo se sustituye sobre el nitrógeno con $-CH_2COH(CH_3)_2$, y el piridilo no está sustituido.

En otra realización de esta invención R^5 es un triazolil-piridil- sustituido donde el triazolilo se sustituye sobre el nitrógeno con $-CH_2CH_2OH$, y el piridilo no está sustituido.

En otra realización de esta invención R^5 es un triazolil-piridil- sustituido donde dicho triazolilo se sustituye sobre el nitrógeno con un grupo alquilo, y el piridilo no está sustituido.

En otra realización de esta invención R^5 es un triazolil-piridil- sustituido donde dicho triazolilo se sustituye sobre el nitrógeno y sobre el carbono con un grupo alquilo, donde cada grupo alquilo se selecciona en forma independiente, y el piridilo no está sustituido.

En otra realización de esta invención R^5 es un triazolil-piridil- sustituido donde dicho triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_3$, y el piridilo no está sustituido.

En otra realización de esta invención R^5 es un triazolil-piridil- sustituido donde dicho triazolilo se sustituye sobre el nitrógeno y sobre el carbono con un grupo $-CH_3$, y el piridilo no está sustituido.

En otra realización de esta invención el resto R^5 es un triazolil-piridil-sustituido donde el triazolilo se sustituye sobre el carbono con un grupo $-NH_2$, y el piridilo no está sustituido.

En otra realización de esta invención R^5 es un triazolil-piridil- sustituido donde el triazolilo se sustituye sobre el nitrógeno con un grupo -alquilen-O-alquilo, y el piridilo no está sustituido, y con la condición de que el resto alquileno de dicho grupo -alquilen-O-alquilo no sea $-CH_2-$ (es decir, que el resto alquileno tenga una longitud de 2 o más carbonos).

En otra realización de esta invención R^5 es un triazolil-piridil- sustituido donde el triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_2CH_2OCH_3$, y el piridilo no está sustituido.

En otra realización de esta invención el resto R^5 es un triazolil-piridil-sustituido donde dicho resto piridilo se sustituye con halo, con la condición de que los átomos de carbono adyacentes al átomo de nitrógeno en dicho piridilo no estén sustituidos con halo, y dicho resto triazolilo se sustituye según lo descripto en cualquiera de las realizaciones anteriores que describen grupos triazolilo sustituidos.

En otra realización de esta invención R^5 es un triazolil-piridil- sustituido donde dicho resto piridilo se sustituye con un halo, con la condición de que un átomo de carbono adyacente al átomo de nitrógeno en dicho piridilo no esté sustituido con dicho halo, y dicho resto triazolilo se sustituye según lo descripto en cualquiera de las realizaciones anteriores, que describen grupos triazolilo.

En otra realización de esta invención R^5 es un triazolil-piridil- sustituido donde dicho resto piridilo se sustituye con F, con la condición de que un átomo de carbono adyacente al átomo de nitrógeno en dicho piridilo no esté sustituido con dicho F, y dicho resto triazolilo se sustituye según lo descripto en cualquiera de las realizaciones anteriores, que describen grupos triazolilo.

En otra realización de esta invención R^5 es un triazolil-piridil- sustituido donde dicho resto piridilo se sustituye con un F, con la condición de que un átomo de carbono adyacente al átomo de nitrógeno en dicho piridilo no esté sustituido con dicho F, y dicho resto triazolilo se sustituye según lo descripto en cualquiera de las realizaciones anteriores que describen grupos triazolilo.

En otra realización de esta invención R^5 es un grupo triazolil-piridil-sustituido donde dicho resto piridilo se sustituye con un F, con la condición de que un átomo de carbono adyacente al átomo de nitrógeno en dicho piridilo no

esté sustituido con dicho F, y dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo sustituido con hidroxilo.

En otra realización de esta invención R^5 es un triazolil-piridil- sustituido donde dicho resto piridilo se sustituye con un F, con la condición de que un átomo de carbono adyacente al átomo de nitrógeno en dicho piridilo no esté sustituido con dicho F, y dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_2CH_2OH$.

En otra realización de esta invención R^5 es un triazolil-piridil- sustituido donde dicho resto piridilo se sustituye con un F, con la condición de que un átomo de carbono adyacente al átomo de nitrógeno en dicho piridilo no esté sustituido con dicho F, y dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo -alquilen-O-alquilo, y el resto alquileno de dicho grupo -alquilen-O-alquilo no sea $-CH_2-$ (es decir, que el resto alquileno tenga una longitud de 2 o más carbonos).

En otra realización de esta invención R^5 es un triazolil-piridil- sustituido donde dicho resto piridilo se sustituye con un F, con la condición de que un átomo de carbono adyacente al átomo de nitrógeno en dicho piridilo no esté sustituido con dicho F, y dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_2CH_2OCH_3$.

En otra realización de esta invención R^5 es un triazolil-piridil- sustituido donde dicho resto piridilo se sustituye con halo, con la condición de que los átomos de carbono adyacentes al átomo de nitrógeno en dicho piridilo no estén sustituidos con halo, y dicho resto triazolilo no está sustituido.

En otra realización de esta invención R^5 es un triazolil-piridil- sustituido donde dicho resto piridilo se sustituye con un halo, con la condición de que un átomo de carbono adyacente al átomo de nitrógeno en dicho piridilo no esté sustituido con dicho halo, y dicho resto triazolilo no está sustituido.

En otra realización de esta invención R^5 es un triazolil-piridil- sustituido donde dicho resto piridilo se sustituye con F, con la condición de que un átomo de carbono adyacente al átomo de nitrógeno en dicho piridilo no esté sustituido con dicho F, y dicho resto triazolilo no está sustituido.

En otra realización de esta invención R^5 es un triazolil-piridil- sustituido donde dicho resto piridilo se sustituye con un F, con la condición de que un átomo de carbono adyacente al átomo de nitrógeno en dicho piridilo no esté sustituido con dicho F, y dicho resto triazolilo no está sustituido.

En otra realización de esta invención el resto R^5 es un triazolil-piridil-sustituido donde dicho resto piridilo se sustituye con alcoxi, y dicho resto triazolilo se sustituye según lo descripto en cualquiera de las realizaciones anteriores que describen grupos triazolilo sustituidos.

En otra realización de esta invención R^5 es un triazolil-piridil- sustituido donde dicho resto piridilo se sustituye con un alcoxi, y dicho resto triazolilo se sustituye según lo descripto en cualquiera de las realizaciones anteriores que describen grupos triazolilo sustituidos.

En otra realización de esta invención R^5 es un triazolil-piridil- sustituido donde dicho resto piridilo se sustituye con $-OCH_3$, y dicho resto triazolilo se sustituye según lo descripto en cualquiera de las realizaciones anteriores que describen grupos triazolilo sustituidos.

En otra realización de esta invención R^5 es un triazolil-piridil- sustituido donde dicho resto piridilo se sustituye con un $-OCH_3$, y dicho resto triazolilo se sustituye según lo descripto en cualquiera de las realizaciones anteriores que describen grupos triazolilo sustituidos.

En otra realización de esta invención R^5 es un grupo triazolil-piridil-sustituido donde dicho resto piridilo se sustituye con un $-OCH_3$, y dicho resto

triazolilo se sustituye sobre el nitrógeno con un grupo alquilo sustituido con hidroxilo.

En otra realización de esta invención R^5 es un triazolil-piridil- sustituido donde dicho resto piridilo se sustituye con un $-OCH_3$, y dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_2CH_2OH$.

En otra realización de esta invención R^5 es un triazolil-piridil- sustituido donde dicho resto piridilo se sustituye con un $-OCH_3$, y dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo -alquilen-O-alquilo, y el resto alquileno de dicho grupo -alquilen-O-alquilo no sea $-CH_2-$ (es decir, que el resto alquileno tenga una longitud de 2 o más carbonos).

En otra realización de esta invención R^5 es un triazolil-piridil- sustituido donde dicho resto piridilo se sustituye con un $-OCH_3$, y dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_2CH_2OCH_3$.

En otra realización de esta invención R^5 es un triazolil-piridil- sustituido donde dicho resto piridilo se sustituye con alcoxi, y dicho resto triazolilo no está sustituido.

En otra realización de esta invención R^5 es un triazolil-piridil- sustituido donde dicho resto piridilo se sustituye con un alcoxi, y dicho resto triazolilo no está sustituido.

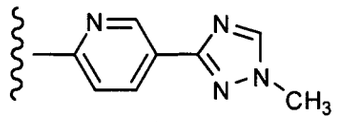
En otra realización de esta invención R^5 es un triazolil-piridil- sustituido donde dicho resto piridilo se sustituye con $-OCH_3$, y dicho resto triazolilo no está sustituido.

En otra realización de esta invención R^5 es un triazolil-piridil- sustituido donde dicho resto piridilo se sustituye con un $-OCH_3$, y dicho resto triazolilo no está sustituido.

En otra realización de esta invención R^5 es un triazolil-piridil- sustituido donde dicho triazolilo se sustituye con 1 o 2 grupos seleccionados en forma

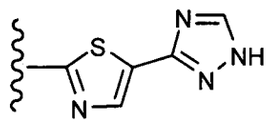
independiente del grupo que consiste en: (a) grupo alquilo sustituido con hidroxilo (por ej., $-CH_2COH(CH_3)_2$, y $-CH_2CH_2OH$), (b) alquilo (por ej., alquilo-C_1-C_6, alquilo-C_1-C_4, alquilo-C_1-C_2, y $-CH_3$), (c) $-NH_2$, y (d) -alquilen-O-alquilo (por ej., $-CH_2CH_2OCH_3$), con la condición de que resto alquileno de dicho grupo -alquilen-O-alquilo no sea $-CH_2-$ (es decir, que el resto alquileno tenga una longitud de 2 o más carbonos) cuando dicho grupo -alquilen-O-alquilo se una al nitrógeno de dicho triazolilo; y dicho piridilo se sustituye con 1 a 3 grupos seleccionados en forma independiente del grupo que consiste en: (a) alquilo (por ej., alquilo-C_1-C_6, alquilo-C_1-C_4, alquilo-C_1-C_2, y $-CH_3$), (b) halo (por ej., Cl, F y Br) y con la condición de que los átomos de carbono adyacentes al átomo de nitrógeno en dicho piridilo no estén sustituidos con halo, y (c) alcoxi (por ej., $-OCH_3$).

En otra realización de esta invención R^5 es



En otra realización de esta invención R^5 es triazolil-tiazolil-.

En otra realización de esta invención R^5 es



En otra realización de esta invención R^5 es un triazolil-piridil- sustituido donde dicho triazolilo se sustituye y dicho tiazolilo no está sustituido.

En otra realización de esta invención R^5 es un triazolil-piridil- sustituido donde dicho triazolilo se sustituye sobre el nitrógeno y dicho tiazolilo no está sustituido.

En otra realización de esta invención R^5 es un triazolil-piridil- sustituido donde dicho triazolilo se sustituye sobre el carbono y dicho tiazolilo no está sustituido.

En otra realización de esta invención R^5 es un triazolil-tiazolil- sustituido donde dicho triazolilo se sustituye sobre el nitrógeno y sobre el carbono, y dicho tiazolilo no está sustituido.

Cuando el resto tiazolilo de R^5 se sustituye con alquilo, los ejemplos de los grupos alquilo incluyen, por ejemplo, alquilo-C_1-C_6, alquilo-C_1-C_4, alquilo-C_1-C_2, y -CH_3.

Cuando el resto tiazolilo de R^5 se sustituye con átomos de halo, los ejemplos de los átomos de halo incluyen, por ejemplo, Cl, F y Br. En una realización de esta invención el halo sobre el tiazolilo es F. En otra realización de esta invención el tiazolilo se sustituye con un F.

Cuando el resto tiazolilo de R^5 se sustituye con un grupo alquilamino, los ejemplos del grupo alquilamino incluyen, por ejemplo, alquil C_1-C_6-NH-, alquil C_1-C_2-NH-, CH_3-NH-, y CH_3CH_2-NH-.

Cuando el resto tiazolilo de R^5 se sustituye con un grupo dialquilamino, los ejemplos del grupo dialquilamino incluyen, por ejemplo, (alquil C_1-C_6)$_2$-N- donde cada alquilo se selecciona en forma independiente, (alquil C_1-C_2)$_2$-N- donde cada alquilo se selecciona en forma independiente, $(CH_3)_2N$-, $(CH_3CH_2)_2$-N-, y $(CH_3)(CH_3CH_2)$N-.

En otra realización de esta invención R^5 es un triazolil-tiazolil- sustituido donde dicho triazolilo se sustituye y dicho tiazolilo está sustituido.

En otra realización de esta invención R^5 es un triazolil-tiazolil- sustituido donde dicho triazolilo se sustituye sobre el nitrógeno y dicho tiazolilo está sustituido.

En otra realización de esta invención R^5 es un triazolil-tiazolil- sustituido donde dicho triazolilo se sustituye sobre el carbono y dicho tiazolilo está sustituido.

En otra realización de esta invención R^5 es un triazolil-tiazolil- sustituido donde dicho triazolilo se sustituye sobre el nitrógeno y sobre el carbono, y dicho tiazolilo está sustituido.

En otra realización de esta invención R^5 es un triazolil-tiazolil- sustituido donde dicho triazolilo no está sustituido y dicho tiazolilo está sustituido.

En otra realización de esta invención R^5 es un triazolil-tiazolil- sustituido donde dicho triazolilo se sustituye sobre el nitrógeno con alquilo, y dicho tiazolilo no está sustituido.

En otra realización de esta invención R^5 es un triazolil-tiazolil- sustituido donde el triazolilo se sustituye sobre el nitrógeno con $-CH_2COH(CH_3)_2$, y dicho tiazolilo no está sustituido.

En otra realización de esta invención R^5 es un triazolil-tiazolil- sustituido donde el triazolilo se sustituye sobre el nitrógeno con $-CH_2CH_2OH$, y dicho tiazolilo no está sustituido.

En otra realización de esta invención R^5 es un triazolil-tiazolil- sustituido donde dicho triazolilo se sustituye sobre el nitrógeno y sobre el carbono con un grupo alquilo, donde dicho grupo alquilo se selecciona en forma independiente, y dicho tiazolilo no está sustituido.

En otra realización de esta invención R^5 es un triazolil-tiazolil- sustituido donde dicho triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_3$, y dicho tiazolilo no está sustituido.

En otra realización de esta invención R^5 es un triazolil-tiazolil- sustituido donde dicho triazolilo se sustituye sobre el nitrógeno y sobre el carbono con un grupo $-CH_3$, y dicho tiazolilo no está sustituido.

En otra realización de esta invención el resto R^5 es un triazolil-tiazolil-sustituido donde el triazolilo se sustituye sobre el carbono con un grupo $-NH_2$, y dicho tiazolilo no está sustituido.

En otra realización de esta invención R^5 es un triazolil-tiazolil- sustituido donde el triazolilo se sustituye sobre el nitrógeno con un grupo -alquilen-O-alquilo, con la condición de que resto alquileno de dicho grupo -alquilen-O-alquilo no sea $-CH_2-$ (es decir, que el resto alquileno tenga una longitud de 2 o más carbonos), y dicho tiazolilo no está sustituido.

En otra realización de esta invención R^5 es un triazolil-tiazolil- sustituido donde el triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_2CH_2OCH_3$, y dicho tiazolilo no está sustituido.

En otra realización de esta invención el resto R^5 es un triazolil-tiazolil-sustituido donde dicho resto tiazolilo se sustituye con halo, y dicho resto triazolilo se sustituye según lo descripto en cualquiera de las realizaciones anteriores que describen grupos triazolilo sustituidos.

En otra realización de esta invención R^5 es un triazolil-tiazolil- sustituido donde dicho resto tiazolilo se sustituye con F, y dicho resto triazolilo se sustituye según lo descripto en cualquiera de las realizaciones anteriores que describen grupos triazolilo sustituidos.

En otra realización de esta invención R^5 es un grupo triazolil-tiazolil-sustituido donde dicho resto tiazolilo se sustituye con un F, y dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo sustituido con hidroxilo.

En otra realización de esta invención R^5 es un triazolil-tiazolil- sustituido donde dicho resto tiazolilo se sustituye con un F, y dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_2CH_2OH$.

En otra realización de esta invención R^5 es un triazolil-tiazolil- sustituido donde dicho resto tiazolilo se sustituye con un F, y dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo -alquilen-O-alquilo.

En otra realización de esta invención R^5 es un triazolil-tiazolil- sustituido donde dicho resto tiazolilo se sustituye con un F, y dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_2CH_2OCH_3$.

En otra realización de esta invención R^5 es un triazolil-tiazolil- sustituido donde dicho resto tiazolilo se sustituye con halo, y dicho resto triazolilo no está sustituido.

En otra realización de esta invención R^5 es un triazolil-tiazolil- sustituido donde dicho resto tiazolilo se sustituye con F, y dicho resto triazolilo no está sustituido.

En otra realización de esta invención el resto R^5 es un triazolil-tiazolil-sustituido donde dicho resto tiazolilo se sustituye con alcoxi, y dicho resto triazolilo se sustituye según lo descripto en cualquiera de las realizaciones anteriores que describen grupos triazolilo sustituidos.

En otra realización de esta invención R^5 es un triazolil-tiazolil- sustituido donde dicho resto tiazolilo se sustituye con $-OCH_3$, y dicho resto triazolilo se sustituye según lo descripto en cualquiera de las realizaciones anteriores que describen grupos triazolilo sustituidos.

En otra realización de esta invención R^5 es un grupo triazolil-tiazolil-sustituido donde dicho resto tiazolilo se sustituye con un $-OCH_3$, y dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo sustituido con hidroxilo.

En otra realización de esta invención R^5 es un triazolil-tiazolil- sustituido donde dicho resto tiazolilo se sustituye con un $-OCH_3$, y dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_2CH_2OH$.

En otra realización de esta invención R^5 es un triazolil-tiazolil- sustituido donde dicho resto tiazolilo se sustituye con un $-OCH_3$, y dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo -alquilen-O-alquilo, y el resto alquileno de dicho grupo -alquilen-O-alquilo no sea $-CH_2-$ (es decir, que el resto alquileno tenga una longitud de 2 o más carbonos).

En otra realización de esta invención R^5 es un triazolil-tiazolil- sustituido donde dicho resto tiazolilo se sustituye con un $-OCH_3$, y dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_2CH_2OCH_3$.

En otra realización de esta invención R^5 es un triazolil-tiazolil- sustituido donde dicho resto tiazolilo se sustituye con alcoxi, y dicho resto triazolilo no está sustituido.

En otra realización de esta invención R^5 es un triazolil-tiazolil- sustituido donde dicho resto tiazolilo se sustituye con $-OCH_3$, y dicho resto triazolilo no está sustituido.

En otra realización de esta invención R^5 es un triazolil-tiazolil- sustituido donde dicho resto tiazolilo se sustituye con un alquilamino, y dicho resto triazolilo se sustituye según lo descripto en cualquiera de las realizaciones anteriores que describen grupos triazolilo.

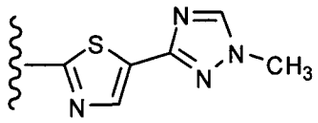
En otra realización de esta invención R^5 es un triazolil-tiazolil- sustituido donde dicho resto tiazolilo se sustituye con un dialquilamino, y dicho resto triazolilo se sustituye según lo descripto en cualquiera de las realizaciones anteriores que describen grupos triazolilo sustituidos.

En otra realización de esta invención R^5 es un triazolil-tiazolil- sustituido donde dicho resto tiazolilo se sustituye con un alquilamino, y dicho resto triazolilo no está sustituido.

En otra realización de esta invención R^5 es un triazolil-tiazolil- sustituido donde dicho resto tiazolilo se sustituye con un dialquilamino, y dicho resto triazolilo no está sustituido.

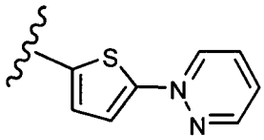
En otra realización de esta invención R^5 es un triazolil-tiazolil- sustituido donde dicho triazolilo se sustituye con 1 o 2 grupos seleccionados en forma independiente del grupo que consiste en: (a) grupo alquilo sustituido con hidroxilo (por ej., $-CH_2COH(CH_3)_2$, y $-CH_2CH_2OH$), (b) alquilo (por ej., alquilo-C_1-C_6, alquilo-C_1-C_4, alquilo-C_1-C_2, y $-CH_3$), $-NH_2$, y (c) -alquilen-O-alquilo (por ej., $-CH_2CH_2OCH_3$), con la condición de que el resto alquileno de dicho grupo -alquilen-O-alquilo no sea $-CH_2-$ (es decir, que el resto alquileno tenga una longitud de 2 o más carbonos) cuando dicho grupo -alquilen-O-alquilo se una al nitrógeno de dicho triazolilo; y dicho tiazolilo se sustituye con 1 grupo seleccionado del grupo que consiste en: (a) alquilo (por ej., -alquilo C_1-C_6, o alquilo-C_1-C_4, o alquilo-C_1-C_2, o $-CH_3$), (b) halo (por ej., Cl, F, o Br), (c) alquilamino (por ej., alquil C_1-C_6-NH-, o alquil C_1-C_2-NH-, o CH_3-NH-, o CH_3CH_2-NH-), y (d) dialquilamino (por ej., (alquil C_1-C_6)$_2$-N- donde cada alquilo se selecciona en forma independiente, o (alquil C_1-C_2)$_2$-N- donde cada alquilo se selecciona en forma independiente, o $(CH_3)_2N$-, o $(CH_3CH_2)_2$-N-, o $(CH_3)(CH_3CH_2)N$-).

En otra realización de esta invención R^5 es



En otra realización de esta invención R^5 es piridazinil-tienil-.

En otra realización de esta invención R^5 es



Cuando el resto piridazinilo de R^5 se sustituye con alquilo, los ejemplos de los grupos alquilo incluyen, por ejemplo, alquilo-C_1-C_6, alquilo-C_1-C_4, alquilo-C_1-C_2, y -CH_3.

Cuando el resto piridazinilo de R^5 se sustituye con átomos de halo, los ejemplos de los átomos de halo incluyen, por ejemplo, Cl, F y Br. En una realización de esta invención el halo sobre el piridazinilo es F. En otra realización de esta invención el piridazinilo se sustituye con un F. Cuando el resto piridazinilo se sustituye con halos, los carbonos adyacentes a los nitrógeno no se sustituyen con halos.

Cuando el resto piridazinilo de R^5 se sustituye con un grupo alquilamino, los ejemplos del grupo alquilamino incluyen, por ejemplo, alquil C_1-C_6-NH-, alquil C_1-C_2-NH-, CH_3-NH-, y CH_3CH_2-NH-.

Cuando el resto piridazinilo de R^5 se sustituye con un grupo dialquilamino, los ejemplos del grupo dialquilamino incluyen, por ejemplo, (alquil C_1-C_6)$_2$-N- donde cada alquilo se selecciona en forma independiente, (alquil C_1-C_2)$_2$-N- donde cada alquilo se selecciona en forma independiente, $(CH_3)_2N$-, $(CH_3CH_2)_2$-N-, y $(CH_3)(CH_3CH_2)$N-.

En otra realización de esta invención R^5 es un piridazinil-tienil- sustituido donde dicho piridazinilo se sustituye y dicho tienilo no está sustituido.

En otra realización de esta invención R^5 es un piridazinil-tienil- sustituido donde dicho piridazinilo se sustituye con un grupo =O, y dicho tienilo no está sustituido.

En otra realización de esta invención R^5 es un piridazinil-tienil- sustituido donde dicho piridazinilo se sustituye con un grupo alquilo, y dicho tienilo no está sustituido.

En otra realización de esta invención R^5 es un piridazinil-tienil- sustituido donde dicho piridazinilo se sustituye con un grupo metilo, y dicho tienilo no está sustituido.

En otra realización de esta invención R^5 es un piridazinil-tienil- sustituido donde dicho piridazinilo se sustituye con un grupo =O, y con un grupo alquilo, y dicho tienilo no está sustituido.

En otra realización de esta invención R^5 es un piridazinil-tienil- sustituido donde dicho piridazinilo se sustituye con un grupo =O, y con un grupo metilo, y dicho tienilo no está sustituido.

En otra realización de esta invención R^5 es un piridazinil-tienil- sustituido donde dicho piridazinilo se sustituye con un grupo amino, y dicho tienilo no está sustituido.

En otra realización de esta invención R^5 es un piridazinil-tienil- sustituido donde dicho piridazinilo se sustituye con un grupo alquilamino, y dicho tienilo no está sustituido.

En otra realización de esta invención R^5 es un piridazinil-tienil- sustituido donde dicho piridazinilo se sustituye con un grupo dialquilamino, y dicho tienilo no está sustituido.

En otra realización de esta invención R^5 es un piridazinil-tienil- sustituido donde dicho piridazinilo se sustituye y dicho tienilo está sustituido.

En otra realización de esta invención R^5 es un piridazinil-tienil- sustituido donde dicho piridazinilo no está sustituido y dicho tienilo está sustituido.

En otra realización de esta invención R^5 es un piridazinil-tienil- sustituido donde dicho piridazinilo no está sustituido y dicho tienilo está sustituido con 1 a 2 halos seleccionados en forma independiente.

En otra realización de esta invención R^5 es un piridazinil-tienil- sustituido donde dicho piridazinilo no está sustituido y dicho tienilo está sustituido con 1 a

2 halos seleccionados en forma independiente del grupo que consiste en: Br, Cl y F.

En otra realización de esta invención R^5 es un piridazinil-tienil- sustituido donde dicho piridazinilo no está sustituido y dicho tienilo está sustituido con 1 a 2 grupos alcoxi seleccionados en forma independiente.

En otra realización de esta invención R^5 es un piridazinil-tienil- sustituido donde dicho piridazinilo no está sustituido y dicho tienilo está sustituido con 1 a 2 grupos $-OCH_3$.

En otra realización de esta invención R^5 es un piridazinil-tienil- sustituido donde dicho piridazinilo se sustituye según lo descripto en cualquiera de las realizaciones anteriores que describen grupos piridazinilo, y dicho tienilo está sustituido.

En otra realización de esta invención R^5 es un piridazinil-tienil- sustituido donde dicho piridazinilo se sustituye según lo descripto en cualquiera de las realizaciones anteriores que describen grupos piridazinilo, y dicho tienilo se sustituye con 1 a 2 halos seleccionados en forma independiente.

En otra realización de esta invención R^5 es un piridazinil-tienil- sustituido donde dicho piridazinilo se sustituye según lo descripto en cualquiera de las realizaciones anteriores que describen grupos piridazinilo, y dicho tienilo se sustituye con 1 a 2 halos seleccionados en forma independiente del grupo que consiste en: Br, Cl y F.

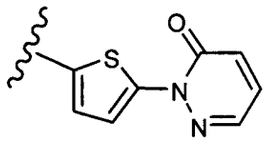
En otra realización de esta invención R^5 es un piridazinil-tienil- sustituido donde dicho piridazinilo se sustituye según lo descripto en cualquiera de las realizaciones anteriores que describen grupos piridazinilo, y dicho tienilo se sustituye con 1 a 2 grupos alcoxi seleccionados en forma independiente.

En otra realización de esta invención R^5 es un piridazinil-tienil- sustituido donde dicho piridazinilo se sustituye según lo descripto en cualquiera de las

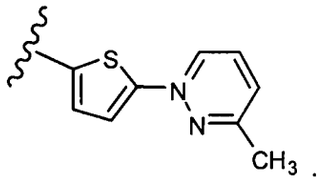
realizaciones anteriores que describen grupos piridazinilo, y dicho tienilo se sustituye con 1 a 2 grupos $-OCH_3$.

En otra realización de esta invención R^5 es un piridazinil-tienil- sustituido donde dicho piridazinilo se sustituye con 1 o 2 grupos seleccionados en forma independiente del grupo que consiste en alquilo (por ej., metilo) y =O, y dicho tienilo se sustituye con 1 a 2 grupos seleccionados en forma independiente del grupo que consiste en: alcoxi (por ej., $-OCH_3$), halo (por ej., Br, Cl y F).

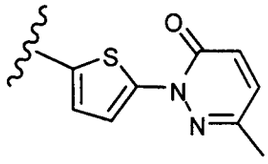
En otra realización de esta invención R^5 es



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 un grupo triazolil-fenil-sustituido donde (a) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un sustituyente seleccionado del grupo que consiste en: $-CH_2COH(CH_3)_2$ y $-CH_2CH_2OH$, (b) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo alquilo, (c) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo alquilo, y sobre el carbono con un grupo alquilo, (d) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo $-CH_3$, (e) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo $-CH_3$, y sobre el

carbono con un grupo $-CH_3$, (f) dicho resto triazolilo se sustituye en forma opcional sobre el carbono con un grupo -NH2, o (g) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo $-CH_2CH_2OCH_3$; y donde dicho resto fenilo se sustituye en forma opcional con halo.

En otra realización de esta invención R^5 es un grupo triazolil-fenil-sustituido donde (a) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un sustituyente seleccionado del grupo que consiste en: $-CH_2COH(CH_3)_2$ y $-CH_2CH_2OH$, (b) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo alquilo, (c) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo alquilo, y sobre el carbono con un grupo alquilo, (d) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo $-CH_3$, (e) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo $-CH_3$, y sobre el carbono con un grupo $-CH_3$, (f) dicho resto triazolilo se sustituye en forma opcional sobre el carbono con un grupo $-NH_2$, o (g) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo $-CH_2CH_2OCH_3$; y donde dicho resto fenilo se sustituye con halo.

En otra realización de esta invención R^5 es un triazolil-fenil- sustituido donde (a) dicho resto triazolilo se sustituye sobre el nitrógeno con un sustituyente seleccionado del grupo que consiste en: $-CH_2COH(CH_3)_2$ y $-CH_2CH_2OH$, (b) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo, (c) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo, y sobre el carbono con un grupo alquilo, (d) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_3$, (e) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_3$, y sobre el carbono con un grupo $-CH_3$, (f) dicho resto triazolilo se sustituye sobre el carbono con un grupo $-NH_2$, o (g) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo –

$CH_2CH_2OCH_3$; y donde dicho resto fenilo se sustituye en forma opcional con halo.

En otra realización de esta invención R^5 es un grupo triazolil-fenil-sustituido donde (a) dicho resto triazolilo se sustituye sobre el nitrógeno con un sustituyente seleccionado del grupo que consiste en: $-CH_2COH(CH_3)_2$ y $-CH_2CH_2OH$, (b) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo, (c) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo, y sobre el carbono con un grupo alquilo, (d) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_3$, (e) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_3$, y sobre el carbono con un grupo $-CH_3$, (f) dicho resto triazolilo se sustituye sobre el carbono con un grupo $-NH_2$, o (g) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_2CH_2OCH_3$; y donde dicho resto fenilo se sustituye con halo.

En otra realización de esta invención R^5 es un grupo triazolil-fenil-sustituido donde (a) dicho resto triazolilo se sustituye sobre el nitrógeno con un sustituyente seleccionado del grupo que consiste en: $-CH_2COH(CH_3)_2$ y $-CH_2CH_2OH$, (b) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo, (c) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo, y sobre el carbono con un grupo alquilo, (d) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_3$, (e) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_3$, y sobre el carbono con un grupo $-CH_3$, (f) dicho resto triazolilo se sustituye sobre el carbono con un grupo $-NH_2$, o (g) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_2CH_2OCH_3$; y donde dicho resto fenilo no está sustituido.

En otra realización de esta invención R^5 es un grupo triazolil-fenil-sustituido donde (a) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un sustituyente seleccionado del grupo que consiste en: –

$CH_2COH(CH_3)_2$ y $-CH_2CH_2OH$, (b) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo alquilo, (c) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo alquilo, y sobre el carbono con un grupo alquilo, (d) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo $-CH_3$, (e) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo $-CH_3$, y sobre el carbono con un grupo $-CH_3$, (f) dicho resto triazolilo se sustituye en forma opcional sobre el carbono con un grupo $-NH_2$, o (g) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo $-CH_2CH_2OCH_3$; y donde dicho resto fenilo se sustituye en forma opcional con alcoxi.

En otra realización de esta invención R^5 es un grupo triazolil-fenil-sustituido donde (a) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un sustituyente seleccionado del grupo que consiste en: $-CH_2COH(CH_3)_2$ y $-CH_2CH_2OH$, (b) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo alquilo, (c) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo alquilo, y sobre el carbono con un grupo alquilo, (d) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo $-CH_3$, (e) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo $-CH_3$, y sobre el carbono con un grupo $-CH_3$, (f) dicho resto triazolilo se sustituye en forma opcional sobre el carbono con un grupo $-NH_2$, o (g) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo $-CH_2CH_2OCH_3$; y donde dicho resto fenilo se sustituye con alcoxi.

En otra realización de esta invención R^5 es un grupo triazolil-fenil-sustituido donde (a) dicho resto triazolilo se sustituye sobre el nitrógeno con un sustituyente seleccionado del grupo que consiste en: $-CH_2COH(CH_3)_2$ y $-CH_2CH_2OH$, (b) dicho resto triazolilo se sustituye sobre el nitrógeno con un

grupo alquilo, (c) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo, y sobre el carbono con un grupo alquilo, (d) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_3$, (e) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_3$, y sobre el carbono con un grupo $-CH_3$, (f) dicho resto triazolilo se sustituye sobre el carbono con un grupo $-NH_2$, o (g) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_2CH_2OCH_3$; y donde dicho resto fenilo se sustituye en forma opcional con alcoxi.

En otra realización de esta invención R^5 es un grupo triazolil-fenil-sustituido donde (a) dicho resto triazolilo se sustituye sobre el nitrógeno con un sustituyente seleccionado del grupo que consiste en: $-CH_2COH(CH_3)_2$ y $-CH_2CH_2OH$, (b) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo, (c) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo, y sobre el carbono con un grupo alquilo, (d) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_3$, (e) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_3$, y sobre el carbono con un grupo $-CH_3$, (f) dicho resto triazolilo se sustituye sobre el carbono con un grupo $-NH_2$, o (g) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_2CH_2OCH_3$; y donde dicho resto fenilo se sustituye con alcoxi.

En otra realización de esta invención R^5 es un grupo triazolil-tienil-sustituido donde (a) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un sustituyente seleccionado del grupo que consiste en: $-CH_2COH(CH_3)_2$ y $-CH_2CH_2OH$, (b) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo alquilo, (c) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo alquilo, y sobre el carbono con un grupo alquilo, (d) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo $-CH_3$, (e) dicho resto triazolilo se

sustituye en forma opcional sobre el nitrógeno con un grupo $-CH_3$, y sobre el carbono con un grupo $-CH_3$, (f) dicho resto triazolilo se sustituye en forma opcional sobre el carbono con un grupo $-NH_2$, o (g) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo $-CH_2CH_2OCH_3$; y donde dicho resto tienilo se sustituye en forma opcional con halo.

En otra realización de esta invención R^5 es un grupo triazolil-tienil-sustituido donde (a) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un sustituyente seleccionado del grupo que consiste en: $-CH_2COH(CH_3)_2$ y $-CH_2CH_2OH$, (b) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo alquilo, (c) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo alquilo, y sobre el carbono con un grupo alquilo, (d) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo $-CH_3$, (e) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo $-CH_3$, y sobre el carbono con un grupo $-CH_3$, (f) dicho resto triazolilo se sustituye en forma opcional sobre el carbono con un grupo $-NH_2$, o (g) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo $-CH_2CH_2OCH_3$; y donde dicho resto tienilo se sustituye con halo.

En otra realización de esta invención R^5 es un grupo triazolil-tienil-sustituido donde (a) dicho resto triazolilo se sustituye sobre el nitrógeno con un sustituyente seleccionado del grupo que consiste en: $-CH_2COH(CH_3)_2$ y $-CH_2CH_2OH$, (b) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo, (c) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo, y sobre el carbono con un grupo alquilo, (d) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_3$, (e) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_3$, y sobre el carbono con un grupo $-CH_3$, (f) dicho resto triazolilo se sustituye sobre el carbono con un grupo

$-NH_2$, o (g) dicho resto triazolilo se sustituye sobre el nitrógeno con un gruop $-CH_2CH_2OCH_3$; y donde dicho resto tienilo se sustituye en forma opcional con halo.

En otra realización de esta invención R^5 es un grupo triazolil-tienil-sustituido donde (a) dicho resto triazolilo se sustituye sobre el nitrógeno con un sustituyente seleccionado del grupo que consiste en: $-CH_2COH(CH_3)_2$ y $-CH_2CH_2OH$, (b) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo, (c) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo, y sobre el carbono con un grupo alquilo, (d) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_3$, (e) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_3$, y sobre el carbono con un grupo $-CH_3$, (f) dicho resto triazolilo se sustituye sobre el carbono con un grupo $-NH_2$, o (g) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_2CH_2OCH_3$; y donde dicho resto tienilo se sustituye con halo.

En otra realización de esta invención R^5 es un grupo triazolil-tienil-sustituido donde (a) dicho resto triazolilo se sustituye sobre el nitrógeno con un sustituyente seleccionado del grupo que consiste en: $-CH_2COH(CH_3)_2$ y $-CH_2CH_2OH$, (b) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo, (c) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo, y sobre el carbono con un grupo alquilo, (d) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_3$, (e) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo –CH3, y sobre el carbono con un grupo $-CH_3$, (f) dicho resto triazolilo se sustituye sobre el carbono con un grupo $-NH_2$, o (g) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_2CH_2OCH_3$; y donde dicho resto tienilo no está sustituido.

En otra realización de esta invención R^5 es un grupo triazolil-tienil-sustituido donde (a) dicho resto triazolilo se sustituye en forma opcional sobre

el nitrógeno con un sustituyente seleccionado del grupo que consiste en: –$CH_2COH(CH_3)_2$, y -CH_2CH_2OH, (b) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo alquilo, (c) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo alquilo, y sobre el carbono con un grupo alquilo, (d) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo –CH_3, (e) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo -CH_3, y sobre el carbono con un grupo –CH_3, (f) dicho resto triazolilo se sustituye en forma opcional sobre el carbono con un grupo -NH_2, o (g) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo –$CH_2CH_2OCH_3$; y donde dicho resto tienilo se sustituye en forma opcional con alcoxi.

En otra realización de esta invención R^5 es un grupo triazolil-tienil-sustituido donde (a) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un sustituyente seleccionado del grupo que consiste en: –$CH_2COH(CH_3)_2$ y -CH_2CH_2OH, (b) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo alquilo, (c) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo alquilo, y sobre el carbono con un grupo alquilo, (d) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo –CH_3, (e) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo -CH_3, y sobre el carbono con un grupo –CH_3, (f) dicho resto triazolilo se sustituye en forma opcional sobre el carbono con un grupo -NH_2, o (g) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo –$CH_2CH_2OCH_3$; y donde dicho resto tienilo se sustituye con alcoxi.

En otra realización de esta invención R^5 es un grupo triazolil-tienil-sustituido donde (a) dicho resto triazolilo se sustituye sobre el nitrógeno con un sustituyente seleccionado del grupo que consiste en: –$CH_2COH(CH_3)_2$ y -

CH_2CH_2OH, (b) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo, (c) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo, y sobre el carbono con un grupo alquilo, (d) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_3$, (e) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_3$, y sobre el carbono con un grupo $-CH_3$, (f) dicho resto triazolilo se sustituye sobre el carbono con un grupo $-NH_2$, o (g) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_2CH_2OCH_3$; y donde dicho resto tienilo se sustituye en forma opcional con alcoxi.

En otra realización de esta invención R^5 es un grupo triazolil-tienil-sustituido donde (a) dicho resto triazolilo se sustituye sobre el nitrógeno con un sustituyente seleccionado del grupo que consiste en: $-CH_2COH(CH_3)_2$, y $-CH_2CH_2OH$, (b) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo, (c) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo, y sobre el carbono con un grupo alquilo, (d) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_3$, (e) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_3$, y sobre el carbono con un grupo $-CH_3$, (f) dicho resto triazolilo se sustituye sobre el carbono con un grupo $-NH_2$, o (g) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_2CH_2OCH_3$; y donde dicho resto tienilo se sustituye con alcoxi.

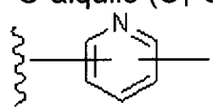
Se describen a continuación otras realizaciones de la invención. Se han numerado las realizaciones para facilitar la referencia.

La realización Nº 1 se dirige a compuestos de fórmula 1.0 donde R^2 es un

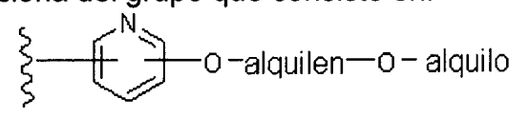
grupo –O-alquilo (C_1-C_2), y R^1 es piridilo sustituido.

La realización Nº 2 se dirige a compuestos de fórmula 1.0 donde R^2 es un grupo –O-alquilo (C_1-C_2), y R^1 es piridilo sustituido con un sustituyente.

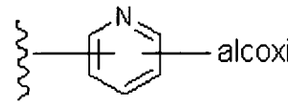
La realización Nº 3 se dirige a compuestos de fórmula 1.0 donde R^2 es un grupo –O-alquilo (C_1-C_2), y R^1 se selecciona del grupo que consiste en:



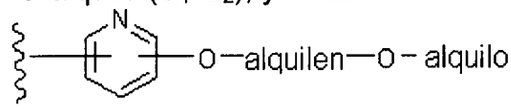
y



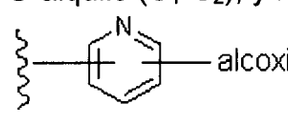
La realización Nº 4 se dirige a compuestos de fórmula 1.0 donde R^2 es un grupo –O-alquilo (C_1-C_2), y R^1 es:



La realización Nº 5 se dirige a compuestos de fórmula 1.0 donde R^2 es un grupo –O-alquilo (C_1-C_2), y R^1 es:

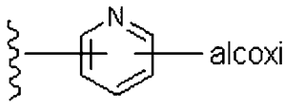


La realización Nº 6 se dirige a compuestos de fórmula 1.0 donde R^2 es un grupo –O-alquilo (C_1-C_2), y R^1 es:



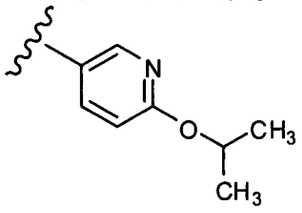
donde dicho grupo alcoxi es $–OCH(CH_3)_2$.

La realización Nº 7 se dirige a compuestos de fórmula 1.0 donde, R^2 es un grupo –O-alquilo (C_1-C_2), y R^1 es:



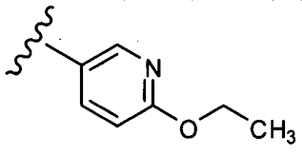
donde dicho grupo alcoxi es $-OC_2H_5$.

La realización Nº 8 se dirige a compuestos de fórmula 1.0 donde R^2 es un grupo –O-alquilo (C_1-C_2), y R^1 es:



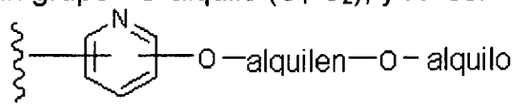
.

La realización Nº 9 se dirige a compuestos de fórmula 1.0 donde R^2 es un grupo –O-alquilo (C_1-C_2), y R^1 es:



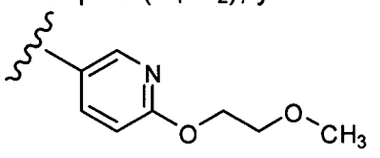
.

La realización Nº 10 se dirige a compuestos de fórmula 1.0 donde z es 1, R^2 es un grupo –O-alquilo (C_1-C_2), y R^1 es:



donde dicho grupo –O-alquilen-O-alquilo es $-OCH_2CH_2OCH_3$.

La realización Nº 11 se dirige a compuestos de fórmula 1.0 donde R^2 es un grupo –O-alquilo (C_1-C_2), y R^1 es:

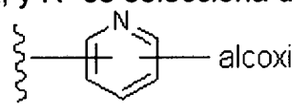


.

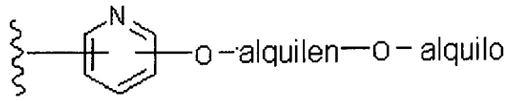
La realización Nº 12 se dirige a compuestos de fórmula 1.0 donde R^2 es $-OCH_3$, y R^1 es piridilo sustituido.

La realización Nº 13 se dirige a compuestos de fórmula 1.0 donde R^2 es $-OCH_3$, y R^1 es piridilo sustituido con un sustituyente.

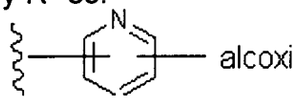
La realización Nº 14 se dirige a compuestos de fórmula 1.0 donde R^2 es $-OCH_3$, y R^1 se selecciona del grupo que consiste en:



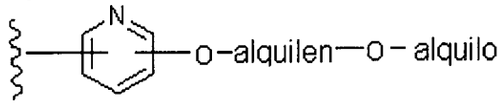
y



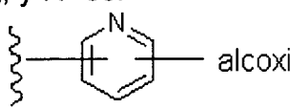
La realización Nº 15 se dirige a compuestos de fórmula 1.0 donde R^2 es $-OCH_3$, y R^1 es:



La realización Nº 16 se dirige a compuestos de fórmula 1.0 donde R^2 es $-OCH_3$, y R^1 es:

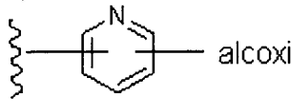


La realización Nº 17 se dirige a compuestos de fórmula 1.0 donde R^2 es $-OCH_3$, y R^1 es:



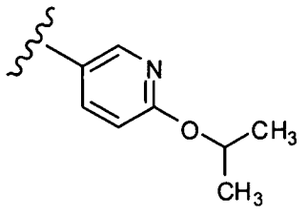
donde dicho grupo alcoxi es $-OCH(CH_3)_2$.

La realización Nº 18 se dirige a compuestos de fórmula 1.0 donde R^2 es $-OCH_3$, y R^1 es:

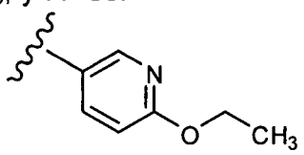


donde dicho grupo alcoxi es $-OC_2H_5$.

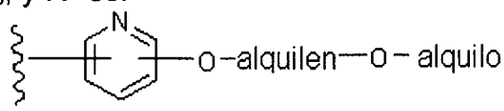
La realización Nº 19 se dirige a compuestos de fórmula 1.0 donde R^2 es $-OCH_3$, y R^1 es:



La realización Nº 20 se dirige a compuestos de fórmula 1.0 donde R^2 es $-OCH_3$, y R^1 es:

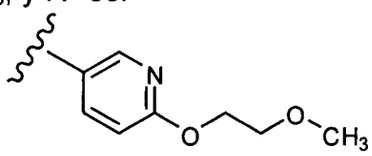


La realización Nº 21 se dirige a compuestos de fórmula 1.0 donde R^2 es $-OCH_3$, y R^1 es:



donde dicho grupo –O-alquilen-O-alquilo es $-OCH_2CH_2OCH_3$.

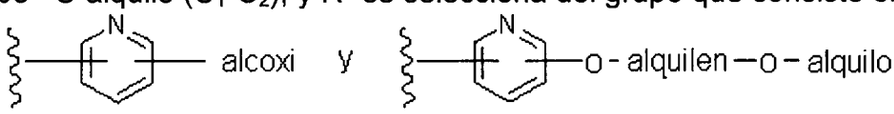
La realización Nº 22 se dirige a compuestos de fórmula 1.0 donde R^2 es $-OCH_3$, y R^1 es:



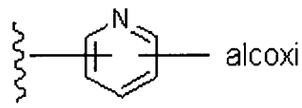
La realización Nº 23 se dirige a compuestos de fórmula 1.0 donde R^2 es un grupo –S-alquilo (C_1-C_2), y R^1 es piridilo sustituido.

La realización Nº 24 se dirige a compuestos de fórmula 1.0 donde R^2 es un grupo –S-alquilo (C_1-C_2), y R^1 es piridilo sustituido con un sustituyente.

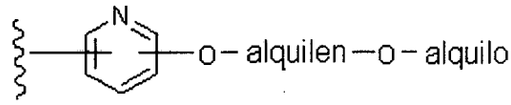
La realización Nº 25 se dirige a compuestos de fórmula 1.0 donde R^2 es un grupo –S-alquilo (C_1-C_2), y R^1 se selecciona del grupo que consiste en:



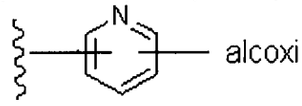
La realización Nº 26 se dirige a compuestos de fórmula 1.0 donde R^2 es un grupo –S-alquilo (C_1-C_2), y R^1 es:



La realización Nº 27 se dirige a compuestos de fórmula 1.0 donde R^2 es un grupo –S-alquilo (C_1-C_2), y R^1 es:

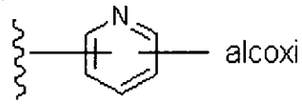


La realización Nº 28 se dirige a compuestos de fórmula 1.0 donde R^2 es un grupo –S-alquilo (C_1-C_2), y R^1 es:



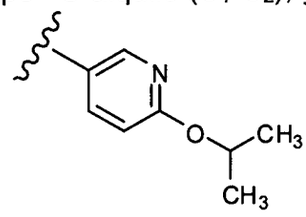
donde dicho grupo alcoxi es $-OCH(CH_3)_2$.

La realización Nº 29 se dirige a compuestos de fórmula 1.0 donde R^2 es un grupo –S-alquilo (C_1-C_2), y R^1 es:

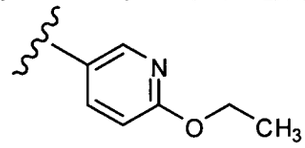


donde dicho grupo alcoxi es $-OC_2H_5$.

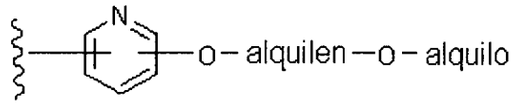
La realización Nº 30 se dirige a compuestos de fórmula 1.0 donde R^2 es un grupo –S-alquilo (C_1-C_2), y R^1 es:



La realización Nº 31 se dirige a compuestos de fórmula 1.0 donde R^2 es un grupo –S-alquilo (C_1-C_2), y R^1 es:

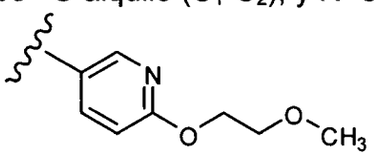


La realización Nº 32 se dirige a compuestos de fórmula 1.0 donde R^2 es un grupo –S-alquilo (C_1-C_2), y R^1 es:



donde dicho grupo –O-alquilen-O-alquilo es $-OCH_2CH_2OCH_3$.

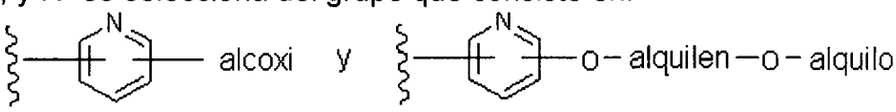
La realización Nº 33 se dirige a compuestos de fórmula 1.0 donde R^2 es un grupo –S-alquilo (C_1-C_2), y R^1 es:



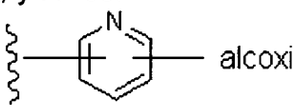
La realización Nº 34 se dirige a compuestos de fórmula 1.0 donde R^2 es $-SCH_3$, y R^1 es piridilo sustituido.

La realización Nº 35 se dirige a compuestos de fórmula 1.0 donde R^2 es $-SCH_3$, y R^1 es piridilo sustituido con un sustituyente.

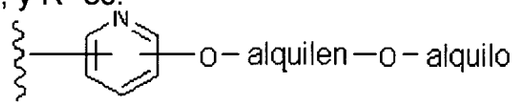
La realización Nº 36 se dirige a compuestos de fórmula 1.0 donde R^2 es $-SCH_3$, y R^1 se selecciona del grupo que consiste en:



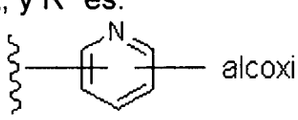
La realización Nº 37 se dirige a compuestos de fórmula 1.0 donde R^2 es $-SCH_3$, y R^1 es:



La realización Nº 38 se dirige a compuestos de fórmula 1.0 donde R^2 es $-SCH_3$, y R^1 es:

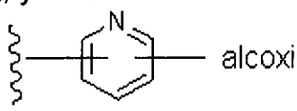


La realización Nº 39 se dirige a compuestos de fórmula 1.0 donde R^2 es $-SCH_3$, y R^1 es:



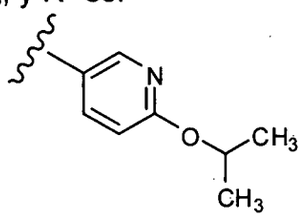
donde dicho grupo alcoxi es $-OCH(CH_3)_2$.

La realización Nº 40 se dirige a compuestos de fórmula 1.0 donde R^2 es $-SCH_3$, y R^1 es:

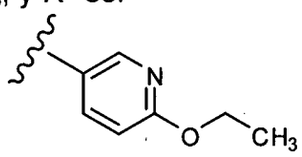


donde dicho grupo alcoxi es $-OC_2H_5$.

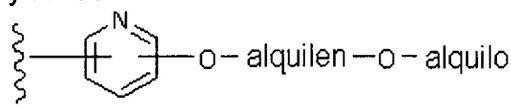
La realización Nº 41 se dirige a compuestos de fórmula 1.0 donde R^2 es $-SCH_3$, y R^1 es:



La realización Nº 42 se dirige a compuestos de fórmula 1.0 donde R^2 es $-SCH_3$, y R^1 es:

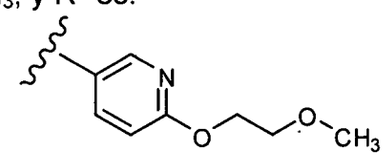


La realización Nº 43 se dirige a compuestos de fórmula 1.0 donde R^2 es $-SCH_3$, y R^1 es:



donde dicho grupo –O-alquilen-O-alquilo es $-OCH_2CH_2OCH_3$.

La realización Nº 44 se dirige a compuestos de fórmula 1.0 donde R^2 es $-SCH_3$, y R^1 es:



La realización Nº 45 se dirige a compuestos de fórmula 1.0 que tienen la fórmula 1.1:

Organizacion y
Digitalizacion CSA Ltda

Industria y Comercio

SUPERINTENDENCIA

DELEGATURA DE PROPIEDAD INDUSTRIAL

División de Nuevas Creaciones

SOLICITUD
PATENTE DE INVENCIÓN

21. **EXPEDIENTE No.** 10-116702 2/2

54. **TÍTULO** _____

_____

_____

_____

51. **CLASIFICACIÓN INTERNACIONAL** _____

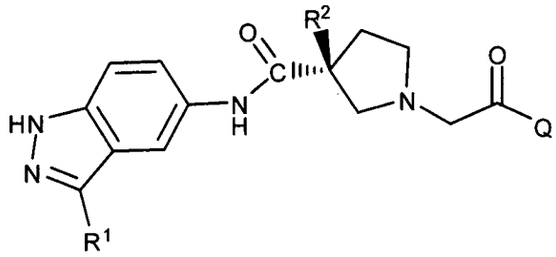
71. **SOLICITANTE** _____

DOMICILIO _____

74. **APODERADO** _____

22. **BOGOTÁ, D.C.,** _____

(FORMA P-10)



(1.1)

La realización Nº 46 se dirige a cualquiera de las Reivindicaciones Nº 1 a 44 donde el compuesto de fórmula 1.0 es un compuesto de fórmula 1.1.

Se describen a continuación otras realizaciones de la invención dirigiadas al sustituyente R^5. La frase "descriptas en cualquiera de las Reivindicaciones Nº 1 a 46" significa que la realización siendo descripta es aplicable a cada una de las Realizaciones Nº 1 a 46. Por ejemplo, otra realización de la invención se dirige a los compuestos descriptos en la realización Nº 1 donde R^5 es lo descripto en cualquiera de los párrafos a continuación. En otro ejemplo, otra realización de la invención se dirige a los compuestos descriptos en la realización Nº2 donde R^5 es lo descripto en cualquiera de los párrafos a continuación, etc.

De este modo, otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde R^5 es un triazolil-fenil- sustituido donde el resto triazolilo se sustituye con uno o dos grupos alquilo seleccionados del grupo que consiste en: alquilo-C_1-C_6, alquilo-C_1-C_4, alquilo-C_1-C_2, y $-CH_3$. .

Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde R^5 es un triazolil-fenil- sustituido donde el resto triazolilo se sustituye con uno o dos grupos alquilo seleccionados del grupo que consiste en: alquilo-C_1-C_4, alquilo-C_1-C_2, y $-CH_3$. Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1

a 46 donde R^5 es un triazolil-fenil- sustituido donde el resto triazolilo se sustituye con uno o dos grupos $-CH_3$.

Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde R^5 es un triazolil-fenil- sustituido donde el resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo seleccionado del grupo que consiste en : alquilo-C_1-C_4, alquilo-C_1-C_2, y $-CH_3$. Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde R^5 es un triazolil-fenil- sustituido donde el resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_3$.

Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde R^5 es un triazolil-fenil- sustituido donde el resto triazolilo se sustituye sobre el nitrógeno con un grupo -alquilen-O-alquilo seleccionado del grupo que consiste en: alquilen-C_2-C_4-O-alquilo C_1-C_6, alquilen-C_2-O-alquilo C_1-C_2, alquilen-C_2-C_4-O-CH_3, y $-CH_2CH_2OCH_3$.

Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde R^5 es un triazolil-fenil- sustituido donde el resto triazolilo se sustituye sobre el nitrógeno con un grupo -alquilen-O-alquilo seleccionado del grupo que consiste en: alquilen-C_2-O-alquilo C_1-C_2, y $-CH_2CH_2OCH_3$. Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde R^5 es un triazolil-fenil- sustituido donde el resto triazolilo se sustituye sobre el nitrógeno con $-CH_2CH_2OCH_3$.

Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde R^5 es un triazolil-fenil- sustituido donde el resto triazolilo se sustituye sobre el

nitrógeno con un grupo alquilo sustituido con hidroxi seleccionado del grupo que consiste en: alquilo-C_1-C_4 sustituido con hidroxi, alquilo-C_1-C_2 sustituido con hidroxi, y -CH_3 sustituido con hidroxi.

Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde R^5 es un triazolil-fenil- sustituido donde el resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo sustituido con hidroxi seleccionado del grupo que consiste en: $CH_2COH(CH_3)_2$, y -CH_2CH_2OH.

Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde los sustituyentes de halo opcionales para el resto fenilo de R^5 se seleccionan en forma independiente del grupo que consiste en: Cl, F y Br.

Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde los sustituyentes de halo opcionales para el resto fenilo de R^5 son F.

Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde el sustituyente de halo opcional para el resto fenilo de R^5 es un F.

Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde R^5 es un grupo triazolil-fenil- sustituido donde (a) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un sustituyente seleccionado del grupo que consiste en: –$CH_2COH(CH_3)_2$ y -CH_2CH_2OH, (b) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo alquilo, (c) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo alquilo, y sobre el carbono con un grupo alquilo, (d) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo –CH_3, (e) dicho

resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo -CH3, y sobre el carbono con un grupo $-CH_3$, (f) dicho resto triazolilo se sustituye en forma opcional sobre el carbono con un grupo $-NH_2$, o (g) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo $-CH_2CH_2OCH_3$; y donde dicho resto fenilo se sustituye en forma opcional con halo (e.g., un halo, tal como por ejemplo, F).

Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde R^5 es un grupo triazolil-fenil- sustituido donde (a) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un sustituyente seleccionado del grupo que consiste en: $-CH_2COH(CH_3)_2$ y $-CH_2CH_2OH$, (b) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo alquilo, (c) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo alquilo, y sobre el carbono con un grupo alquilo, (d) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo $-CH_3$, (e) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo -CH3, y sobre el carbono con un grupo $-CH_3$, (f) dicho resto triazolilo se sustituye en forma opcional sobre el carbono con un grupo $-NH_2$, o (g) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo $-CH_2CH_2OCH_3$; y donde dicho resto fenilo se sustituye con halo (por ej., un halo, tal como por ejemplo, F).

Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde R^5 es un grupo triazolil-fenil- sustituido donde (a) dicho resto triazolilo se sustituye sobre el nitrógeno con un sustituyente seleccionado del grupo que consiste en: $-CH_2COH(CH_3)_2$ y $-CH_2CH_2OH$, (b) dicho resto triazolilo se sustituye sobre el nitrógeno con un

grupo alquilo, (c) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo, y sobre el carbono con un grupo alquilo, (d) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_3$, (e) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_3$, y sobre el carbono con un grupo $-CH_3$, (f) dicho resto triazolilo se sustituye sobre el carbono con un grupo $-NH_2$, o (g) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_2CH_2OCH_3$; y donde dicho resto fenilo se sustituye en forma opcional con halo (por ej., un halo, tal como por ejemplo, F).

Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde R^5 es un grupo triazolil-fenil- sustituido donde (a) dicho resto triazolilo se sustituye sobre el nitrógeno con un sustituyente seleccionado del grupo que consiste en: $-CH_2COH(CH_3)_2$ y $-CH_2CH_2OH$, (b) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo, (c) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo, y sobre el carbono con un grupo alquilo, (d) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_3$, (e) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_3$, y sobre el carbono con un grupo $-CH_3$, (f) dicho resto triazolilo se sustituye sobre el carbono con un grupo $-NH_2$, o (g) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_2CH_2OCH_3$; y donde dicho resto fenilo se sustituye con halo (por ej., un halo, tal como, por ejemplo, F).

Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde los sustituyentes de halo opcionales para el resto fenilo de R^5 se seleccionan en forma independiente del grupo que consiste en: alcoxi.

Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde los sustituyentes de halo opcionales para el resto fenilo de R^5 son $-OCH_3$.

Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde el sustituyente opcional para el resto fenilo de R^5 es un $-OCH_3$.

Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde R^5 es un grupo triazolil-fenil- sustituido donde (a) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un sustituyente seleccionado del grupo que consiste en: $-CH_2COH(CH_3)_2$, y $-CH_2CH_2OH$, (b) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo alquilo, (c) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo alquilo, y sobre el carbono con un grupo alquilo, (d) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo $-CH_3$, (e) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo $-CH_3$, y sobre el carbono con un grupo $-CH_3$, (f) dicho resto triazolilo se sustituye en forma opcional sobre el carbono con un grupo $-NH_2$, o (g) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo $-CH_2CH_2OCH_3$; y donde dicho resto fenilo se sustituye en forma opcional con alcoxi (por ej., un $-OCH_3$).

Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde R^5 es un grupo triazolil-fenil- sustituido donde (a) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un sustituyente seleccionado del grupo que consiste en: $-CH_2COH(CH_3)_2$, y $-CH_2CH_2OH$, (b) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo alquilo,

(c) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo alquilo, y sobre el carbono con un grupo alquilo, (d) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo $-CH_3$, (e) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo $-CH_3$, y sobre el carbono con un grupo $-CH_3$, (f) dicho resto triazolilo se sustituye en forma opcional sobre el carbono con un grupo $-NH_2$, o (g) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo $-CH_2CH_2OCH_3$; y donde dicho resto fenilo se sustituye con alcoxi (e.g., one $-OCH_3$).

Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde R^5 es un grupo triazolil-fenil- sustituido donde (a) dicho resto triazolilo se sustituye sobre el nitrógeno con un sustituyente seleccionado del grupo que consiste en: $-CH_2COH(CH_3)_2$, y $-CH_2CH_2OH$, (b) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo, (c) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo, y sobre el carbono con un grupo alquilo, (d) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_3$, (e) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_3$, y sobre el carbono con un grupo $-CH_3$, (f) dicho resto triazolilo se sustituye sobre el carbono con un grupo $-NH_2$, o (g) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_2CH_2OCH_3$; y donde dicho resto fenilo se sustituye en forma opcional con alcoxi (por ej., un $-OCH_3$).

Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde R^5 es un grupo triazolil-fenil- sustituido donde (a) dicho resto triazolilo se sustituye sobre el nitrógeno con un sustituyente seleccionado del grupo que consiste en:

$-CH_2COH(CH_3)_2$, y $-CH_2CH_2OH$, (b) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo, (c) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo, y sobre el carbono con un grupo alquilo, (d) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_3$, (e) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_3$, y sobre el carbono con un grupo $-CH_3$, (f) dicho resto triazolilo se sustituye sobre el carbono con un grupo $-NH_2$, o (g) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_2CH_2OCH_3$; y donde dicho resto fenilo se sustituye con alcoxi (por ej., un $-OCH_3$).

Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde R^5 es un grupo triazolil-fenil- sustituido donde (a) dicho resto triazolilo se sustituye sobre el nitrógeno con un sustituyente seleccionado del grupo que consiste en: $-CH_2COH(CH_3)_2$, y $-CH_2CH_2OH$, (b) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo, (c) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo, y sobre el carbono con un grupo alquilo, (d) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_3$, (e) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_3$, y sobre el carbono con un grupo $-CH_3$, (f) dicho resto triazolilo se sustituye sobre el carbono con un grupo –NH2, o (g) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_2CH_2OCH_3$; y donde dicho resto fenilo no está sustituido.

Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde dicho resto R^5 sustituido es un grupo triazolil-fenilo sustituido donde dicho resto triazolilo se sustituye con: (a) un sustituyente seleccionado del grupo que

consiste en: $-CH_2COH(CH_3)_2$, y $-CH_2CH_2OH$, (b) un grupo alquilo, (c) dos grupos alquilo, (d) un grupo $-CH_3$, (e) dos grupos $-CH_3$, (f) un grupo $-NH_2$, o (g) un grupo $-CH_2CH_2OCH_3$.

Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde R^5 es un triazolil-tienil- sustituido donde el resto triazolilo se sustituye con uno o dos grupos alquilo seleccionados del grupo que consiste en: alquilo-C_1-C_6, alquilo-C_1-C_4, alquilo-C_1-C_2, y $-CH_3$.

Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde R^5 es un triazolil-tienil- sustituido donde el resto triazolilo se sustituye con uno o dos grupos alquilo seleccionados del grupo que consiste en: alquilo-C_1-C_4, alquilo-C_1-C_2, y $-CH_3$. Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde R^5 es un triazolil-tienil- sustituido donde el resto triazolilo se sustituye con uno o dos grupos $-CH_3$.

Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde R^5 es un triazolil-tienil- sustituido donde el resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo seleccionado del grupo que consiste en : alquilo-C_1-C_4, alquilo-C_1-C_2, y $-CH_3$. Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde R^5 es un triazolil-tienil- sustituido donde el resto triazolilo se sustituye sobre el nitrógeno con $-CH_3$.

Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde R^5

es un triazolil-tienil- sustituido donde el resto triazolilo se sustituye sobre el nitrógeno con un grupo -alquilen-O-alquilo seleccionado del grupo que consiste en: alquilen-C_2-C_4-O-alquilo C_1-C_6, alquilen-C_2-O-alquilo C_1-C_2, alquilen-C_2-C_4-O-CH_3, y $-CH_2CH_2OCH_3$.

Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde R^5 es un triazolil-tienil- sustituido donde el resto triazolilo se sustituye sobre el nitrógeno con un grupo -alquilen-O-alquilo seleccionado del grupo que consiste en: alquilen-C_2-O-alquilo C_1-C_2, y $-CH_2CH_2OCH_3$. Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde R^5 es un triazolil-tienil- sustituido donde el resto triazolilo se sustituye sobre el nitrógeno con $-CH_2CH_2OCH_3$.

Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde R^5 es un triazolil-tienil- sustituido donde el resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo sustituido con hidroxi seleccionado del grupo que consiste en: alquilo-C_1-C_4 sustituido con hidroxi, alquilo-C_1-C_2 sustituido con hidroxi, y -CH_3 sustituido con hidroxi.

Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde R^5 es un triazolil-tienil- sustituido donde el resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo sustituido con hidroxi seleccionado del grupo que consiste en: $CH_2COH(CH_3)_2$, y -CH_2CH_2OH.

Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde los sustituyentes de halo opcionales para el resto tienilo de R^5 se seleccionan en forma independiente del grupo que consiste en: Cl, F y Br.

Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde los sustituyentes de halo opcionales para el resto tienilo de R^5 son F.

Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde el sustituyente de halo opcional para el resto tienilo de R^5 es un F.

Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde R^5 es un grupo triazolil-tienil- sustituido donde (a) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un sustituyente seleccionado del grupo que consiste en: $-CH_2COH(CH_3)_2$, y $-CH_2CH_2OH$, (b) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo alquilo, (c) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo alquilo, y sobre el carbono con un grupo alquilo, (d) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo $-CH_3$, (e) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo $-CH_3$, y sobre el carbono con un grupo $-CH_3$, (f) dicho resto triazolilo se sustituye en forma opcional sobre el carbono con un grupo $-NH_2$, o (g) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo $-CH_2CH_2OCH_3$; y donde dicho resto tienilo se sustituye en forma opcional con halo (por ej., un halo, tal como, por ejemplo, F).

Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde R^5 es un grupo triazolil-tienil- sustituido donde (a) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un sustituyente seleccionado del grupo que consiste en: $-CH_2COH(CH_3)_2$, $-CH_2CH_2OH$, (b) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo alquilo, (c)

dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo alquilo, y sobre el carbono con un grupo alquilo, (d) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo $-CH_3$, (e) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo $-CH_3$, y sobre el carbono con un grupo $-CH_3$, (f) dicho resto triazolilo se sustituye en forma opcional sobre el carbono con un grupo $-NH_2$, o (g) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo $-CH_2CH_2OCH_3$; y donde dicho resto tienilo se sustituye con halo (por ej., un halo, tal como, por ejemplo, F).

Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde R^5 es un grupo triazolil-tienil- sustituido donde (a) dicho resto triazolilo se sustituye sobre el nitrógeno con un sustituyente seleccionado del grupo que consiste en: $-CH_2COH(CH_3)_2$, y $-CH_2CH_2OH$, (b) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo, (c) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo, y sobre el carbono con un grupo alquilo, (d) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_3$, (e) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_3$, y sobre el carbono con un grupo $-CH_3$, (f) dicho resto triazolilo se sustituye sobre el carbono con un grupo $-NH_2$, o (g) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_2CH_2OCH_3$; y donde dicho resto tienilo se sustituye en forma opcional con halo (por ej., un halo, tal como, por ejemplo, F).

Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde R^5 es un grupo triazolil-tienil- sustituido donde (a) dicho resto triazolilo se sustituye sobre el nitrógeno con un sustituyente seleccionado del grupo que consiste en: $-CH_2COH(CH_3)_2$, y $-CH_2CH_2OH$, (b) dicho resto triazolilo se sustituye sobre el

nitrógeno con un grupo alquilo, (c) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo, y sobre el carbono con un grupo alquilo, (d) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_3$, (e) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_3$, y sobre el carbono con un grupo $-CH_3$, (f) dicho resto triazolilo se sustituye sobre el carbono con un grupo $-NH_2$, o (g) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_2CH_2OCH_3$; y donde dicho resto tienilo se sustituye con halo (por ej., un halo, tal como, por ejemplo, F).

Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde R^5 es un grupo triazolil-tienil- sustituido donde (a) dicho resto triazolilo se sustituye sobre el nitrógeno con un sustituyente seleccionado del grupo que consiste en: $-CH_2COH(CH_3)_2$, y $-CH_2CH_2OH$, (b) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo, (c) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo, y sobre el carbono con un grupo alquilo, (d) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_3$, (e) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_3$, y sobre el carbono con un grupo $-CH_3$, (f) dicho resto triazolilo se sustituye sobre el carbono con un grupo $-NH_2$, o (g) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_2CH_2OCH_3$; y donde dicho resto tienilo no está sustituido.

Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde dicho resto R^5 sustituido es un grupo triazolil-tienilo sustituido donde dicho resto triazolilo se sustituye con: (a) un sustituyente seleccionado del grupo que consiste en: $-CH_2COH(CH_3)_2$, y $-CH_2CH_2OH$; (b) un grupo alquilo, (c) dos grupos alquilo, (d)

un grupo $-CH_3$, (e) dos grupos $-CH_3$, (f) un grupo $-NH_2$, o (g) un grupo $-CH_2CH_2OCH_3$.

Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde los sustituyentes opcionales para el resto tienilo de R^5 se seleccionan en forma independiente del grupo que consiste en: alcoxi.

Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde los sustituyentes opcionales para el resto tienilo de R^5 son $-OCH_3$.

Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde el sustituyente opcional para el resto tienilo de R^5 es un $-OCH_3$.

Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde R^5 es un grupo triazolil-tienil- sustituido donde (a) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un sustituyente seleccionado del grupo que consiste en: $-CH_2COH(CH_3)_2$, y $-CH_2CH_2OH$, (b) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo alquilo, (c) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo alquilo, y sobre el carbono con un grupo alquilo, (d) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo $-CH_3$, (e) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo -CH3, y sobre el carbono con un grupo $-CH_3$, (f) dicho resto triazolilo se sustituye en forma opcional sobre el carbono con un grupo $-NH_2$, o (g) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo $-CH_2CH_2OCH_3$; y donde dicho resto tienilo se sustituye en forma opcional con alcoxi (por ej., un $-OCH_3$).

Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde R^5 es un grupo triazolil-tienil- sustituido donde (a) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un sustituyente seleccionado del grupo que consiste en: $-CH_2COH(CH_3)_2$, y $-CH_2CH_2OH$, (b) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo alquilo, (c) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo alquilo, y sobre el carbono con un grupo alquilo, (d) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo $-CH_3$, (e) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo -CH3, y sobre el carbono con un grupo $-CH_3$, (f) dicho resto triazolilo se sustituye en forma opcional sobre el carbono con un grupo $-NH_2$, o (g) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo $-CH_2CH_2OCH_3$; y donde dicho resto tienilo se sustituye con alcoxi (por ej., un $-OCH_3$).

Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde R^5 es un grupo triazolil-tienil- sustituido donde (a) dicho resto triazolilo se sustituye sobre el nitrógeno con un sustituyente seleccionado del grupo que consiste en: $-CH_2COH(CH_3)_2$, y $-CH_2CH_2OH$, (b) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo, (c) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo, y sobre el carbono con un grupo alquilo, (d) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_3$, (e) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_3$, y sobre el carbono con un grupo $-CH_3$, (f) dicho resto triazolilo se sustituye sobre el carbono con un grupo $-NH_2$, o (g) dicho resto triazolilo se sustituye sobre el

nitrógeno con un grupo $-CH_2CH_2OCH_3$; y donde dicho resto tienilo se sustituye en forma opcional con alcoxi (por ej., un $-OCH_3$).

Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde R^5 es un grupo triazolil-tienil- sustituido donde (a) dicho resto triazolilo se sustituye sobre el nitrógeno con un sustituyente seleccionado del grupo que consiste en: $-CH_2COH(CH_3)_2$, y $-CH_2CH_2OH$, (b) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo, (c) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo, y sobre el carbono con un grupo alquilo, (d) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_3$, (e) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_3$, y sobre el carbono con un grupo $-CH_3$, (f) dicho resto triazolilo se sustituye sobre el carbono con un grupo –NH2, o (g) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_2CH_2OCH_3$; y donde dicho resto tienilo se sustituye con alcoxi (por ej., un $-OCH_3$).

Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde R^5 es un triazolil-piridil- sustituido donde el resto triazolilo se sustituye con uno o dos grupos alquilo seleccionados del grupo que consiste en: alquilo-C_1-C_6, alquilo-C_1-C_4, alquilo-C_1-C_2, y $-CH_3$.

Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde R^5 es un triazolil-piridil- sustituido donde el resto triazolilo se sustituye con uno o dos grupos alquilo seleccionados del grupo que consiste en: alquilo-C_1-C_4, alquilo-C_1-C_2, y $-CH_3$. Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1

a 46 donde R^5 es un triazolil-piridil- sustituido donde el resto triazolilo se sustituye con uno o dos grupos $-CH_3$.

Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde R^5 es un triazolil-piridil- sustituido donde el resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo seleccionado del grupo que consiste en: alquilo-C_1-C_4, alquilo-C_1-C_2, y $-CH_3$. Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde R^5 es un triazolil-piridil- sustituido donde el resto triazolilo se sustituye sobre el nitrógeno con $-CH_3$.

Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde R^5 es un triazolil-piridil- sustituido donde el resto triazolilo se sustituye sobre el nitrógeno con un grupo -alquilen-O-alquilo seleccionado del grupo que consiste en: alquilen-C_2-C_4-O-alquilo C_1-C_6, alquilen-C_2-O-alquilo C_1-C_2, alquilen-C_2-C_4-O-CH_3, y $-CH_2CH_2OCH_3$.

Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde R^5 es un triazolil-piridil- sustituido donde el resto triazolilo se sustituye sobre el nitrógeno con un grupo -alquilen-O-alquilo seleccionado del grupo que consiste en: alquilen-C_2-O-alquilo C_1-C_2, y $-CH_2CH_2OCH_3$. Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde R^5 es un triazolil-piridil- sustituido donde el resto triazolilo se sustituye sobre el nitrógeno con $-CH_2CH_2OCH_3$.

Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde R^5 es un triazolil-piridil- sustituido donde el resto triazolilo se sustituye sobre el

nitrógeno con un grupo alquilo sustituido con hidroxi seleccionado del grupo que consiste en: alquilo-C_1-C_4 sustituido con hidroxi, alquilo-C_1-C_2 sustituido con hidroxi, y -CH_3 sustituido con hidroxi.

Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde R^5 es un triazolil-piridil- sustituido donde el resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo sustituido con hidroxi seleccionado del grupo que consiste en: $CH_2COH(CH_3)_2$, y -CH_2CH_2OH.

Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde R^5 es un grupo triazolil-piridil- sustituido donde (a) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un sustituyente seleccionado del grupo que consiste en: –$CH_2COH(CH_3)_2$, y -CH_2CH_2OH, (b) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo alquilo, (c) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo alquilo, y sobre el carbono con un grupo alquilo, (d) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo –CH_3, (e) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo -CH_3, y sobre el carbono con un grupo –CH_3, (f) dicho resto triazolilo se sustituye en forma opcional sobre el carbono con un grupo -NH_2, o (g) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo –$CH_2CH_2OCH_3$; y donde dicho resto piridilo no está sustituido.

Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde R^5 es un grupo triazolil-piridil- sustituido donde (a) dicho resto triazolilo se sustituye sobre el nitrógeno con un sustituyente seleccionado del grupo que consiste en: –$CH_2COH(CH_3)_2$, y -CH_2CH_2OH, (b) dicho resto triazolilo se sustituye sobre el

nitrógeno con un grupo alquilo, (c) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo, y sobre el carbono con un grupo alquilo, (d) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_3$, (e) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_3$, y sobre el carbono con un grupo $-CH_3$, (f) dicho resto triazolilo se sustituye sobre el carbono con un grupo $-NH_2$, o (g) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_2CH_2OCH_3$; y donde dicho resto piridilo no está sustituido.

Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde R^5 es un triazolil-tiazolil- sustituido donde el resto triazolilo se sustituye con uno o dos grupos alquilo seleccionados del grupo que consiste en: alquilo-C_1-C_6, alquilo-C_1-C_4, alquilo-C_1-C_2, y $-CH_3$.

Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde R^5 es un triazolil-tiazolil- sustituido donde el resto triazolilo se sustituye con uno o dos grupos alquilo seleccionados del grupo que consiste en: alquilo-C_1-C_4, alquilo-C_1-C_2, y $-CH_3$. Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde R^5 es un triazolil-tiazolil- sustituido donde el resto triazolilo se sustituye con uno o dos grupos $-CH_3$.

Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde R^5 es un triazolil-tiazolil- sustituido donde el resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo seleccionado del grupo que consiste en : alquilo-C_1-C_4, alquilo-C_1-C_2, y $-CH_3$. Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1

a 46 donde R^5 es un triazolil-tiazolil- sustituido donde el resto triazolilo se sustituye sobre el nitrógeno con $-CH_3$.

Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde R^5 es un triazolil-tiazolil- sustituido donde el resto triazolilo se sustituye sobre el nitrógeno con un grupo -alquilen-O-alquilo seleccionado del grupo que consiste en: alquilen-C_2-C_4-O-alquilo C_1-C_6, alquilen-C_2-O-alquilo C_1-C_2, alquilen-C_2-C_4-O-CH_3, y $-CH_2CH_2OCH_3$.

Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde R^5 es un triazolil-tiazolil- sustituido donde el resto triazolilo se sustituye sobre el nitrógeno con un grupo -alquilen-O-alquilo seleccionado del grupo que consiste en: alquilen-C_2-O-alquilo C_1-C_2, y $-CH_2CH_2OCH_3$. Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde R^5 es un triazolil-tiazolil- sustituido donde el resto triazolilo se sustituye sobre el nitrógeno con $-CH_2CH_2OCH_3$.

Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde R^5 es un triazolil-tiazolil- sustituido donde el resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo sustituido con hidroxi seleccionado del grupo que consiste en: alquilo-C_1-C_4 sustituido con hidroxi, alquilo-C_1-C_2 sustituido con hidroxi, y -CH3 sustituido con hidroxi.

Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde R^5 es un triazolil-tiazolil- sustituido donde el resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo sustituido con hidroxi seleccionado del grupo que consiste en: $CH_2COH(CH_3)_2$, y $-CH_2CH_2OH$.

Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde R^5 es un grupo triazolil-tiazolil- sustituido donde (a) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un sustituyente seleccionado del grupo que consiste en: $-CH_2COH(CH_3)_2$, y $-CH_2CH_2OH$, (b) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo alquilo, (c) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo alquilo, y sobre el carbono con un grupo alquilo, (d) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo $-CH_3$, (e) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo $-CH_3$, y sobre el carbono con un grupo $-CH_3$, (f) dicho resto triazolilo se sustituye en forma opcional sobre el carbono con un grupo $-NH_2$, o (g) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo $-CH_2CH_2OCH_3$; y donde dicho resto tiazolilo no está sustituido.

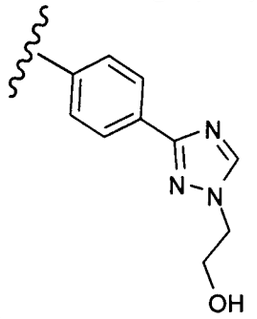
Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde R^5 es un grupo triazolil-tiazolil- sustituido donde (a) dicho resto triazolilo se sustituye sobre el nitrógeno con un sustituyente seleccionado del grupo que consiste en: $-CH_2COH(CH_3)_2$, y $-CH_2CH_2OH$, (b) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo, (c) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo, y sobre el carbono con un grupo alquilo, (d) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_3$, (e) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_3$, y sobre el carbono con un grupo $-CH_3$, (f) dicho resto triazolilo se sustituye sobre el carbono con un grupo $-NH_2$, o (g) dicho resto triazolilo se

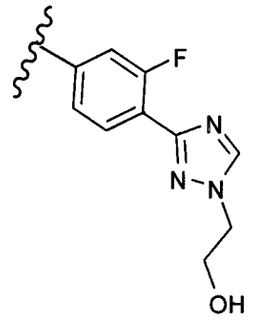
sustituye sobre el nitrógeno con un grupo $-CH_2CH_2OCH_3$; y donde dicho resto tiazolilo no está sustituido.

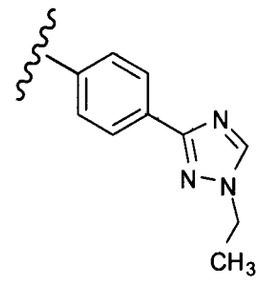
Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde R^5 es un piradizinil-tienil- sustituido donde el resto piridazinilo se sustituye con 1 o 2 grupos seleccionados en forma independiente del grupo que consiste en alquilo (por ej., metilo) y =O, y dicho dicho tienilo no está sustituido.

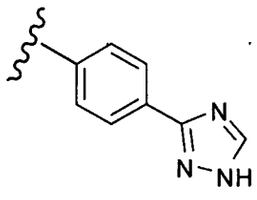
Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde R^5 es un piradizinil-tienil- sustituido donde el resto piridazinilo se sustituye con un resto =O, o dicho grupo piridazinilo se sustituye con un alquilo (por ej., metilo), o dicho piridazinilo se sustituye con un resto =O y un alquilo (por ej., metilo), y dicho dicho tienilo no está sustituido.

Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde R^5 se selecciona del grupo que consiste en:

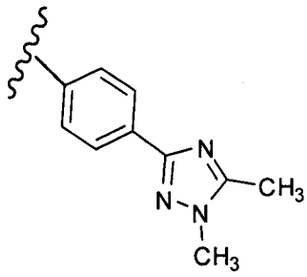
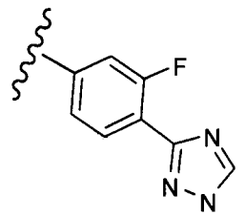
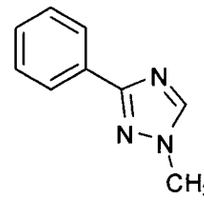
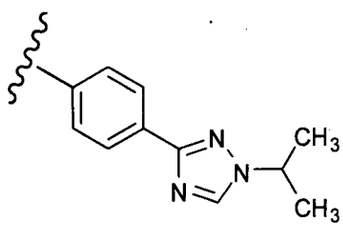
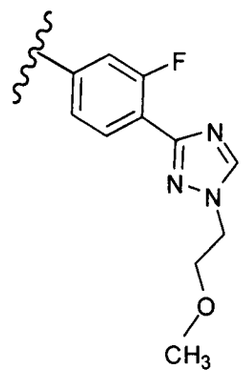
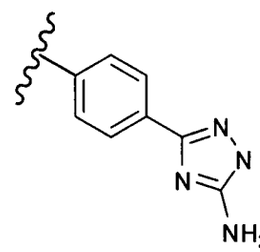
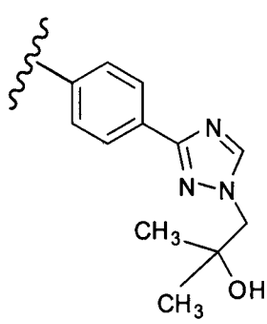
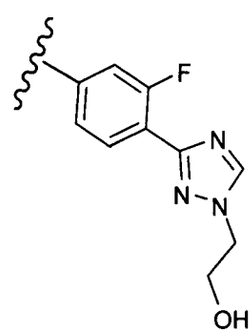
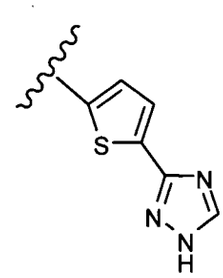
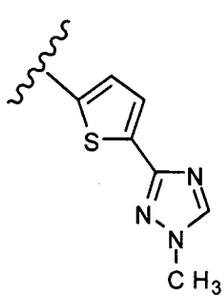
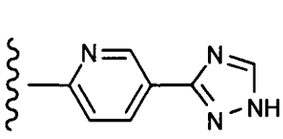
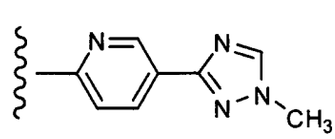
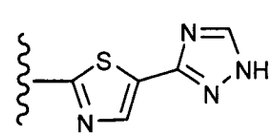


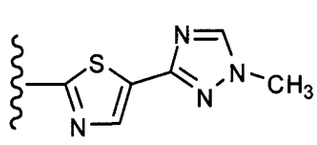
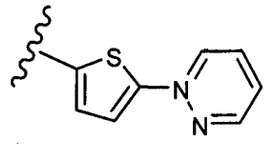
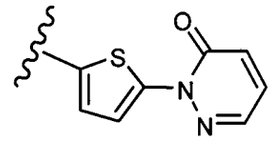
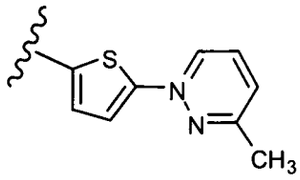
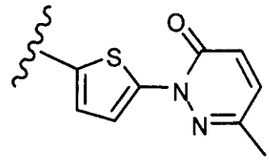
,


,


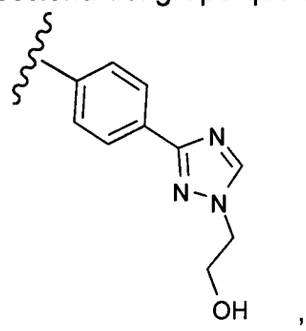
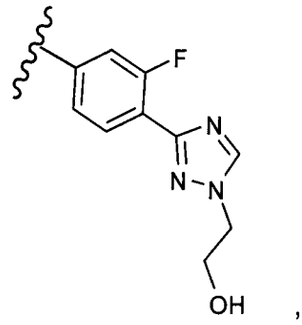
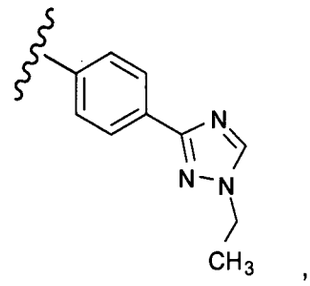
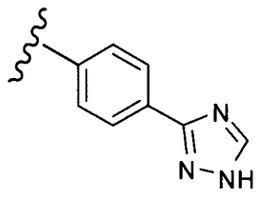
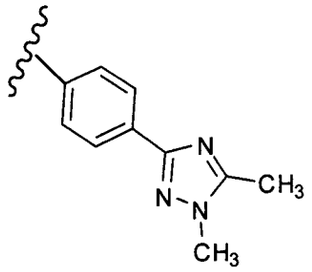
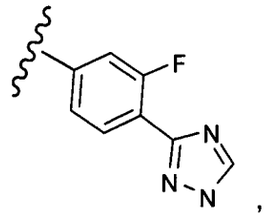
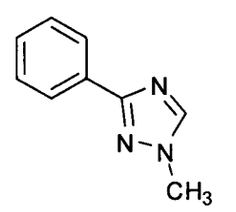
,


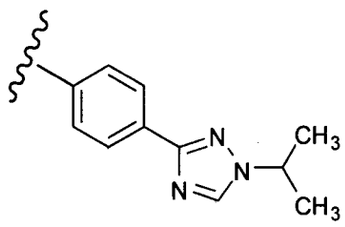
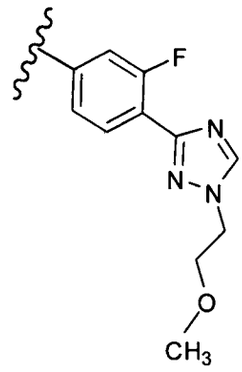
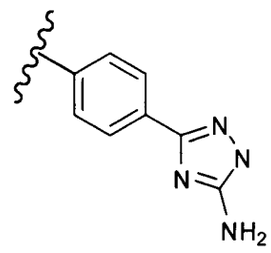
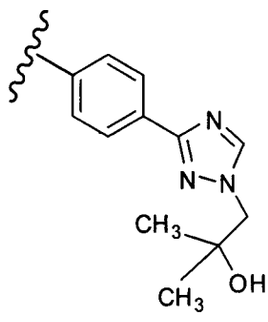
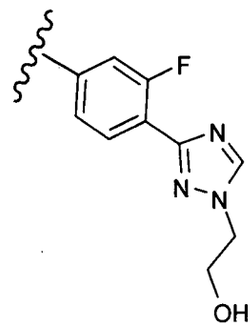
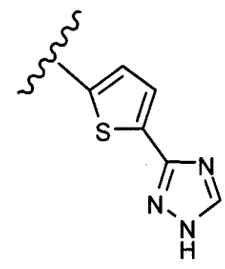
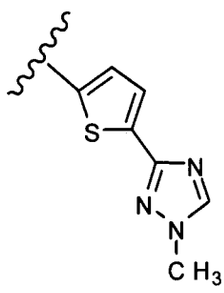
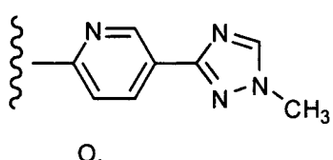
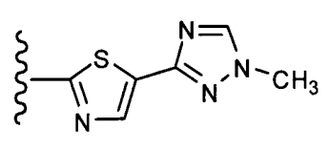
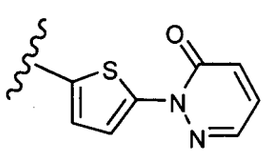
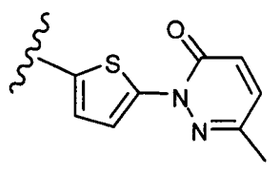
,


,

,

,

,

,

,

,

,

,

,

,

,

,

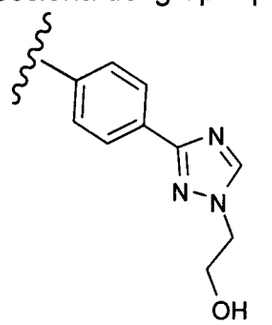

,

,

,

, y

.

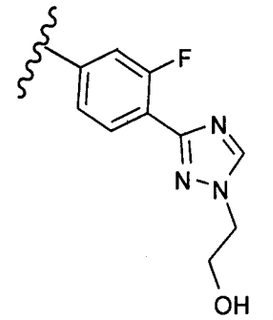
Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde R^5 se selecciona del grupo que consiste en:

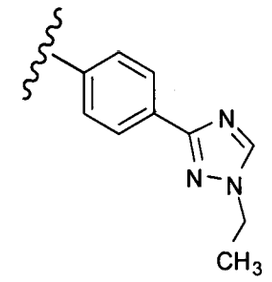

,

,

,

,

,

,

,

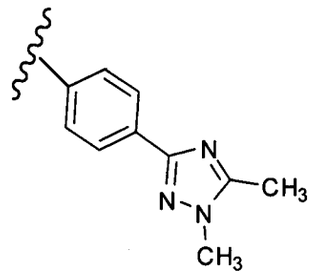










y


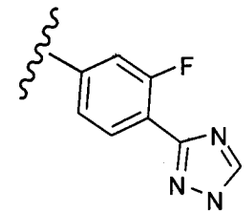
Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde R^5 se selecciona del grupo que consiste en:

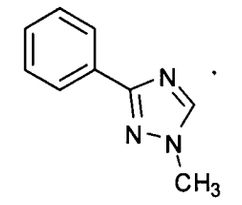


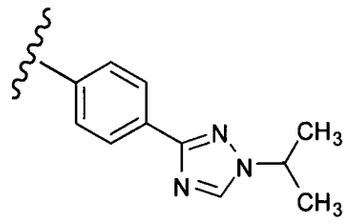
,


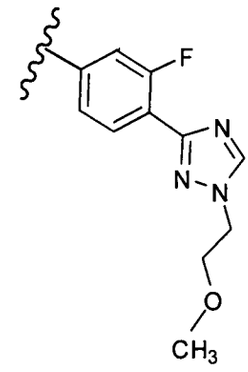
,


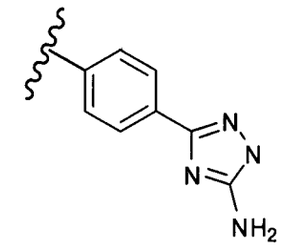
,


,


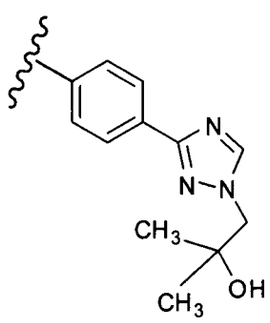
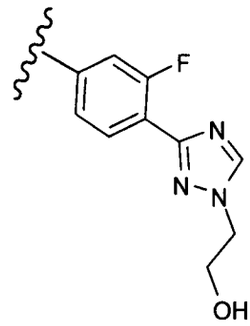
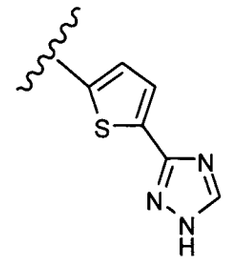
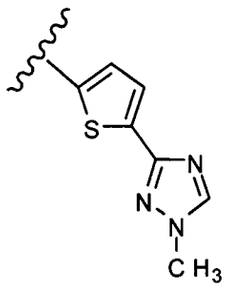
,


,


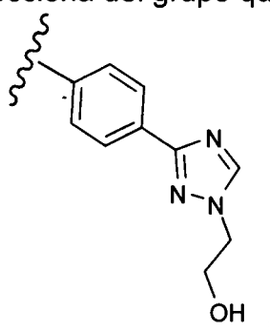
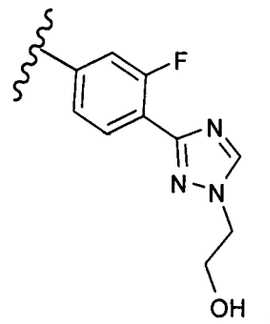
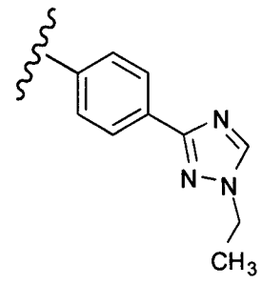
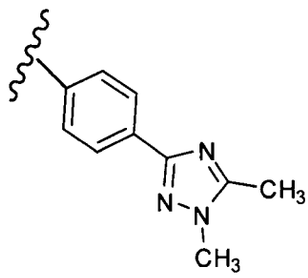
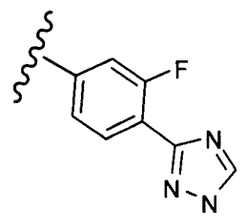
,


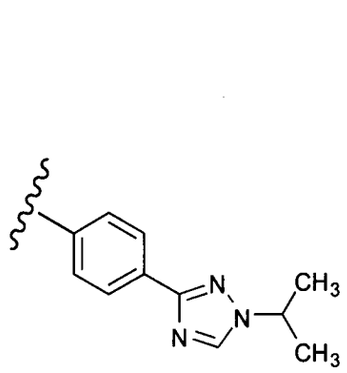
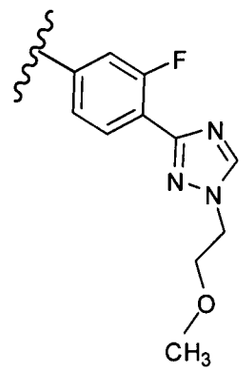
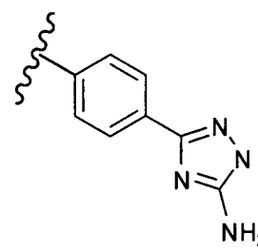
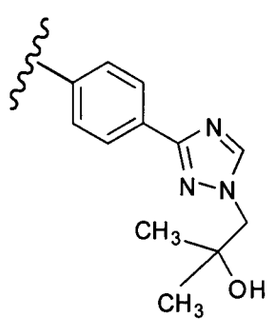
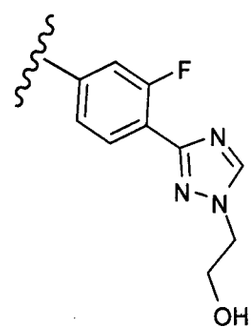
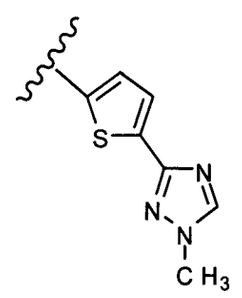
,


,

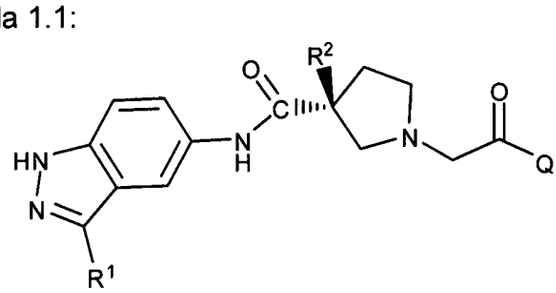



y


Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.0 descriptos en cualquiera de las Realizaciones Nº 1 a 46 donde R^5 se selecciona del grupo que consiste en:



,

,

,

,

, y

.

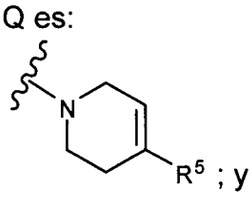
Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.1:


(1.1)

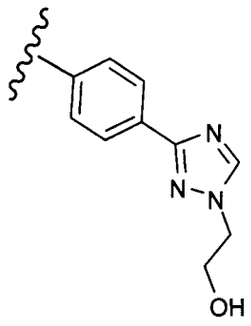
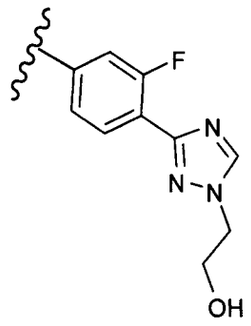
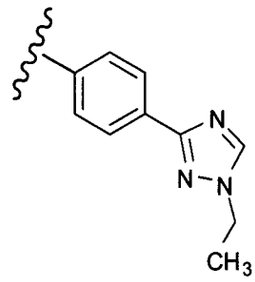
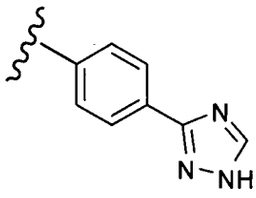
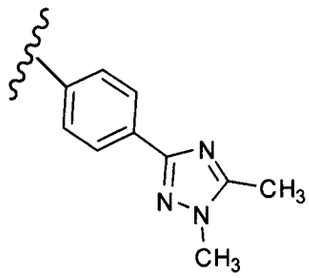
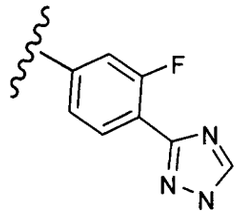
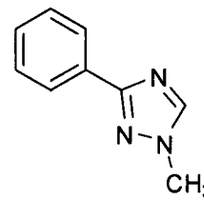
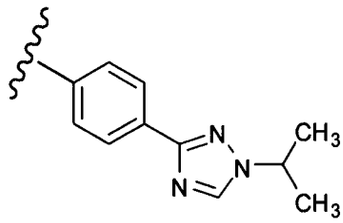
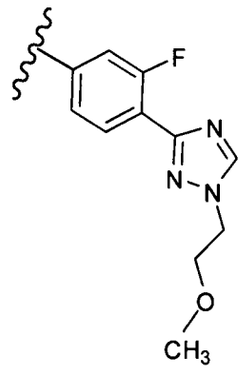
donde:

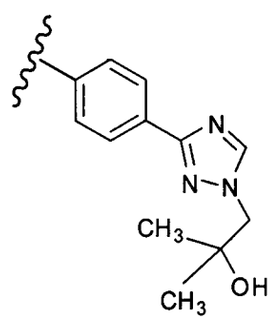
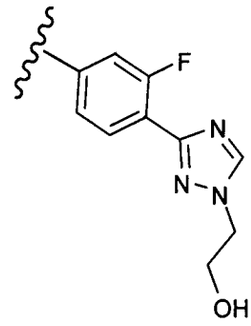
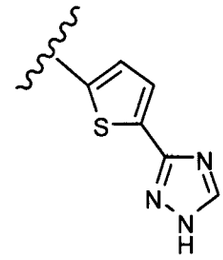
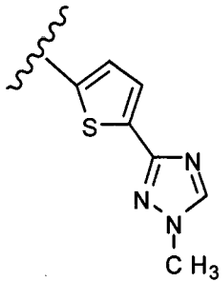
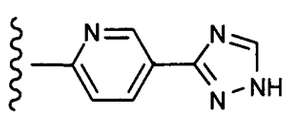
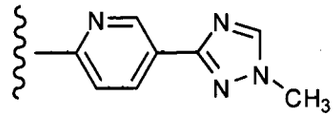
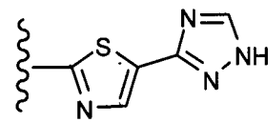
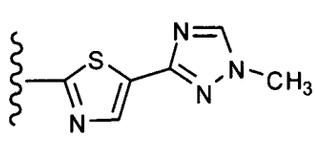
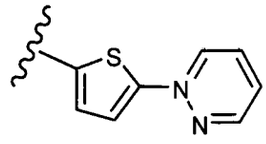
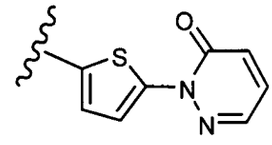
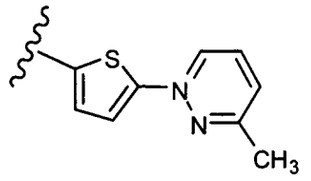
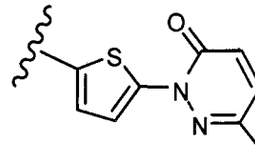
R^1 y R^2 son lo definido en cualquiera de las Realizaciones Nº 1 a 44,

Q es:

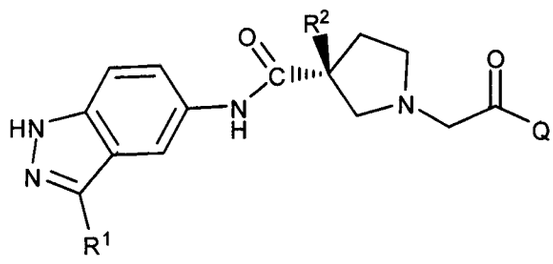

; y

R^5 se selecciona del grupo que consiste en:

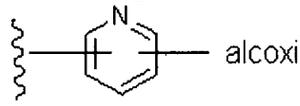
Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.1:



(1.1)

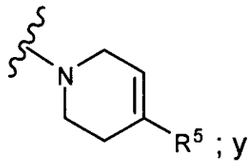
donde:

R^2 es un grupo –O-alquilo (C_1-C_2), y R^1 es:



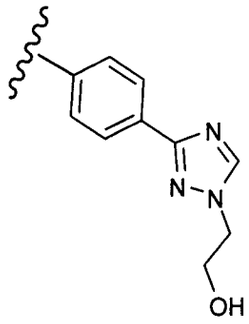
,

Q es:

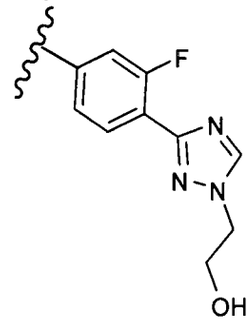


; y

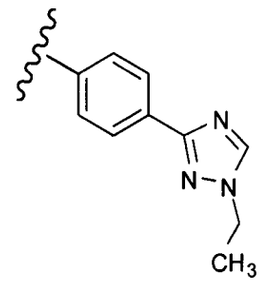
R^5 se selecciona del grupo que consiste en:



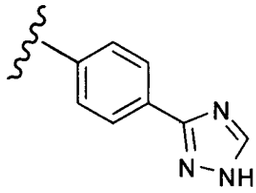
,



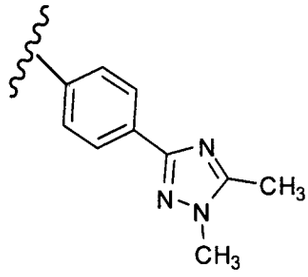
,



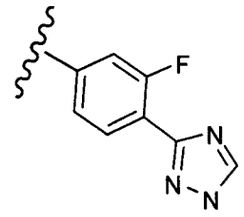
,



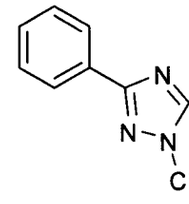
,



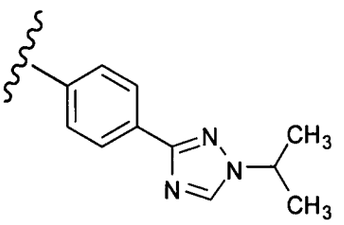
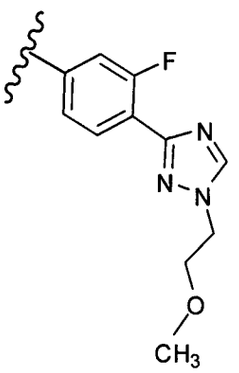
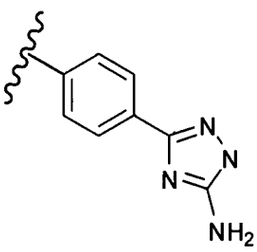
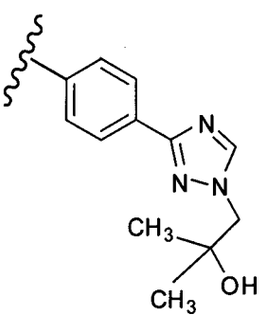
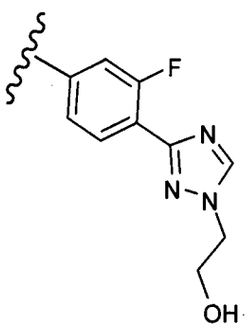
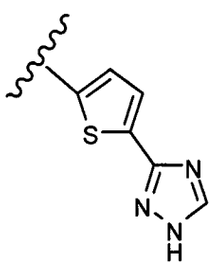
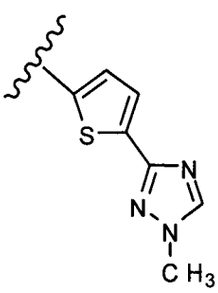
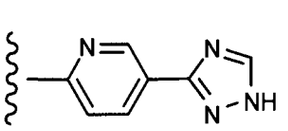
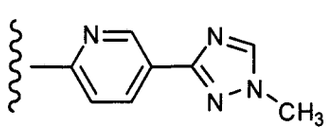
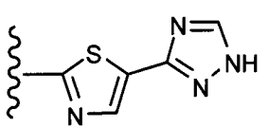
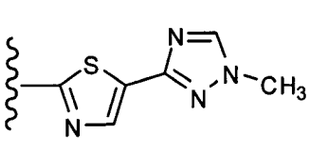
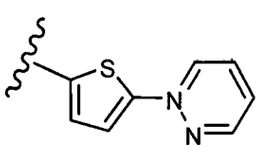
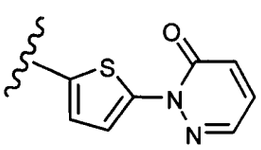
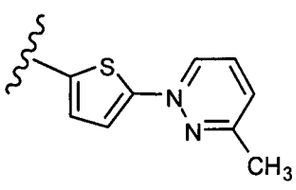
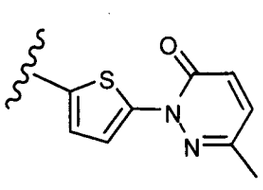
,



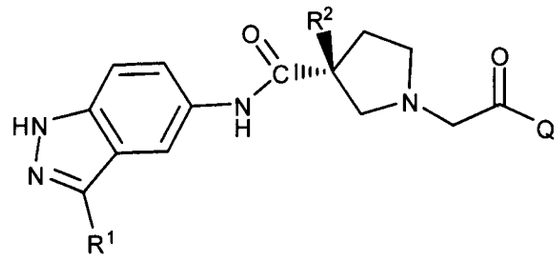
,



,


,

,

,

,

,

,

,

,

,

,

,

,

,

, y

.

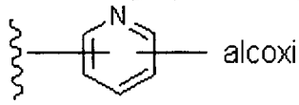
Otras realizaciones de esta invención se dirigen a compuestos de fórmula 1.1:



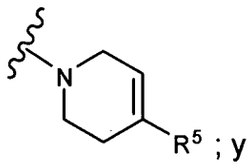
(1.1)

donde:

R^2 es un grupo –S-alquilo (C_1-C_2), y R^1 es:

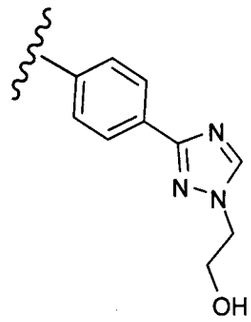


Q es:

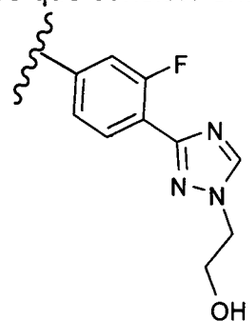


; y

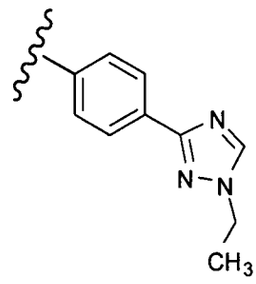
R^5 se selecciona del grupo que consiste en:



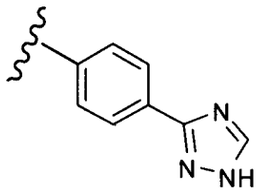
,



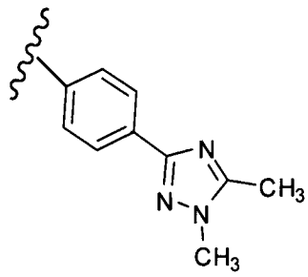
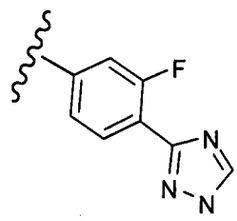
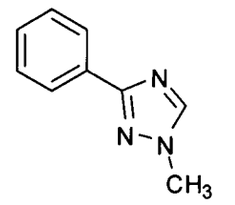
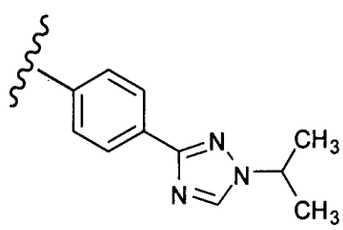
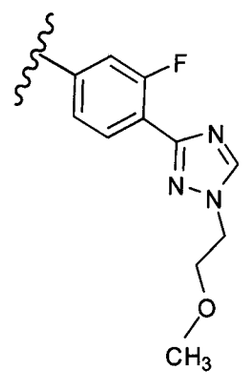
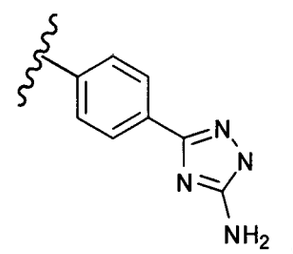
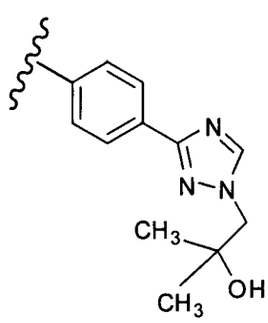
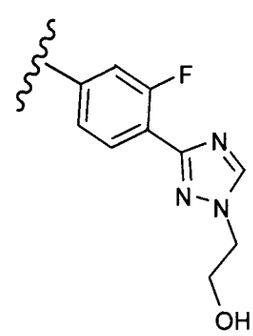
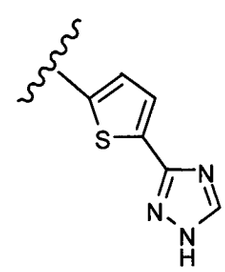
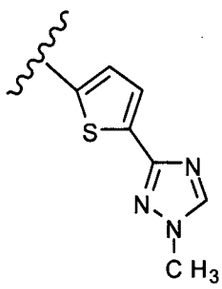
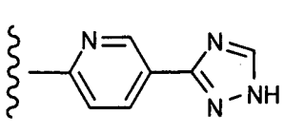
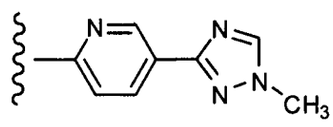
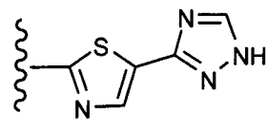
,

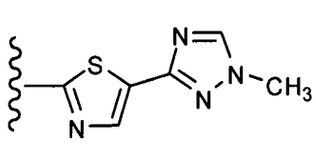
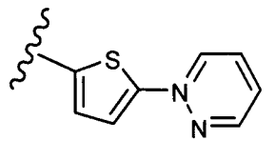
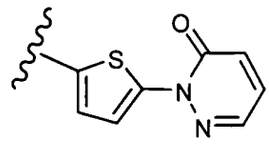
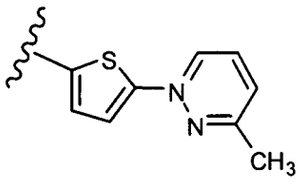
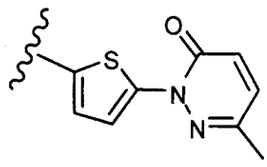


,



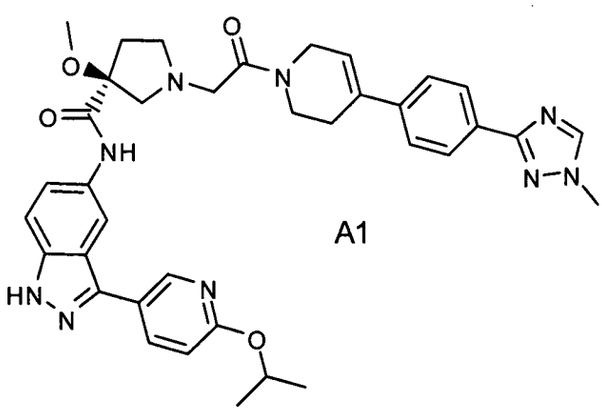
,


,

,

,

,

,

,

,

,

,

,

,

,

,

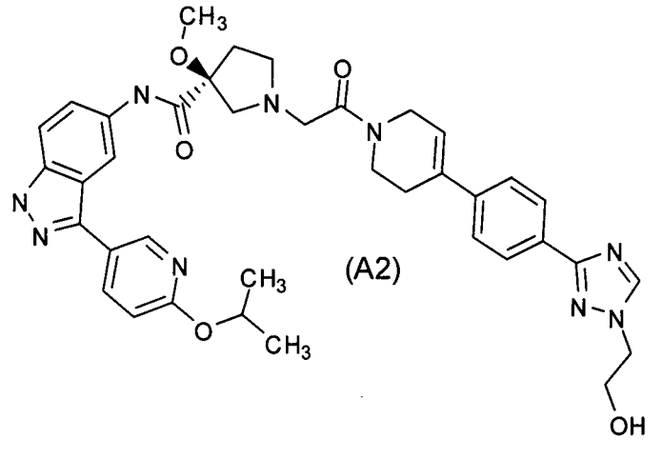






Otras realizaciones de esta invención se dirigen a cualquiera de las realizaciones anteriores (por ejemplo, cualquiera de las Realizaciones Nº 1 a 46, o cualquiera de las realizaciones que siguen a la Realización Nº 46) donde uno o más átomos de hidrógeno son deuterio.

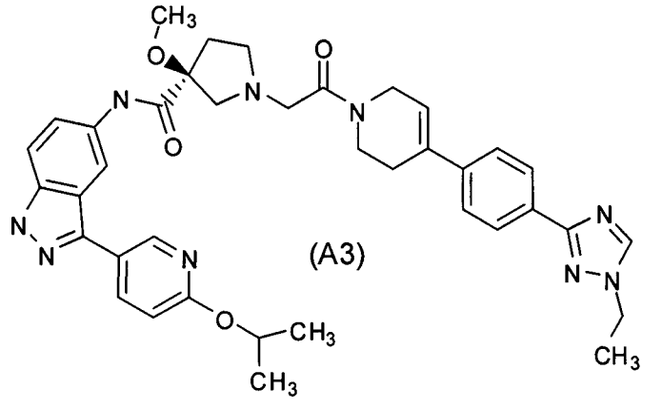
Los compuestos representativos de esta invención incluyen, pero sin limitación:



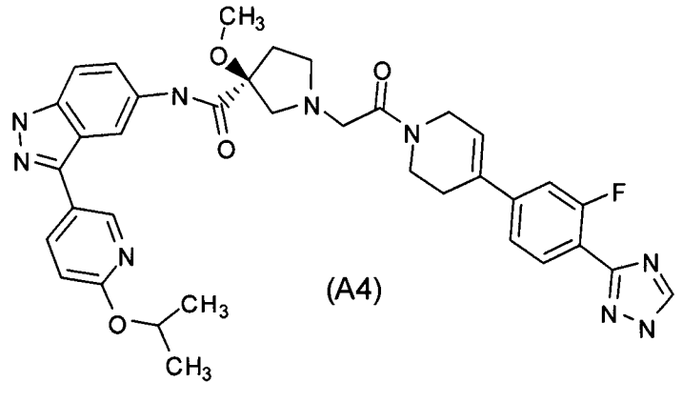
A1



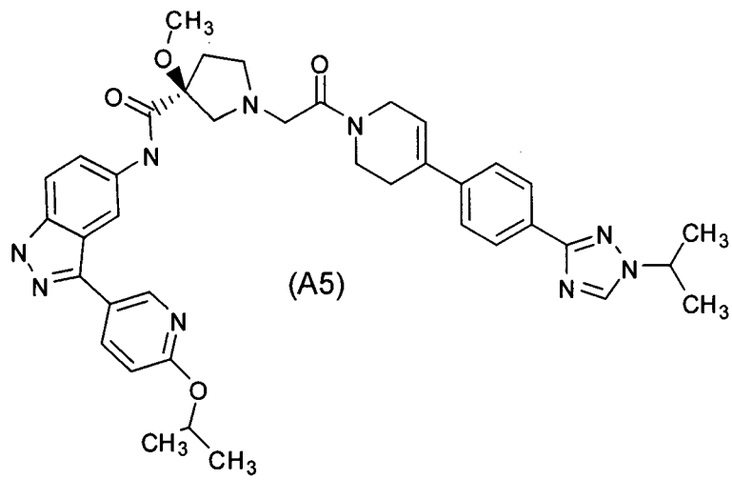
(A2),



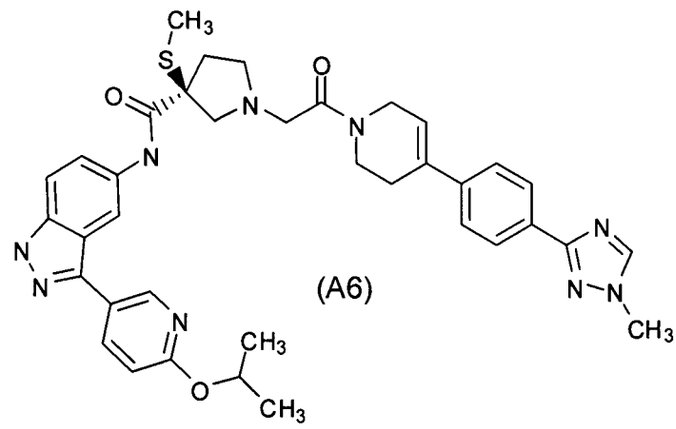
(A3),



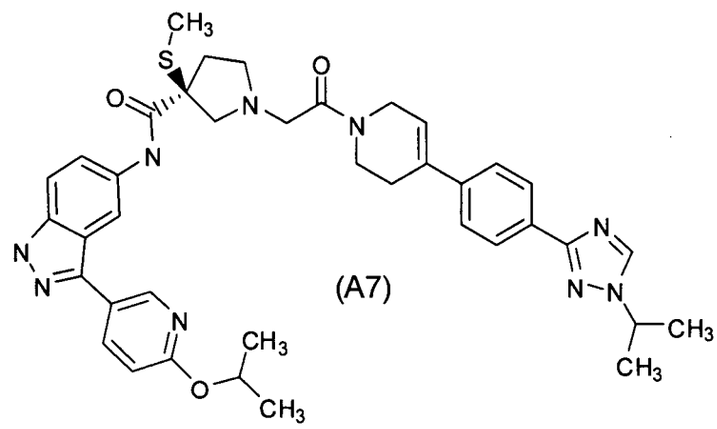
(A4),



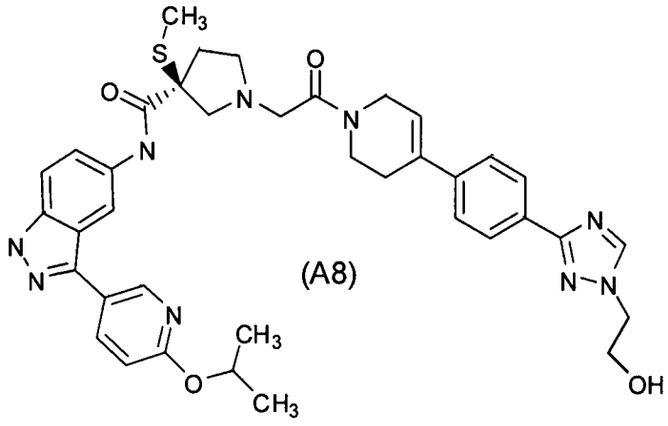
(A5)



(A6)

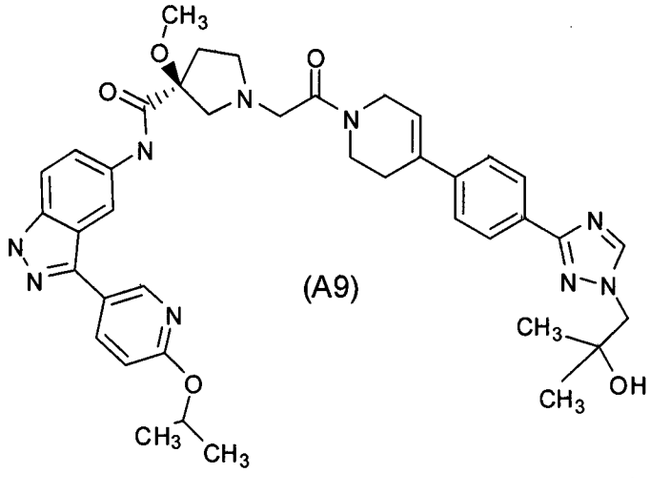


(A7)



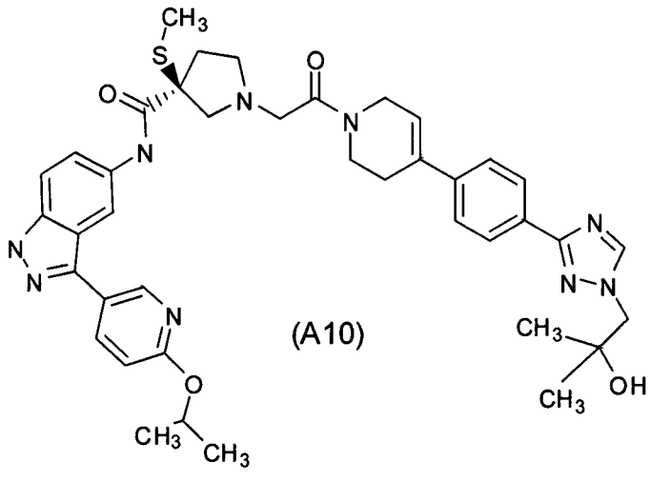
(A8)

,



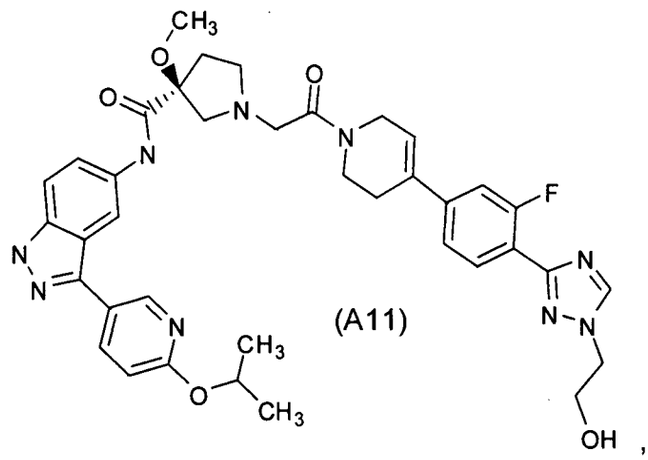
(A9)

,

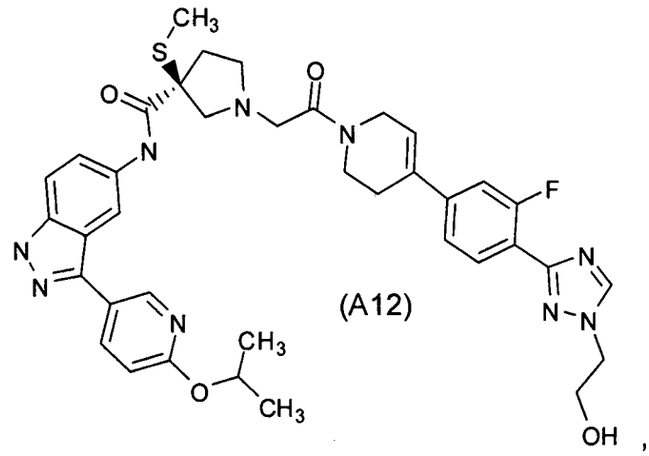


(A10)

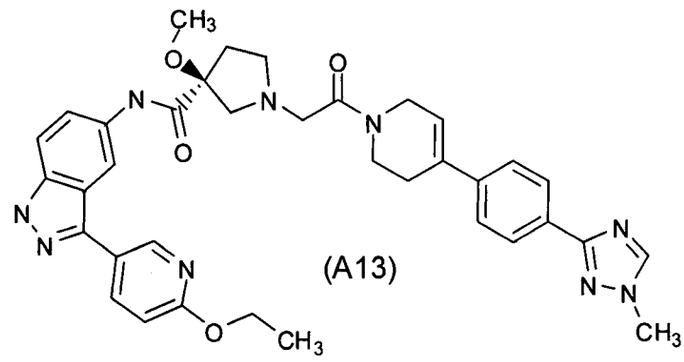
,



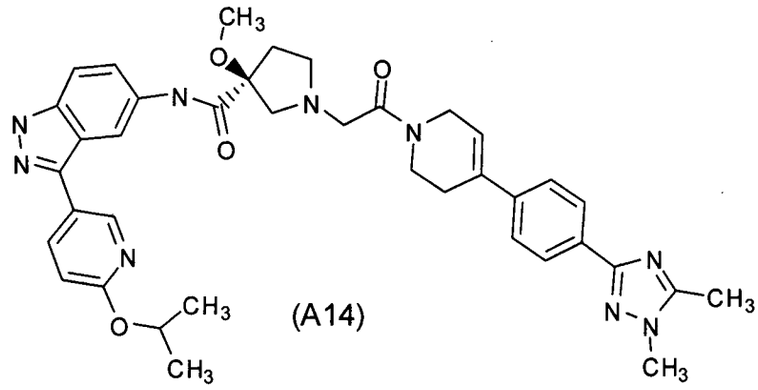
(A11) ,



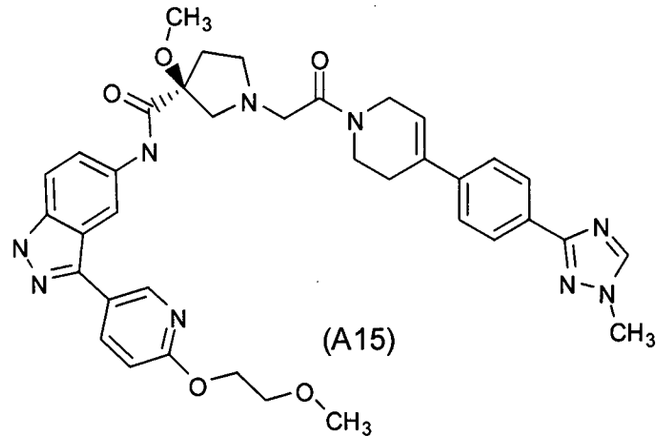
(A12) ,



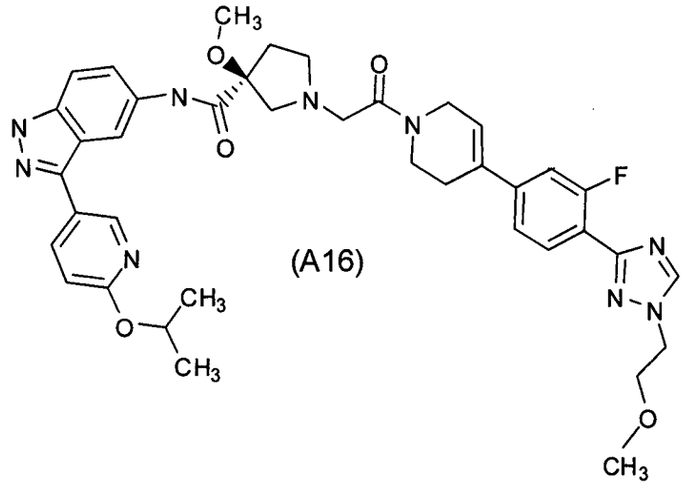
(A13) ,



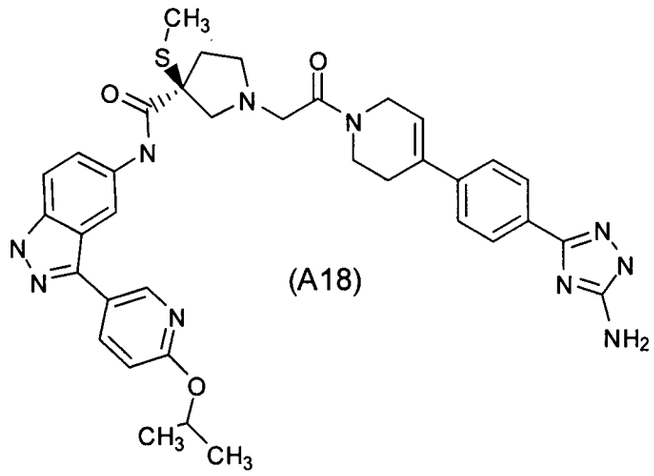
(A14)



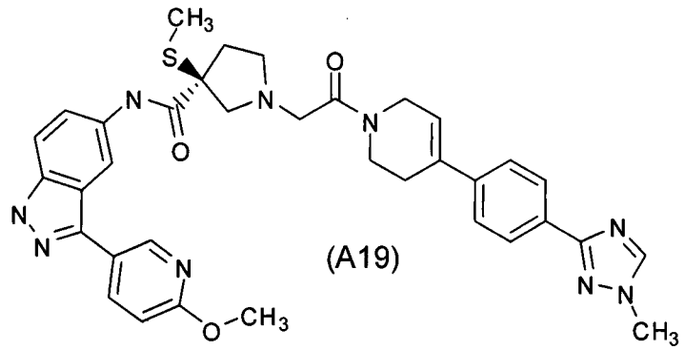
(A15)



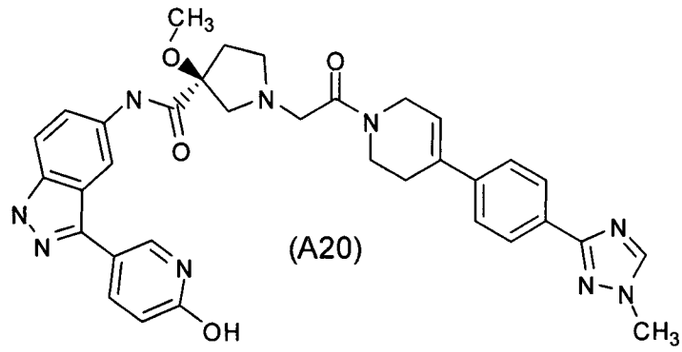
(A16)



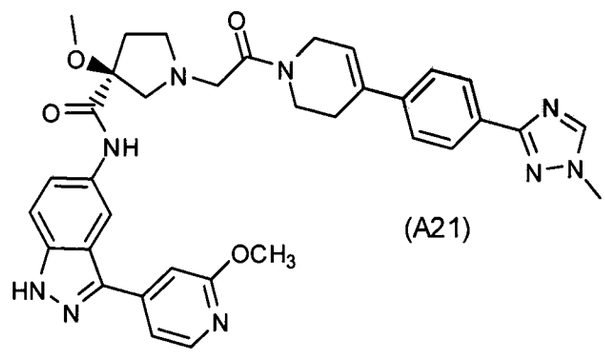
(A18),



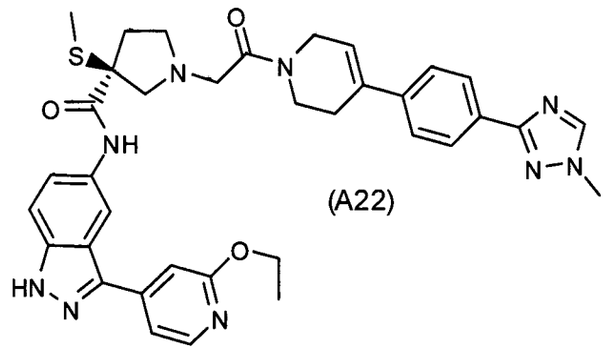
(A19),



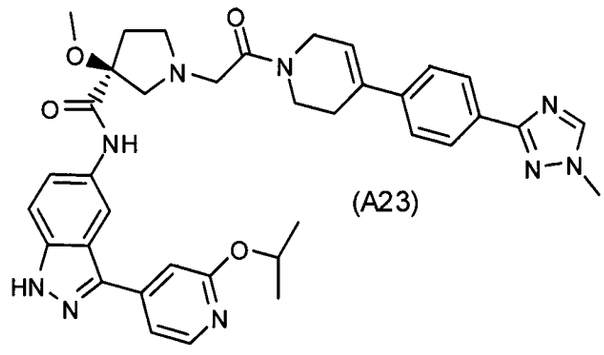
(A20),



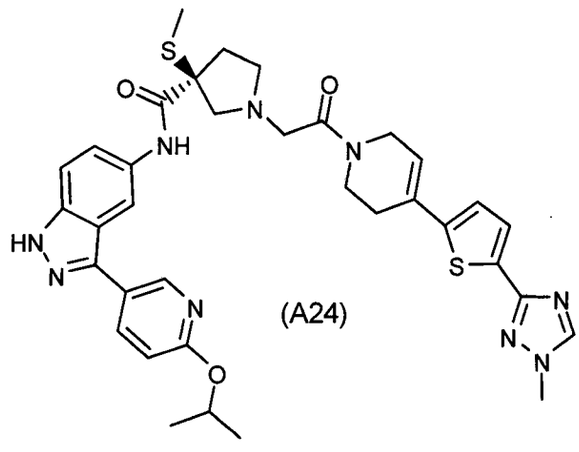
(A21)



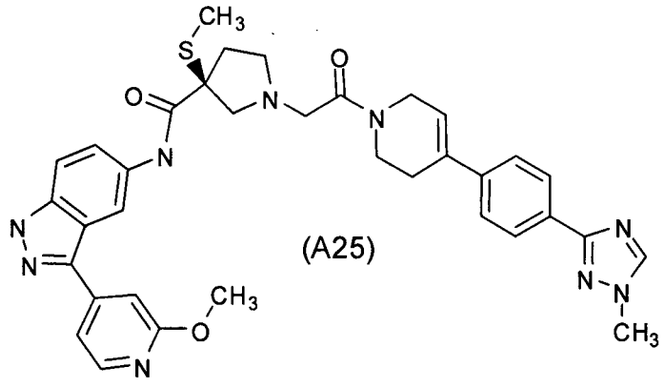
(A22)



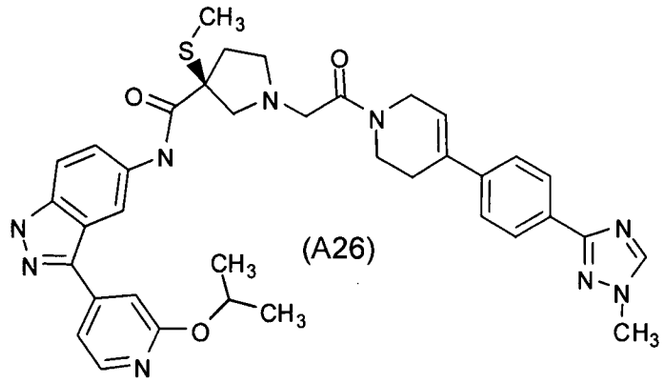
(A23)



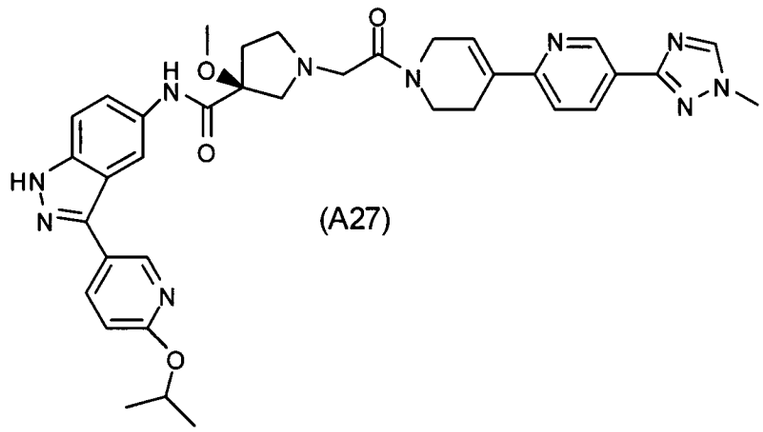
(A24)



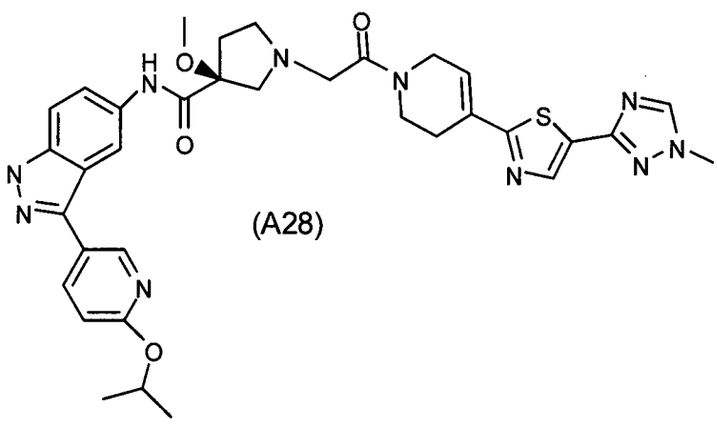
(A25)



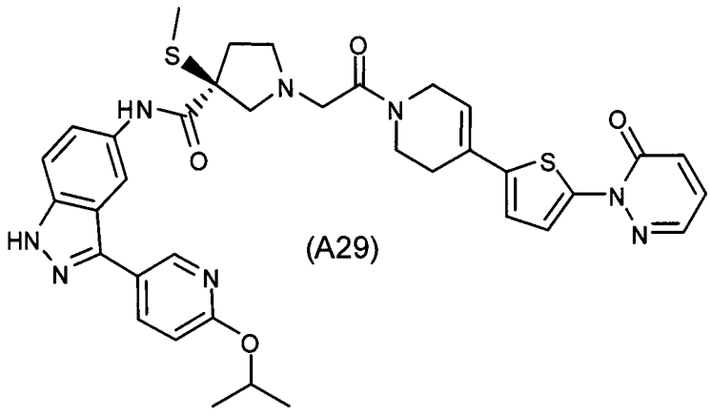
(A26)



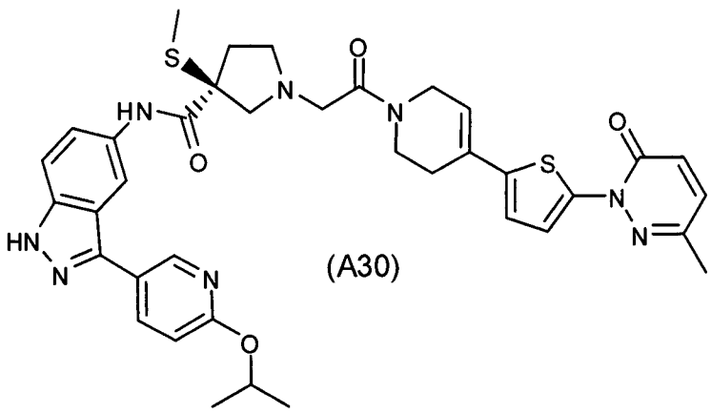
(A27)



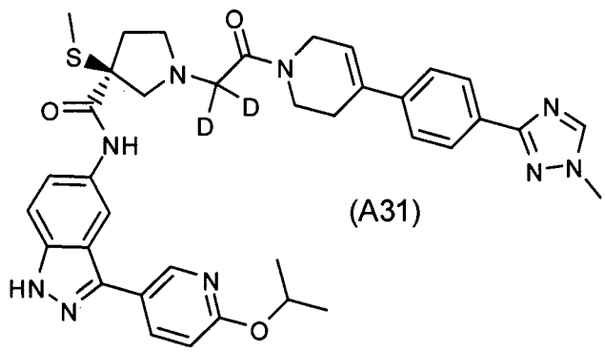
(A28)



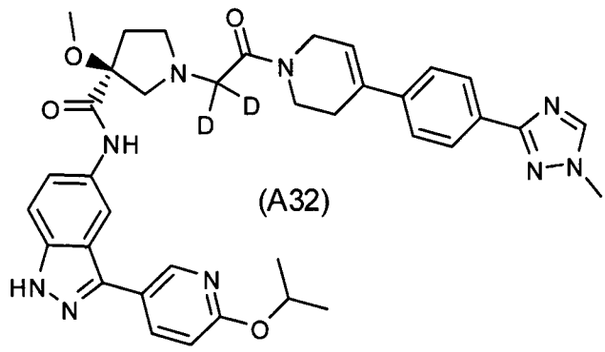
(A29)



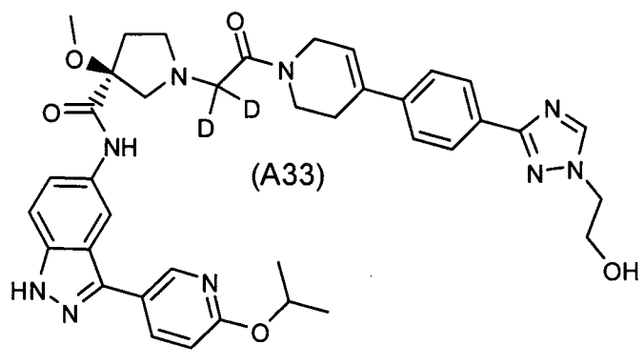
(A30)



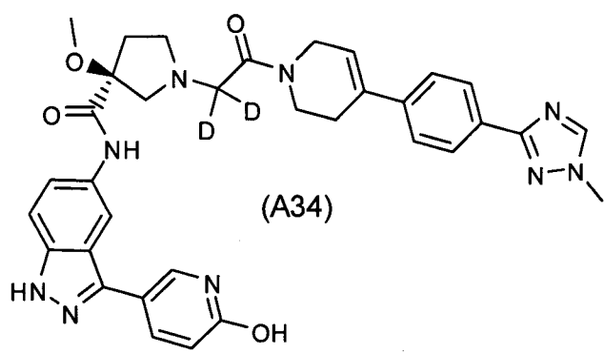
(A31),



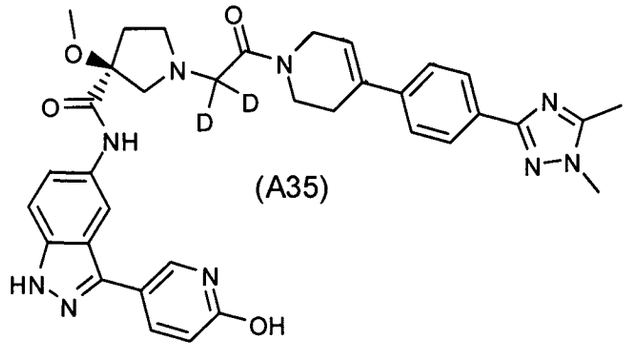
(A32),



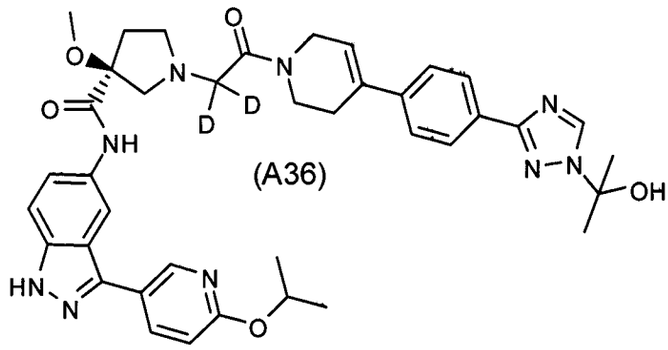
(A33),



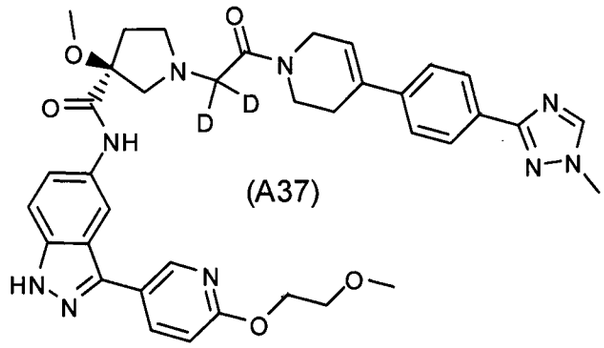
(A34),



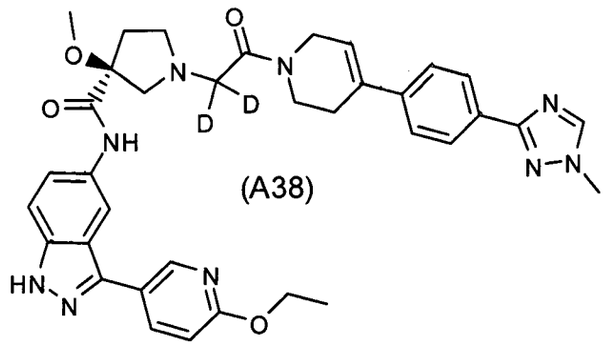
(A35)



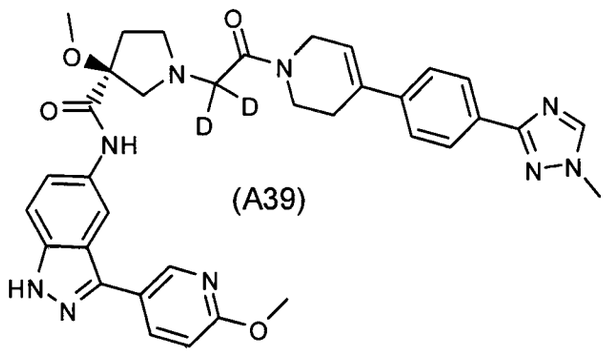
(A36)



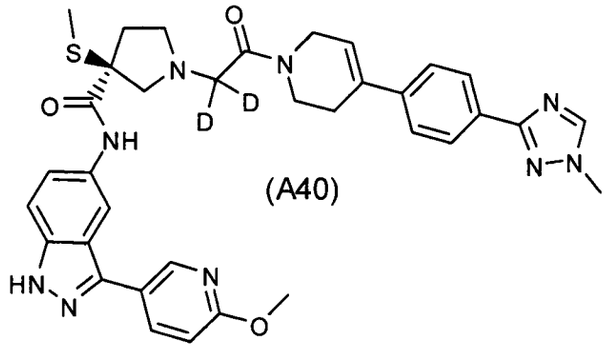
(A37)



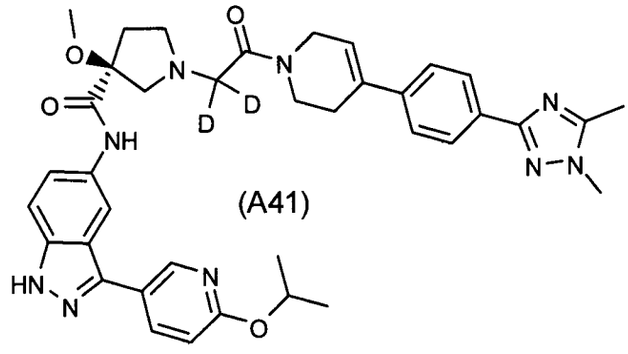
(A38)



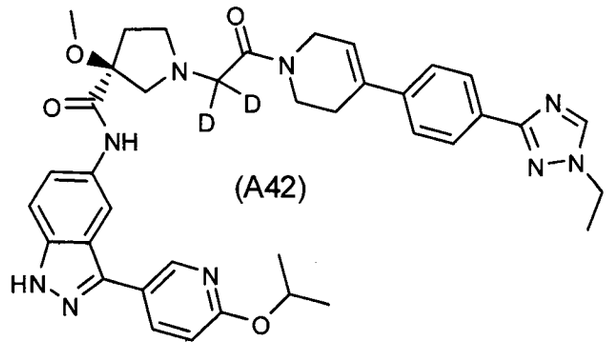
(A39)



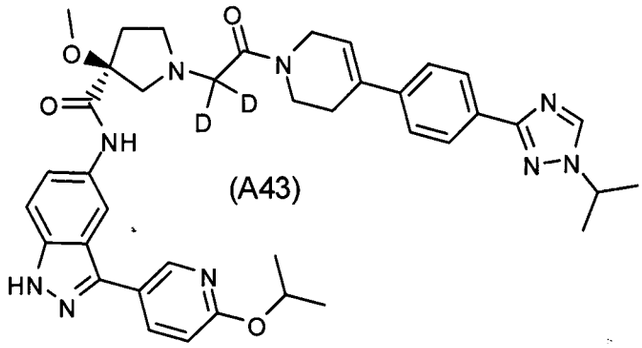
(A40)



(A41)

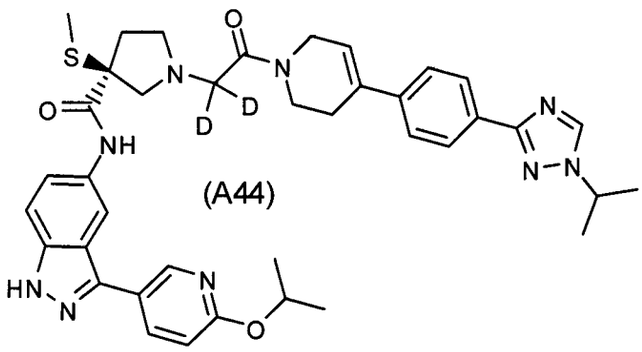


(A42)



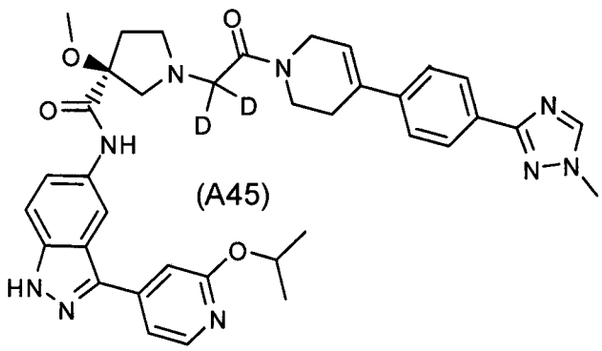
(A43)

,



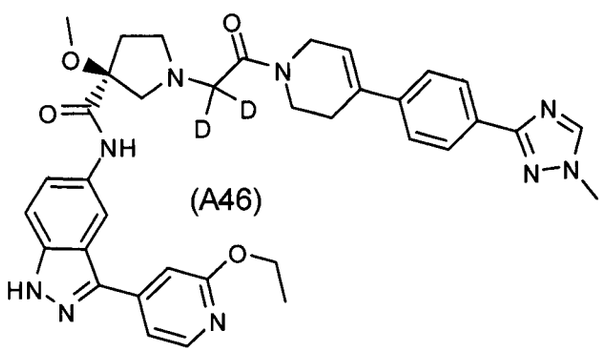
(A44)

,



(A45)

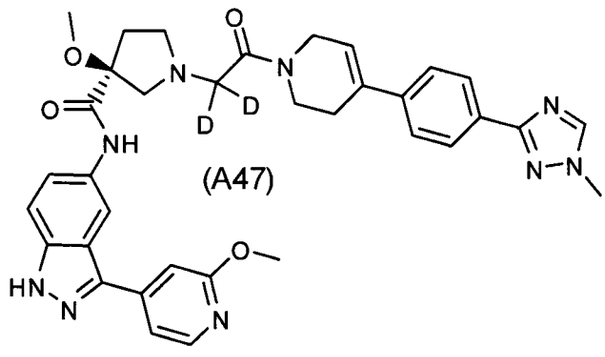
,



(A46)

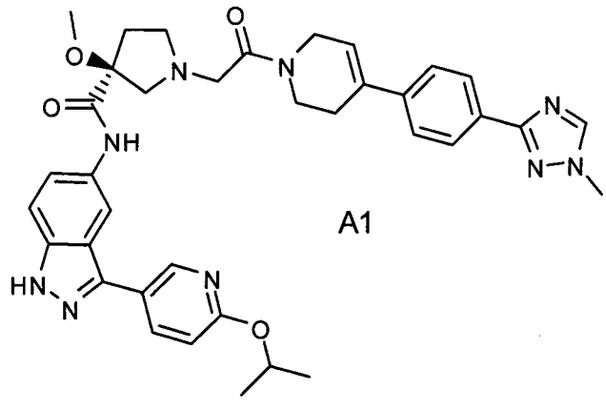
, y

246

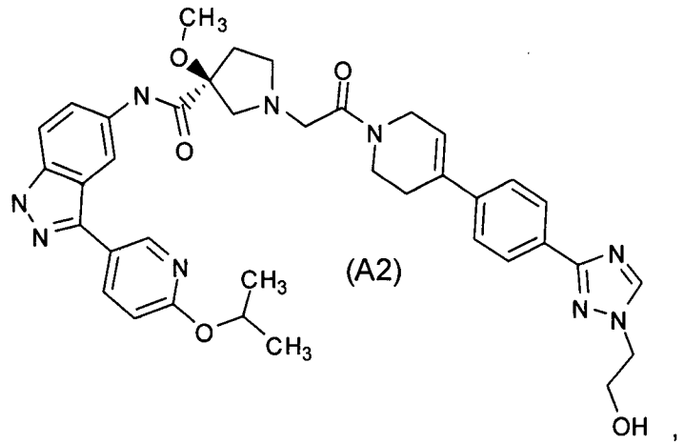


(A47)

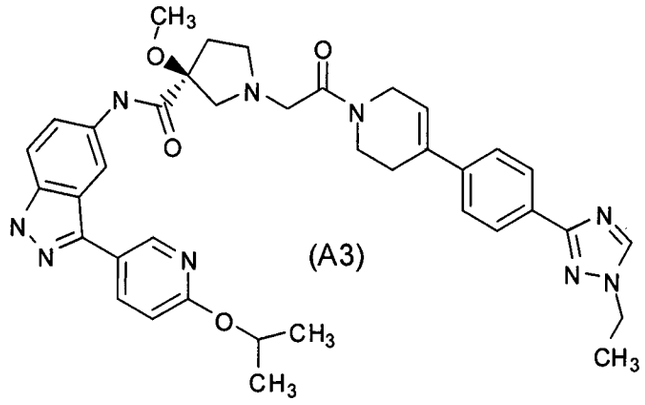
Los compuestos representativos de esta invención incluyen, pero sin limitación:



A1

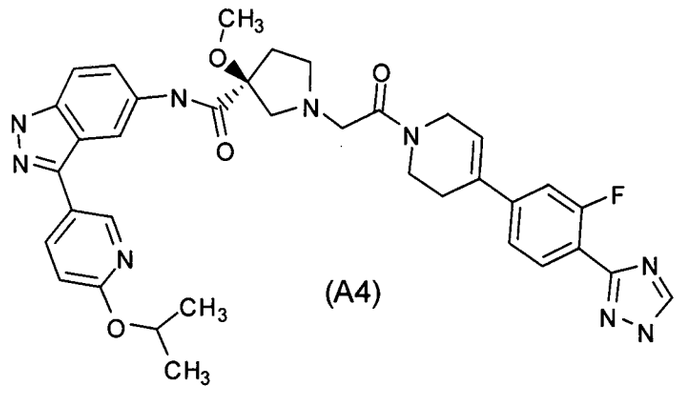


(A2)



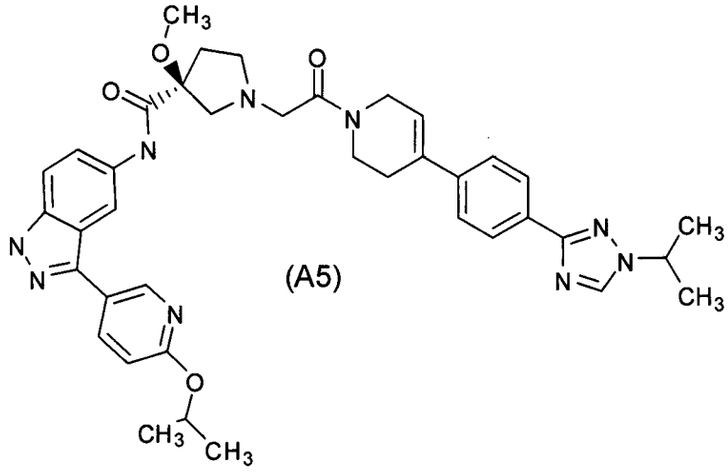
(A3)

,



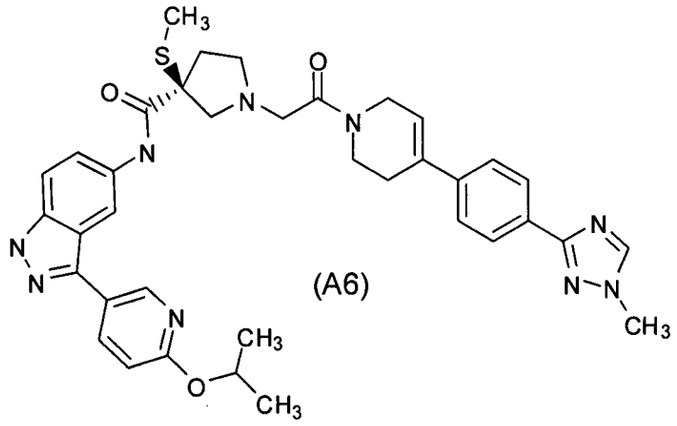
(A4)

,

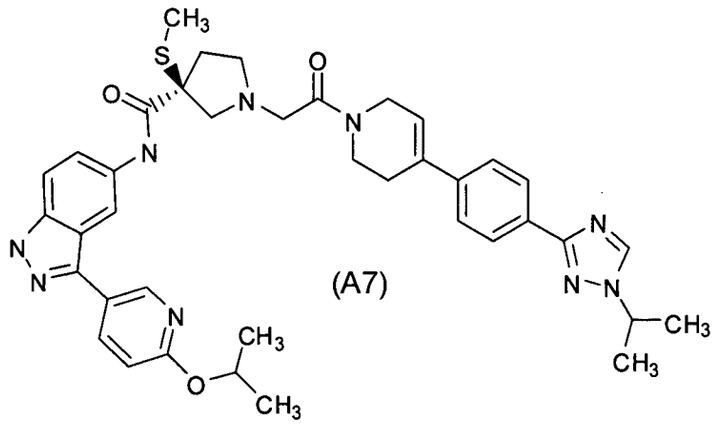


(A5)

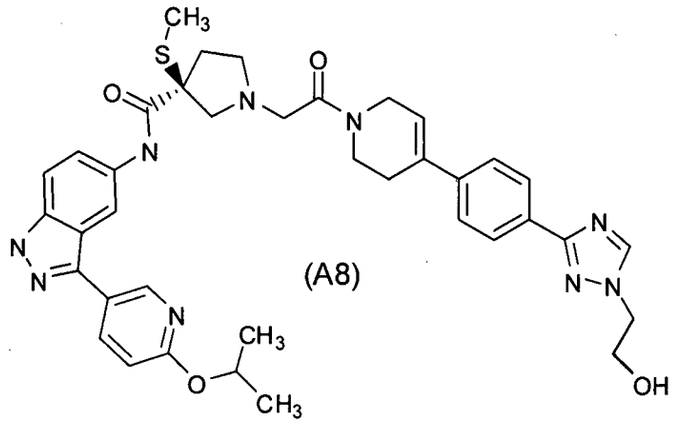
,



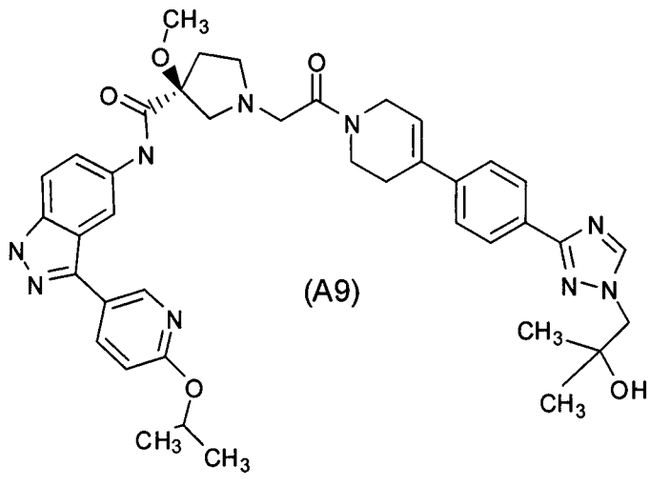
(A6)



(A7)

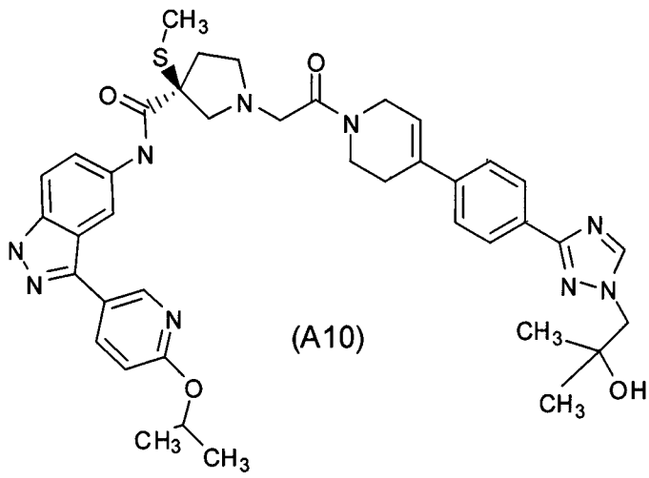


(A8)



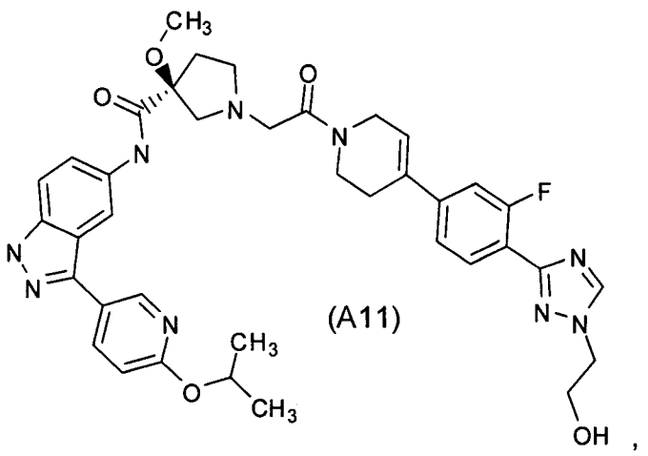
(A9)

,



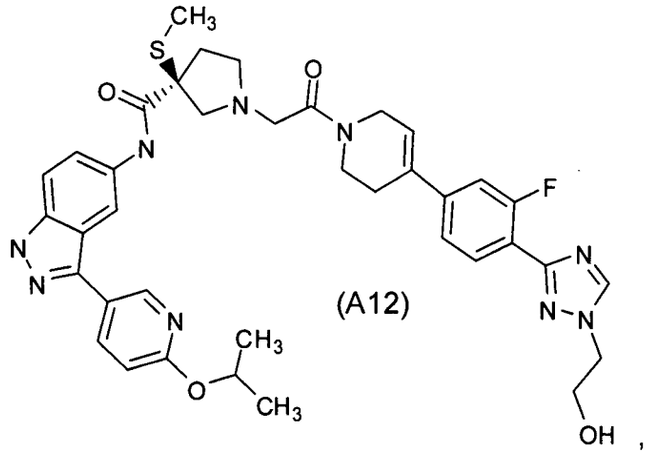
(A10)

,

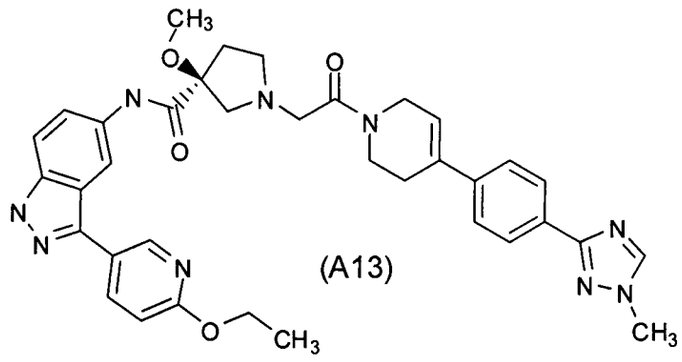


(A11)

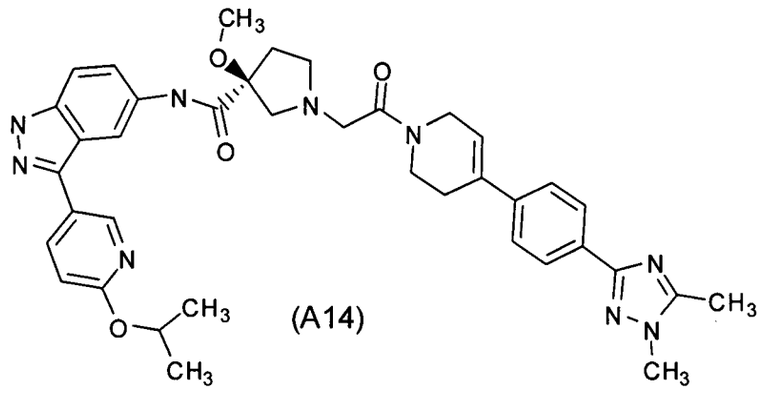
,



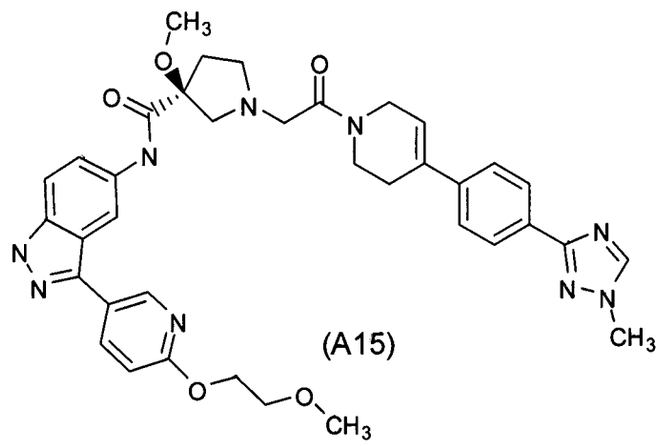
(A12) ,



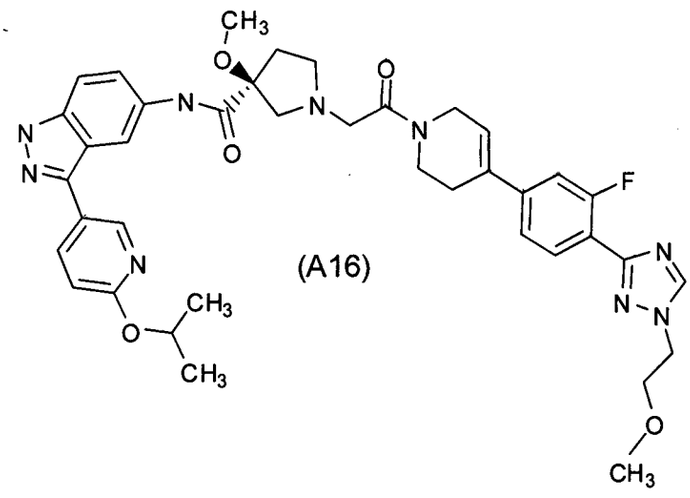
(A13) ,



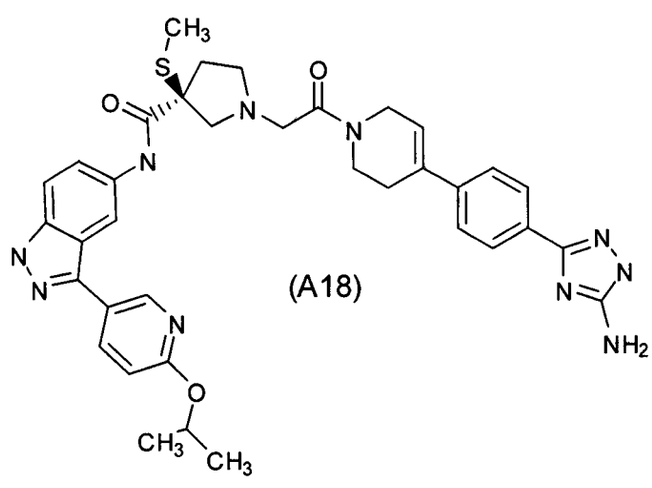
(A14) ,



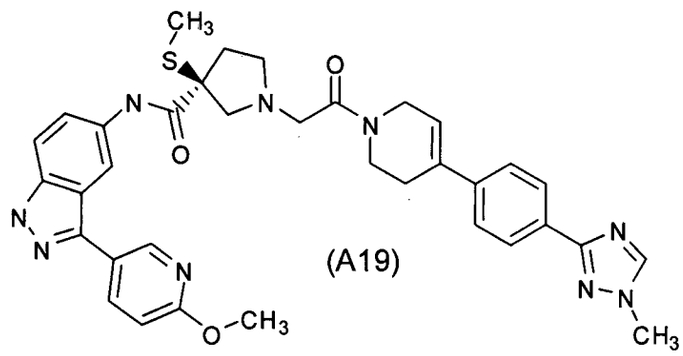
(A15)



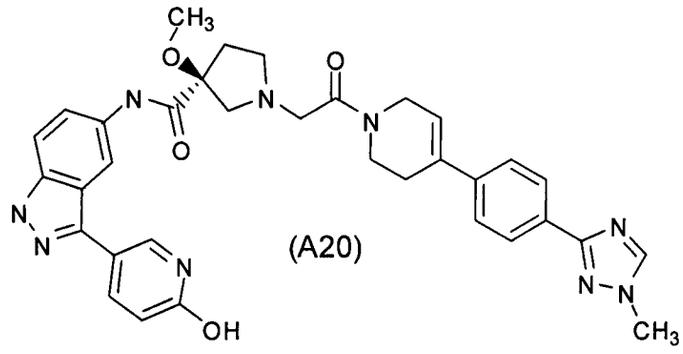
(A16)



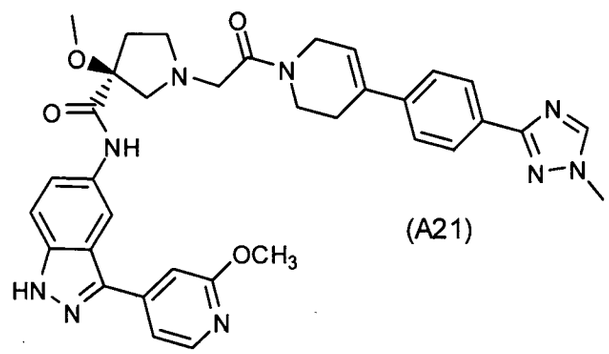
(A18)



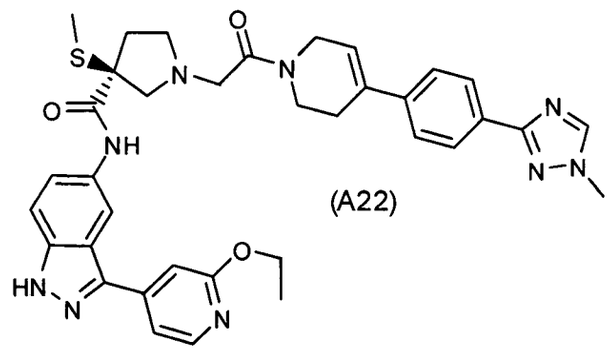
(A19)



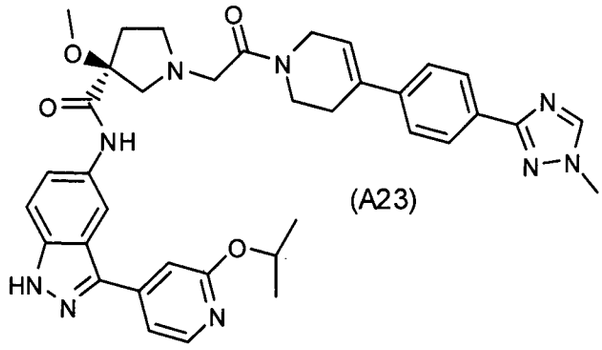
(A20)



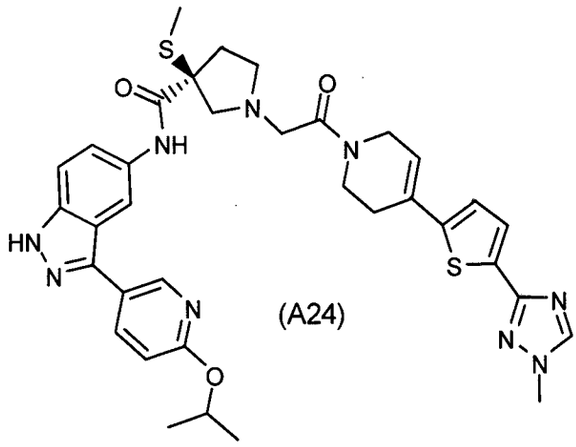
(A21)



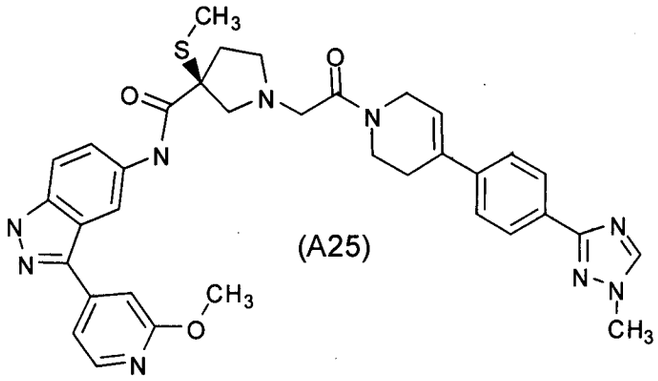
(A22)



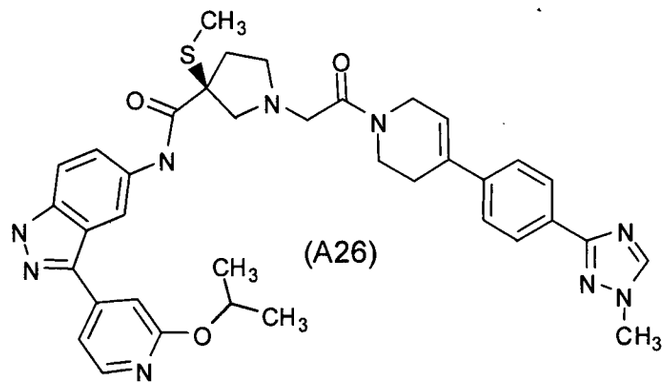
(A23)



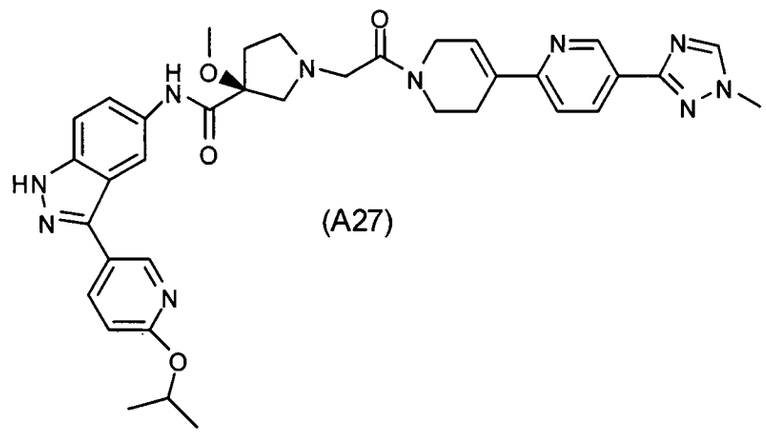
(A24)



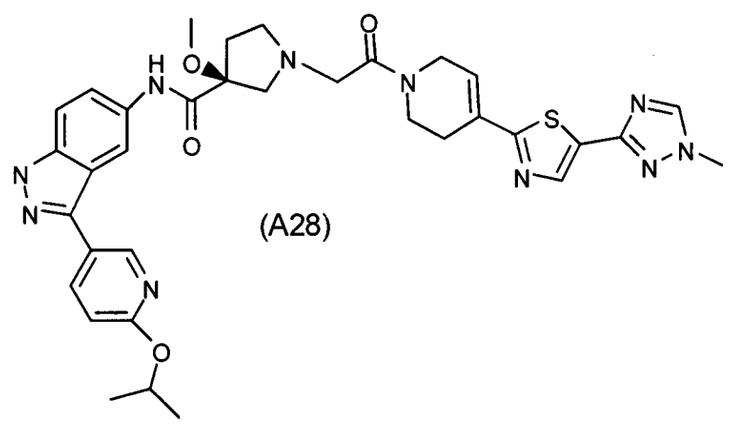
(A25)



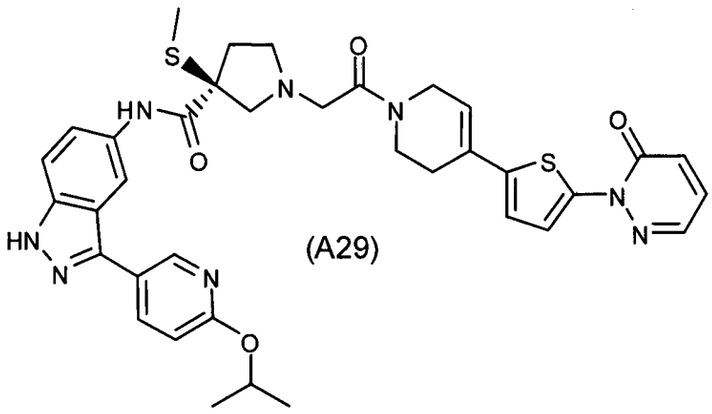
(A26)



(A27)

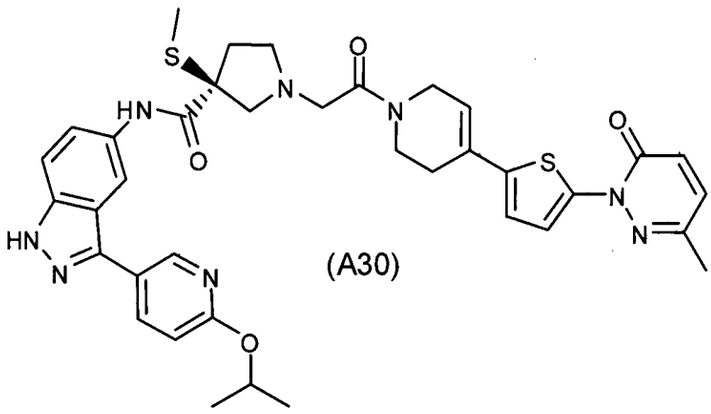


(A28)



(A29)

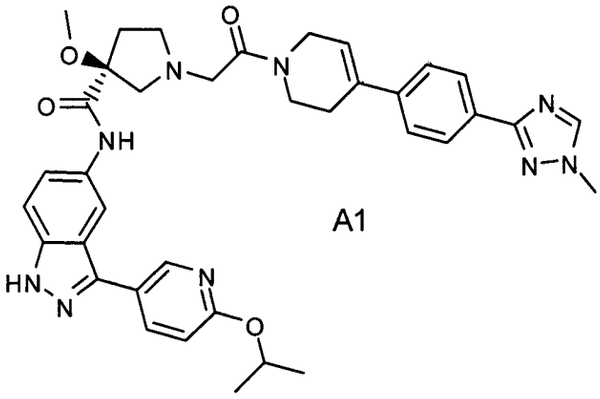
, y



(A30)

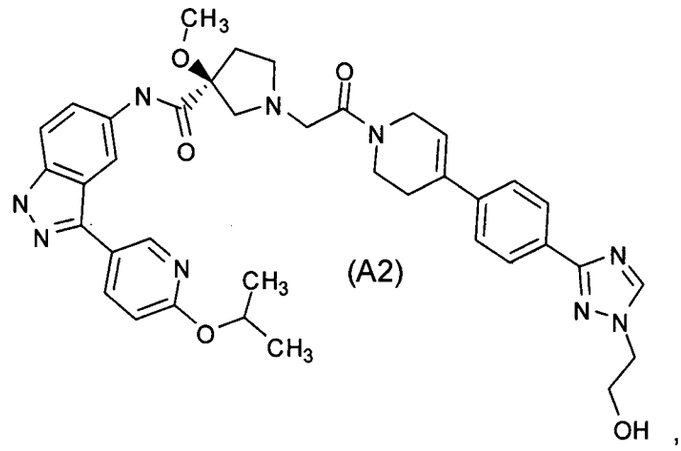
.

Los compuestos representativos de esta invención incluyen, pero sin limitación:

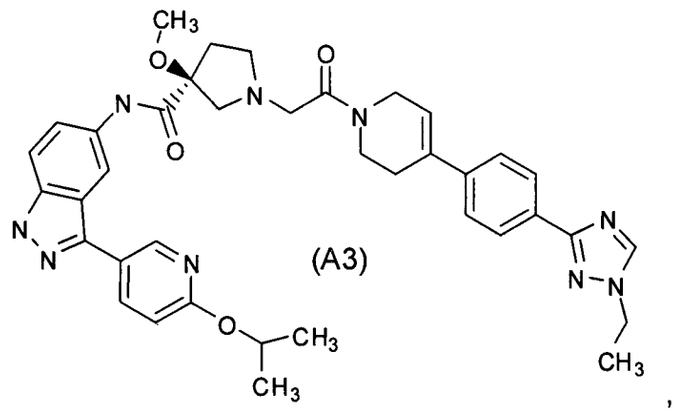


A1

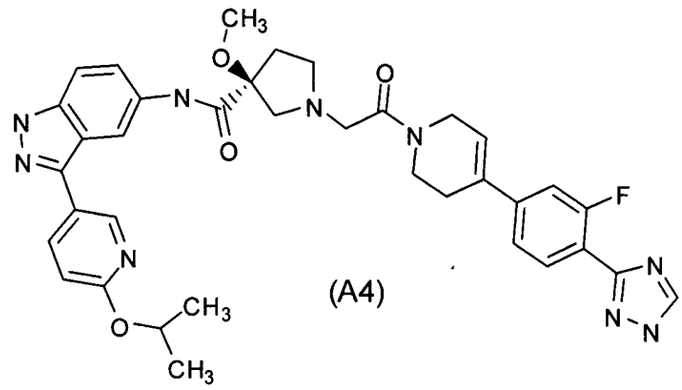
,



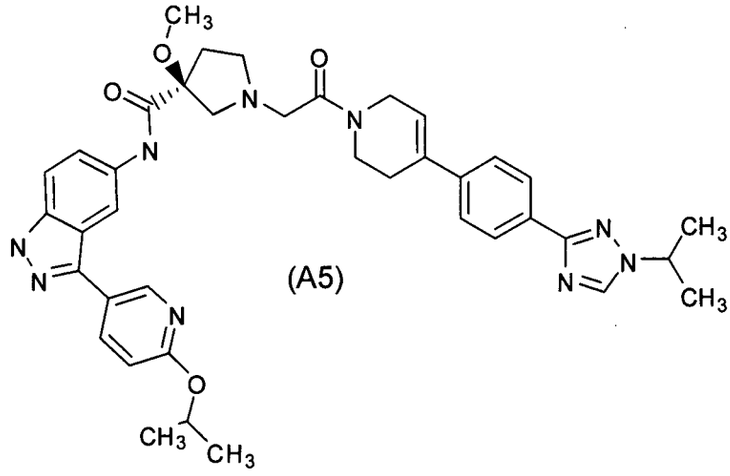
(A2),



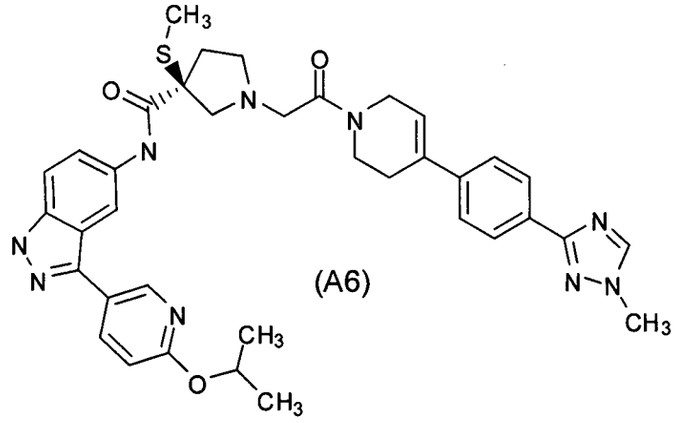
(A3),



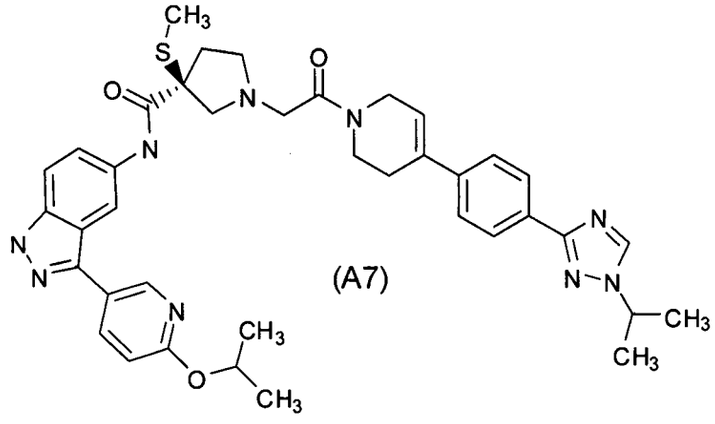
(A4),



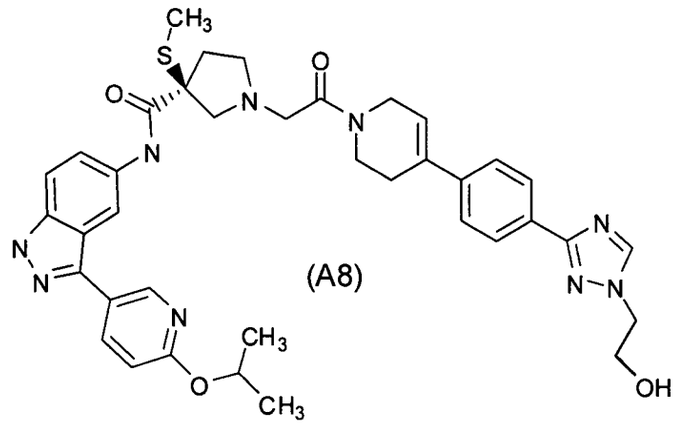
(A5)



(A6)

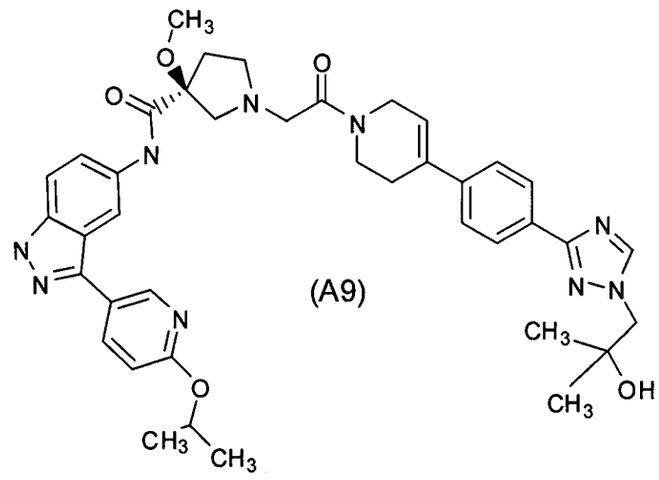


(A7)



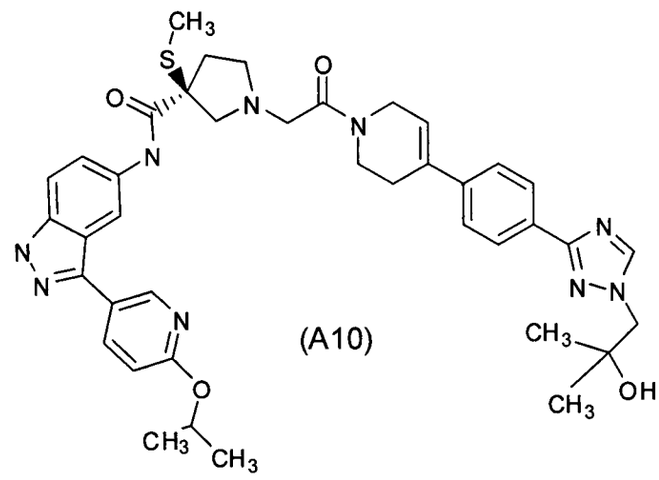
(A8)

,



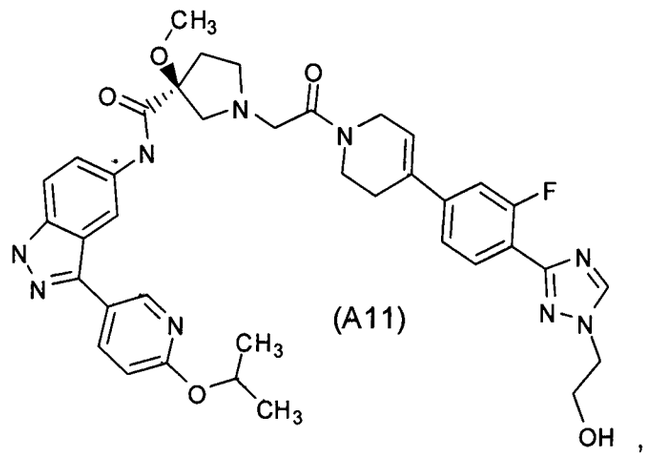
(A9)

,

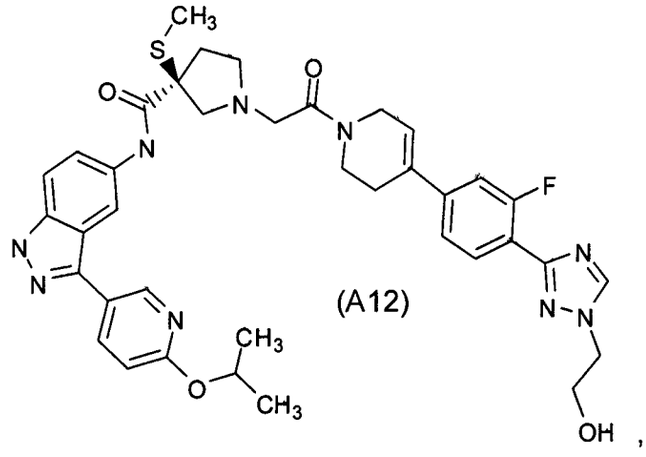


(A10)

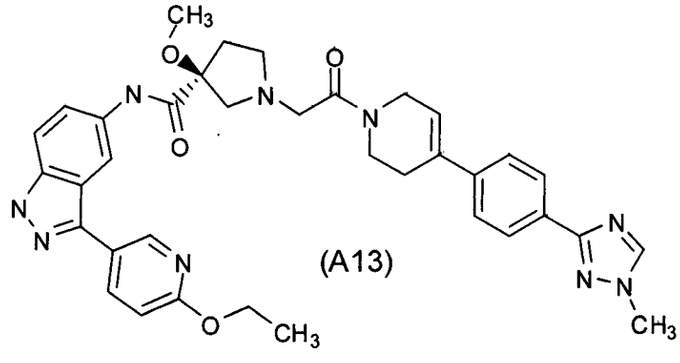
,



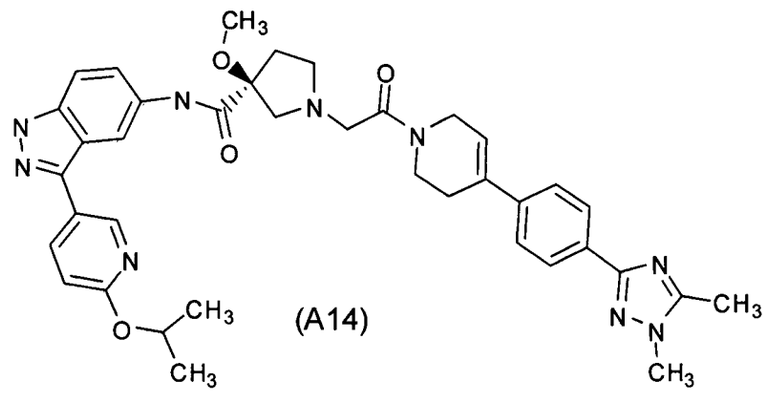
(A11) ,



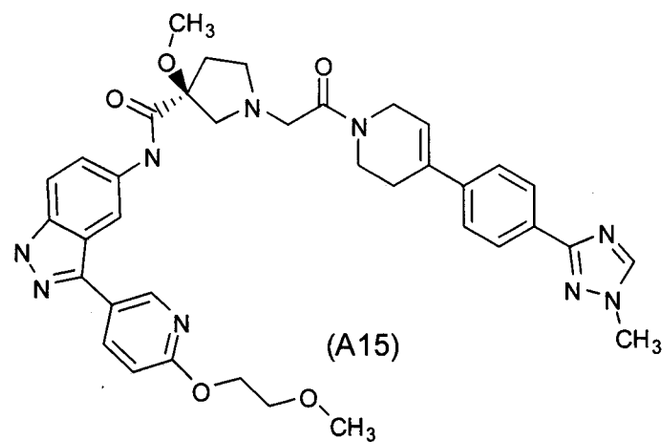
(A12) ,



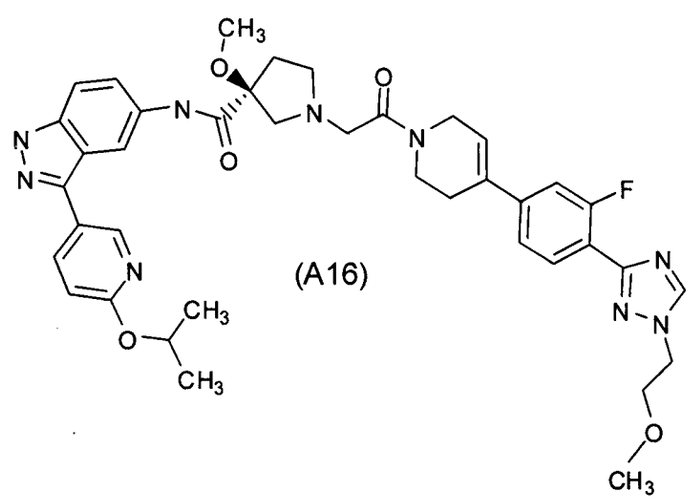
(A13) ,



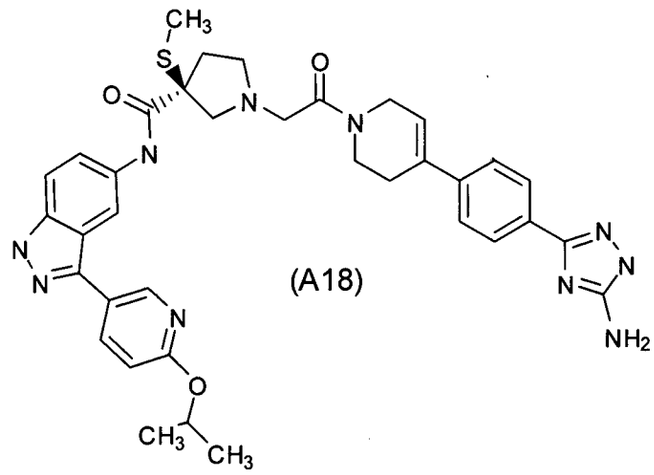
(A14)



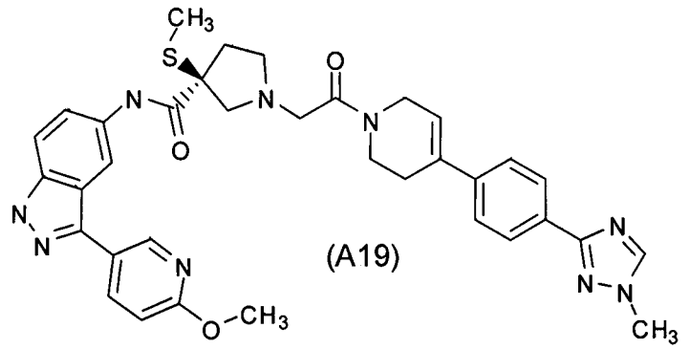
(A15)



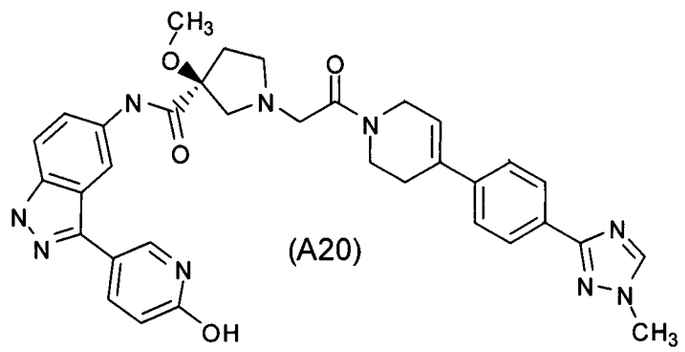
(A16)



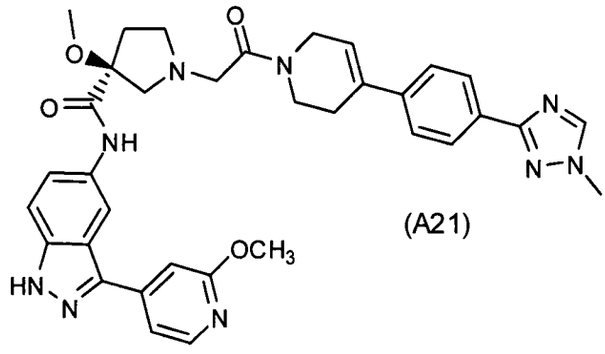
(A18)



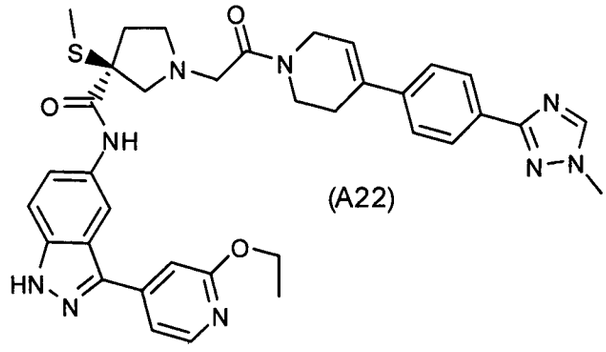
(A19),



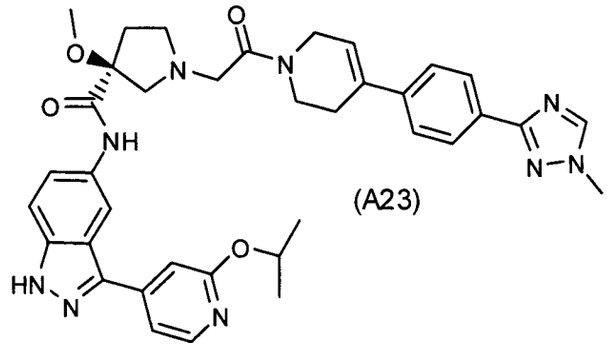
(A20),



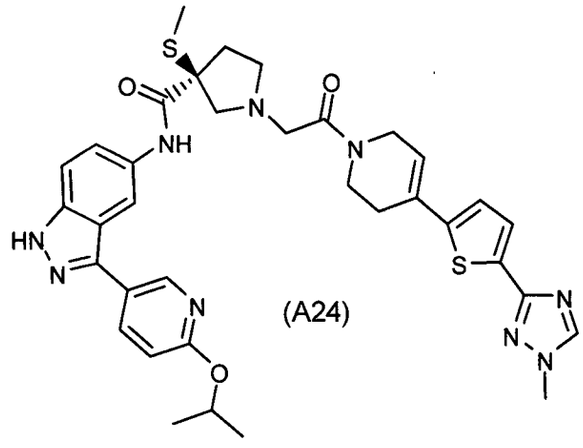
(A21)



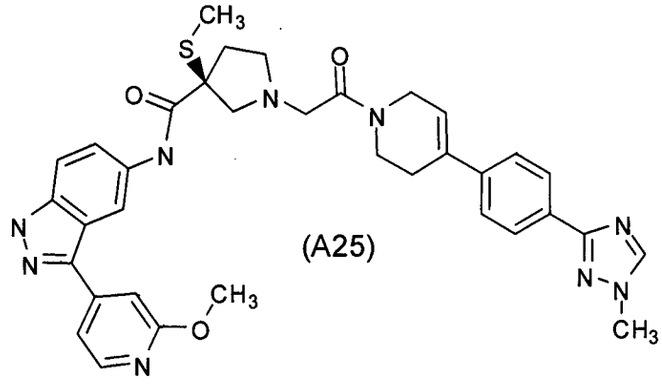
(A22)



(A23)

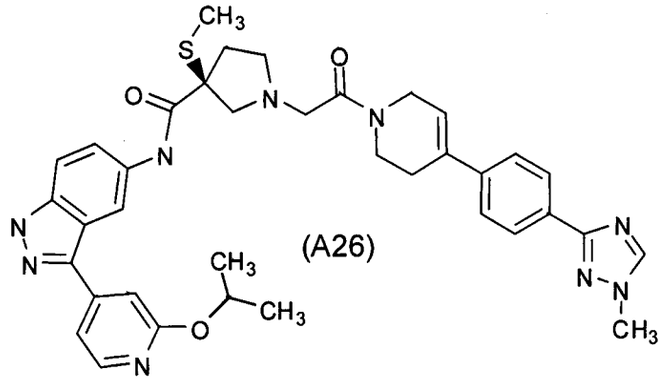


(A24)



(A25)

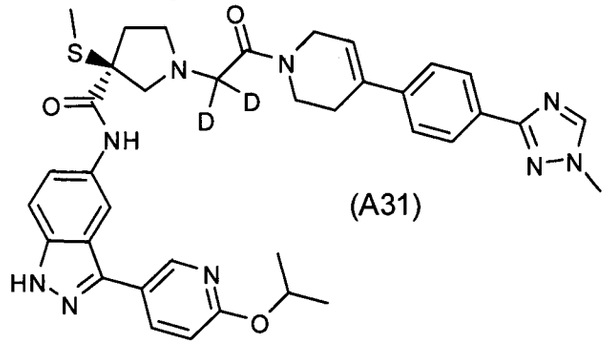
, y



(A26)

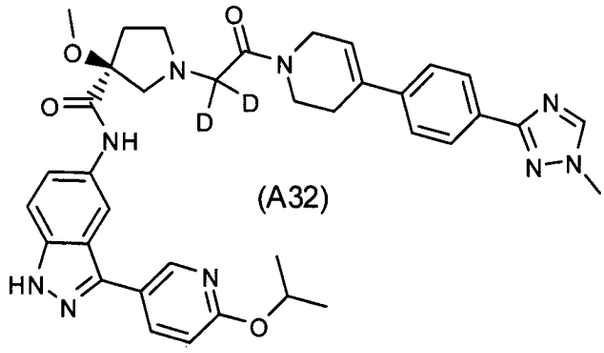
.

Los compuestos representativos de esta invención donde se ha reemplazado hidrógeno con deuterio incluyen, pero sin limitación:

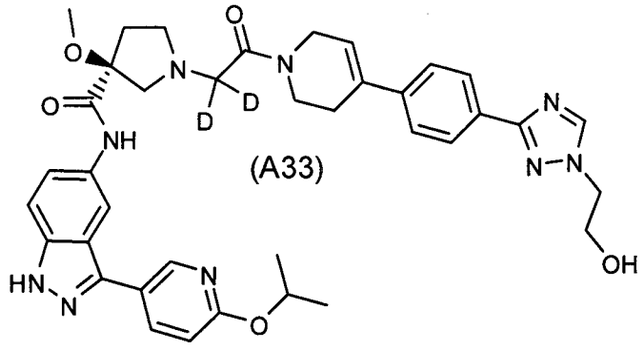


(A31)

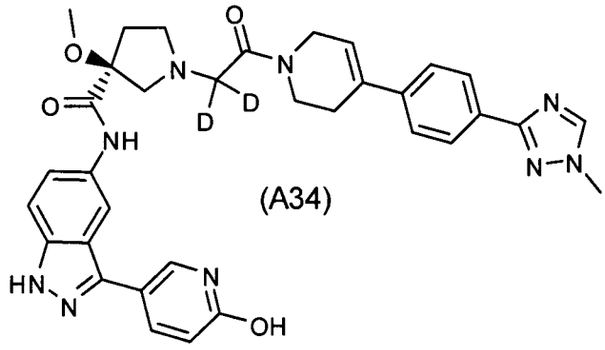
,



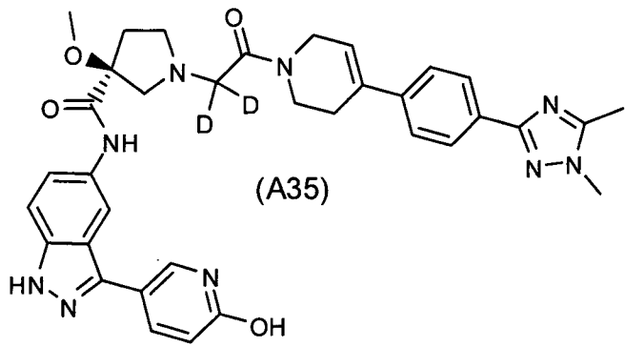
(A32)



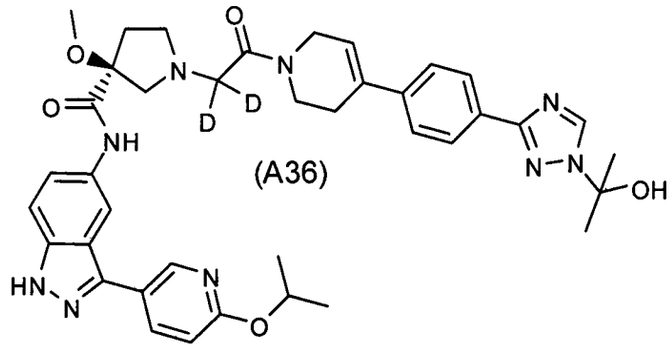
(A33)



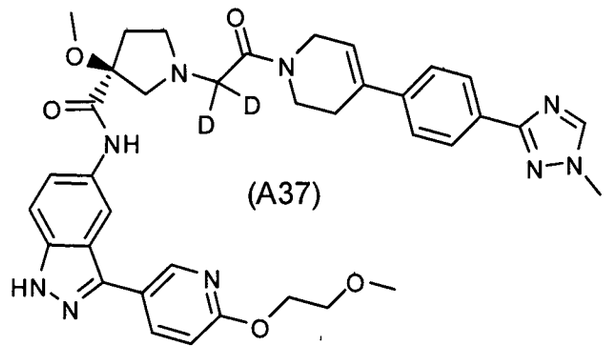
(A34)



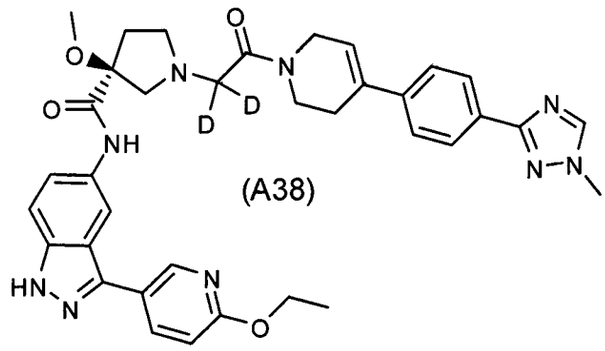
(A35)



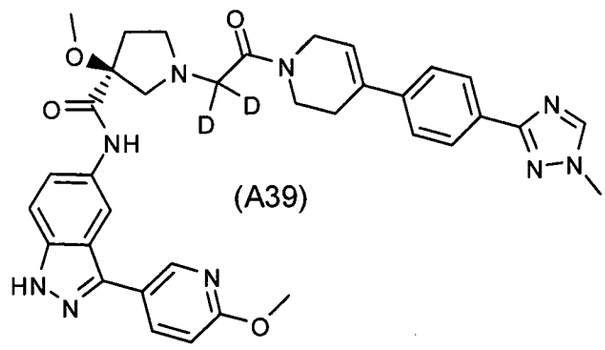
(A36)



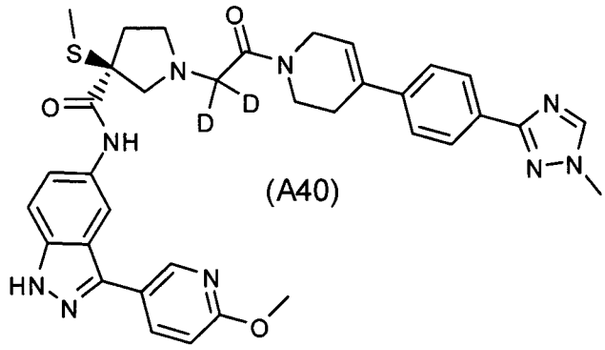
(A37)



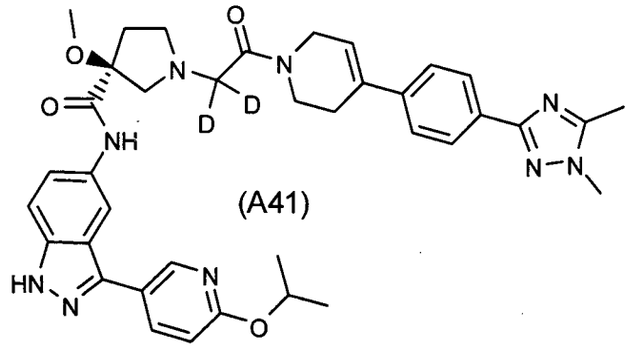
(A38)



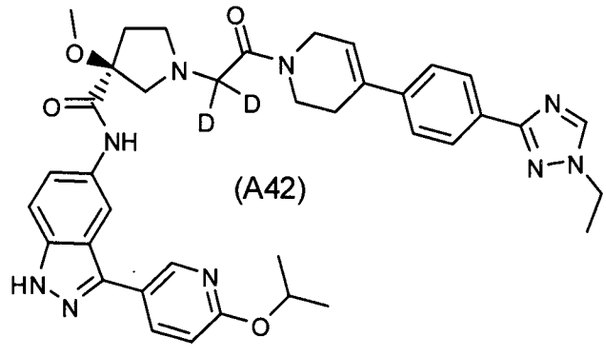
(A39)



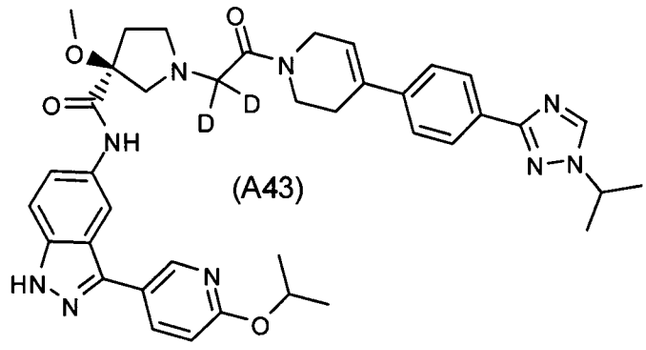
(A40)



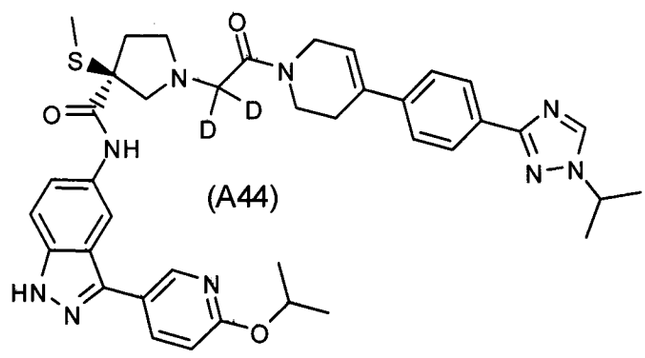
(A41)



(A42)

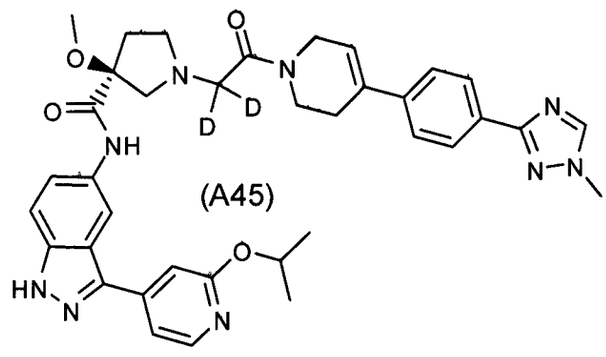


(A43)



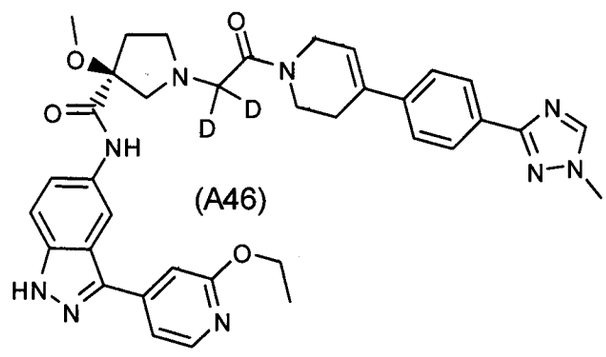
(A44)

,



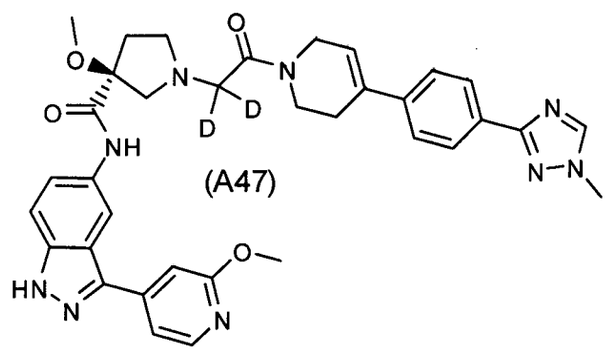
(A45)

,



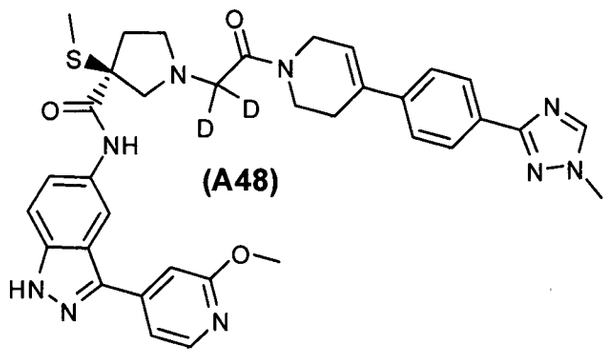
(A46)

,



(A47)

y



(A48)

Otra realización de esta invención se dirige al compuesto A1.

Otra realización de esta invención se dirige al compuesto A2.

Otra realización de esta invención se dirige al compuesto A3.

Otra realización de esta invención se dirige al compuesto A4.

Otra realización de esta invención se dirige al compuesto A5.

Otra realización de esta invención se dirige al compuesto A6.

Otra realización de esta invención se dirige al compuesto A7.

Otra realización de esta invención se dirige al compuesto A8.

Otra realización de esta invención se dirige al compuesto A9.

Otra realización de esta invención se dirige al compuesto A10.

Otra realización de esta invención se dirige al compuesto A11.

Otra realización de esta invención se dirige al compuesto A12.

Otra realización de esta invención se dirige al compuesto A13.

Otra realización de esta invención se dirige al compuesto A14.

Otra realización de esta invención se dirige al compuesto A15.

Otra realización de esta invención se dirige al compuesto A16.

Otra realización de esta invención se dirige al compuesto A18.

Otra realización de esta invención se dirige al compuesto A19.

Otra realización de esta invención se dirige al compuesto A20.

Otra realización de esta invención se dirige al compuesto A21.

Otra realización de esta invención se dirige al compuesto A22.

Otra realización de esta invención se dirige al compuesto A23.

Otra realización de esta invención se dirige al compuesto A24.

Otra realización de esta invención se dirige al compuesto A25.

Otra realización de esta invención se dirige al compuesto A26.

Otra realización de esta invención se dirige al compuesto A27.

Otra realización de esta invención se dirige al compuesto A28.

Otra realización de esta invención se dirige al compuesto A29.

Otra realización de esta invención se dirige al compuesto A30.

Otra realización de esta invención se dirige al compuesto A31.

Otra realización de esta invención se dirige al compuesto A32.

Otra realización de esta invención se dirige al compuesto A33.

Otra realización de esta invención se dirige al compuesto A34.

Otra realización de esta invención se dirige al compuesto A35.

Otra realización de esta invención se dirige al compuesto A36.

Otra realización de esta invención se dirige al compuesto A37.

Otra realización de esta invención se dirige al compuesto A38.

Otra realización de esta invención se dirige al compuesto A39.

Otra realización de esta invención se dirige al compuesto A40.

Otra realización de esta invención se dirige al compuesto A41.

Otra realización de esta invención se dirige al compuesto A42.

Otra realización de esta invención se dirige al compuesto A43.

Otra realización de esta invención se dirige al compuesto A44.

Otra realización de esta invención se dirige al compuesto A45.

Otra realización de esta invención se dirige al compuesto A46.

Otra realización de esta invención se dirige al compuesto A47.

Otra realización de esta invención se dirige al compuesto A48.

Otra realización de esta invención se dirige a una sal aceptable para uso farmacéutico del compuesto A1.

Otra realización de esta invención se dirige a una sal aceptable para uso farmacéutico del compuesto A2.

Otra realización de esta invención se dirige a una sal aceptable para uso farmacéutico del compuesto A3.

Otra realización de esta invención se dirige a una sal aceptable para uso farmacéutico del compuesto A4.

Otra realización de esta invención se dirige a una sal aceptable para uso farmacéutico del compuesto A5.

Otra realización de esta invención se dirige a una sal aceptable para uso farmacéutico del compuesto A6.

Otra realización de esta invención se dirige a una sal aceptable para uso farmacéutico del compuesto A7.

Otra realización de esta invención se dirige a una sal aceptable para uso farmacéutico del compuesto A8.

Otra realización de esta invención se dirige a una sal aceptable para uso farmacéutico del compuesto A9.

Otra realización de esta invención se dirige a una sal aceptable para uso farmacéutico del compuesto A10.

Otra realización de esta invención se dirige a una sal aceptable para uso farmacéutico del compuesto A11.

Otra realización de esta invención se dirige a una sal aceptable para uso farmacéutico del compuesto A12.

Otra realización de esta invención se dirige a una sal aceptable para uso farmacéutico del compuesto A13.

Otra realización de esta invención se dirige a una sal aceptable para uso farmacéutico del compuesto A14.

Otra realización de esta invención se dirige a una sal aceptable para uso farmacéutico del compuesto A15.

Otra realización de esta invención se dirige a una sal aceptable para uso farmacéutico del compuesto A16.

Otra realización de esta invención se dirige a una sal aceptable para uso farmacéutico del compuesto A18.

Otra realización de esta invención se dirige a una sal aceptable para uso farmacéutico del compuesto A19.

Otra realización de esta invención se dirige a una sal aceptable para uso farmacéutico del compuesto A20.

Otra realización de esta invención se dirige a una sal aceptable para uso farmacéutico del compuesto A21.

Otra realización de esta invención se dirige a una sal aceptable para uso farmacéutico del compuesto A22.

Otra realización de esta invención se dirige a una sal aceptable para uso farmacéutico del compuesto A23.

Otra realización de esta invención se dirige a una sal aceptable para uso farmacéutico del compuesto A24.

Otra realización de esta invención se dirige a una sal aceptable para uso farmacéutico del compuesto A25.

Otra realización de esta invención se dirige a una sal aceptable para uso farmacéutico del compuesto A26.

Otra realización de esta invención se dirige a una sal aceptable para uso farmacéutico del compuesto A27.

Otra realización de esta invención se dirige a una sal aceptable para uso farmacéutico del compuesto A28.

Otra realización de esta invención se dirige a una sal aceptable para uso farmacéutico del compuesto A29.

Otra realización de esta invención se dirige a una sal aceptable para uso farmacéutico del compuesto A30.

Otra realización de esta invención se dirige a una sal aceptable para uso farmacéutico del compuesto A31.

Otra realización de esta invención se dirige a una sal aceptable para uso farmacéutico del compuesto A32.

Otra realización de esta invención se dirige a una sal aceptable para uso farmacéutico del compuesto A33.

Otra realización de esta invención se dirige a una sal aceptable para uso farmacéutico del compuesto A34.

Otra realización de esta invención se dirige a una sal aceptable para uso farmacéutico del compuesto A35.

Otra realización de esta invención se dirige a una sal aceptable para uso farmacéutico del compuesto A36.

Otra realización de esta invención se dirige a una sal aceptable para uso farmacéutico del compuesto A37.

Otra realización de esta invención se dirige a una sal aceptable para uso farmacéutico del compuesto A38.

Otra realización de esta invención se dirige a una sal aceptable para uso farmacéutico del compuesto A39.

Otra realización de esta invención se dirige a una sal aceptable para uso farmacéutico del compuesto A40.

Otra realización de esta invención se dirige a una sal aceptable para uso farmacéutico del compuesto A41.

Otra realización de esta invención se dirige a una sal aceptable para uso farmacéutico del compuesto A42.

Otra realización de esta invención se dirige a una sal aceptable para uso farmacéutico del compuesto A43.

Otra realización de esta invención se dirige a una sal aceptable para uso farmacéutico del compuesto A44.

Otra realización de esta invención se dirige a una sal aceptable para uso farmacéutico del compuesto A45.

Otra realización de esta invención se dirige a una sal aceptable para uso farmacéutico del compuesto A46.

Otra realización de esta invención se dirige a una sal aceptable para uso farmacéutico del compuesto A47.

Otra realización de esta invención se dirige a una sal aceptable para uso farmacéutico del compuesto A48.

Otra realización de esta invención se dirige a un solvato del compuesto A1.

Otra realización de esta invención se dirige a un solvato del compuesto A2.

Otra realización de esta invención se dirige a un solvato del compuesto A3.

Otra realización de esta invención se dirige a un solvato del compuesto A4.

Otra realización de esta invención se dirige a un solvato del compuesto A5.

Otra realización de esta invención se dirige a un solvato del compuesto A6.

Otra realización de esta invención se dirige a un solvato del compuesto A7.

Otra realización de esta invención se dirige a un solvato del compuesto A8.

Otra realización de esta invención se dirige a un solvato del compuesto A9.

Otra realización de esta invención se dirige a un solvato del compuesto A10.

Otra realización de esta invención se dirige a un solvato del compuesto A11.

Otra realización de esta invención se dirige a un solvato del compuesto A12.

Otra realización de esta invención se dirige a un solvato del compuesto A13.

Otra realización de esta invención se dirige a un solvato del compuesto A14.

Otra realización de esta invención se dirige a un solvato del compuesto A15.

Otra realización de esta invención se dirige a un solvato del compuesto A16.

Otra realización de esta invención se dirige a un solvato del compuesto A18.

Otra realización de esta invención se dirige a un solvato del compuesto A19.

Otra realización de esta invención se dirige a un solvato del compuesto A20.

Otra realización de esta invención se dirige a un solvato del compuesto A21.

Otra realización de esta invención se dirige a un solvato del compuesto A22.

Otra realización de esta invención se dirige a un solvato del compuesto A23.

Otra realización de esta invención se dirige a un solvato del compuesto A24.

Otra realización de esta invención se dirige a un solvato del compuesto A25.

Otra realización de esta invención se dirige a un solvato del compuesto A26.

Otra realización de esta invención se dirige a un solvato del compuesto A27.

Otra realización de esta invención se dirige a un solvato del compuesto A28.

Otra realización de esta invención se dirige a un solvato del compuesto A29.

Otra realización de esta invención se dirige a un solvato del compuesto A30.

Otra realización de esta invención se dirige a un solvato del compuesto A31.

Otra realización de esta invención se dirige a un solvato del compuesto A32.

Otra realización de esta invención se dirige a un solvato del compuesto A33.

Otra realización de esta invención se dirige a un solvato del compuesto A34.

Otra realización de esta invención se dirige a un solvato del compuesto A35.

Otra realización de esta invención se dirige a un solvato del compuesto A36.

Otra realización de esta invención se dirige a un solvato del compuesto A37.

Otra realización de esta invención se dirige a un solvato del compuesto A38.

Otra realización de esta invención se dirige a un solvato del compuesto A39.

Otra realización de esta invención se dirige a un solvato del compuesto A40.

Otra realización de esta invención se dirige a un solvato del compuesto A41.

Otra realización de esta invención se dirige a un solvato del compuesto A42.

Otra realización de esta invención se dirige a un solvato del compuesto A43.

Otra realización de esta invención se dirige a un solvato del compuesto A44.

Otra realización de esta invención se dirige a un solvato del compuesto A45.

Otra realización de esta invención se dirige a un solvato del compuesto A46.

Otra realización de esta invención se dirige a un solvato del compuesto A47.

Otra realización de esta invención se dirige a un solvato del compuesto A48.

Otras realizaciones de esta invención se dirigen a cualquiera de las realizaciones de fórmula 1.0 donde el compuesto está en forma pura y aislada.

Otras realizaciones de esta invención se dirigen a cualquiera de las realizaciones de fórmula 1.0 donde el compuesto está en forma pura.

Otras realizaciones de esta invención se dirigen a cualquiera de las realizaciones de fórmula 1.0 donde el compuesto está en forma aislada.

Otras realizaciones de esta invención se dirigen a cualquiera de los compuestos de A1 a A16 y A18 a A48 en forma pura y aislada.

Otras realizaciones de esta invención se dirigen a cualquiera de los compuestos de A1 a A16 y A18 a A30 en forma pura y aislada.

Otras realizaciones de esta invención se dirigen a cualquiera de los compuestos de A1 a A16 y A18 a A26 en forma pura y aislada.

Otras realizaciones de esta invención se dirigen a cualquiera de los compuestos de A31 a A48 en forma pura y aislada.

Otras realizaciones de esta invención se dirigen a cualquiera de los compuestos de A1 a A16 y A18 a A48 en forma pura.

Otras realizaciones de esta invención se dirigen a cualquiera de los compuestos de A1 a A16 y A18 a A30 en forma pura.

Otras realizaciones de esta invención se dirigen a cualquiera de los compuestos de A1 a A16 y A18 a A26 en forma pura.

Otras realizaciones de esta invención se dirigen a cualquiera de los compuestos de A31 a A48 en forma pura.

Otras realizaciones de esta invención se dirigen a cualquiera de los compuestos de A1 a A16 y A18 a A48 en forma aislada.

Otras realizaciones de esta invención se dirigen a cualquiera de los compuestos de A1 a A16 y A18 a A30 en forma aislada.

Otras realizaciones de esta invención se dirigen a cualquiera de los compuestos de A1 a A16 y A18 a A26 en forma aislada.

Otras realizaciones de esta invención se dirigen a cualquiera de los compuestos de A31 a A48 en forma aislada.

Otra realización de esta invención se dirige a una composición farmacéutica que comprende una cantidad efectiva de al menos un compuesto (por ej., 1, 2 o 3, o 1 o 2, o 1, y normalmente 1) de fórmula 1.0 (preferentemente de fórmula 1.1) y un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se dirige a una composición farmacéutica que comprende una cantidad efectiva de un compuesto de fórmula 1.0 (preferentemente de fórmula 1.1) y un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se dirige a una composición farmacéutica que comprende una cantidad efectiva de al menos un compuesto (por ej., 1, 2 o 3, o 1 o 2, o 1, y normalmente 1) seleccionado del grupo que consiste en: A1 a A16 y A18 a A48, y un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se dirige a una composición farmacéutica que comprende una cantidad efectiva de al menos un compuesto (por ej., 1, 2 o 3, o 1 o 2, o 1, y normalmente 1) seleccionado del grupo que consiste en: A1 a A16 y A18 a A30, y un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se dirige a una composición farmacéutica que comprende una cantidad efectiva de al menos un compuesto (por ej., 1, 2 o 3, o 1 o 2, o 1, y normalmente 1) seleccionado del grupo que consiste en: A1 a A16 y A18 a A26, y un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se dirige a una composición farmacéutica que comprende una cantidad efectiva de al menos un compuesto (por ej., 1, 2 o 3, o 1 o 2, o 1, y normalmente 1) seleccionado del grupo que consiste en: A31 a A48, y un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se dirige a una composición farmacéutica que comprende una cantidad efectiva de un compuesto seleccionado del grupo que consiste en: A1 a A16 y A18 a A48, y un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se dirige a una composición farmacéutica que comprende una cantidad efectiva de un compuesto seleccionado del grupo que consiste en: A1 a A16 y A18 a A30, y un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se dirige a una composición farmacéutica que comprende una cantidad efectiva de un compuesto seleccionado del grupo que consiste en: A1 a A16 y A18 a A26, y un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se dirige a una composición farmacéutica que comprende una cantidad efectiva de un compuesto seleccionado del grupo que consiste en: A31 a A48, y un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se dirige a una composición farmacéutica que comprende una cantidad efectiva de al menos un compuesto

(por ej., 1, 2 o 3, o 1 o 2, o 1, y normalmente 1) de fórmula 1.0 (preferentemente de fórmula 1.1), al menos otro (por ej., 1, 2 o 3, o 1 o 2, o 1, y normalmente 1) componente farmacéuticamente activo, y un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se dirige a una composición farmacéutica que comprende una cantidad efectiva de un compuesto de fórmula 1.0 (preferentemente de fórmula 1.1), otro componente farmacéuticamente activo, y un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se dirige a una composición farmacéutica que comprende una cantidad efectiva de al menos un compuesto (por ej., 1, 2 o 3, o 1 o 2, o 1, y normalmente 1) seleccionado del grupo que consiste en: A1 a A16 y A18 a A48, al menos otro (por ej., 1, 2 o 3, o 1 o 2, o 1, y normalmente 1) componente farmacéuticamente activo, y un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se dirige a una composición farmacéutica que comprende una cantidad efectiva de al menos un compuesto (por ej., 1, 2 o 3, o 1 o 2, o 1, y normalmente 1) seleccionado del grupo que consiste en: A1 a A16 y A18 a A30, al menos otro (por ej., 1, 2 o 3, o 1 o 2, o 1, y normalmente 1) componente farmacéuticamente activo, y un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se dirige a una composición farmacéutica que comprende una cantidad efectiva de al menos un compuesto (por ej., 1, 2 o 3, o 1 o 2, o 1, y normalmente 1) seleccionado del grupo que consiste en: A1 a A16 y A18 a A26, al menos otro (por ej., 1, 2 o 3, o 1 o 2, o 1, y normalmente 1) componente farmacéuticamente activo, y un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se dirige a una composición farmacéutica que comprende una cantidad efectiva de al menos un compuesto (por ej., 1, 2 o 3, o 1 o 2, o 1, y normalmente 1) seleccionado del grupo que consiste en: A31 a A48, al menos otro (por ej., 1, 2 o 3, o 1 o 2, o 1, y normalmente 1) componente farmacéuticamente activo, y un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se dirige a una composición farmacéutica que comprende una cantidad efectiva de un compuesto seleccionado del grupo que consiste en: A1 a A16 y A18 a A48, otro componente farmacéuticamente activo, y un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se dirige a una composición farmacéutica que comprende una cantidad efectiva de un compuesto seleccionado del grupo que consiste en: A1 a A16 y A18 a A30, otro componente farmacéuticamente activo, y un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se dirige a una composición farmacéutica que comprende una cantidad efectiva de un compuesto seleccionado del grupo que consiste en: A1 a A16 y A18 a A26, otro componente farmacéuticamente activo, y un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se dirige a una composición farmacéutica que comprende una cantidad efectiva de un compuesto seleccionado del grupo que consiste en: A31 a A48, otro componente farmacéuticamente activo, y un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se dirige a una composición farmacéutica que comprende una cantidad efectiva de al menos un compuesto

(por ej., 1, 2 o 3, o 1 o 2, o 1, y normalmente 1) de fórmula 1.0 (preferentemente de fórmula 1.1), al menos un (por ej., 1, 2 o 3, o 1 o 2, o 1, y normalmente 1) agente quimioterapéutico, y un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se dirige a una composición farmacéutica que comprende una cantidad efectiva de un compuesto de fórmula 1.0 (preferentemente de fórmula 1.1), un agente quimioterapéutico, y un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se dirige a una composición farmacéutica que comprende una cantidad efectiva de al menos un compuesto (por ej., 1, 2 o 3, o 1 o 2, o 1, y normalmente 1) seleccionado del grupo que consiste en: A1 a A16 y A18 a A48, al menos un (por ej., 1, 2 o 3, o 1 o 2, o 1, y normalmente 1) agente quimioterapéutico, y un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se dirige a una composición farmacéutica que comprende una cantidad efectiva de al menos un compuesto (por ej., 1, 2 o 3, o 1 o 2, o 1, y normalmente 1) seleccionado del grupo que consiste en: A1 a A16 y A18 a A30, al menos un (por ej., 1, 2 o 3, o 1 o 2, o 1, y normalmente 1) agente quimioterapéutico, y un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se dirige a una composición farmacéutica que comprende una cantidad efectiva de al menos un compuesto (por ej., 1, 2 o 3, o 1 o 2, o 1, y normalmente 1) seleccionado del grupo que consiste en: A1 a A16 y A18 a A26, al menos un (por ej., 1, 2 o 3, o 1 o 2, o 1, y normalmente 1) agente quimioterapéutico, y un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se dirige a una composición farmacéutica que comprende una cantidad efectiva de al menos un compuesto (por ej., 1, 2 o 3, o 1 o 2, o 1, y normalmente 1) seleccionado del grupo que consiste en: A31 a A48, al menos un (por ej., 1, 2 o 3, o 1 o 2, o 1, y normalmente 1) agente quimioterapéutico, y un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se dirige a una composición farmacéutica que comprende una cantidad efectiva de un compuesto seleccionado del grupo que consiste en: A1 a A16 y A18 a A48, un agente quimioterapéutico, y un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se dirige a una composición farmacéutica que comprende una cantidad efectiva de un compuesto seleccionado del grupo que consiste en: A1 a A16 y A18 a A30, un agente quimioterapéutico, y un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se dirige a una composición farmacéutica que comprende una cantidad efectiva de un compuesto seleccionado del grupo que consiste en: A1 a A16 y A18 a A26, un agente quimioterapéutico, y un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se dirige a una composición farmacéutica que comprende una cantidad efectiva de un compuesto seleccionado del grupo que consiste en: A31 a A48, un agente quimioterapéutico, y un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se dirige a un método para tratar el cáncer en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de al menos un (1, 2 o 3, o 1 o 2, o 1, y normalmente 1) compuesto de fórmula 1.0 (preferentemente de fórmula 1.6).

Otra realización de esta invención se dirige a un método para tratar el cáncer en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de un compuesto de fórmula 1.0 (preferentemente de fórmula 1.6).

Otra realización de esta invención se dirige a un método para tratar el cáncer en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de al menos un (1, 2 o 3, o 1 o 2, o 1, y normalmente 1) compuesto de A1 a A16 y A18 a A48.

Otra realización de esta invención se dirige a un método para tratar el cáncer en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de al menos un (1, 2 o 3, o 1 o 2, o 1, y normalmente 1) compuesto de A1 a A16 y A18 a A30.

Otra realización de esta invención se dirige a un método para tratar el cáncer en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de al menos un (1, 2 o 3, o 1 o 2, o 1, y normalmente 1) compuesto de A1 a A16 y A18 a A26.

Otra realización de esta invención se dirige a un método para tratar el cáncer en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de al menos un (1, 2 o 3, o 1 o 2, o 1, y normalmente 1) compuesto de A31 a A48.

Otra realización de esta invención se dirige a un método para tratar el cáncer en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de un compuesto de A1 a A16 y A18 a A48.

Otra realización de esta invención se dirige a un método para tratar el cáncer en un paciente necesitado de dicho tratamiento, dicho método

comprende administrar a dicho paciente una cantidad efectiva de un compuesto de A1 a A16 y A18 a A30.

Otra realización de esta invención se dirige a un método para tratar el cáncer en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de un compuesto de A1 a A16 y A18 a A26.

Otra realización de esta invención se dirige a un método para tratar el cáncer en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de un compuesto de A31 a A48.

Otra realización de esta invención se dirige a un método para tratar el cáncer en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de al menos un (1, 2 o 3, o 1 o 2, o 1, y normalmente 1) compuesto de fórmula 1.0, y una cantidad efectiva de al menos un (1, 2 o 3, o 1 o 2, o 1, y normalmente 1) agente quimioterapéutico.

Otra realización de esta invención se dirige a un método para tratar el cáncer en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de un compuesto de fórmula 1.0, y una cantidad efectiva de al menos un (1, 2 o 3, o 1 o 2, o 1, y normalmente 1) agente quimioterapéutico.

Otra realización de esta invención se dirige a un método para tratar el cáncer en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de al menos un (1, 2 o 3, o 1 o 2, o 1, y normalmente 1) compuesto de A1 a A16 y A18 a A48, y una cantidad efectiva de al menos un (1, 2 o 3, o 1 o 2, o 1, y normalmente 1) agente quimioterapéutico.

Otra realización de esta invención se dirige a un método para tratar el cáncer en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de al menos un (1, 2 o 3, o 1 o 2, o 1, y normalmente 1) compuesto de A1 a A16 y A18 a A30, y una cantidad efectiva de al menos un (1, 2 o 3, o 1 o 2, o 1, y normalmente 1) agente quimioterapéutico.

Otra realización de esta invención se dirige a un método para tratar el cáncer en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de al menos un (1, 2 o 3, o 1 o 2, o 1, y normalmente 1) compuesto de A1 a A16 y A18 a A26, y una cantidad efectiva de al menos un (1, 2 o 3, o 1 o 2, o 1, y normalmente 1) agente quimioterapéutico.

Otra realización de esta invención se dirige a un método para tratar el cáncer en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de al menos un (1, 2 o 3, o 1 o 2, o 1, y normalmente 1) compuesto de A31 a A48, y una cantidad efectiva de al menos un (1, 2 o 3, o 1 o 2, o 1, y normalmente 1) agente quimioterapéutico.

Otra realización de esta invención se dirige a un método para tratar el cáncer en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de un compuesto de A1 a A16 y A18 a A48, y una cantidad efectiva de al menos un (1, 2 o 3, o 1 o 2, o 1, y normalmente 1) agente quimioterapéutico.

Otra realización de esta invención se dirige a un método para tratar el cáncer en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de un

compuesto de A1 a A16 y A18 a A30, y una cantidad efectiva de al menos un (1, 2 o 3, o 1 o 2, o 1, y normalmente 1) agente quimioterapéutico.

Otra realización de esta invención se dirige a un método para tratar el cáncer en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de un compuesto de A1 a A16 y A18 a A26, y una cantidad efectiva de al menos un (1, 2 o 3, o 1 o 2, o 1, y normalmente 1) agente quimioterapéutico.

Otra realización de esta invención se dirige a un método para tratar el cáncer en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de un compuesto de A31 a A48, y una cantidad efectiva de al menos un (1, 2 o 3, o 1 o 2, o 1, y normalmente 1) agente quimioterapéutico.

Los compuestos de esta invención inhiben la actividad de ERK1 y ERK2. Por lo tanto, esta invención además provee un método para inhibir ERK en mamíferos, en especial humanos, mediante la administración de una cantidad efectiva (por ej., una cantidad efectiva para uso terapéutico) 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 del cáncer.

En cualquiera de los métodos para tratar el cáncer descriptos en la presente, a menos que lo indique lo contrario, los métodos pueden incluir 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 currently o secuencial con los compuestos de esta invención.

Los métodos para tratar el cáncer descriptos en la presente incluyen métodos donde se utiliza (es decir, los métodos para tratar el cáncer de esta

invención incluyen terapias combinadas) una combinación de drogas (es decir, compuestos, o componentes farmacéuticamente activos, o composiciones farmacéuticas). Aquellos con experiencia en la técnica apreciarán que, en general, las drogas se administran individualmente como una composición farmacéutica. Se encuentra dentro del alcance de esta invención el uso de una composición farmacéutica que comprende más de una droga.

En cualquiera de los métodos para tratar el cáncer descriptos en la presente, a menos que lo indique lo contrario, los métodos pueden incluir en forma opcional la administración de una cantidad efectiva de terapia de radiación. En cuanto a la terapia de radiación, se prefiere γ-radiación.

Los ejemplos de cáncer que pueden tratarse con los métodos de esta invención incluyen, pero sin limitación: (A) cáncer de pulmón (por ej., adenocarcinoma pulmonar y cáncer de pulmón de células no pequeñas), (B) cánceres pancreáticos (por ej., carcinoma pancreático tal como, por ejemplo, carcinoma pancreático exocrino), (C) cánceres de colon (por ej., carcinomas colorectales, tal como, por ejemplo, adenocarcinoma de colon y adenoma de colon), (D) leucemias mieloides (por ejemplo, leucemia mielógena aguda (AML), 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 cabeza y cuello (por ej., cáncer de células escamosas de la cabeza y cuello), (M) cáncer de ovarios, (N) cánceres cerebrales (por ej., gliomas, tal como glioblastoma multiforme), (O) cánceres de origen mesenquimal (por ej., fibrosarcomas y rabdomiosarcomas), (P) sarcomas, (Q) tetracarcinomas, (R) nuroblastomas, (S) carcinomas renales, (T) hepatomas, (U) linfoma no Hodgkin, (V) mieloma múltiple, y (W) carcinoma anaplásico de tiroides.

De este modo, otra realización de esta invención se dirige a un método para tratar el cáncer de pulmón, cáncer pancreático, cáncer de colon (por ej., cáncer colorectal), 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 cabeza y cuello (por ej., cáncer de células escamosas de la cabeza y cuello), cáncer de ovarios, cánceres cerebrales (por ej., gliomas, tal como glioblastoma multiforme), cánceres de origen mesenquimal (por ej., fibrosarcomas y rabdomiosarcomas), sarcomas, tetracarcinomas, nuroblastomas, carcinomas renales, hepatomas, linfoma no Hodgkin, mieloma múltiple, o carcinoma anaplásico de tiroides, en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0.

Otra realización de esta invención se dirige a un método para tratar el cáncer de pulmón, cáncer pancreático, cáncer de colon (por ej., cáncer colorectal), 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 cabeza y cuello (por ej., cáncer de células escamosas de la cabeza y cuello), cáncer de ovarios, cánceres cerebrales (por ej., gliomas, tal como glioblastoma multiforme), cánceres de origen mesenquimal (por ej., fibrosarcomas y rabdomiosarcomas), sarcomas, tetracarcinomas, nuroblastomas, carcinomas renales, hepatomas, linfoma no Hodgkin, mieloma múltiple, o carcinoma anaplásico de tiroides en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0,

en combinación con una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Otra realización de esta invención se dirige a un método para tratar el cáncer de pulmón, cáncer pancreático, cáncer de colon (por ej., cáncer colorectal), 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 cabeza y cuello (por ej., cáncer de células escamosas de la cabeza y cuello), cáncer de ovarios, cánceres cerebrales (por ej., gliomas, tal como glioblastoma multiforme), cánceres de origen mesenquimal (por ej., fibrosarcomas y rabdomiosarcomas), sarcomas, tetracarcinomas, nuroblastomas, carcinomas renales, hepatomas, linfoma no Hodgkin, mieloma múltiple, o carcinoma anaplásico de tiroides en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0.

Otra realización de esta invención se dirige a un método para tratar el cáncer de pulmón, cáncer pancreático, cáncer de colon (por ej., cáncer colorectal), 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 cabeza y cuello (por ej., cáncer de células escamosas de la cabeza y cuello), cáncer de ovarios, cánceres cerebrales (por ej., gliomas, tal como glioblastoma multiforme), cánceres de origen mesenquimal (por ej., fibrosarcomas y rabdomiosarcomas), sarcomas, tetracarcinomas, nuroblastomas, carcinomas renales, hepatomas, linfoma no Hodgkin, mieloma múltiple, o carcinoma anaplásico de tiroides en un paciente necesitado de dicho tratamiento, dicho

método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0, en combinación con una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Otra realización de esta invención se dirige a un método para tratar el cáncer en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0, donde dicho cáncer se selecciona del grupo que consiste en: melanoma, cáncer pancreático, cáncer de tiroides, cáncer colorectal, cáncer de pulmón, cáncer de mama y cáncer de ovarios.

Otra realización de esta invención se dirige a un método para tratar el cáncer en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0, en combinación con una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico donde dicho cáncer se selecciona del grupo que consiste en: melanoma, cáncer pancreático, cáncer de tiroides, cáncer colorectal, cáncer de pulmón, cáncer de mama y cáncer de ovarios.

Otra realización de esta invención se dirige a un método para tratar el cáncer en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0, donde dicho cáncer se selecciona del grupo que consiste en: melanoma, cáncer

pancreático, cáncer de tiroides, cáncer colorectal, cáncer de pulmón, cáncer de mama y cáncer de ovarios.

Otra realización de esta invención se dirige a un método para tratar el cáncer en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0, en combinación con una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico donde dicho cáncer se selecciona del grupo que consiste en: melanoma, cáncer pancreático, cáncer de tiroides, cáncer colorectal, cáncer de pulmón, cáncer de mama y cáncer de ovarios.

Otra realización de esta invención se dirige a un método para tratar melanoma en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0.

Otra realización de esta invención se dirige a un método para tratar melanoma en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0, en combinación con una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Otra realización de esta invención se dirige a un método para tratar melanoma en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0.

Otra realización de esta invención se dirige a un método para tratar melanoma en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0, en combinación con una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Otra realización de esta invención se dirige a un método para tratar el cáncer pancreático en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0.

Otra realización de esta invención se dirige a un método para tratar el cáncer pancreático en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0, en combinación con una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Otra realización de esta invención se dirige a un método para tratar el cáncer pancreático en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0.

Otra realización de esta invención se dirige a un método para tratar el cáncer pancreático en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0, en

combinación con una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Otra realización de esta invención se dirige a un método para tratar el cáncer de tiroides en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0.

Otra realización de esta invención se dirige a un método para tratar el cáncer de tiroides en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0, en combinación con una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Otra realización de esta invención se dirige a un método para tratar el cáncer de tiroides en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0.

Otra realización de esta invención se dirige a un método para tratar el cáncer de tiroides en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0, en combinación con una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Otra realización de esta invención se dirige a un método para tratar el cáncer colorectal en un paciente necesitado de dicho tratamiento, dicho método

comprende administrar a dicho paciente una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0.

Otra realización de esta invención se dirige a un método para tratar el cáncer colorectal en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0, en combinación con una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Otra realización de esta invención se dirige a un método para tratar el cáncer colorectal en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0.

Otra realización de esta invención se dirige a un método para tratar el cáncer colorectal en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0, en combinación con una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Otra realización de esta invención se dirige a un método para tratar el cáncer de pulmón en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0.

Otra realización de esta invención se dirige a un método para tratar el cáncer de pulmón en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de al

menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0, en combinación con una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Otra realización de esta invención se dirige a un método para tratar el cáncer de pulmón en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0.

Otra realización de esta invención se dirige a un método para tratar el cáncer de pulmón en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0, en combinación con una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Otra realización de esta invención se dirige a un método para tratar el cáncer de mama en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0.

Otra realización de esta invención se dirige a un método para tratar el cáncer de mama en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0, en combinación con una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Otra realización de esta invención se dirige a un método para tratar el cáncer de mama en un paciente necesitado de dicho tratamiento, dicho método

comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0.

Otra realización de esta invención se dirige a un método para tratar el cáncer de mama en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0, en combinación con una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Otra realización de esta invención se dirige a un método para tratar el cáncer de ovarios en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0.

Esta invención también provee un método para tratar el cáncer de ovarios en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0, en combinación con una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Otra realización de esta invención se dirige a un método para tratar el cáncer de ovarios en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0.

Otra realización de esta invención se dirige a un método para tratar el cáncer de ovarios en un paciente necesitado de dicho tratamiento, dicho

método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0, en combinación con una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Otras realizaciones de esta invención se dirigen a métodos para tratar el cáncer de mama (es decir, cáncer de mama postmenopaúsico y premenopaúsico, por ej., cáncer de mama hormona-dependiente) en un paciente necesitado de dicho tratamiento, dicho tratamiento comprende la administración de una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0 en combinación con terapias hormonales (es decir, agentes antihormonales).

Otras realizaciones de esta invención se dirigen a métodos para tratar el cáncer de mama (es decir, cáncer de mama postmenopaúsico y premenopaúsico, por ej., cáncer de mama hormona-dependiente) en un paciente necesitado de dicho tratamiento, dicho tratamiento comprende la administración de una cantidad efectiva de a composición farmacéutica que comprende una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0 en combinación con terapias hormonales (es decir, agentes antihormonales).

Otras realizaciones de esta invención se dirigen a métodos para tratar el cáncer de mama (es decir, cáncer de mama postmenopaúsico y premenopaúsico, por ej., cáncer de mama hormona-dependiente) en un paciente necesitado de dicho tratamiento, dicho tratamiento comprende la administración de una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0 en combinación con terapias hormonales (es decir, agentes antihormonales), y en combinación con una

cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Otras realizaciones de esta invención se dirigen a métodos para tratar el cáncer de mama (es decir, cáncer de mama postmenopaúsico y premenopaúsico, por ej., cáncer de mama hormona-dependiente) en un paciente necesitado de dicho tratamiento, dicho tratamiento comprende la administración de una cantidad efectiva de a composición farmacéutica que comprende una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0 en combinación con terapias hormonales (es decir, agentes antihormonales), y en combinación con una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Los métodos para tratar el cáncer de mama descriptos en la presente incluyen el tratamiento de cánceres de mama hormona-dependientes metastáticos y avanzados, terapia adyuvante para cáncer de mama hormona-dependiente primario y temprano, el tratamiento de carcinoma ductal in situ, y el tratamiento de cáncer de mama inflamatorio in situ.

Los métodos para tratar el cáncer de mama hormona-dependiente pueden también utilizarse para prevenir el cáncer de mama en paciente con alto riesgo de desarrollar el mismo.

Así, otras realizaciones de esta invención se dirigen a métodos para prevenir el cáncer de mama (es decir, cáncer de mama postmenopaúsico y premenopaúsico, por ej., cáncer de mama hormona-dependiente) en un paciente necesitado de dicho tratamiento, dicho tratamiento comprende la administración de una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0 en combinación con terapias hormonales (es decir, agentes antihormonales).

Otras realizaciones de esta invención se dirigen a métodos para prevenir el cáncer de mama (es decir, cáncer de mama postmenopaúsico y premenopaúsico, por ej., cáncer de mama hormona-dependiente) en un paciente necesitado de dicho tratamiento, dicho tratamiento comprende la administración de una cantidad efectiva de a composición farmacéutica que comprende una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0 en combinación con terapias hormonales (es decir, agentes antihormonales).

Otras realizaciones de esta invención se dirigen a métodos para prevenir el cáncer de mama (es decir, cáncer de mama postmenopaúsico y premenopaúsico, por ej., cáncer de mama hormona-dependiente) en un paciente necesitado de dicho tratamiento, dicho tratamiento comprende la administración de una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0 en combinación con terapias hormonales (es decir, agentes antihormonales), y en combinación con una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Otras realizaciones de esta invención se dirigen a métodos para prevenir el cáncer de mama (es decir, cáncer de mama postmenopaúsico y premenopaúsico, por ej., cáncer de mama hormona-dependiente) en un paciente necesitado de dicho tratamiento, dicho tratamiento comprende la administración de una cantidad efectiva de a composición farmacéutica que comprende una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0 en combinación con terapias hormonales (es decir, agentes antihormonales), y en combinación con una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Otra realización de esta invención se dirige a un método para tratar el cáncer cerebral (por ej., glioma, tal como glioblastoma multiforme) en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0.

Otra realización de esta invención se dirige a un método para tratar el cáncer cerebral (por ej., glioma, tal como glioblastoma multiforme) en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0, en combinación con una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Otra realización de esta invención se dirige a un método para tratar el cáncer cerebral (por ej., glioma, tal como glioblastoma multiforme) a en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0.

Otra realización de esta invención se dirige a un método para tratar el cáncer cerebral (por ej., glioma, tal como glioblastoma multiforme) en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0, en combinación con una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Otra realización de esta invención se dirige a un método para tratar el cáncer cerebral (por ej., glioma, tal como glioblastoma multiforme) en un paciente necesitado de dicho tratamiento, dicho método comprende administrar

a dicho paciente una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0, en combinación con una cantidad efectiva de un agente quimioterapéutico donde dicho agente quimioterapéutico es temozolomide.

Otra realización de esta invención se dirige a un método para tratar el cáncer cerebral (por ej., glioma, tal como glioblastoma multiforme) en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0, en combinación con una cantidad efectiva de un agente quimioterapéutico, donde dicho agente quimioterapéutico es temozolomide.

Otra realización de esta invención se dirige a un método para tratar el cáncer de próstata en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0.

Otra realización de esta invención se dirige a un método para tratar el cáncer de próstata en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0, en combinación con una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Otra realización de esta invención se dirige a un método para tratar el cáncer de próstata en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0.

Otra realización de esta invención se dirige a un método para tratar el cáncer de próstata en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0, en combinación con una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Otra realización de esta invención se dirige a un método para tratar el síndrome mielodisplásico en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0.

Otra realización de esta invención se dirige a un método para tratar el síndrome mielodisplásico en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0, en combinación con una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Otra realización de esta invención se dirige a un método para tratar el síndrome mielodisplásico en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0.

Otra realización de esta invención se dirige a un método para tratar el síndrome mielodisplásico en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de al

menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1, en combinación con una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Otra realización de esta invención se dirige a un método para tratar leucemias mieloides en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0.

Otra realización de esta invención se dirige a un método para tratar leucemias mieloides en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0, en combinación con una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Otra realización de esta invención se dirige a un método para tratar leucemias mieloides en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0.

Otra realización de esta invención se dirige a un método para tratar leucemias mieloides en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0, en combinación con una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Otra realización de esta invención se dirige a un método para tratar la leucemia mielógena aguda (AML) en un paciente necesitado de dicho

tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0.

Otra realización de esta invención se dirige a un método para tratar la leucemia mielógena aguda (AML) en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0, en combinación con una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Otra realización de esta invención se dirige a un método para tratar la leucemia mielógena aguda (AML) en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0.

Otra realización de esta invención se dirige a un método para tratar la leucemia mielógena aguda (AML) en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0, en combinación con una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Otra realización de esta invención se dirige a un método para tratar la leucemia mielomonocítica crónica (CMML) en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0.

Otra realización de esta invención se dirige a un método para tratar la leucemia mielomonocítica crónica (CMML) en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0, en combinación con una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Otra realización de esta invención se dirige a un método para tratar la leucemia mielomonocítica crónica (CMML) en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0.

Otra realización de esta invención se dirige a un método para tratar la leucemia mielomonocítica crónica (CMML) en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0, en combinación con una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Otra realización de esta invención se dirige a un método para tratar la leucemia mielógena crónica (leucemia mieloide crónica, CML) en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0.

Otra realización de esta invención se dirige a un método para tratar la leucemia mielógena crónica (leucemia mieloide crónica, CML) en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho

paciente una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0, en combinación con una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Otra realización de esta invención se dirige a un método para tratar la leucemia mielógena crónica (leucemia mieloide crónica, CML) en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0.

Otra realización de esta invención se dirige a un método para tratar la leucemia mielógena crónica (leucemia mieloide crónica, CML) en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0, en combinación con una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Otra realización de esta invención se dirige a un método para tratar leucemias mieloides en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0.

Otra realización de esta invención se dirige a un método para tratar leucemias mieloides en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0, en combinación con una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Otra realización de esta invención se dirige a un método para tratar leucemias mieloides en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0.

Otra realización de esta invención se dirige a un método para tratar leucemias mieloides en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0, en combinación con una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Otra realización de esta invención se dirige a un método para tratar el cáncer de vejiga en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0.

Otra realización de esta invención se dirige a un método para tratar el cáncer de vejiga en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0, en combinación con una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Otra realización de esta invención se dirige a un método para tratar el cáncer de vejiga en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0.

Otra realización de esta invención se dirige a un método para tratar el cáncer de vejiga en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0, en combinación con una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Otra realización de esta invención se dirige a un método para tratar el linfoma no Hodgkin en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0.

Otra realización de esta invención se dirige a un método para tratar el linfoma no Hodgkin en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0, en combinación con una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Otra realización de esta invención se dirige a un método para tratar el linfoma no Hodgkin en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0.

Otra realización de esta invención se dirige a un método para tratar el linfoma no Hodgkin en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0, en

combinación con una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Otra realización de esta invención se dirige a un método para tratar el mieloma múltiple en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0.

Otra realización de esta invención se dirige a un método para tratar el mieloma múltiple en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0, en combinación con una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Otra realización de esta invención se dirige a un método para tratar el mieloma múltiple en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0.

Otra realización de esta invención se dirige a un método para tratar el mieloma múltiple en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de una composición farmacéutica que comprende una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, y normalmente 1) compuesto de fórmula 1.0, en combinación con una cantidad efectiva de al menos un (por ej., 1, 2 o 3, 1 o 2, o 1) agente quimioterapéutico.

Los agentes quimioterapéuticos (agente antineoplásico) incluyen, pero sin limitación: agentes que afectan los microtúbulos, agentes alquilantes,

antimetabolitos, productos naturales y sus derivados, hormonas y esteroides (que incluyen análogos sintéticos), y sintéticos.

Los ejemplos de agentes alquilantes (que incluyen mostazas de nitrógeno, derivados de etilenimina, alquil sulfonatos, nitrosoureas y triazenos) incluyen: mostaza Uracil, Clormetina, Ciclofosfamida (Cytoxan®), Ifosfamida, Melfalan, Clorambucil, Pipobroman, Trietilen-melamina, Trietilentiofosforamina, Busulfan, Carmustina, Lomustina, Estreptozocina, Dacarbazina, y Temozolomida.

Los ejemplos de antimetabolitos (que incluyen antagonistas del ácido fólico, análogos de pirimidina, análogos de purina e inhibidores de adenosina deaminasa) incluyen: Metotrexato, 5-Fluoruracilo, Floxuridina, Citarabina, 6-Mercaptopurina, 6-Tioguanina, Fludarabin fosfato, Pentostatina, y Gemcitabina.

Los ejemplos de productos naturales y sus derivados (que incluyen alcaloides de la vinca, antiobióticos antitumorales, enzimas, linfoquinas y epipodofilotoxinas) incluyen: Vinblastina, Vincristina, Vindesina, Bleomicina, Dactinomicina, Daunorubicina, Doxorubicina, Epirubicina, Idarubicina, Paclitaxel (paclitaxel es un agente que afecta los microtúbulos y se encuentra comercialmente disponible como Taxol®), derivados de Paclitaxel (por ej., taxotero), Mitramicina, Deoxico-formicina, Mitomicin-C, L-Asparaginasa, Interferonas (en especial IFN-a), Etoposida, y Teniposida.

Los ejemplos de hormonas y esteroides (que incluyen análogos sintéticos) incluyen: 17α-Etinilestradiol, Dietilstilbestrol, Testosterona, Prednisona, Fluoximesterona, Propionato de dromostanolona, Testolactona, Megestrolacetato, Tamoxifen, Metilprednisolona, Metil-testosterona, Prednisolona, Triamcinolona, Clorotrianisene, Hidroxiprogesterona,

Aminoglutetimida, Estramustina, Acetato de medroxiprogesterona, Leuprolida, Flutamida, Toremifeno, y Zoladex.

Los ejemplos de sintéticos (que incluyen complejos inorgánicos tal como complejos de coordinación de platino): Cisplatina, Carboplatina, Hidroxiurea, Amsacrina, Procarbazina, Mitotano, Mitoxantrona, Levamisol, y Hexametilmelamina.

Los ejemplos de otros quimioterapéuticos incluyen: Navelbeno, CPT-11, Anastrazol, Letrazol, Capecitabina, Reloxafina, y Droloxafina.

Un agente que afecta los microtúbulos (por ej., paclitaxel, un derivado de paclitaxel o un compuesto tipo paclitaxel), utilizado en la presente, es un compuesto que interfiere con la mitosis celular, es decir, que tiene un efecto antimitótico, afectando la formación y/o acción de los microtúbulos. Por ejemplo, tales agentes pueden ser agentes estabilizadores de microtúbulos o agentes que interrumpan la formación de los microtúbulos.

Los agentes que afectan los microtúbulos, útiles en los métodos de esta invención, son bien conocidos por aquellos con experiencia en la técnica e incluyen, pero sin limitación: Alocolquicina (NSC 406042), Halicondrina B (NSC 609395), Colquicina (NSC 757), derivados de Colquicina (por ej., NSC 33410), Dolastatina 10 (NSC 376128), Maitansina (NSC 153858), Rizoxina (NSC 332598), Paclitaxel (Taxol®, NSC 125973), derivados de Paclitaxel (por ej., Taxotero, 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. Se describen ejemplos de tales agentes 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.

Los agentes quimioterapéuticos con actividad similar a la de paclitaxel incluyen, pero sin limitación, paclitaxel y derivados de paclitaxel (compuestos de tipo paclitaxel) y análogos. Paclitaxel y sus derivados (por ej., Taxol y Taxotero) se encuentran comercialmente disponibles. Además, métodos de preparación de paclitaxel y derivados de paclitaxel y análogos son bien conocidos por aquellos con experiencia en la técnica (ver, por ej., las Patentes de los Estados Unidos Nº: 5569729; 5565478; 5530020; 5527924; 5508447; 5489589; 5488116; 5484809; 5478854; 5478736; 5475120; 5468769; 5461169; 5440057; 5422364; 5411984; 5405972; y 5296506).

En forma más específica, el término "paclitaxel" utilizado en la presente hace referencia a la droga comercialmente disponible como Taxol® (Nº de NSC: 125973). Taxol® inhibe la replicación de las células eucarióticas mediante la mejora de la polimerización de restos de tubulina en paquetes de microtúbulos estabilizados que son incapaces de reorganizarse en la estructuras apropiadas para la mitosis. Entre las numerosas drogas quimioterapéuticas disponibles, paclitaxel ha generado interés a causa de su eficacia en los ensayos clínicos frente a tumores refractarios a las drogas, que incluyen 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).

Pueden evaluarse agentes adicionales que afectan los microtúbulos utilizando uno o más de muchos ensayos conocidos en la práctica, por ej., un ensayo semiautomático que mide la actividad polimerizante de la tubulina de análogos de paclitaxel en combinación con un ensayo celular para calcular el

potencial de estos compuestos para bloquear células en mitosis (ver Lopes (1997) Cancer Chemother. Pharmacol. 41:37-47).

En general, la actividad de un compuesto de ensayo se determina poniendo en contacto una célula con dicho compuesto y determinando si el ciclo celular se interrumpe o no, en particular, a través de la inhibición de un evente mitótico. Tal inhibición puede ser mediada por la interrupción del aparato mitótico, por ej., interrupción de la formación de ejes normales. Las células donde se interrumpe la mitosis pueden caracterizarse por la presencia de una alteración en la morfología (por ej., compactación de los microtúbulos, aumento del número de cromosomas, etc.).

Compuestos con posible actividad de polimerización de tubulina pueden observarse in vitro. Por ejemplo, los compuestos se observan contra células cultivadas WR21 (derivadas de la línea de ratones 69-2 wap-ras) para inhibición de la proliferación y/o para morfología celular alterada, en particular para compactación de microtúbulos. Luego, puede llevarse a cabo la observación in vivo de compuestos de ensayo con resultados positivos utilizando ratones desnudos que porten las células tumorales WR21. Se describen protocolos detallados para este método de observación en Porter (1995) Lab. Anim. Sci., 45(2):145-150.

Otros métodos de observación de compuestos para actividad deseada son bien conocidos por aquellos con experiencia en la técnica. Típicamente tales ensayos incluyen ensayos para la inhibición del armado y desarmado de los microtúbulos. Se describen ensayos para el armado de microtúbulos, por ejemplo, en Gaskin et al. (1974) J. Molec. Biol., 89: 737-758. La Patente de los Estados Unidos Nº 5569720 también provee ensayos in vitro e in vivo para compuestos con actividad similar a la de paclitaxel.

Así, en los métodos de esta invención donde se utilice al menos un agente quimioterapéutico, los ejemplos de dichos agentes quimioterapéuticos incluyen los seleccionados del grupo que consiste en: agentes que afectan los microtúbulos, agentes alquilantes, antimetabolitos, productos naturales y sus derivados, hormonas y esteroides (que incluyen análogos sintéticos), y sintéticos.

En los métodos de esta invención donde se utilice al menos un agente quimioterapéutico, los ejemplos de dichos agentes quimioterapéuticos también incluyen: (1) taxanos, (2) compuestos coordinadores de platino, (3) inhibidores del factor de crecimiento epidérmico (EGF) que son anticuerpos, (4) inhibidores de EGF que son pequeñas moléculas, (5) inhibidores del factor de crecimiento endotelial vascular (VEGF) que son anticuerpos, (6) Inhbidores de la quinasa VEGF que son pequeñas moléculas, (7) antagonistas del receptor de estrógenos o moduladores selectivos del receptor de estrógenos (SERM), (8) derivados nucleósidos antitumorales, (9) epotilonas, (10) inhibidores de la topoisomerasa, (11) vinca alcaloides, (12) anticuerpos que son inhibidores de □V□3 integrinas, (13) antagonistas de folato, (14) inhibidores de la ribonucleótido reductasa, (15) antraciclinas, (16) biológicos; (17) inhibidores de angiogénesis y/o supresores de factor de necrosis tumoral alfa (TNF-alfa) tal como talidomida (o imida relacionada), (18) Inhibidores de la bcr/abl quinasa, (19) inhibidores de MEK1 y/o MEK 2 que son pequeñas moléculas, (20) inhibidores de IGF-1 y IGF-2 que son pequeñas moléculas, (21) inhibidores de pequeñas moléculas de las RAF y BRAF quinasas, (22) inhibidores de pequeñas moléculas de quinasas dependientes de ciclos celulares tal como CDK1, CDK2, CDK4 y CDK6, (23) agentes alquilantes, e (24) inhibidores de la farnesil proteína transferasa (también denominados inhibidores FPT o FTI (es decir, inhibidores de la farnesil transferasa)).

En los métodos de esta invención donde se utilice al menos un agente quimioterapéutico, los ejemplos de dichos agentes quimioterapéuticos incluyen:

(1) taxanos tal como paclitaxel (TAXOL®) y/o docetaxel (Taxotere®);

(2) compuestos coordinadores de platino, tal como, por ejemplo, carboplatin, cisplatin y oxaliplatin (por ej. Eloxatin);

(3) inhibidores de EGF que son anticuerpos, tal como: anticuerpos de HER2 (tal 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 and Ribozyme Pharmaceuticals), PKI 166 (Novartis), EKB 569 (Wyeth-Ayerst), GW 572016 (GlaxoSmithKline), CI 1033 (Pfizer Global Research and Development), conjugado trastuzmab-maitansinoide (Genentech, Inc.), mitumomab (Imclone Systems and Merck KGaA) y Melvax II (Imclone Systems and Merck KgaA);

(4) inhibidores de EGF que son moléculas pequeñas, tal como, Tarceva (TM) (OSI-774, OSI Pharmaceuticals, Inc.), and Iressa (ZD 1839, Astra Zeneca);

(5) inhibidores de VEGF que son anticuerpos tal como: bevacizumab (Genentech, Inc.), e IMC-1C11 (ImClone Systems), DC 101 (un Receptor 2 de KDR VEGF de ImClone Systems);

(6) inhibidores de la VEGF quinasa que son moléculas pequeñas, tal como, SU 5416 (from Sugen, Inc), SU 6688 (de Sugen, Inc.), Bay 43-9006 (un inhibidor dual de VEGF y bRAF de Bayer Pharmaceuticals and Onyx Pharmaceuticals);

(7) antagonistas del receptor de estrógenos o moduladores selectivos del receptor de estrógenos (SERM), tal como tamoxifeno, idoxifeno, raloxifeno, trans-2,3-dihidroraloxifeno, levormeloxifeno, droloxifeno, MDL 103323, y acolbifeno (Schering Corp.);

(8) derivados nucleósidos antitumorales tal como 5-fluoruracil, gemcitabina, capecitabina, citarabina (Ara-C), fludarabina (F-Ara-A), decitabina, y clorodeoxiadenosina (Cda, 2-Cda);

(9) epotilonas tal como BMS-247550 (Bristol-Myers Squibb), y EPO906 (Novartis Pharmaceuticals);

(10) inhibidores de la topoisomerasa tal como topotecan (Glaxo SmithKline), y Camptosar (Pharmacia);

(11) alcaloides de la vinca, tal como, navelbina (Anvar and Fabre, France), vincristina y vinblastina;

(12) anticuerpos que son inhibidores de $\alpha V\beta 3$ integrinas, tal como, LM-609 (ver, Clinical Cancer Research, Vol. 6, pag. 3056-3061, August 2000, cuyos descubrimientos se incorporan en la presente como referencia);

(13) antagonistas de folato, tal como Metotrexato (MTX), y Premetrexed (Alimta);

(14) inhibidores de la ribonucleótido reductasa, tal como Hidroxiurea (HU);

(15) antraciclinas, tal como Daunorubicina, Doxorubicina (Adriamicina), e Idarubicina;

(16) biológicos, tal como interferón (por ej., Intron-A y Roferon), interferón pegilado (por ej., Peg-Intron y Pegasys), y Rituximab (Rituxan, anticuerpo utilizado para el tratamiento del linfoma no Hodgkin);

(17) talidomida (o imida relacionada);

(18) inhibidores de la bcr/abl quinasa, tal como, por ejemplo Gleevec (STI-571), AMN-17, ONO12380, SU11248 (Sunitinib) y BMS-354825

(19) inhibidores de MEK1 y/o MEK2, tal como PD0325901 y Arry-142886 (AZD6244);

(20) inhibidores de IGF-1 e IGF-2 que son moléculas pequeñas, tal como, por ejemplo, NVP-AEW541;

(21) inhibidores de moléculas pequeñas de RAF y BRAF quinasas, tal como, por ejemplo, BAY 43-9006 (Sorafenib);

(22) inhibidores de moléculas pequeñas de quinasas dependientes de ciclos celulares tal como CDK1, CDK2, CDK4 y CDK6, tal como, por ejemplo, CYC202, BMS387032, y Flavopiridol;

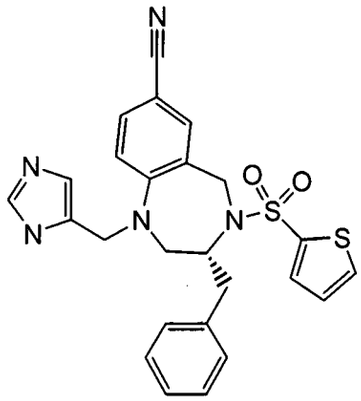
(23) agentes alquilantes, tal como, por ejemplo, temozolomida de la marca Temodar®;

(24) inhibidores de la farnesil proteína transferasa, tal como, por ejemplo:

(a) lonifarnib de la marca Sarasar® (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, U.S. 5874442, presentada el 23 de febrero de 1999, y U.S. 6632455 presentada el 14 de octubre de 2003, cuyos descubrimientos se incorporan en la presente como referencia),

(b) tipifarnib de la mraca Zarnestra® (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 U.S. 5968952 presentada el 19 de octubre de 1999, cuyos descubrimientos se incorporan en la presente como referencia), y

(c) Bristol-Myers Squibb 214662:



(ver WO97/30992 publicada el 28 de agosto de 1997, U.S. 6011029 presentada el 4 de enero de 2000, y U.S. 6455523, cuyos descubrimientos se incorporan en la presente como referencia).

Los inhibidores de la bcr/abl quinasa, inhibidores del receptor de EGF, y anticuerpos HER-2 (inhibidores del receptor de EGF que son anticuerpos) descriptos con anterioridad también son conocidos como por su faceta de inhibidores de la transducción de señales. Por lo tanto, los agentes quimioterapéuticos, utilizados en la presente, incluyen inhibidores de la transducción de señales.

Los inhibidores típicos de la transducción de señales, que son agentes quimioterapéuticos, incluyen, pero sin limitación: (i) Inhibidores de la bcr/abl quinasa tal como, por ejemplo, STI 571 (Gleevec), (ii) Inhibidor del receptor del factor de crecimiento epidérmico (EGF) tal como, por ejemplo, inhibidores de la Quinasa (Iressa, OSI-774) y anticuerpos (Imclone: C225 [Goldstein et al. (1995), Clin Cancer Res. 1:1311-1318], y Abgenix: ABX-EGF) e (iii) inhibidores del receptor hER-2/neu tal como, por ejemplo, Herceptin® (trastuzumab).

También son conocidos por aquellos con experiencia en la técnica numerosos métodos para la administración segura y efectiva de la mayoría de los agentes quimioterapéuticos. Más aún, su administración se describe en la literatura estándar. Por ejemplo, la administración de muchos de los agentes quimioterapéuticos se describe en la "Physicians' Desk Reference" (PDR), por

ej., 1996 ed. (Medical Economics Company, Montvale, NJ 07645-1742, USA), la Physician's Desk Reference, 56th Ed., 2002 (publicada por la Medical Economics company, Inc. Montvale, NJ 07645-1742), la Physician's Desk Reference, 57th Ed., 2003 (publicada por Thompson PDR, Montvale, NJ 07645-1742); y la Physician's Desk Reference, 60th Ed., 2006 (publicada por Thompson PDR, Montvale, NJ 07645-1742); cuyos descubrimientos se incorporan en la presente como referencia.

Por ejemplo, el compuesto de fórmula 1.0 (por ej., una composición farmacéutica que comprende el compuesto de fórmula 1.0); puede administrarse en forma oral (por ej., como una cápsula), y los agentes quimioterapéuticos pueden administrarse en forma intravenosa, normalmente como una solución IV. Se encuentra dentro del alcance de esta invención el uso de una composición farmacéutica que comprende más de una droga.

El compuesto de fórmula 1.0 y los agentes quimioterapéuticos se administran en dosis efectivas para uso terapéutico para obtener resultados clínicamente aceptables, por ej., reducción o eliminación de síntomas o del tumor. De este modo, el compuesto de fórmula 1.0 y los agentes quimioterapéuticos pueden administrarse en forma concurrente o consecutiva en un protocolo de tratamiento. La administración de los agentes quimioterapéuticos puede llevarse a cabo de acuerdo con protocolos de tratamiento conocidos en la técnica.

En general, cuando se utiliza más de un agente quimioterapéutico en los métodos de esta invención, los agentes quimioterapéuticos se administrant el mismo día ya sea en forma concurrente o consecutiva, en su forma de dosificación estándar. Por ejemplo, los agentes quimioterapéuticos normalmente se administran en forma intravenosa, preferentemente mediante

un goteo IV utilizando soluciones IV bien conocidas en la técnica (por ej., salina isotónica (NaCl 0,9%) o solución de dextrosa (por ej., dextrosa 5%)).

Cuando se utilizan dos o más agentes quimioterapéuticos, éstos generalmente se administran el mismo día; sin embargo, aquellos con experiencia en la técnica apreciarán que los agentes quimioterapéuticos pueden administrarse en días distintos y en semanas distintas. El profesional a cargo experimentado cuenta con la capacidad de administrar los agentes quimioterapéuticos de acuerdo con el programa de dosificación recomendado por el fabricante del agente y puede ajustar el programa de acuerdo con las necesidades del paciente, por ej., basándose en la respuesta del paciente al tratamiento. Por ejemplo, cuando se utiliza gemcitabina en combinación con un compuesto coordinador de platino, tal como, por ejemplo, cisplatin, para tratar el cáncer de pulmón, la gemcitabina y la cisplatin se administran el mismo día, el primer día del ciclo de tratamiento, y luego se administra sólo gemcitabina el día 8 y nuevamente sólo dicho producto el día 15.

Los compuestos de esta invención y los agentes quimioterapéuticos pueden administrarse en un protocolo de tratamiento que normalmente dura de una a siete semanas, y que típicamente se repite de 6 a 12 veces. En general, el protocolo de tratamiento puede durar de una a cuatro semanas. Pueden también utilizarse protocolos de tratamiento de una a tres semanas. Puede también utilizarse un protocolo de tratamiento de una a dos semanas. Durante este ciclo o protocolo de tratamiento, los compuestos de esta invención pueden administrarse a diario mientras que los agentes quimioterapéuticos pueden administrarse una o más veces a la semana. En general, un compuesto de esta invención puede administrarse a diario (es decir, una vez al día), y en una realización dos veces al día, y el agente quimioterapéutico se administra una vez a la 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 a la semana o una vez cada tres semanas.

Sin embargo, aquellos con experiencia en la técnica apreciarán que los protocolos de tratamiento pueden variarse de acuerdo con las necesidades del paciente. Así, la combinación de compuestos (drogas) utilizados en los métodos de esta invención pueden administrarse en variaciones de los protocolos descriptos con anteriorida. Por ejemplo, los compuestos de esta invención pueden administrarse en forma discontinua más que continua durante el ciclo de tratamiento. Así, por ejemplo, durante el ciclo de tratamiento los compuestos de esta invención pueden administrarse a diario durante una semana y en forma discontinua durante una semana, repitiéndose dicha administración durante el ciclo de tratamiento. O los compuestos de esta invención pueden administrarse a diario durante dos semanas y en forma discontinua durante una semana, repitiéndose dicha administración durante el ciclo de tratamiento. Así, los compuestos de esta invención pueden administrarse a diario durante una o más semanas durante el ciclo y en forma discontinua durante el ciclo, repitiéndose este patrón de administración durante el ciclo de tratamiento. Este tratamiento discontinuo puede también basarse en números de días más que en una semana completa. Por ejemplo, dosis diaria durante 1 a 6 días, ninguna dosis durante 1 a 6 días, repitiéndose este patrón de administración durante el ciclo de tratamiento. El número de días (o semanas) en que no se administran los compuestos de esta invención no tienen que igualar el número de días (o semanas) en que se administran. Normalmente, si se utiliza un protocolo de dosificación discontinua, el número de días (o semanas) en que se administran los compuestos de esta invención es al menos igual o mayor que el número de días o semanas en que no se administran.

El agente quimioterapéutico puede administrarse en forma de bolus o mediante infusión continua. El agente quimioterapéutico puede administrarse de a diario a una vez a la 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 a diario durante un ciclo de tratamiento, esta dosificación diaria puede ser discontinua durante el número de semanas del ciclo de tratamiento. Por ejemplo, dosificación durante una semana (o un número de días), sin dosificación dosing durante una semana (o un número de días), repitiéndose este patrón de administración durante el ciclo de tratamiento.

Los compuestos de esta invención pueden administrarse en forma oral, preferentemente como una forma de dosificación sólida, y en una realización como una cápsula, y aunque la dosis diaria efectiva para uso terapéutico total puede administrarse en una a cuatro, o una a dos dosis divididas por día, en general, la dosis efectiva para uso terapéutico se administra una o dos veces al día, y en una realización dos veces al día. Los compuestos de esta invención pueden administrarse en una cantidad de aproximadamente 50 a aproximadamente 400 mg una vez al día, y pueden administrarse en una cantidad de aproximadamente 50 a aproximadamente 300 mg una vez al día. En general, los compuestos de esta invención se administran en una cantidad de aproximadamente 50 a aproximadamente 350 mg dos veces al día, normalmente 50 mg a aproximadamente 200 mg dos veces al día, y en una realización aproximadamente 75 mg a aproximadamente 125 mg administrada dos veces al día, y en otra realización aproximadamente 100 mg administrada dos veces al día.

Si el paciente responde, o se encuentra estable, luego de la finalización del ciclo de terapia, el ciclo de terapia puede repetirse de acuerdo con el juicio

del profesional a cargo. Luego de la finalización de los ciclos de terapia, el paciente puede continuar con los compuestos de esta invención en la misma dosis administrada en el protocolo de tratamiento, o, si la dosis era menor que 200 mg dos veces al día, la dosis puede elevarse a 200 mg dos veces al día. Puede continuarse con esta dosis de mantenimiento hasta que el paciente progrese o ya no pueda tolerar la dosis (caso en el que la dosis puede reducirse y el paciente puede continuar recibiendo la dosis reducida).

Los agentes quimioterapéuticos, utilizados con los compuestos de esta invención, se administran en sus dosis normalmente prescriptas durante el ciclo de tratamiento (es decir, los agentes quimioterapéuticos se administran de acuerdo con el estándar de práctica para la administración de estas drogas). Por ejemplo: (a) aproximadamente 30 a aproximadamente 300 mg/m^2 para los taxanos; (b) aproximadamente 30 a aproximadamente 100 mg/m^2 para Cisplatin; (c) AUC de aproximadamente 2 a aproximadamente 8 para Carboplatin; (d) aproximadamente 2 a aproximadamente 4 mg/m^2 para los inhibidores de EGF que son anticuerpos; (e) aproximadamente 50 a aproximadamente 500 mg/m^2 para los inhibidores de EGF que son moléculas pequeñas; (f) aproximadamente 1 a aproximadamente 10 mg/m^2 para los inhibidores de la VEGF quinasa que son anticuerpos; (g) aproximadamente 50 a aproximadamente 2400 mg/m^2 para los inhibidores de VEGF que son moléculas pequeñas; (h) aproximadamente 1 a aproximadamente 20 mg para SERM; (i) aproximadamente 500 a aproximadamente 1250 mg/m^2 para los nucleósidos antitumorales 5-Fluoruracil, Gemcitabina y Capecitabina; (j) para el nucleósido antitumoral Citarabina (Ara-C) 100-200mg/m^2/día durante 7 a 10 días cada 3 a 4 semanas, y dosis elevadas para la leucemia y linfoma refractario, es decir, 1 a 3 gm/m^2 durante una hora cada 12 horas durante 4-8 dosis cada 3 a 4 semanas; (k) para el nucleósido antitumoral Fludarabina (F-

ara-A) 10-25mg/m^2/día cada 3 a 4 semanas; (l) para el nucleósido antitumoral Decitabina 30 a 75 mg/m^2 durante tres días cada 6 semanas durante un máximo de 8 ciclos; (m) para el nucleósido antitumoral Clorodeoxiadenosina (CdA, 2-CdA) 0,05-0,1 mg/kg/día como una infusión continua durante hasta 7 días cada 3 a 4 semanas; (n) aproximadamente 1 a aproximadamente 100 mg/m^2 para las epotilonas; (o) aproximadamente 1 a aproximadamente 350 mg/m^2 para los inhibidores de la topoisomerasa; (p) aproximadamente 1 a aproximadamente 50 mg/m^2 para los alcaloides de la vinca; (q) para el antagonista de folato, Metotrexato, (MTX) 20-60 mg/m^2 en forma oral, IV o IM cada 3 a 4 semanas, el régimen de dosificación intermedio es 80-250 mg/m^2 IV durante 60 minutos cada 3 a 4 semanas, y el régimen de dosificación elevada es 250-1000mg/m^2 IV administrado con leucovorin cada 3 a 4 semanas; (r) para el antagonista de folato Premetrexed (Alimta) 300-600 mg/m^2 (infusion IV durante 10 minutos el día 1) cada 3 semanas; (s) para el inhibidor de la ribonucleótido reductasa Hidroxiurea (HU) 20-50 mg/kg/día (según lo requerido para reducir los recuentos de los glóbulos rojos); (t) el compuesto coordinador de platino, Oxaliplatin (Eloxatin) 50-100 mg/m^2 cada 3 a 4 semanas (preferentemente utilizado para tumores sólidos tal como cáncer de pulmón de células no pequeñas, cáncer colorectal y cáncer de ovarios); (u) para la antraciclina daunorubicin IV 10-50 mg/m^2/día durante 3-5 días cada 3 a 4 semanas; (v) para la antraciclina Doxorubicin (Adriamicin) IV continua 50-100 mg/m^2 durante 1-4 días cada 3 a 4 semanas, o IV semanal 10-40 mg/m^2; (w) para la antraciclina Idarubicin 10-30 mg/m^2 a diario durante 1-3 días como una infusión IV lenta durante 10-20 minutos cada 3 a 4 semanas; (x) para el interferón biológico (Intron-A, Roferon) IU 5 a 20 millones tres veces a la semana; (y) para el interferón biológico pegilado (Peg-intron, Pegasys) administración subcutánea crónica de 3 a 4 microgramos/kg/día (hasta una

recaída o pérdida de la actividad); (z) para el biológico Rituximab (Rituxan) (anticuerpo utilizado para el linfoma no Hodgkin) IV 200-400mg/m^2 durante 4-8 semanas durante 6 meses; (aa) para el agente alquilante temozolomida 75 mg/m^2 a 250mg/m^2, por ejemplo, 150 mg/m^2, o por ejemplo, 200 mg/m^2, tal como 200mg/m^2 durante 5 días; y (bb) para el inhibidor PD0325901 MEK1 y/o MEK2, 15 mg a 30 mg, por ejemplo, 15 mg por día duante 21 días cada 4 semanas.

Puede utilizarse gleevec en forma oral en una cantidad de aproximadamente 200 a aproximadamente 800 mg/día.

Puede utilizarse talidomida (e imidas relacionadas) en forma oral en cantidades de aproximadamente 200 a aproximadamente 800 mg/día, y puede administrarse en forma continua o utilizarse hasta una recaída o toxicidad. Ver, por ejemplo, Mitsiades et al., "Apoptotic signaling induced by immunomodulatory thalidomide analoqs in human mieloma múltiple cells; therapeutic implications", Blood, 99(12):4525-30, June 15, 2002, cuyos descubrimientos se incorporan en la presente como referencia.

El inhibidor FPT Sarasar® (marca de lonifarnib) puede administrarse en forma oral (por ej., cápsula) en cantidades de aproximadamente 50 a aproximadamente 200 mg administradas dos veces al día, o en cantidades de aproximadamente 75 a aproximadamente 125 mg administradas dos veces al día, o en cantidades de aproximadamente 100 a aproximadamente 200 mg administradas dos veces al día, o en una cantidad de aproximadamente 100 mg administrada dos veces al día.

Paclitaxel (por ej., Taxol®), por ejemplo, puede administrarse una vez a la semana en una cantidad de aproximadamente 50 a aproximadamente 100 mg/m^2 y en otro ejemplo aproximadamente 60 a 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 a aproximadamente 250 mg/m^2 y en otro ejemplo aproximadamente 175 a aproximadamente 225 mg/m^2.

En otro ejemplo, Docetaxel (por ej., Taxotere®) puede administrarse una vez a la semana en una cantidad de aproximadamente 10 a 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 a aproximadamente 100 mg/m^2.

En otro ejemplo Cisplatin puede administrarse una vez a la semana en una cantidad de aproximadamente 20 a aproximadamente 40 mg/m^2. En otro ejemplo Cisplatin puede administrarse una vez cada tres semanas en una cantidad de aproximadamente 60 a aproximadamente 100 mg/m^2.

En otro ejemplo Carboplatin puede administrarse una vez a la semana en una cantidad para proveer un AUC de aproximadamente 2 a aproximadamente 3. En otro ejemplo Carboplatin puede administrarse una vez cada tres semanas en una cantidad para proveer un AUC de aproximadamente 5 a aproximadamente 8.

Otras realizaciones de esta invención se dirigen a cualquiera de los métodos de las realizaciones para tratar el cáncer donde los compuestos de fórmula 1.0 y los agentes quimioterapéuticos se administran como una composición farmacéutica que comprende una cantidad efectiva de los compuestos de fórmula 1.0, una cantidad efectiva de los agentes quimioterapéuticos, y un vehículo aceptable para uso farmacéutico.

Otras realizaciones de esta invención se dirigen a cualquiera de los métodos de las realizaciones para tratar el cáncer donde se utilice un agente quimioterapéutico, donde el agente quimioterapéutico se selecciona del grupo que consiste en: paclitaxel, docetaxel, carboplatin, cisplatin, gemcitabina,

tamoxifen, Herceptin, Cetuximab, Tarceva, Iressa, bevacizumab, navelbina, IMC-1C11, SU5416 y SU6688.

Otras realizaciones de esta invención se dirigen a cualquiera de los métodos de las realizaciones para tratar el cáncer dónde se utilice un agente quimioterapéutico, donde el agente quimioterapéutico se selecciona del grupo que consiste en: paclitaxel, docetaxel, carboplatin, cisplatin, navelbina, gemcitabina, y Herceptin.

Otras realizaciones de esta invención se dirigen a cualquiera de los métodos de las realizaciones para tratar el cáncer donde se utilice un agente quimioterapéutico, donde el agente quimioterapéutico se selecciona del grupo que consiste en: ciclofasfamida, 5-Fluoruracil, Temozolomida, Vincristina, Cisplatin, Carboplatin, y Gemcitabina.

Otras realizaciones de esta invención se dirigen a cualquiera de los métodos de las realizaciones para tratar el cáncer donde se utilice un agente quimioterapéutico, donde el agente quimioterapéutico se selecciona del grupo que consiste en: Gemcitabina, Cisplatin y Carboplatin.

Esta invención también provee un método para tratar el cáncer en un paciente necesitado de dicho tratamiento, dicho tratamiento comprende administrar a dicho paciente una cantidad efectiva para uso terapéutico de al menos un (por ej., 1, 2 o 3, o 1 o 2, o 1, y normalmente 1) compuesto de fórmula 1.0, y cantidades efectivas para uso terapéutico de al menos un (por ej., 1, 2 o 3, o 1 o 2, o 2, o 1) agente quimioterapéutico seleccionado del grupo que consiste en: (1) taxanos, (2) compuestos coordinadores de platino, (3) inhibidores del factor de crecimiento epidérmico (EGF) que son anticuerpos, (4) inhibidores de EGF que son pequeñas moléculas, (5) inhibidores del factor de crecimiento endotelial vascular (VEGF) que son anticuerpos, (6) Inhbidores de la quinasa VEGF que son pequeñas moléculas, (7) antagonistas del receptor

de estrógenos o moduladores selectivos del receptor de estrógenos (SERM), (8) derivados nucleósidos antitumorales, (9) epotilonas, (10) inhibidores de la topoisomerasa, (11) vinca alcaloides, (12) anticuerpos que son inhibidores de $\alpha V\beta 3$ integrinas, (13) antagonistas de folato, (14) inhibidores de la ribonucleótido reductasa, (15) antraciclinas, (16) biológicos; (17) inhibidores de angiogénesis y/o supresores de factor de necrosis tumoral alfa (TNF-alfa) tal como talidomida (o imida relacionada), (18) Inhibidores de la bcr/abl quinasa, (19) inhibidores de MEK1 y/o MEK 2 que son pequeñas moléculas, (20) inhibidores de IGF-1 y IGF-2 que son pequeñas moléculas, (21) inhibidores de pequeñas moléculas de las RAF y BRAF quinasas, (22) inhibidores de pequeñas moléculas de quinasas dependientes de ciclos celulares tal como CDK1, CDK2, CDK4 y CDK6, (23) agentes alquilantes, e (24) inhibidores de la farnesil proteína transferasa (también denominados inhibidores FPT o FTI (es decir, inhibidores de la farnesil transferasa)).

Esta invención también provee un método para tratar el cáncer en un paciente necesitado de dicho tratamiento, dicho tratamiento comprende administrar a dicho paciente una cantidad efectiva para uso terapéutico de al menos un (por ej., 1, 2 o 3, o 1 o 2, o 1, y normalmente 1) compuesto de fórmula 1.0, y cantidades efectivas para uso terapéutico de al menos dos (por ej., 2 o 3, o 2, y normalmente 2) agentes antineoplásicos diferentes seleccionados del grupo que consiste en: (1) taxanos, (2) compuestos coordinadores de platino, (3) inhibidores del factor de crecimiento epidérmico (EGF) que son anticuerpos, (4) inhibidores de EGF que son pequeñas moléculas, (5) inhibidores del factor de crecimiento endotelial vascular (VEGF) que son anticuerpos, (6) Inhbidores de la quinasa VEGF que son pequeñas moléculas, (7) antagonistas del receptor de estrógenos o moduladores selectivos del receptor de estrógenos (SERM), (8) derivados nucleósidos

antitumorales, (9) epotilonas, (10) inhibidores de la topoisomerasa, (11) vinca alcaloides, (12) anticuerpos que son inhibidores de αVβ3 integrinas, (13) antagonistas de folato, (14) inhibidores de la ribonucleótido reductasa, (15) antraciclinas, (16) biológicos; (17) inhibidores de angiogénesis y/o supresores de factor de necrosis tumoral alfa (TNF-alfa) tal como talidomida (o imida relacionada), (18) Inhibidores de la bcr/abl quinasa, (19) inhibidores de MEK1 y/o MEK 2 que son pequeñas moléculas, (20) inhibidores de IGF-1 y IGF-2 que son pequeñas moléculas, (21) inhibidores de pequeñas moléculas de las RAF y BRAF quinasas, (22) inhibidores de pequeñas moléculas de quinasas dependientes de ciclos celulares tal como CDK1, CDK2, CDK4 y CDK6, (23) agentes alquilantes, e (24) inhibidores de la farnesil proteína transferasa (también denominados inhibidores FPT o FTI (es decir, inhibidores de la farnesil transferasa)).

Esta invención también provee un método para tratar el cáncer en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente cantidades efectivas para uso terapéutico de al menos un (por ej., 1, 2 o 3, o 1 o 2, o 1, y normalmente 1) compuesto de fórmula 1.0, y un agente antineoplásico seleccionado del grupo que consiste en: (1) Inhibidores de EGF que son anticuerpos, (2) Inhibidores de EGF que son moléculas pequeñas, (3) Inhibidores de EGF que son anticuerpos, y (4) Inhibidores de EGF que son moléculas pequeñas. También puede utilizarse terapia de radiación, en conjunto con esta terapia combinada anterior, es decir, el método anterior donde se utiliza una combinación de compuestos de esta invención y un agente antineoplásico puede también comprender la administración de una cantidad efectiva para uso terapéutico de radiación.

Esta invención también provee un método para tratar leucemias (por ej., leucemia mieloide aguda (AML), y leucemia mieloide crónica (CML)) en un

paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente cantidades efectivas para uso terapéutico de al menos un (por ej., 1, 2 o 3, o 1 o 2, o 1, y normalmente 1) compuesto de fórmula 1.0, y: (1) Gleevec e interferón para tratar la CML; (2) Gleevec e interferon pegilado para tratar la CML; (3) Gleevec para tratar la CML; (4) un derivado de un nucleósido antitumoral (por ej., Ara-C) para tratar la AML; o (5) un derivado de un nucleósido antitumoral (por ej., Ara-C) en combinación con una antraciclina para tratar la AML.

Esta invención también provee un método para tratar el linfoma no Hodgkin en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente cantidades efectivas para uso terapéutico de al menos un (por ej., 1, 2 o 3, o 1 o 2, o 1, y normalmente 1) compuesto de fórmula 1.0 y: (1) un biológico (por ej., Rituxan); (2) un biólogico (por ej., Rituxan) y un derivado de un nucleósido antitumoral (por ej., Fludarabina); o (3) Genasense (antisentido a BCL-2).

Esta invención también provee un método para tratar el mieloma múltiple en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente cantidades efectivas para uso terapéutico de al menos un (por ej., 1, 2 o 3, o 1 o 2, o 1, y normalmente 1) compuesto de fórmula 1.0 y: (1) un inhibidor de la proteosoma (por ej., PS-341 de Millenium); o (2) Talidomida (o una imida relacionada).

Esta invención también provee un método para tratar el cáncer en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente cantidades efectivas para uso terapéutico de: (a) al menos un (por ej., 1, 2 o 3, o 1 o 2, o 1, y normalmente 1) compuesto de fórmula 1.0, y (b) al menos un (por ej., 1, 2 o 3, o 1 o 2, o 2, o 1) agente antineoplásico seleccionado del grupo que consiste en: (1) taxanos, (2) compuestos

coordinadores de platino, (3) Inhibidores de EGF que son anticuerpos, (4) Inhibidores de EGF que son moléculas pequeñas, (5) Inhibidores de EGF que son anticuerpos, (6) Inhibidores de la VEGF quinasa que son moléculas pequeñas, (7) antagonistas del receptor de estrógenos o moduladores selectivos del receptor de estrógenos, (8) derivados de nucleósidos antitumorales, (9) epotilonas, (10) inhibidores de la topoisomerasa, (11) alcaloides de la vinca, y (12) anticuerpos que son inhibidores de $\alpha V\beta 3$ integrinas.

Esta invención también provee un método para tratar el cáncer de pulmón de células no pequeñas en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente cantidades efectivas para uso terapéutico de: (a) al menos un (por ej., 1, 2 o 3, o 1 o 2, o 1, y normalmente 1) compuesto de fórmula 1.0, y (b) al menos un (por ej., 1, 2 o 3, o 1 o 2, o 2, o 1) agente antineoplásico seleccionado del grupo que consiste en: (1) taxanos, (2) compuestos coordinadores de platino, (3) Inhibidores de EGF que son anticuerpos, (4) Inhibidores de EGF que son moléculas pequeñas, (5) Inhibidores de EGF que son anticuerpos, (6) Inhibidores de la VEGF quinasa que son moléculas pequeñas, (7) antagonistas del receptor de estrógenos o moduladores selectivos del receptor de estrógenos, (8) derivados de nucleósidos antitumorales, (9) epotilonas, (10) inhibidores de la topoisomerasa, (11) alcaloides de la vinca, y (12) anticuerpos que son inhibidores de $\alpha V\beta 3$ integrinas.

Esta invención también provee un método para tratar el cáncer de pulmón de células no pequeñas en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente cantidades efectivas para uso terapéutico de: (a) al menos un (por ej., 1, 2 o 3, o 1 o 2, o 1, y normalmente 1) compuesto de fórmula 1.0, y (b) al menos un (por ej., 1, 2 o

3, o 1 o 2, o 2, o 1) agente antineoplásico seleccionado del grupo que consiste en: (1) taxanos, (2) compuestos coordinadores de platino, (3) derivados de nucleósidos antitumorales, (4) inhibidores de la topoisomerasa, y (5) alcaloides de la vinca.

Esta invención también provee un método para tratar el cáncer de pulmón de células no pequeñas en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente cantidades efectivas para uso terapéutico de: (a) al menos un (por ej., 1, 2 o 3, o 1 o 2, o 1, y normalmente 1) compuesto de fórmula 1.0, (b) carboplatin, y (c) paclitaxel.

Esta invención también provee un método para tratar el cáncer de pulmón de células no pequeñas en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente cantidades efectivas para uso terapéutico de: (a) al menos un (por ej., 1, 2 o 3, o 1 o 2, o 1, y normalmente 1) compuesto de fórmula 1.0, (b) cisplatin, y (c) gemcitabina.

Esta invención también provee un método para tratar el cáncer de pulmón de células no pequeñas en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente cantidades efectivas para uso terapéutico de: (a) al menos un (por ej., 1, 2 o 3, o 1 o 2, o 1, y normalmente 1) compuesto de fórmula 1.0, (b) carboplatin, y (c) gemcitabina.

Esta invención también provee un método para tratar el cáncer de pulmón de células no pequeñas en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente cantidades efectivas para uso terapéutico de: (a) al menos un (por ej., 1, 2 o 3, o 1 o 2, o 1, y normalmente 1) compuesto de fórmula 1.0, (b) Carboplatin, y (c) Docetaxel.

Esta invención también provee un método para tratar el cáncer en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente cantidades efectivas para uso terapéutico de: (a) al menos un

(por ej., 1, 2 o 3, o 1 o 2, o 1, y normalmente 1) compuesto de fórmula 1.0, y (b) un agente antineoplásico seleccionado del grupo que consiste en: (1) Inhibidores de EGF que son anticuerpos, (2) Inhibidores de EGF que son moléculas pequeñas, (3) Inhibidores de EGF que son anticuerpos, (4) Inhibidores de la VEGF quinasa que son moléculas pequeñas.

Esta invención también provee un método para tratar el cáncer de células escamosas de cabeza y cuello, en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente cantidades efectivas para uso terapéutico de: (a) al menos un (por ej., 1, 2 o 3, o 1 o 2, o 1, y normalmente 1) compuesto de fórmula 1.0, y (b) al menos un (por ej., 1, 2 o 3, o 1 o 2, o 2, o 1) agente antineoplásico seleccionado del grupo que consiste en: (1) taxanos, y (2) compuestos coordinadores de platino.

Esta invención también provee un método para tratar el cáncer de células escamosas de cabeza y cuello, en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente cantidades efectivas para uso terapéutico de: (a) al menos un (por ej., 1, 2 o 3, o 1 o 2, o 1, y normalmente 1) compuesto de fórmula 1.0, y (b) al menos un (por ej., 1, 2 o 3, o 1 o 2, o 2, o 1) agente antineoplásico seleccionado del grupo que consiste en: (1) taxanos, (2) compuestos coordinadores de platino, y (3) derivados de nucleósidos antitumorales (por ej., 5-Fluoruracil).

Esta invención también provee un método para tratar la CML en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente cantidades efectivas para uso terapéutico de: (a) al menos un (por ej., 1, 2 o 3, o 1 o 2, o 1, y normalmente 1) compuesto de fórmula 1.0, (b) Gleevec, e (c) interferón (por ej., Intron-A).

Esta invención también provee un método para tratar la CML en un paciente necesitado de dicho tratamiento, dicho método comprende administrar

a dicho paciente cantidades efectivas para uso terapéutico de: (a) de al menos un (por ej., 1, 2 o 3, o 1 o 2, o 1, y normalmente 1) compuesto de fórmula 1.0, (b) Gleevec; e (c) interferón pegilado (por ej., Peg-Intron, y Pegasys).

Esta invención también provee un método para tratar la CML en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente cantidades efectivas para uso terapéutico de: (a) de al menos un (por ej., 1, 2 o 3, o 1 o 2, o 1, y normalmente 1) compuesto de fórmula 1.0 y (b) Gleevec.

Esta invención también provee un método para tratar CMML en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente cantidades efectivas para uso terapéutico de al menos un (por ej., 1, 2 o 3, o 1 o 2, o 1, y normalmente 1) compuesto de fórmula 1.0.

Esta invención también provee un método para tratar AML en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente cantidades efectivas para uso terapéutico de: (a) al menos un (por ej., 1, 2 o 3, o 1 o 2, o 1, y normalmente 1) compuesto de fórmula 1.0, y (b) un derivado de un nucleósido antitumoral (por ej., Citarabina (es decir, Ara-C)).

Esta invención también provee un método para tratar AML en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente cantidades efectivas para uso terapéutico de: (a) al menos un (por ej., 1, 2 o 3, o 1 o 2, o 1, y normalmente 1) compuesto de fórmula 1.0, (b) un derivado de un nucleósido antitumoral (por ej., Citarabina (es decir, Ara-C)), y (c) una antraciclina.

Esta invención también provee un método para tratar el linfoma no Hodgkin en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente cantidades efectivas para uso

terapéutico de: (a) al menos un (por ej., 1, 2 o 3, o 1 o 2, o 1, y normalmente 1) compuesto de fórmula 1.0, y (b) Rituximab (Rituxan).

Esta invención también provee un método para tratar el linfoma no Hodgkin en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente cantidades efectivas para uso terapéutico de: (a) al menos un (por ej., 1, 2 o 3, o 1 o 2, o 1, y normalmente 1) compuesto de fórmula 1.0, (b) Rituximab (Rituxan), y (c) un derivado de un nucleósido antitumoral (por ej., Fludarabina (es decir, F-ara-A).

Esta invención también provee un método para tratar el linfoma no Hodgkin en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente cantidades efectivas para uso terapéutico de: (a) al menos un (por ej., 1, 2 o 3, o 1 o 2, o 1, y normalmente 1) compuesto de fórmula 1.0, y (b) Genasense (antisentido a BCL-2).

Esta invención también provee un método para tratar el mieloma múltiple en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente cantidades efectivas para uso terapéutico de: (a) al menos un (por ej., 1, 2 o 3, o 1 o 2, o 1, y normalmente 1) compuesto de fórmula 1.0, y (b) un inhibidor de la proteosoma (por ej., PS-341 (Millenium)).

Esta invención también provee un método para tratar el mieloma múltiple en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente cantidades efectivas para uso terapéutico de: (a) al menos un (por ej., 1, 2 o 3, o 1 o 2, o 1, y normalmente 1) compuesto de fórmula 1.0, y (b) Talidomida o una imida relacionada.

Esta invención también provee un método para tratar el mieloma múltiple en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente cantidades efectivas para uso terapéutico de: (a)

al menos un (por ej., 1, 2 o 3, o 1 o 2, o 1, y normalmente 1) compuesto de fórmula 1.0, y (b) Talidomida.

Esta invención también se dirige a los métodos para tratar el cáncer descriptos en la presente, en particular a aquellos descriptos con anterioridad, donde además de la administración del compuesto de fórmula 1.0 y agentes antineoplásicos, también se administra terapia de radiación antes, durante, o después del ciclo de tratamiento.

Esta invención también provee un método para tratar el cáncer (por ej., cáncer de pulmón, cáncer de próstata y leucemias mieloides) en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente (1) una cantidad efectiva de al menos un (por ej., 1, 2 o 3, o 1 o 2, o 1, y normalmente 1) compuesto de fórmula 1.0, en combinación con (2) al menos un (por ej., 1, 2 o 3, o 1 o 2, o 2, o 1) agente antineoplásico, agente que afecta los microtúbulos y/o terapia de radiación.

Esta invención también provee un método para tratar el cáncer en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de de al menos un (por ej., 1, 2 o 3, o 1 o 2, o 1, y normalmente 1) compuesto de fórmula 1.0 en combinación con una cantidad efectiva de al menos un (por ej., 1, 2 o 3, o 1 o 2, o 1, y normalmente 1) inhibidor de la transducción de señales.

Así, en un ejemplo (por ej., en el tratamiento del cáncer de pulmón de células no pequeñas): (1) el compuesto de fórmula 1.0 se administra en una cantidad de aproximadamente 50 mg a aproximadamente 200 mg dos veces al día, y en otro ejemplo aproximadamente 75 mg a aproximadamente 125 mg administrada dos veces al día, y en aún otro ejemplo aproximadamente 100 mg administrada dos veces al día, (2) Paclitaxel (por ej., Taxol® se administra una vez a la semana en una cantidad de aproximadamente 50 a aproximadamente

100 mg/m^2, y en otro ejemplo about 60 a aproximadamente 80 mg/m^2, y (3) Carboplatin se administra una vez a la semana en una cantidad para proveer un AUC de aproximadamente 2 a aproximadamente 3.

En otro ejemplo (por ej., en el tratamiento del cáncer de pulmón de células no pequeñas): (1) el compuesto de fórmula 1.0 se administra en una cantidad de aproximadamente 50 mg a aproximadamente 200 mg dos veces al día, y en otro ejemplo aproximadamente 75 mg a aproximadamente 125 mg administrada dos veces al día, y aún en otro ejemplo aproximadamente 100 mg administrada dos veces al día, (2) Paclitaxel (por ej., Taxol® se administra una vez a la semana en una cantidad de aproximadamente 50 a aproximadamente 100 mg/m^2, y en otro ejemplo aproximadamente 60 a aproximadamente 80 mg/m^2, y (3) Cisplatin se administra una vez a la semana en una cantidad de aproximadamente 20 a aproximadamente 40 mg/m^2.

En otro ejemplo (por ej., en el tratamiento del cáncer de pulmón de células no pequeñas): (1) el compuesto de fórmula 1.0 se administra en una cantidad de aproximadamente 50 mg a aproximadamente 200 mg dos veces al día, y en otro ejemplo aproximadamente 75 mg a aproximadamente 125 mg administrada dos veces al día, y en aún otro ejemplo aproximadamente 100 mg administrada dos veces al día, (2) Docetaxel (por ej., Taxotere®) se administra una vez a la semana en una cantidad de aproximadamente 10 a aproximadamente 45 mg/m^2, y (3) Carboplatin se administra una vez a la semana en una cantidad para proveer un AUC de aproximadamente 2 a aproximadamente 3.

En otro ejemplo (por ej., en el tratamiento del cáncer de pulmón de células no pequeñas): (1) el compuesto de fórmula 1.0 se administra en una cantidad de aproximadamente 50 mg a aproximadamente 200 mg dos veces al día, y en otro ejemplo aproximadamente 75 mg a aproximadamente 125 mg

administrada dos veces al día, y en aún otro ejemplo aproximadamente 100 mg administrada dos veces al día, (2) Docetaxel (por ej., Taxotere®) se administra una vez a la semana en una cantidad de aproximadamente 10 a aproximadamente 45 mg/m^2, y (3) Cisplatin se administra una vez a la semana en una cantidad de aproximadamente 20 a aproximadamente 40 mg/m^2.

En otro ejemplo (por ej., en el tratamiento del cáncer de pulmón de células no pequeñas): (1) el compuesto de fórmula 1.0 se administra en una cantidad de aproximadamente 50 mg a aproximadamente 200 mg dos veces al día, y en otro ejemplo aproximadamente 75 mg a aproximadamente 125 mg administrada dos veces al día, y en aún otro ejemplo aproximadamente 100 mg administrada dos veces al día, (2) Paclitaxel (por ej., Taxol® se administra una vez cada tres semanas en una cantidad de aproximadamente 150 a aproximadamente 250 mg/m^2, y en otro ejemplo aproximadamente 175 a aproximadamente 225 mg/m^2, y en aún otro ejemplo 175 mg/m^2, y (3) Carboplatin se administra una vez cada tres semanas en una cantidad para proveer un AUC de aproximadamente 5 a aproximadamente 8, y en otro ejemplo 6.

En otro ejemplo del tratamiento del cáncer de pulmón de células no pequeñas: (1) el compuesto de fórmula 1.0 se administra en una cantidad de 100 mg administrada dos veces al día, (2) Paclitaxel (por ej., Taxol® se administra una vez cada tres semanas en una cantidad de 175 mg/m^2, y (3) Carboplatin se administra una vez cada tres semanas en una cantidad para proveer un AUC de 6.

En otro ejemplo (por ej., en el tratamiento del cáncer de pulmón de células no pequeñas): (1) el compuesto de fórmula 1.0 se administra en una cantidad de aproximadamente 50 mg a aproximadamente 200 mg dos veces al día, y en otro ejemplo aproximadamente 75 mg a aproximadamente 125 mg

administrada dos veces al día, y en aún otro ejemplo aproximadamente 100 mg administrada dos veces al día, (2) Paclitaxel (por ej., Taxol® se administra una vez cada tres semanas en una cantidad de aproximadamente 150 a aproximadamente 250 mg/m^2, y en otro ejemplo aproximadamente 175 a aproximadamente 225 mg/m^2, y (3) Cisplatin se administra una vez cada tres semanas en una cantidad de aproximadamente 60 a aproximadamente 100 mg/m^2.

En otro ejemplo (por ej., en el tratamiento del cáncer de pulmón de células no pequeñas): (1) el compuesto de fórmula 1.0 se administra en una cantidad de aproximadamente 50 mg a aproximadamente 200 mg dos veces al día, y en otro ejemplo aproximadamente 75 mg a aproximadamente 125 mg administrada dos veces al día, y en aún otro ejemplo aproximadamente 100 mg administrada dos veces al día, (2) Docetaxel (por ej., Taxotere® se administra una vez cada tres semanas en una cantidad de aproximadamente 50 a aproximadamente 100 mg/m^2, y (3) Carboplatin se administra una vez cada tres semanas en una cantidad para proveer un AUC de aproximadamente 5 a aproximadamente 8.

En otro ejemplo (por ej., en el tratamiento del cáncer de pulmón de células no pequeñas): (1) el compuesto de fórmula 1.0 se administra en una cantidad de aproximadamente 50 mg a aproximadamente 200 mg dos veces al día, en otro ejemplo aproximadamente 75 mg a aproximadamente 125 mg administrada dos veces al día, y en aún otro ejemplo aproximadamente 100 mg administrada dos veces al día, (2) Docetaxel (por ej., Taxotere® se administra una vez cada tres semanas en una cantidad de aproximadamente 50 a aproximadamente 100 mg/m^2, y (3) Cisplatin se administra una vez cada tres semanas en una cantidad de aproximadamente 60 a aproximadamente 100 mg/m^2.

En otro ejemplo del tratamiento del cáncer de pulmón de células no pequeñas utilizando los compuestos de fórmula 1.0, Docetaxel y Carboplatin: (1) el compuesto de fórmula 1.0 se administra en una cantidad de aproximadamente 50 mg a aproximadamente 200 mg dos veces al día, y en otro ejemplo aproximadamente 75 mg a aproximadamente 125 mg administrada dos veces al día, y en aún otro ejemplo aproximadamente 100 mg administrada dos veces al día, (2) Docetaxel (por ej., Taxotere®) se administra una vez cada tres semanas en una cantidad de aproximadamente 75 mg/m^2, y (3) Carboplatin se administra una vez cada tres semanas en una cantidad para proveer un AUC de aproximadamente 6.

En otro ejemplo de los tratamientos de cáncer de pulmón de células no pequeñas descriptos con anterioridad, se administran Docetaxel (por ej., Taxotere®) y Cisplatin, el Docetaxel (por ej., Taxotere®) y Carboplatin, el Paclitaxel (por ej., Taxol®) y Carboplatin, o el Paclitaxel (por ej., Taxol®) y Cisplatin se administran el mismo día.

En otro ejemplo (por ej., CML): (1) el compuesto de fórmula 1.0 se administra en una cantidad de aproximadamente 100 mg a aproximadamente 200 mg administrada dos veces al día, (2) Gleevec se administra en una cantidad de aproximadamente 400 a aproximadamente 800 mg/día en forma oral, y (3) se administra interferón (Intron-A) en una cantidad de aproximadamente 5 a aproximadamente 20 millones IU tres veces a la semana.

En otro ejemplo (por ej., CML): (1) el compuesto de fórmula 1.0 se administra en una cantidad de aproximadamente 100 mg a aproximadamente 200 mg administrada dos veces al día, (2) Gleevec se administra en una cantidad de aproximadamente 400 aproximadamente 800 mg/día en forma oral, e (3) interferón pegilado (Peg-Intron o Pegasys) se administra en una cantidad de aproximadamente 3 a aproximadamente 6 microgramos/kg/día.

En otro ejemplo (por ej., linfoma no Hodgkin): (1) el compuesto de fórmula 1.0 se administra en una cantidad de aproximadamente 50 mg a aproximadamente 200 mg dos veces al día, y en otro ejemplo aproximadamente 75 mg a aproximadamente 125 mg administrada dos veces al día, y en aún otro ejemplo aproximadamente 100 mg administrada dos veces al día, y (2) Genasense (antisentido a BCL-2) se administra como una infusión IV continua en una dosis de aproximadamente 2 a aproximadamente 5 mg/kg/día (por ej., 3 mg/kg/día) durante 5 a 7 días cada 3 a 4 semanas.

En otro ejemplo (por ej., mieloma múltiple): (1) el compuesto de fórmula 1.0 se administra en una cantidad de aproximadamente 50 mg a aproximadamente 200 mg dos veces al día, y en otro ejemplo aproximadamente 75 mg a aproximadamente 125 mg administrada dos veces al día, y en aún otro ejemplo aproximadamente 100 mg administrada dos veces al día, y (2) el inhibidor de la proteosoma (por ej., PS-341 – Millenium) se administra en una cantidad de aproximadamente 1,5mg/m^2 dos veces a la semana durante dos semanas consecutives con un período de descanso de una semana.

En otro ejemplo (por ej., mieloma múltiple): (1) el compuesto de fórmula 1.0 se administra en una cantidad de aproximadamente 50 mg a aproximadamente 200 mg dos veces al día, y en otro ejemplo aproximadamente 75 mg a aproximadamente 125 mg administrada dos veces al día, y en aún otro ejemplo aproximadamente 100 mg administrada dos veces al día, y (2) la Talidomida (o una imida relacionada) se administra en forma oral en una cantidad de aproximadamente 200 a aproximadamente 800 mg/day, siendo esta dosificación continua hasta una recaída o toxicidad.

En una realización de los métodos para tratar el cáncer de esta invención, los agentes quimioterapéuticos se seleccionan del grupo que

consiste en: paclitaxel, docetaxel, carboplatin, cisplatin, gemcitabina, tamoxifen, Herceptin, Cetuximab, Tarceva, Iressa, bevacizumab, navelbina, IMC-1C11, SU5416 y SU6688.

En otra realización de los métodos para tratar el cáncer de esta invención, the agente quimioterapéuticos se seleccionan del grupo que consiste en: paclitaxel, docetaxel, carboplatin, cisplatin, navelbina, gemcitabina, y Herceptin.

Así, una realización de esta invención se dirige a un método para tratar el cáncer que comprende administrar a un paciente necesitado de dicho tratamiento cantidades efectivas para uso terapéutico del compuesto de fórmula 1.0, un taxano, y un compuesto de coordinación de platino.

Otra realización de esta invención se dirige a un método para tratar el cáncer que comprende administrar a un paciente necesitado de dicho tratamiento cantidades efectivas para uso terapéutico del compuesto de fórmula 1.0, 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 a la semana por ciclo, y dicho compuesto coordinador de platino se administra una vez a la semana por ciclo. En otra realización, el tratamiento es de una a cuatro semanas por ciclo.

Otra realización de esta invención se dirige a un método para tratar el cáncer que comprende administrar a un paciente necesitado de dicho tratamiento cantidades efectivas para uso terapéutico del compuesto de fórmula 1.0, 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 ciclo, y dicho compuesto coordinador de platino se administra una vez cada tres semanas por ciclo. En otra realización, el tratamiento es de una a tres semanas por ciclo.

Otra realización de esta invención se dirige a un método para tratar el cáncer que comprende administrar a un paciente necesitado de dicho tratamiento cantidades efectivas para uso terapéutico del compuesto de fórmula 1.0, paclitaxel, y carboplatin. En otra realización, dicho compuesto de fórmula 1.0 se administra todos los días, dicho paclitaxel se administra una vez a la semana por ciclo, y dicha carboplatin se administra una vez a la semana por ciclo. En otra realización, el tratamiento es de una a cuatro semanas por ciclo.

Otra realización de esta invención se dirige a un método para tratar el cáncer que comprende administrar a un paciente necesitado de dicho tratamiento cantidades efectivas para uso terapéutico del compuesto de fórmula 1.0, paclitaxel, y carboplatin. En otra realización, dicho compuesto de fórmula 1.0 se administra todos los días, dicho paclitaxel se administra una vez cada tres semanas por ciclo, y dicho carboplatin se administra una vez cada tres semanas por ciclo. En otra realización, el tratamiento es de una a tres semanas por ciclo.

Otra realización de esta invención se dirige a un método para tratar el cáncer de pulmón de células no pequeñas en un paciente necesitado de dicho tratamiento que comprende administrar a diario una cantidad efectiva para uso terapéutico del compuesto de fórmula 1.0, administrar una cantidad efectiva para uso terapéutico de carboplatin una vez a la semana por ciclo, y administrar una cantidad efectiva para uso terapéutico de paclitaxel una vez a la semana por ciclo, donde el tratamiento se administra durante una a cuatro semanas por ciclo. En otra realización dicho compuesto de fórmula 1.0 se administra dos veces al día. En otra realización dicha carboplatin y dicho paclitaxel se administran el mismo día, y en otra realización dicha carboplatin y

dicho paclitaxel se administran en forma consecutiva, y en otra realización dicha carboplatin se administra luego de dicho paclitaxel.

Otra realización de esta invención se dirige a un método para tratar el cáncer de pulmón de células no pequeñas en un paciente necesitado de dicho tratamiento que comprende administrar a diario una cantidad efectiva para uso terapéutico de un compuesto de fórmula 1.0, administrar una cantidad efectiva para uso terapéutico de carboplatin una vez cada tres semanas por ciclo, y administrar una cantidad efectiva para uso terapéutico de paclitaxel una vez cada tres semanas por ciclo, donde el tratamiento se administra durante una a tres semanas. En otra realización el compuesto de fórmula 1.0 se administra dos veces al día. En otra realización dicha carboplatin y dicho paclitaxel se administran el mismo día, y en otra realización dicha carboplatin y dicho paclitaxel se administran en forma consecutiva, y en otra realización dicha carboplatin se administra luego de dicho paclitaxel.

Otra realización de esta invención se dirige a un método para tratar el cáncer de pulmón de células no pequeñas en un paciente necestiado de dicho tratamiento que comprende administrar aproximadamente 50 a aproximadamente 200 mg de un compuesto de fórmula 1.0 dos veces al día, administrar carboplatin una vez a la semana por ciclo en una cantidad para proveer un AUC de aproximadamente 2 a aproximadamente 8 (y en otra realización aproximadamente 2 a aproximadamente 3), y administrar una vez a la semana por ciclo aproximadamente 60 a aproximadamente 300 mg/m^2 (y en otra realización aproximadamente 50 a 100mg/m2, y en aún otra realización aproximadamente 60 a aproximadamente 80 mg/m2) de paclitaxel, donde el tratamiento se administra durante una a cuatro semanas por ciclo. En otra realización dicho compuesto de fórmula 1.0 se administra en una cantidad de aproximadamente 75 a aproximadamente 125 mg dos veces al día, y en otra

realización aproximadamente 100 mg dos veces al día. En otra realización dicha carboplatin y dicho paclitaxel se administran el mismo día, y en otra realización dicha carboplatin y dicho paclitaxel se administran en forma consecutiva, y en otra realización dicha carboplatin se administra luego de dicho paclitaxel.

En otra realización, esta invención se dirige a un método para tratar el cáncer de pulmón de células no pequeñas en un paciente necestiado de dicho tratamiento que comprende administrar aproximadamente 50 a aproximadamente 200 mg de un compuesto de fórmula 1.0 dos veces al día, administrar carboplatin una vez cada tres semanas por ciclo en una cantidad para proveer un AUC de aproximadamente 2 a aproximadamente 8 (en otra realización aproximadamente 5 a aproximadamente 8, y en otra realización 6), y administrar una vez cada tres semanas por ciclo aproximadamente 150 a aproximadamente 250 mg/m^2 (y en otra realización aproximadamente 175 a aproximadamente 225 mg/m^2, y en otra realización 175 mg/m^2) de paclitaxel, donde el tratamiento se administra durante una a tres semanas. En otra realización dicho compuesto de fórmula 1.0 se administra en una cantidad de aproximadamente 75 a aproximadamente 125 mg dos veces al día, y en otra realización aproximadamente 100 mg dos veces al día. En otra realización dicha carboplatin y dicho paclitaxel se administran el mismo día, y en otra realización dicha carboplatin y dicho paclitaxel se administran en forma consecutiva, y en otra realización dicha carboplatin se administra luego de dicho paclitaxel.

Otras realizaciones de esta invención se dirigen a métodos para tratar el cáncer descriptos en las realizaciones anteriores (es decir, las realizaciones dirigidas al tratamiento del cáncer y al tratamiento del cáncer de pulmón de células no pequeñas con un taxano y un compuesto coordinador de platino)

con la excepción de que en lugar de paclitaxel y carboplatin, los taxanos y los compuestos coordinadores de platino utilizados en conjunto en los métodos, son: (1) docetaxel (Taxotere®) y cisplatin; (2) paclitaxel y cisplatin; y (3) docetaxel y carboplatin. En otra realización de los métodos de esta invención se utiliza cisplatin en cantidades de aproximadamente 30 a aproximadamente 100 mg/m^2. En otra realización de los métodos de esta invención se utiliza docetaxel en cantidades de aproximadamente 30 a aproximadamente 100 mg/m^2.

En otra realización esta invención se dirige a un método para tratar el cáncer que comprende administrar a un paciente necesitado de dicho tratamiento cantidades efectivas para uso terapéutico de un compuesto de fórmula 1.0, un taxano, y un inhibidor de EGF que es un anticuerpo. En otra realización el taxano utilizado es paclitaxel, y el inhibidor de EGF es un anticuerpo HER2 (en una realización, Herceptin) o Cetuximab, y en otra realización se utiliza Herceptin. La longitud del tratamiento, y las cantidades y administración de dicho compuesto de fórmula 1.0 y el taxano son las descriptas en las realizaciones anteriores. El inhibidor de EGF que es un anticuerpo se administra una vez a la semana por ciclo, y en otra realización se administra al mismo día que el taxano, y en otra realización se administra en forma consecutiva con el taxano. Por ejemplo, Herceptin se administra en una carga de dosis de aproximadamente 3 a 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 a la semana por ciclo durante el resto del ciclo de tratamiento (normalmente, el ciclo es de 1 a 4 semanas). En una realización, el cáncer tratado es cáncer de mama.

En otra realización esta invención se dirige a un método para tratar el cáncer que comprende administrar a un paciente necesitado de dicho

tratamiento cantidades efectivas para uso terapéutico de: (1) un compuesto de fórmula 1.0, (2) un taxano, y (3) un agente antineoplásico 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 la VEGF quinasa que es una molécula pequeña. En otra realización, se utiliza el taxano paclitaxel o docetaxel. En otra realización el agente antineoplásico se selecciona del grupo que consiste en: tarceva, Iressa, bevacizumab, SU5416, SU6688 y BAY 43-9006. La longitud del tratamiento, y las cantidades y administración de dicho compuesto de fórmula 1.0 y el taxano son las descriptas en las realizaciones anteriores. Normalmente, el inhibidor de la VEGF quinasa que es un anticuerpo se administra una vez a la semana por ciclo. Normalmente, los inhibidores de EGF y VEGF que son moléculas pequeñas se administran a diario por 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 se administra el mismo día que el taxano, la administración es concurrente con la del taxano. En general, el inhibidor de EGF o VEGF quinasa se administra en una cantidad de aproximadamente 10 a aproximadamente 500 mg/m^2.

En otra realización esta invención se dirige a un método para tratar el cáncer que comprende administrar a un paciente necesitado de dicho tratamiento cantidades efectivas para uso terapéutico de un compuesto de fórmula 1.0, un derivado de un nucleósido antitumoral, y un compuesto de coordinación de platino.

Otra realización de esta invención se dirige a un método para tratar el cáncer que comprende administrar a un paciente necesitado de dicho

tratamiento cantidades efectivas para uso terapéutico de un compuesto de fórmula 1.0, un derivado de un nucleósido antitumoral, y un compuesto de coordinación de platino, donde dicho compuesto de fórmula 1.0 se administra todos los días, dicho derivado nucleósido antitumoral se administra una vez a la semana por ciclo, y dicho compuesto coordinador de platino se administra una vez a la semana por ciclo. Aunque el tratamiento puede ser de una a cuatro semanas por ciclo, en una realización, el tratamiento es de una a siete semanas por ciclo.

Otra realización de esta invención se dirige a un método para tratar el cáncer que comprende administrar a un paciente necesitado de dicho tratamiento cantidades efectivas para uso terapéutico de un compuesto de fórmula 1.0, un derivado de un nucleósido antitumoral, y un compuesto de coordinación de platino, donde dicho compuesto de fórmula 1.0 se administra todos los días, dicho derivado de un nucleósido antitumoral se administra una vez a la semana por ciclo, y dicho compuesto coordinador de platino se administra una vez cada tres semanas por ciclo. Aunque el tratamiento puede ser de una a cuatro semanas por ciclo, en una realización, el tratamiento es de una a siete semanas por ciclo.

Otra realización de esta invención se dirige a un método para tratar el cáncer que comprende administrar a un paciente necesitado de dicho tratamiento cantidades efectivas para uso terapéutico de un compuesto de fórmula 1.0, gemcitabina, y cisplatin. En otra realización, dicho compuesto de fórmula 1.0 se administra todos los días, dicha gemcitabina se administra una vez a la semana por ciclo, y dicha cisplatin se administra una vez a la semana por ciclo. En una realización, el tratamiento es de una a siete semanas por ciclo.

Otra realización de esta invención se dirige a un método para tratar el cáncer que comprende administrar a un paciente necesitado de dicho tratamiento cantidades efectivas para uso terapéutico de un compuesto de fórmula 1.0, gemcitabina, y cisplatin. En otra realización, dicho compuesto de fórmula 1.0 se administra todos los días, dicha gemcitabina se administra una vez a la semana por ciclo, y dicha cisplatin se administra una vez cada tres semanas por ciclo. En otra realización el tratamiento es de una a siete semanas.

Otra realización de esta invención se dirige a un método para tratar el cáncer que comprende administrar a un paciente necesitado de dicho tratamiento cantidades efectivas para uso terapéutico de un compuesto de fórmula 1.0, gemcitabina, y carboplatin. En otra realización dicho compuesto de fórmula 1.0 se administra todos los días, dicha gemcitabina se administra una vez a la semana por ciclo, y dicha carboplatin se administra una vez a la semana por ciclo. En otra realización el tratamiento es de una a siete semanas por ciclo.

Otra realización de esta invención se dirige a un método para tratar el cáncer que comprende administrar a un paciente necesitado de dicho tratamiento cantidades efectivas para uso terapéutico de un compuesto de fórmula 1.0, gemcitabina, y carboplatin. En otra realización dicho compuesto de fórmula 1.0 se administra todos los días, dicha gemcitabina se administra una vez a la semana por ciclo, y dicha carboplatin se administra una vez cada tres semanas por ciclo. En otra realización el tratamiento es de una a siete semanas por ciclo.

En las realizaciones anteriores donde se utiliza gemcitabina, el compuesto de fórmula 1.0 y el compuesto coordinador de platino se administran según lo descripto con anterioridad para las realizaciones donde se

utilizan taxanos. Se administra gemcitabina en una cantidad de aproximadamente 500 a aproximadamente 1250 mg/m^2. En una realización, la gemcitabina se administra el mismo día que el compuesto coordinador de platino, y en otra realización en forma consecutive con el compuesto coordinador de platino, y en otra realización, la gemcitabina se administra después que el compuesto coordinador de platino.

Otra realización de esta invención se dirige a un método para tratar el cáncer en un paciente necesitado de dicho tratamiento que comprende administrar a dicho paciente un compuesto de fórmula 1.0 y un agente antineoplásico seleccionado de: (1) Inhibidores de EGF que son anticuerpos, (2) Inhibidores de EGF que son moléculas pequeñas, (3) Inhibidores de EGF que son anticuerpos, e (4) Inhibidores de la VEGF quinasa que son moléculas pequeñas, todos descriptos con anterioridad. El tratamiento es de una a siete semanas por ciclo, y en general de una a cuatro semanas por ciclo. El compuesto de fórmula 1.0 se administra en igual forma a la descripta con anterioridad para las otras realizaciones de esta invención. Normalmente, los agentes antineoplásicos de molécula pequeña se administran a diario, y los agentes antineoplásicos anticuerpos normalmente se administran una vez a la semana por ciclo. En una realización, los agentes antineoplásicos se seleccionan del grupo que consiste en: Herceptin, Cetuximab, Tarceva, Iressa, bevacizumab, IMC-1C11, SU5416, SU6688 y BAY 43-9006.

En las realizaciones de esta invención donde se utiliza un compuesto coordinador de platino así como al menos otro agente antineoplásico, y estas drogas se administran en forma consecutiva, en general, el compuesto coordinador de platino se administran después de la administración de los otros agentes antineoplásicos.

Otras realizaciones de esta invención incluyen la administración de una cantidad efectiva para uso terapéutico de radiación al paciente además de la administración de un compuesto de fórmula 1.0 y agentes antineoplásicos en las realizaciones descriptas con anterioridad. La radiación se administra de acuerdo con técnicas y protocolos bien conocidos por aquellos con experiencia en la técnica.

Otra realización de esta invención se dirige a una composición farmacéutica que comprende al menos dos agentes quimioterapéuticos diferentes y un vehículo aceptable para uso farmacéutico para administración intravenosa. Preferentemente, el vehículo aceptable para uso farmacéutico es una solución salina isotónica (NaCl 0,9%) o una solución de dextrosa (por ej., dextrosa 5%).

Otra realización de esta invención se dirige a una composición farmacéutica que comprende un compuesto de fórmula 1.0 y al menos dos agentes antineoplásicos diferentes y un vehículo aceptable para uso farmacéutico para administración intravenosa. Preferentemente, el vehículo aceptable para uso farmacéutico es una solución salina isotónica (NaCl 0,9%) o una solución de dextrosa (por ej., dextrosa 5%).

Otra realización de esta invención se dirige a una composición farmacéutica que comprende un compuesto de fórmula 1.0 y al menos un agente antineoplásico y un vehículo aceptable para uso farmacéutico para administración intravenosa. Preferentemente, el vehículo aceptable para uso farmacéutico es una solución salina isotónica (NaCl 0,9%) o una solución de dextrosa (por ej., dextrosa 5%).

Otras realizaciones de esta invención se dirigen al uso de una combinación de al menos un (por ej., un) compuesto de fórmula 1.0 y drogas para el tratamiento del cáncer de mama, es decir, esta invención se dirige a

una terapia combinada para el tratamiento del cáncer de mama. Aquellos con experiencia en la técnica apreciarán que, en general, los compuestos de fórmula 1.0 y las drogas se administran como composiciones farmacéuticas individuales. Se encuentra dentro del alcance de esta invención el uso de una composición farmacéutica que comprende más de una droga.

De este modo, otra realización de esta invención se dirige a un método para tratar (o prevenir) el cáncer de mama (es decir, cáncer de mama postmenopáusico y premenopáusico, por ej., cáncer de mama hormona-dependiente) en un paciente necesitado de dicho tratamiento que comprende administrar a dicho paciente una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0 y una cantidad efectiva para uso terapéutico de al menos un agente antihormonal seleccionado del grupo que consiste en: (a) inhibidores de la aromatasa, (b) antiestrógenos, y (c) análogos de LHRH; y dicho tratamiento incluye en forma opcional la administración de al menos un agente quimioterapéutico.

El compuesto de fórmula 1.0 preferentemente se administra en forma oral, y en una realización se administra en forma de cápsula.

Los ejemplos de inhibidores de la aromatasa incluyen, pero sin limitación: Anastrozol (por ej., Arimidex), Letrozol (por ej., Femara), Exemestano (Aromasin), Fadrozol y Formestano (por ej., Lentaron).

Los ejemplos de antiestrógenos incluyen, pero sin limitación: Tamoxifen (por ej., Nolvadex), Fulvestrant (por ej., Faslodex), Raloxifeno (por ej., Evista), y Acolbifeno.

Los ejemplos de análogos de LHRH incluyen, pero sin limitación: Goserelin (por ej., Zoladex) y Leuprolida (por ej., Acetato de leuprolida, tal como Lupron o Lupron Depot).

Los ejemplos de agente quimioterapéuticos incluyen, pero sin limitación: Trastuzumab (por ej., Herceptin), Gefitinib (por ej., Iressa), Erlotinib (por ej., Erlotinib HCl, tal como Tarceva), Bevacizumab (por ej., Avastin), Cetuximab (por ej., Erbitux), y Bortezomib (por ej., Velcade).

Preferentemente, cuando se utiliza más de un agente antihormonal, cada agente se selecciona de una categoría de agente diferente. Por ejemplo, un agente es un inhibidor de la aromatasa (por ej., Anastrozol, Letrozol, o Exemestano) y un agente es un antiestrógeno (por ej., Tamoxifen o Fulvestrant).

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0 y al menos un agente antihormonal seleccionado del grupo que consiste en: (a) inhibidores de la aromatasa, (b) antiestrógenos, y (c) análogos de LHRH; y administrar una cantidad efectiva de al menos un agente quimioterapéutico.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0 y al menos un agente antihormonal seleccionado del grupo que consiste en: (a) inhibidores de la aromatasa, (b) antiestrógenos, y (c) análogos de LHRH.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0 y al menos

un agente antihormonal seleccionado del grupo que consiste en: (a) inhibidores de la aromatasa, y (b) antiestrógenos.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0, y al menos un agente antihormonal seleccionado del grupo que consiste en: (a) inhibidores de la aromatasa, y (b) antiestrógenos; y al menos un agente quimioterapéutico.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0 y al menos un inhibidor de la aromatasa.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0, al menos un inhibidor de la aromatasa, y al menos un agente quimioterapéutico.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de: (1) al menos un (por ej., uno) compuesto de fórmula 1.0; y (2) al menos un agente antihormonal seleccionado del grupo que consiste en: (a) inhibidores de la aromatasa seleccionados del grupo que consiste en Anastrozol, Letrozole, Exemestane, Fadrozol y Formestano, (b) antiestrógenos seleccionados del grupo que consiste en: Tamoxifen, Fulvestrant, Raloxifeno, y Acolbifeno, y (c) Análogos de LHRH seleccionados del grupo que consiste en:

Goserelin y Leuprolida; y administrar una cantidad efectiva de al menos un agente quimioterapéutico seleccionado del grupo que consiste en: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, y Bortezomib.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de: (1) al menos un (por ej., uno) compuesto de fórmula 1.0; y (2) al menos un agente antihormonal seleccionado del grupo que consiste en: (a) inhibidores de la aromatasa seleccionados del grupo que consiste en Anastrozol, Letrozol, Exemestano, Fadrozol y Formestano, (b) antiestrógenos seleccionados del grupo que consiste en: Tamoxifen, Fulvestrant, Raloxifeno, y Acolbifeno, y (c) Análogos de LHRH seleccionados del grupo que consiste en: Goserelin y Leuprolida.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de: (1) al menos un (por ej., uno) compuesto de fórmula 1.0; y (2) al menos un agente antihormonal seleccionado del grupo que consiste en: (a) inhibidores de la aromatasa seleccionados del grupo que consiste en Anastrozol, Letrozol, Exemestano, Fadrozol y Formestano, y (b) antiestrógenos seleccionados del grupo que consiste en: Tamoxifen, Fulvestrant, Raloxifeno, y Acolbifeno.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de: (1) al menos un (por ej., uno) compuesto de fórmula 1.0; y (2) al menos un agente antihormonal seleccionado del grupo que consiste en: (a)

inhibidores de la aromatasa seleccionados del grupo que consiste en Anastrozol, Letrozol, Exemestano, Fadrozol y Formestano, (b) antiestrógenos seleccionados del grupo que consiste en: Tamoxifen, Fulvestrant, Raloxifeno, y Acolbifeno; y administrar una cantidad efectiva de al menos un agente quimioterapéuticos se seleccionan del grupo que consiste en: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, y Bortezomib.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de: (1) al menos un (por ej., uno) compuesto de fórmula 1.0; y (2) al menos un inhibidor de la aromatasa seleccionado del grupo que consiste en Anastrozol, Letrozol, Exemestano, Fadrozol y Formestano.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de: (1) al menos un (por ej., uno) compuesto de fórmula 1.0; (2) al menos un inhibidor de la aromatasa seleccionado del grupo que consiste en Anastrozol, Letrozol, Exemestano, Fadrozol y Formestano; y (3) administrar una cantidad efectiva de al menos un agente quimioterapéutico seleccionado del grupo que consiste en: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, y Bortezomib.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de: (1) al menos un (por ej., uno) compuesto de fórmula 1.0; (2) al menos un inhibidor de la aromatasa; y (3) al menos un análogo de LHRH.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de:(1) al menos un (por ej., uno) compuesto de fórmula 1.0; (2) al menos un antiestrógeno; y (3) al menos un análogo de LHRH.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de: (1) al menos un (por ej., uno) compuesto de fórmula 1.0; (2) al menos un inhibidor de la aromatasa seleccionado del grupo que consiste en Anastrozol, Letrozol, Exemestano, Fadrozol y Formestano; y (3) al menos un análogo de LHRH that se selecciona del grupo que consiste en: Goserelin y Leuprolida.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un páciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de: (1) al menos un (por ej., uno) compuesto de fórmula 1.0; (2) al menos un antiestrógeno seleccionado del grupo que consiste en: Tamoxifen, Fulvestrant, Raloxifeno, y Acolbifeno; y (3) al menos un análogo de LHRH that se selecciona del grupo que consiste en: Goserelin y Leuprolida.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0 y Anastrozol.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento

donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0 y Letrazol.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0 y Exemestano.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0 y Fadrozol.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0 y Formestano.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0 y Tamoxifen.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0 y Fulvestrant.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0 y Raloxifeno.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0 y Acolbifeno.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0 y Goserelin.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0 y Leuprolida.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0, Anastrozol, y un antiestrógeno seleccionado del grupo que consiste en: Tamoxifen, Fulvestrant, Raloxifeno, y Acolbifeno.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0, Letrozol, y un antiestrógeno seleccionado del grupo que consiste en: Tamoxifen, Fulvestrant, Raloxifeno, y Acolbifeno.



Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0, Exemestane, y un antiestrógeno seleccionado del grupo que consiste en: Tamoxifen, Fulvestrant, Raloxifeno, y Acolbifeno.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0, Fadrozole, y un antiestrógeno seleccionado del grupo que consiste en: Tamoxifen, Fulvestrant, Raloxifeno, y Acolbifeno.



Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0, Formestano, y un antiestrógeno seleccionado del grupo que consiste en: Tamoxifen, Fulvestrant, Raloxifeno, y Acolbifeno.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso

terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0, Anastrozol, y Tamoxifen.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0, Letrozol, y Tamoxifen.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0, Exemestano, y Tamoxifen.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0, Fadrozol, y Tamoxifen.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0, Formestano, y Tamoxifen.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0, Anastrozol, y Fulvestrant.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0, Letrozol, y Fulvestrant.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0, Exemestano, y Fulvestrant.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0, Fadrozol, y Fulvestrant.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0, Formestano, y Fulvestrant.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0, Anastrozol, y un agente quimioterapéutico seleccionado del grupo que consiste en: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, y Bortezomib.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0, Letrozol, y un agente quimioterapéutico seleccionado del grupo que consiste en: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, y Bortezomib.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0, Exemestano, y un agente quimioterapéutico seleccionado del grupo que consiste en: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, y Bortezomib.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0, Fadrozol, y un agente quimioterapéutico seleccionado del grupo que consiste en: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, y Bortezomib.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0, Formestano, y un agente quimioterapéutico seleccionado del grupo que consiste en: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, y Bortezomib.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0, Tamoxifen, y un agente quimioterapéutico seleccionado del grupo que consiste en: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, y Bortezomib.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0, Fulvestrant, y un agente quimioterapéutico seleccionado del grupo que consiste en: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, y Bortezomib.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0, Raloxifeno, y un agente quimioterapéutico seleccionado del grupo que consiste en: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, y Bortezomib.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0, Acolbifeno, y un agente quimioterapéutico seleccionado del grupo que consiste en: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, y Bortezomib.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso

terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0, Goserelin, y un agente quimioterapéutico seleccionado del grupo que consiste en: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, y Bortezomib.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0, Leuprolein, y un agente quimioterapéutico seleccionado del grupo que consiste en: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, y Bortezomib.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0, Anastrozole, un antiestrógeno seleccionado del grupo que consiste en: Tamoxifen, 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 dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0, Letrozol, un antiestrógeno seleccionado del grupo que consiste en: Tamoxifen, 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 dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento

donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0, Exemestano, un antiestrógeno seleccionado del grupo que consiste en: Tamoxifen, 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 dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0, Fadrozol, un antiestrógeno seleccionado del grupo que consiste en: Tamoxifen, 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 dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0, Formestano, un antiestrógeno seleccionado del grupo que consiste en: Tamoxifen, 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 dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0, Anastrozol,

Tamoxifen, y un agente quimioterapéutico seleccionado del grupo que consiste en: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, y Bortezomib.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0, Letrozol, Tamoxifen, y un agente quimioterapéutico seleccionado del grupo que consiste en: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, y Bortezomib.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0, Exemestano, Tamoxifen, y un agente quimioterapéutico seleccionado del grupo que consiste en: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, y Bortezomib.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0, Fadrozol, Tamoxifen, y un agente quimioterapéutico seleccionado del grupo que consiste en: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, y Bortezomib.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0, Formestano, Tamoxifen, y un agente quimioterapéutico seleccionado del grupo

que consiste en: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, y Bortezomib.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0, 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 dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0, 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 dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0, 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 dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0, 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 dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0, 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 dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0, Goserelin y Tamoxifen.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0, Goserelin, y Fulvestrant.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0, Goserelin, y Raloxifeno.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0, Goserelin y Acolbifeno.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0, Leuprolida, y Tamoxifen.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0, Leuprolida, y Fulvestrant.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0, Leuprolida, y Raloxifeno.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0, Leuprolida y Acolbifeno.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0, Goserelin y Anastrozol.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento

donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0, Goserelin y Letrozol.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0, Goserelin y Exemestano.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0, Goserelin y Fadrozol.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0, Goserelin y Formestano.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0, Leuprolida y Anastrozol.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso

terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0, Leuprolida y Letrozola.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0, Leuprolida y Exemestano.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0, Leuprolida y Fadrozol.

Otra realización de esta invención se dirige a un método para tratar o prevenir el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0, Leuprolida y Formestano.

Otra realización de esta invención se dirige al tratamiento o prevención del cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende la administración de una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0 y Anastrozol.

Otra realización de esta invención se dirige al tratamiento o prevención del cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende la administración de una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0 y Letrozol.

Otra realización de esta invención se dirige al tratamiento o prevención del cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende la administración de una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0 y Exemestano.

Otra realización de esta invención se dirige al tratamiento o prevención del cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende la administración de una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0 y Tamoxifen.

Otra realización de esta invención se dirige al tratamiento o prevención del cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende la administración de una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0 y Fulvestrant.

Otra realización de esta invención se dirige al tratamiento o prevención del cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende la administración de una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0, Anastrozol, y Fulvestrant.

Otra realización de esta invención se dirige al tratamiento o prevención del cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende la administración de una cantidad efectiva para uso terapéutico of al menos un compuesto de fórmula 1.0 (por ej., uno), Letrozol, y Fulvestrant.

Otra realización de esta invención se dirige al tratamiento o prevención del cáncer de mama en un paciente necesitado de dicho tratamiento donde

dicho tratamiento comprende la administración de una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0, Exemestano, y Fulvestrant.

Otra realización de esta invención se dirige al tratamiento o prevención del cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende la administración de una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0, Anastrozol, y Tamoxifen.

Otra realización de esta invención se dirige al tratamiento o prevención del cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende la administración de una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0, Letrozol, y Tamoxifen.

Otra realización de esta invención se dirige al tratamiento o prevención del cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende la administración de una cantidad efectiva para uso terapéutico de al menos un (por ej., uno) compuesto de fórmula 1.0, Exemestano, y Tamoxifen.

Otras realizaciones de esta invención se dirigen a cualquiera de las realizaciones descriptas con anterioridad para el tratamiento del Cáncer de mama donde el agente quimioterapéutico es Trastuzumab.

Otras realizaciones de esta invención se dirigen a cualquiera de las realizaciones descriptas con anterioridad para el tratamiento o prevención del Cáncer de mama donde el método se dirige al tratamiento de cáncer de mama.

El compuesto de fórmula 1.0, los agentes antihormonales y los agentes quimioterapéuticos pueden administrarse en forma concurrente o secuencial.

Los agentes antihormonales y los agentes quimioterapéuticos opcionales se administrant de acuerdo con sus protocolos, cantidades de dosificación, y formas de dosificación que son bien conocidas por aquellos con experiencia en la técnica dosage (por ej., la Physician's Desk Reference o literatura publicada). Por ejemplo, para Tamoxifen, Fulvestrant, Raloxifeno, Anastrozol, Letrozol, Exemestano, Leuprolida y Goserelin, ver la Physician's Desk Reference, 57th Ed., 2003, publicada por Thomas PDR at Montvale, N.J. 07645-1742, cuyos descubrimientos se incorporan en la presente como referencia.

En general, en las realizaciones dirigidas a los métodos para tratar el Cáncer de mama: (1) el compuesto de fórmula 1.0 puede administrarse a diario (por ej., una vez al día, y en una realización dos veces al día), (2) los inhibidores de la aromatasa pueden administrarse de acuerdo con el protocolo conocido para el inhibidor de la aromatasa utilizado (por ej., una vez al día), (3) los antiestrógenos pueden administrarse de acuerdo con el protocolo conocido para el antiestrógeno utilizado (por ej., de una vez al día a una vez al mes), (4) el análogo de LHRH puede administrarse de acuerdo con el protocolo conocido para el análogo de LHRH utilizado (por ej., de una vez al mes a una vez cada tres meses), y (5) el agente quimioterapéutico puede administrarse de acuerdo con el protocolo conocido para el agente quimioterapéutico utilizado (por ej., de una vez al día a una vez a la semana).

Si se administra terapia de radiación en los tratamientos anteriores para el cáncer de mama, en general se administran de acuerdo con protocolos conocidos antes de la administración del compuesto de fórmula 1.0, de los agentes antihormonales y de los agentes quimioterapéuticos opcionales.

El tratamiento de acuerdo con los métodos para tratar el cáncer de mama es continuo (es decir, se sigue un programa de dosificación continua). El

tratamiento se continúa hasta que se produzca una respuesta completa, o hasta que el profesional a cargo determine que el paciente no obtienen beneficios de parte del tratamiento (por ejemplo, cuando se observa una progresión de la enfermedad).

El protocolo de tratamiento continuo para el cáncer de mama puede cambiarse a un programa de tratamiento discontinuo si, de acuerdo con el juicio del profesional a cargo, el paciente se viera beneficiado con un programa de dosificación discontinua con una o más de las drogas administradas. Por ejemplo, el compuesto de fórmula 1.0 puede administrarse utilizando un programa de tratamiento mientras que las drogas restantes utilizadas en el tratamiento se administran de acuerdo con lo descripto con anterioridad. Un ejemplo de un protocolo de tratamiento discontinuo para el compuesto de fórmula 1.0 es un ciclo de repetición de tres semanas con el compuesto de fórmula 1.0 seguido por una semana sin el compuesto de fórmula 1.0.

Una vez obtenida una respuesta completa con el tratamiento del cáncer de mama, puede continuarse una terapia de mantenimiento con el compuesto de fórmula 1.0 utilizando las dosis descriptas en los métodos de la invención. La terapia de mantenimiento puede también incluir la administración de los agentes antihormonales utilizando las dosis descriptas en los métodos de la invención. La terapia de mantenimiento puede sólo comprender agentes antihormonales. Por ejemplo, una vez obtenida una respuesta completa, puede continuarse con un inhibidor de la aromatasa (por ej., Anastrozol, Letrozol o Exemestano) durante hasta cinco años. O, por ejemplo, puede utilizarse un antiestrógeno, por ej., Tamoxifen, durante hasta cinco años luego de obtenerse una respuesta completa. O, por ejemplo, puede utilizarse un antiestrógeno, (por ej., Tamoxifen) durante hasta cinco años luego de obtenerse una respuesta completa seguido por el uso de un inhibidor de la

aromatasa (por ej., Anastrozol, Letrozol o Exemestano) durante hasta cinco años.

En las realizaciones dirigidas al tratamiento del cáncer de mama descriptas con anterioridad, el compuesto de fórmula 1.0 se administra en forma continua en una dosis diaria total de aproximadamente 100 mg a aproximadamente 600 mg. Normalmente, esta cantidad se administra en dosis divididas, y en una realización esta cantidad se administra dos veces al día. En una realización el compuesto de fórmula 1.0 se dosifica dos veces al día en una cantidad de aproximadamente 50 mg a aproximadamente 300 mg por dosis. En otra realización el compuesto de fórmula 1.0 se dosifica dos veces al día en una cantidad de aproximadamente 100 mg a aproximadamente 200 mg por dosis. Los ejemplos incluyen el compuesto de fórmula 1.0 siendo dosificado dos veces al día a 100 mg por dosis. Los ejemplos también incluyen el compuesto de fórmula 1.0 siendo dosificado dos veces al día a 200 mg por dosis.

Anastrozol se administra p.o. y se dosifica una vez al día en cantidades de aproximadamente 0,5 a aproximadamente 10 mg por dosis, y en una realización en una cantidad de aproximadamente 1,0 mg por dosis.

Letrozol se administra p.o. y se dosifica una vez al día en cantidades de aproximadamente 1.0 a aproximadamente 10 mg por dosis, y en una realización en una cantidad de aproximadamente 2,5 mg por dosis.

Exemestano se administra p.o. y se dosifica una vez al día en cantidades de aproximadamente 10 a aproximadamente 50 mg por dosis, y en una realización en una cantidad de aproximadamente 25 mg por dosis.

Fadrozol se administra p.o. y se dosifica dos veces al día en cantidades de aproximadamente 0,5 a aproximadamente 10 mg por dosis, y en una realización en una cantidad de aproximadamente 2,0 mg por dosis.

Formestano se administra i.m. y se dosifica una vez cada dos semanas en cantidades de aproximadamente 100 a aproximadamente 500 mg por dosis, y en una realización en una cantidad de aproximadamente 250 mg por dosis.

Tamoxifen se administra p.o. y se dosifica una vez al día en cantidades de aproximadamente 10 a aproximadamente 100 mg por dosis, y en una realización en una cantidad de aproximadamente 20 mg por dosis.

Fulvestrant se administra i.m. y se dosifica once a month en cantidades de aproximadamente 100 a aproximadamente 1000 mg por dosis, y en una realización en una cantidad de aproximadamente 250 mg por dosis.

Raloxifeno se administra p.o. y se dosifica una vez al día en cantidades de aproximadamente 10 a aproximadamente 120 mg por dosis, y en una realización en una cantidad de aproximadamente 60 mg por dosis.

Acolbifeno se administra p.o. y se dosifica una vez al día en cantidades de aproximadamente 5 a aproximadamente 20 mg por dosis, y en una realización en una cantidad de aproximadamente 20 mg por dosis.

Goserelin se administra s.c. y se dosifica una vez al mes, o cada tres meses, en cantidades de aproximadamente 2 a aproximadamente 20 mg por dosis, y en una realización en una cantidad de aproximadamente 3,6 mg por dosis cuando se administra una vez al mes, y en otra realización en una cantidad de aproximadamente 10,8 mg por dosis cuando se administra cada tres meses.

Leuprolida se administra s.c. y se dosifica una vez al mes, o cada tres meses, en cantidades de aproximadamente 2 a aproximadamente 20 mg por dosis, y en una realización en una cantidad de aproximadamente 3,75 mg por dosis cuando se administra una vez al mes, y en otra realización en una cantidad de aproximadamente 11,25 mg por dosis cuando se administra cada tres meses.

Trastuzumab se administra i.v. y se dosifica una vez a la semana en cantidades de aproximadamente 2 a aproximadamente 20 mpk por dosis, y en una realización en una cantidad de aproximadamente 2 mpk por dosis. En general, trastuzumab se administra en un principio en una dosis de carga que es generalmente de dos veces la dosis semanal. Así, por ejemplo, se administra una dosis de carga de 4 mpk y luego se dosifican 2 mpk por dosis por semana.

Gefitinib se administra p.o. y se dosifica una vez al día en cantidades de aproximadamente 100 a aproximadamente 1000 mg por dosis, y en una realización en una cantidad de aproximadamente 250 mg por dosis.

Erlotinib se administra p.o. y se dosifica una vez al día en cantidades de aproximadamente 100 a aproximadamente 500 mg por dosis, y en una realización en una cantidad de aproximadamente 150 mg por dosis.

Bevacizumab se administra i.v. y se dosifica una vez cada dos semanas en cantidades de aproximadamente 2.5 a aproximadamente 15 mg per kilogram of body weight por dosis, Y en una realización en una cantidad de aproximadamente 10 mg per kilogram por dosis.

Cetuximab se administra i.v. y se dosifica una vez a la semana en cantidades de aproximadamente 200 a aproximadamente 500 mg por dosis por metro cuadrado, y en una realización en una cantidad de aproximadamente 250 mg por dosis por metro cuadrado.

Bortezomib se administra i.v. y se dosifica una vez a la semana durante 2 semanas seguido por una período de descanso de 10 días (ciclo de tratamiento de 21 días) durante un máximo de ciclos de tratamiento en cantidades de aproximadamente 1,0 a aproximadamente 2,5 mg por dosis por metro cuadrado, y en una realización en una cantidad de aproximadamente 1,3 mg por dosis por metro cuadrado.

De este modo, en una realización de esta invención se trata (o previene) el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar a dicho paciente: (1) el compuesto de fórmula 1.0 en forma oral en una cantidad de aproximadamente 50 mg a aproximadamente 300 mg por dosis donde cada dosis se administra dos veces al día, y (2) Anastrozol p.o. en una cantidad de aproximadamente 0.5 a aproximadamente 10 mg por dosis donde cada dosis se administra una vez al día.

En otra realización de esta invención se trata (o previene) el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar a dicho paciente: (1) el compuesto de fórmula 1.0 en forma oral en una cantidad de aproximadamente 100 a 200 mg por dosis, donde cada dosis se administra dos veces al día, y (2) Anastrozol en una cantidad de aproximadamente 1,0 mg por dosis donde cada dosis se administra una vez al día.

En otra realización de esta invención se trata (o previene) el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar a dicho paciente: (1) el compuesto de fórmula 1.0 en forma oral en una cantidad de aproximadamente 50 mg a aproximadamente 300 mg por dosis donde cada dosis se administra dos veces al día, y (2) Letrozol p.o. en una cantidad de aproximadamente 1,0 a aproximadamente 10 mg por dosis donde cada dosis se administra una vez al día.

En otra realización de esta invención se trata (o previene) el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar a dicho paciente: (1) el compuesto de fórmula 1.0 en forma oral en una cantidad de aproximadamente 100 a 200 mg por dosis, donde cada dosis se administra dos veces al día, y (2) Letrozol p.o. en una

cantidad de aproximadamente 2,5 mg por dosis donde cada dosis se administra una vez al día.

En otra realización de esta invención se trata (o previene) el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar a dicho paciente: (1) el compuesto de fórmula 1.0 en forma oral en una cantidad de aproximadamente 50 mg a aproximadamente 300 mg por dosis donde cada dosis se administra dos veces al día, y (2) Exemestano p.o. en una cantidad de aproximadamente 10 a aproximadamente 50 mg por dosis donde cada dosis se administra una vez al día.

En otra realización de esta invención se trata (o previene) el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar a dicho paciente: (1) el compuesto de fórmula 1.0 en forma oral en una cantidad de aproximadamente 100 a 200 mg por dosis, donde cada dosis se administra dos veces al día, y (2) Exemestano en una cantidad de aproximadamente 25 mg por dosis donde cada dosis se administra una vez al día.

En otra realización de esta invención se trata (o previene) el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar a dicho paciente: (1) el compuesto de fórmula 1.0 en forma oral en una cantidad de aproximadamente 50 mg a aproximadamente 300 mg por dosis donde cada dosis se administra dos veces al día, y (2) Fulvestrant i.m. en una cantidad de aproximadamente 100 a aproximadamente 1000 mg por dosis donde cada dosis se administra una vez al mes.

En otra realización de esta invención se trata (o previene) el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar a dicho paciente: (1) el compuesto de fórmula 1.0 en forma oral en una cantidad de aproximadamente 100 a 200 mg por dosis,

donde cada dosis se administra dos veces al día, y (2) Fulvestrant i.m. en una cantidad de aproximadamente 250 mg por dosis donde cada dosis se administra una vez al mes.

En otra realización de esta invención se trata (o previene) el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar a dicho paciente: (1) el compuesto de fórmula 1.0 p.o. en una cantidad de aproximadamente 50 mg a aproximadamente 300 mg por dosis donde cada dosis se administra dos veces al día, y (2) Tamoxifen p.o. en una cantidad de aproximadamente 10 a aproximadamente 100 mg por dosis donde cada dosis se administra una vez al día.

En otra realización de esta invención se trata (o previene) el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar a dicho paciente: (1) el compuesto de fórmula 1.0 p.o. en una cantidad de aproximadamente 100 a 200 mg por dosis, donde cada dosis se administra dos veces al día, y (2) Tamoxifen p.o. en una cantidad de aproximadamente 20 mg por dosis donde cada dosis se administra una vez al día.

En otras realizaciones de la invención, se trata el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende la administración del compuesto de fórmula 1.0, uno de los inhibidores de la aromatasa (por ej., Anastrozol, Letrozol, o Exemestano, y en una realización Anastrozol), y uno de los antiestrógenos (por ej., Fulvestrant o Tamoxifen), donde el compuesto de fórmula 1.0, el inhibidor de la aromatasa y el antiestrógeno se administran en las dosis descriptas con anterioridad.

De este modo, por ejemplo, en otra realización de esta invención se trata (o previene) el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar a dicho paciente: (1) el

compuesto de fórmula 1.0 p.o. en una cantidad de aproximadamente 50 mg a aproximadamente 300 mg por dosis donde cada dosis se administra dos veces al día, (2) Anastrozol p.o. en una cantidad de aproximadamente 0,5 a aproximadamente 10 mg por dosis donde cada dosis se administra una vez al día, y (3) Fulvestrant i.m. en una cantidad de aproximadamente 100 a aproximadamente 1000 mg por dosis donde cada dosis se administra una vez al mes.

En otra realización de esta invención se trata (o previene) el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar a dicho paciente: (1) el compuesto de fórmula 1.0 p.o en una cantidad de aproximadamente 100 a 200 mg por dosis, donde cada dosis se administra dos veces al día, (2) Anastrozol p.o. en una cantidad de aproximadamente 1,0 mg por dosis donde cada dosis se administra una vez al día, y (3) Fulvestrant i.m. en una cantidad de aproximadamente 250 mg por dosis donde cada dosis se administra una vez al mes.

En otra realización de esta invención se trata (o previene) el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar a dicho paciente: (1) el compuesto de fórmula 1.0 p.o. en una cantidad de aproximadamente 50 mg a aproximadamente 300 mg por dosis donde cada dosis se administra dos veces al día, (2) Letrozol p.o en una cantidad de aproximadamente 1.0 a aproximadamente 10 mg por dosis donde cada dosis se administra una vez al día, y (3) Fulvestrant en una cantidad de aproximadamente 100 a aproximadamente 1000 mg por dosis donde cada dosis se administra una vez al mes.

En otra realización de esta invención se trata (o previene) el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar a dicho paciente: (1) el compuesto de fórmula 1.0 p.o.

en una cantidad de aproximadamente 100 a 200 mg por dosis, donde cada dosis se administra dos veces al día, (2) Letrozol p.o. en una cantidad de aproximadamente 2,5 mg por dosis donde cada dosis se administra una vez al día, y (3) Fulvestrant i.m. en una cantidad de aproximadamente 250 mg por dosis donde cada dosis se administra una vez al mes.

En otra realización de esta invención se trata (o previene) el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar a dicho paciente: (1) el compuesto de fórmula 1.0 p.o. en una cantidad de aproximadamente 50 mg a aproximadamente 300 mg por dosis donde cada dosis se administra dos veces al día, (2) Exemestano p.o. en una cantidad de aproximadamente 10 a aproximadamente 50 mg por dosis donde cada dosis se administra una vez al día, y (3) Fulvestrant i.m. en una cantidad de aproximadamente 100 a aproximadamente 1000 mg por dosis donde cada dosis se administra una vez al mes.

En otra realización de esta invención se trata (o previene) el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar a dicho paciente: (1) el compuesto de fórmula 1.0 p.o. en una cantidad de aproximadamente 100 a 200 mg por dosis, donde cada dosis se administra dos veces al día, (2) Exemestano p.o. en una cantidad de aproximadamente 25 mg por dosis donde cada dosis se administra una vez al día, y (3) Fulvestrant i.m. en una cantidad de aproximadamente 250 mg por dosis donde cada dosis se administra una vez al mes.

En otra realización de esta invención se trata (o previene) el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar a dicho paciente: (1) el compuesto de fórmula 1.0 p.o. en una cantidad de aproximadamente 50 mg a aproximadamente 300 mg por dosis donde cada dosis se administra dos veces al día, (2) Anastrozole p.o. en

una cantidad de aproximadamente 0,5 a aproximadamente 10 mg por dosis donde cada dosis se administra una vez al día, y (3) Tamoxifen p.o.en una cantidad de aproximadamente 10 a aproximadamente 100 mg por dosis donde cada dosis se administra una vez al día.

En otra realización de esta invención se trata (o previene) el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar a dicho paciente: (1) el compuesto de fórmula 1.0 p.o. en una cantidad de aproximadamente 100 a 200 mg por dosis, donde cada dosis se administra dos veces al día, (2) Anastrozol p.o. en una cantidad de aproximadamente 1,0 mg por dosis donde cada dosis se administra una vez al día, y (3) Tamoxifen p.o. en una cantidad de aproximadamente 20 mg por dosis donde cada dosis se administra una vez al día.

En otra realización de esta invención se trata (o previene) el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar a dicho paciente: (1) el compuesto de fórmula 1.0 p.o. en una cantidad de aproximadamente 50 mg a aproximadamente 300 mg por dosis donde cada dosis se administra dos veces al día, (2) Letrozole p.o. en una cantidad de aproximadamente 1,0 a aproximadamente 10 mg por dosis donde cada dosis se administra una vez al día, y (3) Tamoxifen p.o. en una cantidad de aproximadamente 10 a aproximadamente 100 mg por dosis donde cada dosis se administra una vez al día.

En otra realización de esta invención se trata (o previene) el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar a dicho paciente: (1) el compuesto de fórmula 1.0 p.o. en una cantidad de aproximadamente 100 a 200 mg por dosis, donde cada dosis se administra dos veces al día, (2) Letrozol p.o. en una cantidad de aproximadamente 2,5 mg por dosis donde cada dosis se administra una vez al

día, y (3) Tamoxifen p.o. en una cantidad de aproximadamente 20 mg por dosis donde cada dosis se administra una vez al día.

En otra realización de esta invención se trata (o previene) el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar a dicho paciente: (1) el compuesto de fórmula 1.0 p.o. en una cantidad de aproximadamente 50 mg a aproximadamente 300 mg por dosis donde cada dosis se administra dos veces al día, (2) Exemestane p.o. en una cantidad de aproximadamente 10 a aproximadamente 50 mg por dosis donde cada dosis se administra una vez al día, y (3) Tamoxifen p.o. en una cantidad de aproximadamente 10 a aproximadamente 100 mg por dosis donde cada dosis se administra una vez al día.

En otra realización de esta invención se trata (o previene) el cáncer de mama en un paciente necesitado de dicho tratamiento donde dicho tratamiento comprende administrar a dicho paciente: (1) el compuesto de fórmula 1.0 p.o. en una cantidad de aproximadamente 100 a 200 mg por dosis, donde cada dosis se administra dos veces al día, (2) Exemestano p.o. en una cantidad de aproximadamente 25 mg por dosis donde cada dosis se administra una vez al día, y (3) Tamoxifen p.o. en una cantidad de aproximadamente 20 mg por dosis donde cada dosis se administra una vez al día.

Aquellos con experiencia en la técnica apreciarán que cuando se utilicen otras combinaciones de agentes antihormonales, el agente antihormonal se utiliza en las cantidades especificadas para el agente antihormonal individual.

Otras realizaciones del tratamiento del Cancér de mama se dirigen a los métodos para el tratar el Cáncer de mama descriptos con anterioridad donde el compuesto de fórmula 1.0 se dosifica dos veces al día en una cantidad de aproximadamente 100 mg por dosis.

Otras realizaciones del tratamiento del Cancér de mama se dirigen a los métodos para el tratar el Cáncer de mama descriptos con anterioridad donde el compuesto de fórmula 1.0 se dosifica dos veces al día en una cantidad de aproximadamente 200 mg por dosis.

Otras realizaciones del tratamiento del Cancér de mama se dirigen a los métodos para el tratar el Cáncer de mama descriptos con anterioridad donde un agente quimioterapéutico se administra en adición al compuesto de fórmula 1.0 y al agente antihormonal (o agentes antihormonales). En tales realizaciones, los rangos de dosificación del compuesto de fórmula 1.0 y de los agentes antihormonales son los descriptos con anterioridad en las terapias combinadas, o los descriptos con anterioridad para el compuesto individual de fórmula I y agentes antihormonales, y las dosis de los agentes quimioterapéuticos son las descriptas con anterioridad para el agente quimioterapéutico individual. Las dosis para los agentes quimioterapéuticos son bien conocidas en la técnica.

Otras realizaciones de esta invención se dirigen a composiciones farmacéuticas que comprenden el compuesto de fórmula 1.0 y al menos un agente antihormonal y un vehículo aceptable para uso farmacéutico.

Otras realizaciones de esta invención se dirigen a composiciones farmacéuticas que comprenden el compuesto de fórmula 1.0, al menos un agente antihormonal, al menos un agente quimioterapéutico, y un vehículo aceptable para uso farmacéutico.

Otras realizaciones de esta invención se dirigen a composiciones farmacéuticas que comprenden el compuesto de fórmula 1.0, al menos un agente quimioterapéutico, y un vehículo aceptable para uso farmacéutico.

Aquellos con experiencia en la técnica apreciarán que los compuestos (drogas) utilizados en los métodos de esta invención se encuentran disponibles

para aquellos con experiencia en la técnica en la forma de composiciones farmacéuticas (formas de dosificación) por parte del fabricante y se utilizan en tales composiciones. Por lo tanto, la mención del compuesto o clase de compuestos en los métodos descriptos con anterioridad puede reemplazarse con una mención de una composición farmacéutica que comprenda el compuesto o clase de compuestos. Por ejemplo, la realización dirigida a un método para tratar el cáncer que comprende administrar a un paciente necesitado de dicho tratamiento cantidades efectivas para uso terapéutico del compuesto de fórmula 1.0, un taxano, y un compuesto de coordinación de platino, incluye dentro de su alcance un método para tratar el cáncer que comprende administrar a un paciente necesitado de dicho tratamiento cantidades efectivas para uso terapéutico de una composición farmacéutica que comprenda el compuesto de fórmula 1.0, una composición farmacéutica que comprenda un taxano, y una composición farmacéutica que comprenda un compuesto de coordinación de platino.

Aquellos con experiencia en la técnica reconocerán que las dosis y protocolos para administración reales empleados en los métodos de esta invención pueden variar de acuerdo con el juicio del profesional a cargo. La dosis real empleada puede variar dependiendo de los requerimientos del paciente y de la severidad de la afección bajo tratamiento. La determinación de la dosis adecuada para una situación particular es parte del conocimiento de a quellos con experiencia en la técnica. Una determinación de variar las dosis y protocolos para la administración puede tomarse luego de que el profesional a cargo tome en consideración factores tal como la edad del paciente, la condición y tamaño, así como la severidad del cáncer bajo tratamiento y la respuesta del paciente al tratamiento.

La cantidad y frecuencia de administración del compuesto de fórmula 1.0 y los agentes quimioterapéuticos será regulada de acuerdo con el juicio del profesional a cargo en consideración de factores tal como la edad, condición y tamaño del paciente, y la severidad del cáncer bajo tratamiento.

El agente quimioterapéutico puede administrarse de acuerdo con protocolos terapéuticos bien conocidos en la técnica. Será aparente a aquellos con experiencia en la técnica que la administración del agente quimioterapéutico puede variar dependiendo del cáncer bajo tratamiento y de los efectos conocidos del agente quimioterapéutico sobre la enfermedad. También, de acuerdo con los conocimientos del profesional a cargo, pueden variarse los protocolos terapéuticos (por ej., cantidades de dosificación y tiempos de administración) en vista de los efectos observados de los agentes terapéuticos administrados al paciente, y en vista de los respuestas observadas del cáncer a los agentes terapéuticos administrados.

La administración inicial puede llevarse a cabo de acuerdo con protocolos establecidos conocidos en la técnica, y luego, con base en los efectos observados, pueden modificarse las dosis, los modos y los tiempos de administración por parte del profesional a cargo.

La elección particular del agente quimioterapéutico dependerá del diagnóstico de los profesionales a cargo y de su juicio de la condición del paciente y del protocolo de tratamiento adecuado.

La determinación del orden de administración, y del número de repeticiones de administración del agente quimioterapéutico durante un protocolo de tratamiento, es parte del conocimiento de los profesionales experimentados luego de la evaluación del cáncer bajo tratamiento y de la condición del paciente.

De este modo, de acuerdo con la experiencia y conocimientos, el profesional a cargo puede modificar cada protocolo para la administración de un agente quimioterapéutico de acuerdo con las necesidades individuales del paciente, a medida que el tratamiento proceda. Todas las tales modificaciones son parte del alcance de la presente invención.

La elección particular de los agentes antihormonales, de los agentes quimioterapéuticos opcionales y de la radiación opcional dependerá del diagnóstico de los profesionales a cargo y de su juicio de la condición del paciente y del protocolo de tratamiento adecuado.

La determinación del orden de administración, y del número de repeticiones de administración de los agentes antihormonales, de los agentes quimioterapéuticos opcionales y de la radiación opcional durante un protocolo de tratamiento, es parte del conocimiento de los profesionales experimentados luego de la evaluación del cáncer de mama bajo tratamiento y de la condición del paciente.

De este modo, de acuerdo con la experiencia y conocimientos, el profesional a cargo puede modificar cada protocolo para la administración de un agente quimioterapéutico de acuerdo con las necesidades individuales del paciente, a medida que el tratamiento proceda. Todas las tales modificaciones son parte del alcance de la presente invención.

El profesional a cargo, en consideración de si el tratamiento es efectivo a la dosis administrada, considerará el bienestar general del paciente así como signos más definidos tal como alivio de los síntomas relacionados con el cáncer (por ej., dolor, tos (para el cáncer de pulmón), y falta de aliento (para el cáncer de pulmón)), inhibición del crecimiento de tumor, encongimiento real del tumor, o inhibición de las metástasis. El tamaño del tumor puede medirse con métodos estándar tal como estudios radiológicos, por ej., CAT o barrido por MRI, y

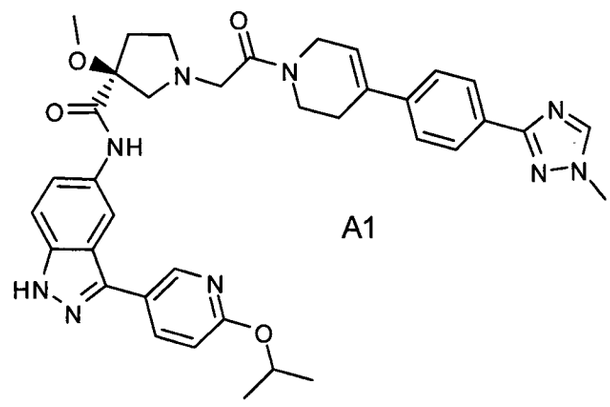
pueden utilizarse mediciones sucesivas para juzgar si se ha retrasado o incluso revertido el crecimiento del tumor. El alivio de síntomas relacionados con el cáncer tal como dolor, y la mejora en la condición general también pueden utilizarse para juzgar la efectividad del tratamiento.

Los compuestos de la invención pueden prepararse de acuerdo con los procesos descriptos en US 2007/0191604 publicada el 16 de agosto de 2007, U.S. con Nº de Serie 11/810282 presentada el 5 de junio de 2007, así como de acuerdo con los procesos descriptos a continuación. Los descubrimientos de US 2007/0191604 y de U.S. con Nº de Serie 11/810282 se incorporan en la presente como referencia.

Las condiciones de LCMS son: (1) columna: C-18 en fase reversa, 5um, 4,6 x 50 mm, (2) MS:PE Sciex API-150EX, y (3) HPLC: Shimadzu LC-10 ADvp, 1ml/min., gradiente lineal acetonitrilo en agua 10% a acetonitrilo en agua 95%, ambos contienen TFA 0,05%.

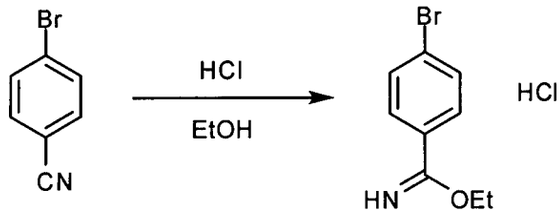
Ejemplo 1

Síntesis de [3-(6-isopropoxi-piridin-3-il)-1H-indazol-5-il]-amida del ácido 3-metoxi-1-(2-{4-[4-(1-metil-1H-[1,2,4]triazol-3-il)-fenil]-3,6-dihidro-2H-piridin-1-il}-2-oxo-etil)-pirrolidin-3-carboxílico



A1

Síntesis de 2-cloro-1-{4-[4-(1-metil-1*H*-[1,2,4]triazol-3-il)-fenil]-3,6-dihidro-2*H*-piridin-1-il}-etanona

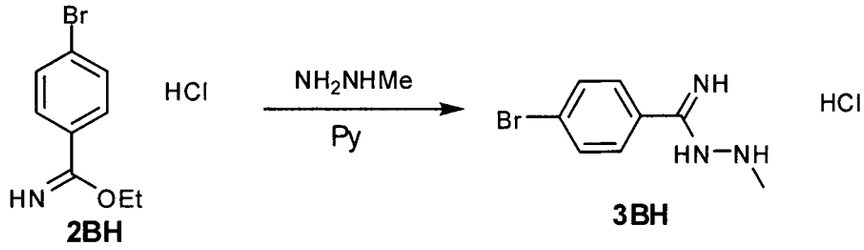


1BH **2BH**

Paso 1: Preparación de etiléster del ácido 4-bromo-bencimídico

Se suspendió 4-bromo-benzonitrilo (5 g) en EtOH absoluto (100 ml) y se enfrió a 0-5°C. Se burbujeó gas de HCl a través del mismo, en un principio en forma vigorosa durante varios minutos y luego lentamente durante 5 horas. La solución resultante se dejó agitar hasta el día siguiente. La mayor parte del solvente se retiró y el precipitado se filtró, se lavó dos veces con EtOH y se secó para dar el compuesto **2BH** (4,1 g) como un sólido blanco.

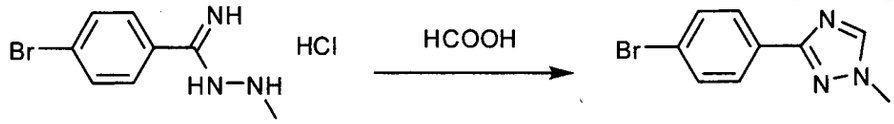
Paso 2: Preparación del Compuesto 3BH



2BH **3BH**

El etiléster del ácido 4-bromo-bencimídico (2,12 g, 8 mmoles) se disolvió en piridina (20 ml). Metilhidrazina (640 µl, 12 mmols) se agregó con agitación y la mezcla resultante se dejó agitar hasta el día siguiente. La mezcla de reacción se concentró bajo presión reducida, y se agregó éter, se filtró y lavó tres veces con éter y se secó para proveer el compuesto **3BH** (2,2 g).

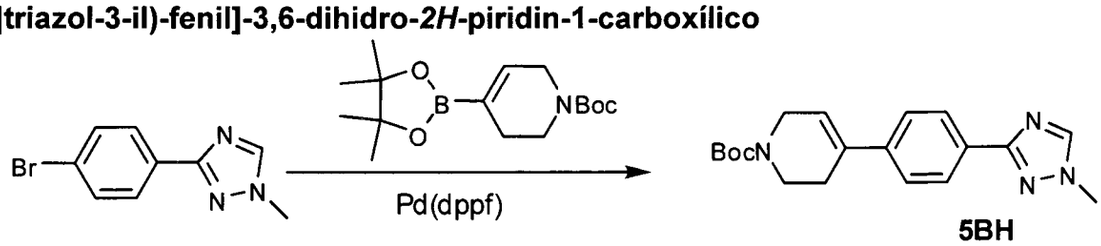
Paso 3: Preparación de 3-(4-bromo-phenil)-1-metil-*1H*-[1, 2, 4]triazol



3BH **4BH**

Una mezcla del compuesto **3BH** (2,2 g) en ácido fórmico (30 ml) se calentó a reflujo hasta el día siguiente y se concentró. El residuo se trató con $NaHCO_3$ saturado, y se extrajo tres veces con EtOAc. Los orgánicos combinados se secaron sobre $MgSO_4$. Luego de la concentración, se obtuvo el compuesto **4BH** como cristales incoloros (1,39 g). (Nota: se ha descubierto que la reacción puede llevarse a cabo en sólo dos horas. En síntesis a gran escala, utilizar NaOH 10% para reemplazar $NaHCO_3$).

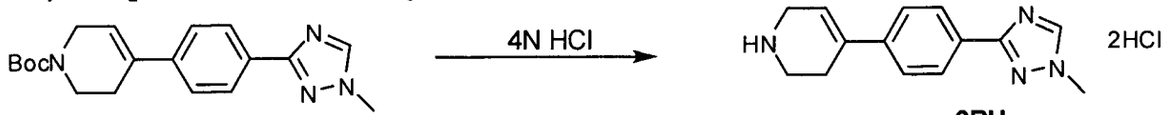
Paso 4: Preparación de ter-butil éster del ácido 4-[4-(1-metil-*1H*-[1,2,4]triazol-3-il)-fenil]-3,6-dihidro-*2H*-piridin-1-carboxílico



4BH **5BH**

Se cargaron en un matraz de alta presión, el compuesto **4BH** (13,3 g, 55,9 mmoles), 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 (19 g, 61,5 mmols), [1,1'-bis(difenilfosfino)-ferroceno]dicloropaladio (II), complejo con diclorometano (1:1) (2,3 g, 2,8 mmoles), K_2CO_3 (23,2 g, 168 mmols) y DME/agua (5:1, 120 ml). La mezcla se desgasificó brevemente con Ar durante ~0,5 minutos, se tapó y agitó a 80°C hasta el día siguiente. Luego del enfriamiento, la mezcla de reacción se diluyó con EtOAc y salmuera. La capa orgánica se aisló y secó ($MgSO_4$). Luego de la concentración, el residuo se purificó sobre gel de sílice. La elución con MeOH/EtOAc (0-10%) dio el producto deseado **5BH** (13,9 g, 73%).

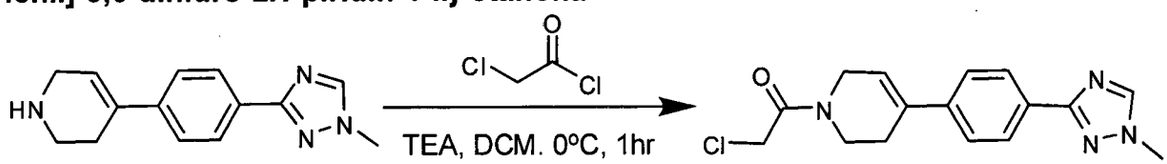
Paso 5: Preparación de clorhidrato de 4-[4-(1-metil-1*H*-[1,2,4]triazol-3-il)-fenil]-1,2,3,6-tetrahidro-piridina



5BH **6BH**

El grupo Boc puede retirarse tratando el compuesto **5BH** con HCl 4N en dioxano a ta durante dos horas. El retiro del solvente al vacío dio el compuesto **6BH**.

Paso 6: Preparación de 2-cloro-1-{4-[4-(1-metil-1*H*-[1,2,4]triazol-3-il)-fenil]-3,6-dihidro-2*H*-piridin-1-il}-etanona



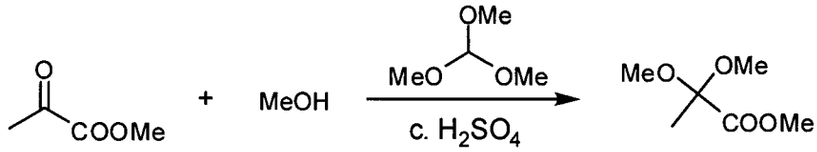
6BH .2HCl **7BH**

A una solución fría (0°C) de 4-[4-(1-metil-1*H*-[1,2,4]triazol-3-il)-fenil]-1,2,3,6-tetrahidro-piridina **6BH** (13,7g, 44mmol) in diclorometano (450 ml) se agregó TEA (37 ml, 264 mmol) gota a gota. Luego de agitación a 0°C durante 10 minutos, se agregó cloruro de cloroacetilo (10,5 ml, 132 mmoles) a la mezcla de reacción. La mezcla resultante se agitó a 0°C durante 1hora, y se

desactivó con agua (165 ml). La mezcla de reacción se diluyó con diclorometano (600 ml). La capa orgánica se separó y lavó con salmuera, se secó sobre $MgSO_4$. La mezcla de reacción se concentró a ~50ml, se agregó éter y el sólido se filtró para obtener el producto deseado **7BH** (8,74 g).

Síntesis de metiléster del ácido 3-metoxi-pirrolidin-3-carboxílico

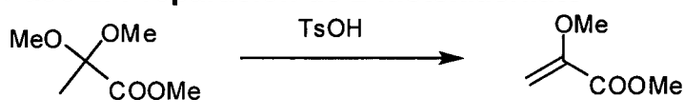
Paso 1: Preparación de α,α–dimetoxipropionato de metilo



8BH

Se siguió el procedimiento de Ernest Wenkert, et al. (JACS, **1983**, *105*, 2021-2029). Una solución de piruvato de metilo (44 g), ortoformato de trimetilo (62 ml), H_2SO_4 concentrado (0,2 ml) en MeOH (120 ml) se calentó a reflujo durante 4 horas. En el próximo período de una hora, se destiló el solvente (aproximadamente 80 ml). La mezcla de reacción se enfrió a 10°C, se vertió en una solución de KOH (KOH 1,2 g en 600 ml de agua), y se extrajo con éter (3x). Los extractos de éter combinados se lavaron con salmuera y se secaron ($MgSO_4$). Luego de la concentración, el residuo se destiló al vacío para proveer el acetal (**8BH**) (40g, 62%, 40-43C/1 torr).

Paso 2: Preparación de 2-metoxiacrilato

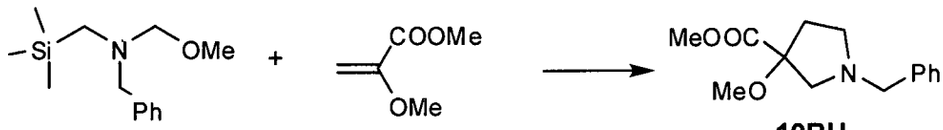


8BH **9BH**

Se siguió el procedimiento de Ernest Wenkert, et al. (JACS, **1983**, *105*, 2021-2029). Se cargó a un matraz de un cuello α,α-dimetoxipropionato (**8BH**) (150 g) y monohidrato del ácido toluensulfónico (3g) y se adjuntó una cabeza de destilación corta. La mezcla se calentó a 140°C (temperatura de un baño de aceite) y primero comenzó a salir el metanol. Luego, el producto (76 g) de

(**9BH**) se destiló luego de que la temperatura de un baño de aceite se elevara a más de 190°C.

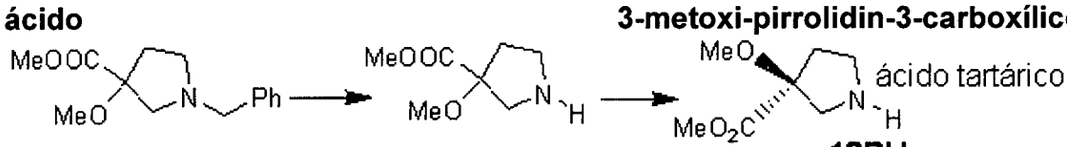
Paso 3: Preparación de metiléster del ácido 1-bencil-3-metoxi-pirrolidin-3-carboxílico



9BH **10BH**

A una solución agitada de 2-metoxiacrilato de metilo (20,8 g, 179 mmoles) y *N*-(metoximetil)-*N*-(trimetilsililmetil)bencilamina (55 ml, 215 mmoles) en diclorometano (160 ml) se agregó a 0°C una solución de ácido trifluoracético (2 ml) en diclorometano (10 ml). La solución resultante se calentó a temperatura ambiente y se agitó hasta el día siguiente. Luego de la concentración, producto bruto se purificó por cromatografía en columna sobre gel de sílice eluyendo con una solución de acetate de etilo/hexanos/Et_3N (1000:3000:4 a 1000:1000:3) para dar el compuesto del título (**10BH**) (17,7 mg, 40%). (Nota: la adición de Et_3N es esencial para asegurar una separación precisa.)

Paso 4: Preparación de sal del ácido tartárico de metiléster del ácido 3-metoxi-pirrolidin-3-carboxílico

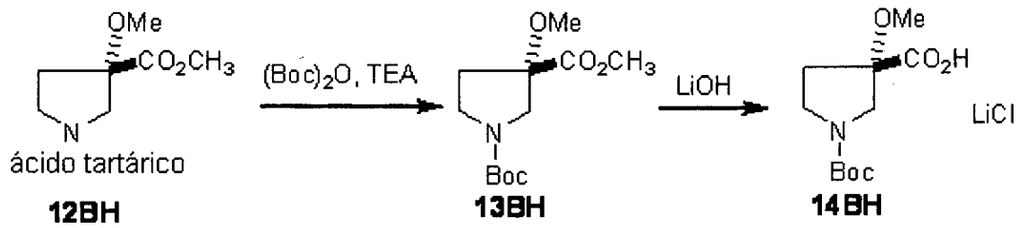


10BH **11BH** **12BH**

2,49 gm de metiléster del ácido 1-bencil-3-metoxi-pirrolidin-3-carboxílico (**10BH**) se hidrogenaron en etanol utilizando Pd/C 10% a hidrógeno 3793,14 Hpa durante 24 horas. La filtración del Pd/C fue seguida por la evaporación del etanol 1,6 gm de producto bruto desbencilado (**11BH**). El producto bruto se disolvió en 95 ml de metanol y se agregaron 1,35 gm de ácido L-tartárico.

Luego de 24 horas, los cristales se filtraron y recristalizaron a partir de metanol para dar 13,4 gramos del producto del título (**12BH**).

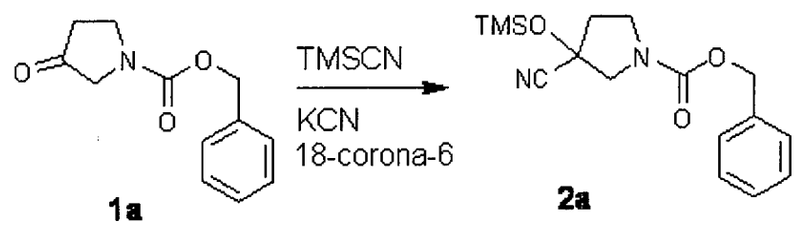
Paso 5: Preparación de 1-ter-butil éster del ácido 3-metoxi-pirrolidin-1,3-dicarboxílico



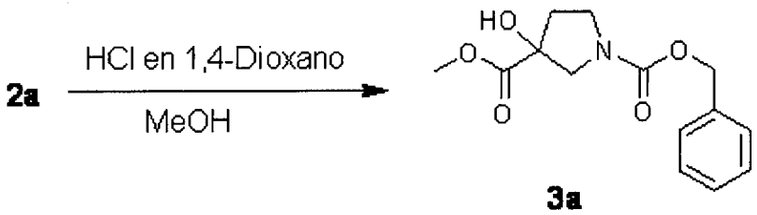
A una solución fría (0°C) de **12BH** (28 g, 90,52 mmol) en CH_2Cl_2 seco (250 ml) se agregó trietilamina (31,5 ml, 226,32 mmol, 2,5 equiv.) seguido por $(Boc)_2O$ (25,7 g, 117,68 mmol, 1,3 equiv.). La mezcla resultante se agitó de 0°C a ta durante toda la noche, luego se diluyó con CH_2Cl_2, que se lavó con una solución saturada acuosa de $NaHCO_3$ y salmuera, se secó ($MgSO_4$) y concentró. La cromatografía sobre gel de sílice (hexanos/acetato de etilo, 4:1) dio **13BH** (23,5 mg, 90,52 mmol, 100%) como un aceite incoloro.

A una solución agitada de **13BH** (23.5 mg, 90.52 mmol) en THF/MeOH (175 ml/175 ml) se agregó 135 ml de LiOH (1M en H_2O, 135 mmol, 1,5 equiv.). La mezcla de reacción se agitó a ta hasta el día siguiente, a lo que se agregó 135 ml de HCl 1N. La mezcla resultante se agitó durante 15 minutos adicionales y se concentró, se destiló azeotrópicamente con dioxano (150 ml x 3) para dar **14BH** (42,32 g) como un sólido blanco, que puede utilizarse en el próximo paso sin purificación adicional.

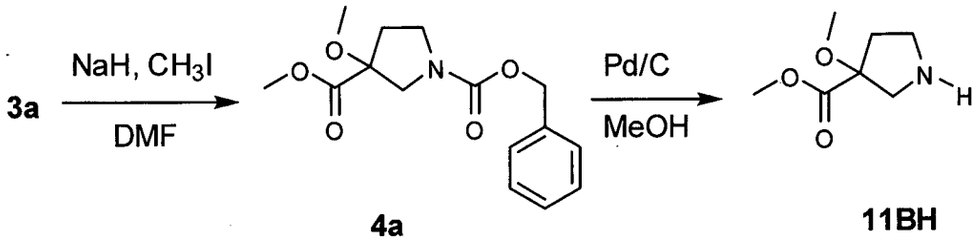
Alternativamente, el compuesto 11BH puede prepararse como sigue:



1a **2a**



2a **3a**



3a **4a** **11BH**

A una solución helada de benciléster del ácido 3-oxo-pirrolidin-1-carboxílico **1a** (250 g, 1,14 mol) en diclorometano anhidro 3,5 l se agregó KCN (7.5g, 0.12 mol), seguido por 18-corona-6 (30 g, 0,11 mol), aunque no se disolvió en forma completa, se agregó TMSCN (183 ml, 1,37 mol) lentamente durante un período de 20 minutos. La reacción se agitó a temperatura ambiente durante una noche.

Se agregó una solución semisaturada de $NaHCO_3$ (2 l) a 15°C, se agitó durante 10 minutos y luego se separó la capa orgánica, se secó sobre sulfato de magnesio, se filtró y evaporó para dar benciléster del ácido 3-ciano-3-trimetilsilaniloxi-pirrolidin-1-carboxílico **2a**, 422 g (>100%).

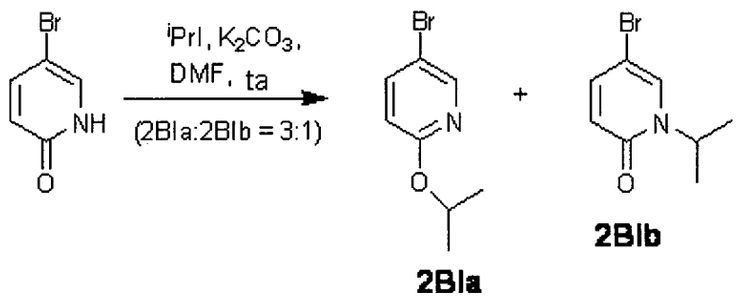
A benciléster del ácido 3-ciano-3-trimetilsilaniloxi-pirrolidin-1-carboxílico **2a** (422 g) en 4 l de anhidrous MeOH, se agregó 2,2 l de HCl 4N en dioxano. La reacción se calentó a reflujo durante 13 horas y se agitó a temperatura

ambiente durante una nocha. Se retiraron los solventes, se suspendieron en 5 l de CH_2Cl_2, se lavaron con 4+3l de agua, se ajustó el pH a 6-7 con $NaHCO_3$ acuoso, se secaron sobre sulfato de magnesio, se filtraron y evaporaron para dar 1-benciléster 3-metiléster del ácido 3-hidroxi-pirrolidin-1,3-dicarboxílico **3a**, 278 g (2 pasos, 87%).

A una suspensión de NaH (52 g, 1,3 mol) en 2,2 l de DMF anhidro a 8°C, se agregó una solución de 1-benciléster 3-metiléster del ácido 3-hidroxi-pirrolidin-1,3-dicarboxílico **3a** (278 g, 1,0 mol) en DMF 700, manteniendo la temperatura de reacción a menos de 11°C. Una vez completa la adición (~20 minutos), se retiró el baño de hielo, se agitó a 16-18°C durante 1 hora, y luego a temperatura ambiente durante 1 hora. Se enfrió nuevamente a 15^0C, se agregó MeI (81 ml, 1,3 mol) lentamente. La mezcla de reacción se agitó a temperatura ambiente durante una noche. Luego, la mezcla de reacción se vertió en agua helada (4 l) y luego se extrajo con Et_2O (6 l) y EtOAc (2 l), se lavó la capa orgánica con agua (5 l), salmuera (700 ml), se secó sobre sulfato de magnesio, se filtró y evaporó para dar 1-benciléster 3-metiléster del ácido 3-metoxi-pirrolidin-1,3-dicarboxílico crudo **4a** 289 g (rendimiento bruto 99%, contiene aceite mineral) (la agitación/separación con lavado con pentano dio **4a**, 268.2 g (92%).

A 1-benciléster 3-metiléster del ácido 3-metoxi-pirrolidin-1,3-dicarboxílico **4a** en MeOH (2200 ml), se agregó 14 g de Pd/C 10% (~50% en agua). La mezcla de reacción se hidrogenó utilizando H_2 a una presión de ~3793,14 Hpa (válvula abierta) durante una noche. La mezcla de reacción se filtró, secó para dar metiléster del ácido 3-metoxi-pirrolidin-3-carboxílico **11BH** 126 g. (Rendimiento total de 70% en 4 pesos, sin purificación en columna).

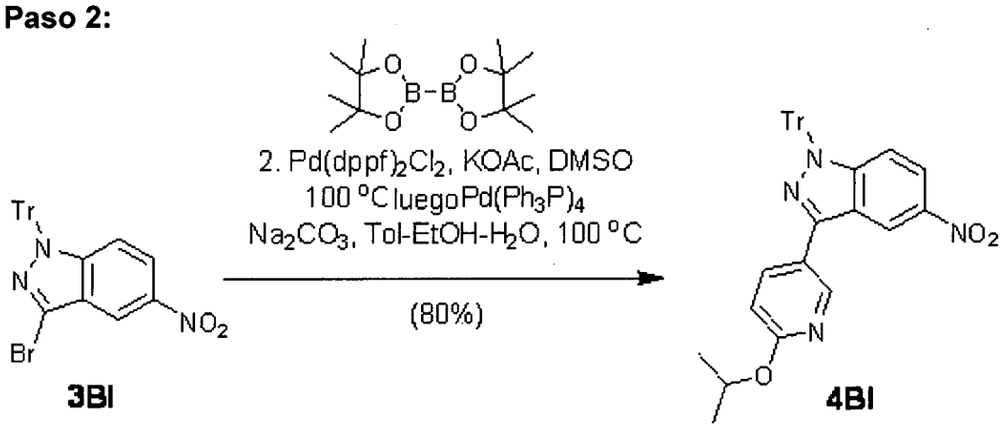
Síntesis de [3-(6-isopropoxi-piridin-3-il)-1H-indazol-5-il]-amida del ácido 3-Metoxi-pirrolidin-3-carboxílico



Paso 1:

5-bromo-1H-piridona **1BI** (100 g, 0,58 mol), carbonato de potasio (238g, 1,73 mol) y 2-iodopropano (86 ml, 0,86 mol) se agitaron en DMF (1 l) a ta durante 1 día. La mezcla se diluyó con acetato de etilo y agua, se separaron las capas. La capa orgánica separada se lavó con agua (X2), se secó (Mg SO_4) y filtró. Los solventes se retiraron al vacío y la purificación en columna [acetato de etilo 5% en hexanos] dio la primera 5-isopropoxipiridina menos polar **2BIa** (73g, 59%) como un líquido incoloro. La continuación de la elución con [acetato de etilo 50% en hexanos] dio la 5-bromo-1-isopropilpiridona más polar **2BIb** como un sólido blanco (22g, 18%).

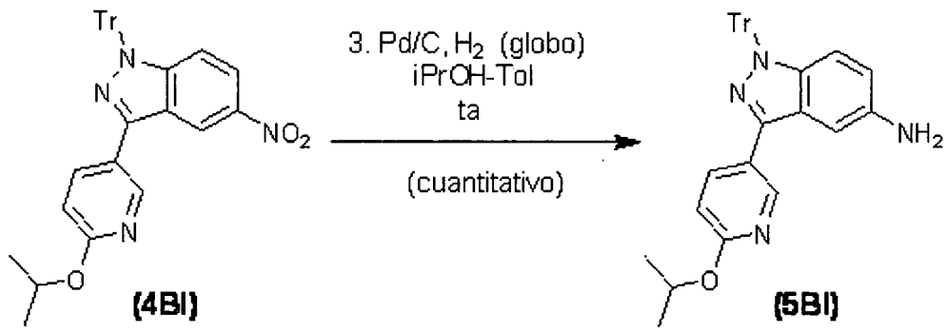
Paso 2:



5-isopropoxipiridina **2BIa** (10g, 0,046 mol), bis(pinacolato)diboro (14,1 g, 0,056 mol), acetato de potasio (13,6 g, 0,14 mol) y $PdCl_2(dppf)_2.CH_2Cl_2$ (3.78g, 0.0046mol) se pesaron en un matraz de 1 l de 2 cuellos equipado con un condensador de agua. DMSO (100 ml) se agregó y la mezcla se purgó con

nitrógeno durante 15 minutos. La mezcla se calentó a 100ºC bajo nitrógeno durante 2 horas. Luego del enfriamiento a ta, se agregaron agua (100 ml), tolueno (100 ml), etanol (100 ml), carbonato de potasio (32 g, 0,23 mol) y bromoindazol **3BI** (22,4 g, 0,046 mol). La mezcla se purgó con nitrógeno durante 10 minutos a ta y se agregó $Pd(Ph_3P)_4$ (5.35g, 0.0046mol). La mezcla final se calentó a 100ºC durante 2 horas y se enfrió a ta. se agregaron agua y acetato de etilo. Los sólidos se filtraron a través de Celite. Se separaron las capas y la capa orgánica separada se lavó con agua (X2). Las capas acuosas combinadas se reextrajeron con acetato de etilo (X1). Las capas orgánicas combinadas se secaron ($MgSO_4$), se filtraron y los solventes se retiraron al vacío. La purificación en columna [Hexanos-acetato de etilo = 9:1 (v/v)] dio isopropoxiindazol **4BI** (20g, 80%) como un sólido amarillo.

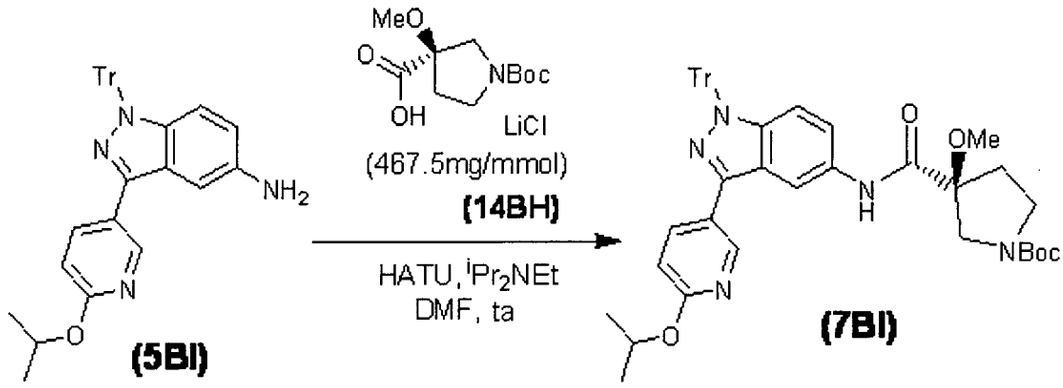
Paso 3:



(4BI) **(5BI)**

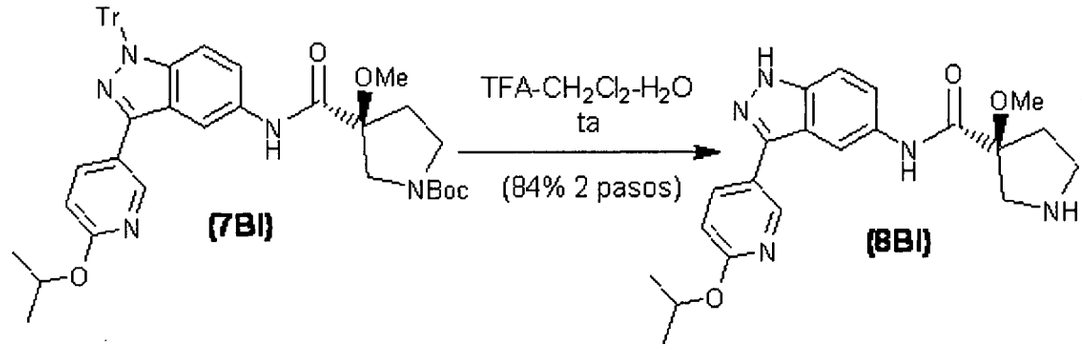
Isopropoxiindazol **4BI** (20 g, 0,037 mol) y Pd/C (10%, 50% húmedo, 7,8 g, 0,0037 mol) se agitaron en tolueno (100ml) y 2-propanol (200 ml) bajo H_2 (globo) a ta durante 1 día. El catalizador sólido se filtró a través de Celite y los solventes se eliminaron al vacío para dar aminoindazol **5BI** (cuant.) como un sólido blancuzco.

Paso 4:



Aminoindazol **5BI** (39 g, 0,076 mol) y ácido pirrolidincarboxílico **14BH** (32 g, 0,069 mol) se disolvieron en DMF (300 ml) a ta. Se agregaron HATU (29 g, 0,076 mol) seguido por $^{i}Pr_2NEt$ (14,5 ml, 0,083 mol). La mezcla se agitó a ta hasta el día siguiente y se diluyó con acetato de etilo y agua. Se separaron las capas. La capa orgánica separada se lavó con agua (X2), se secó ($MgSO_4$) y filtró. La concentración al vacío seguida por la purificación en columna [hexanos – acetato de etilo = 4:1 (v/v)] dio **7BI** bruto como una espuma blancuzca.

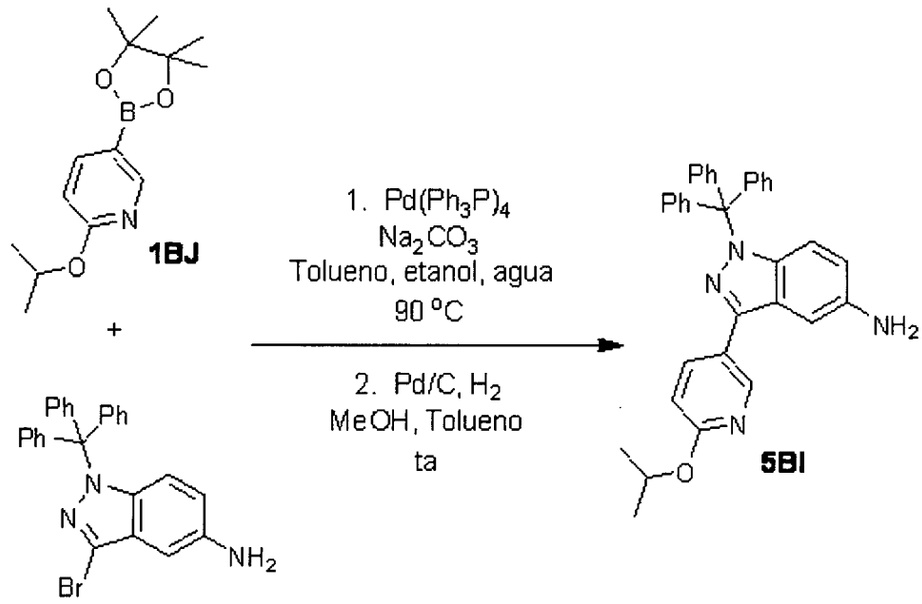
Paso 5:



El **7BI** bruto se agitó en una mezcla de diclorometano (300 ml), ácido trifluoracético (100 ml) y agua (50 ml) a ta hasta el día siguiente. La mezcla se enfrió a 0°C y se desactivó cuidadosamente con bicarbonato de sodio saturado acuoso. Los solventes se retiraron al vacío. Se diluyeron con agua y acetato de etilo. Se separaron las capas y la capa acuosa separada se extrajo con acetato de etilo (X3). Las capas orgánicas combinadas se secaron ($MgSO_4$), se filtraron

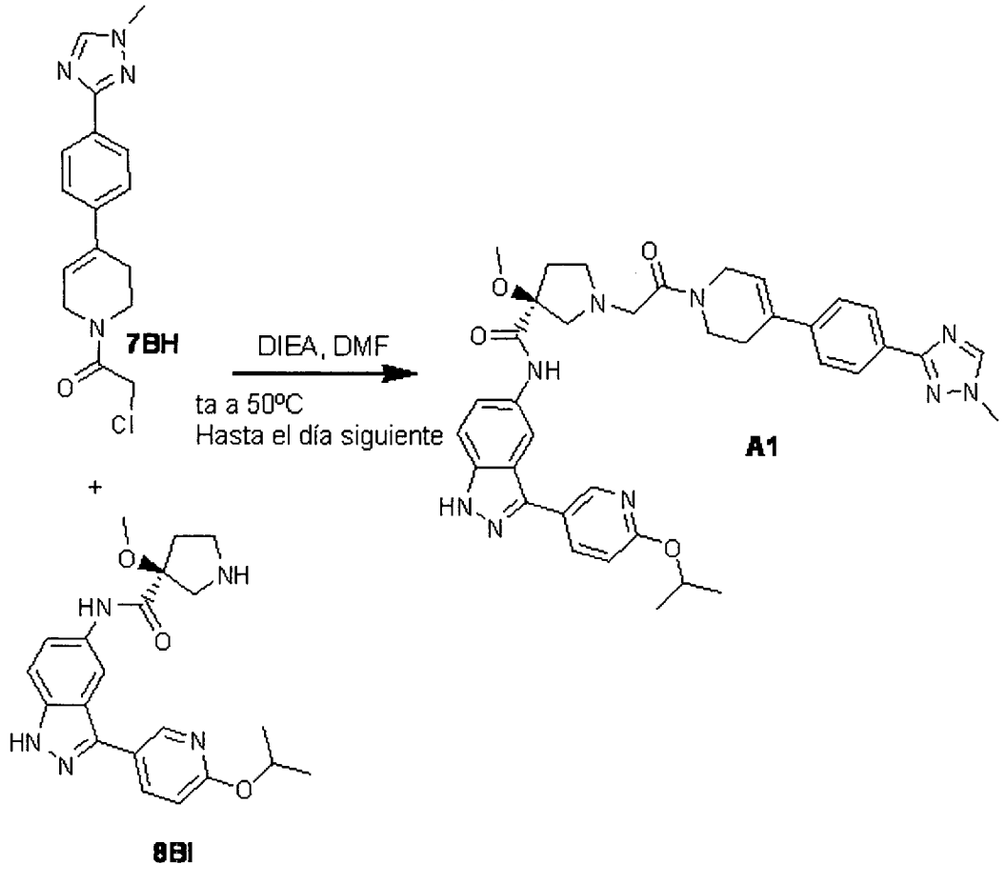
y los solventes se retiraron al vacío. La purificación en columna [MeOH 5 a 10% (amoníaco 7N) en diclorometano] dio pirrolidina **8BI** (23g, 84%) como un sólido blancuzco.

Alternativamente:



Boronato **1BJ** (1,0g, 3,80 mmol), bromoindazol **2BJ** (1,84 g, 3,80 mmol), bicarbonato de sodio (1,21 g, 11,4 mmol) se cargaron en un tubo sellado. Se agregaron tolueno (30 ml), etanol (30 ml) y agua (15 ml). La suspensión se purgó con nitrógeno durante 15 minutos y se agregó $Pd(Ph_3P)_4$ (439 mg, 0,38mmol) en una porción. La mezcla se calentó en el tubo sellado a 90ºC hasta el día siguiente. Luego del enfriamiento a ta, se agregaron agua y acetato de etilo y se separaron las capas. La capa orgánica separada se lavó con agua, se secó ($MgSO_4$) y filtró. Los solventes se retiraron al vacío. El residuo se disolvió en tolueno (100 ml). Se agregaron metanol (100 ml) seguido por Pd/C (809mg, 0,38 mmol, húmedo 50%). La mezcla se agitó bajo H_2 (globo) hasta el día sigiente. El catalizador se filtró y los solventes se eliminaron al vacío. La

Síntesis de [3-(6-isopropoxi-piridin-3-il)-1H-indazol-5-il]-amida del ácido 3-metoxi-1-(2-{4-[4-(1-metil-1H-[1,2,4]triazol-3-il)-fenil]-3,6-dihidro-2H-piridin-1-il}-2-oxo-etil)-pirrolidin-3-carboxílico

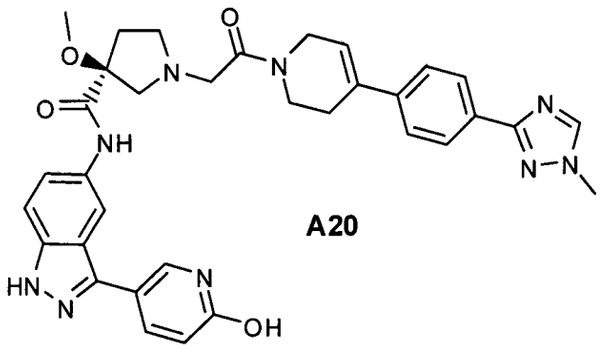


Una mezcla del compuesto **7BH** (7,88 g, 24,93 mmol), compuesto **8BI** (9,86 gm, 24,93 mmol), y DIEA (26,1 ml, 149,62 mmol) en DMF (200 ml) se agitó a temperatura ambiente durante 5 horas. La reacción se completó a aproximadamente 89%, con base en la LCMS. Luego, esta se calentó a 50ºC hasta el día siguiente (16 horas.) LCMS mostró que la reacción estaba completa. El DMF se retiró a presión reducida. El bruto se disolvió en 700 ml de DCM y se lavó una vez con 35 ml de agua. La capa acuosa se extrajo con MeOH/DCM 2% (2 x 120 ml). Los extractos orgánicos combinados se homogeneizaron con MeOH y se secaron sobre $MgSO_4$. El solvente se retiró y

el bruto se purificó mediante cromatografía en columna utilizando MeOH/EtoAc 20% para dar el producto deseado **A1** como un sólido amarillo (70%). (LCMS M+1= 674, tiempo de retención= 2.91 min.) 1H RMN (400 MHz, CD3OD):δ8,67 (S, 1H), 8,42 (S, 1H), 8,35 (S, 1H), 8,15-8,19 (m, 1H), 7,94(dd, 2H, J= 8,4 & 10 Hz), 7,64 (m, 1H), 7,49 (m, 3H), 6,84 (m, 1H), 6,20 (d, 1H, J= 11,2 Hz), 5,3 (m, 1H), 4,28 (s, 1H), 4,23 (m, 1H), 3,97 (s, 3H), 3,8 (m, 2H), 3,56 (d, 1H, 2,4 Hz), 3,52(d, 1H, 6,4 Hz), 3,31 (s, 3H), 3,17 (t, 1H, J= 10 Hz), 3,07 (t, 1H, J= 12 Hz), 2,81 (m, 1H), 2,81 (m, 1H), 2,65 (s, 1H), 2,58 (s, 1H), 2,43 (m, 1H), 2,17 (m, 1H), 1,32 (d, 6H, J=6,4 Hz)

Ejemplo 2

Síntesis de [3-(6-hidroxi-piridin-3-il)-1H-indazol-5-il]-amida del ácido 3-Metoxi-1-(2-{4-[4-(1-metil-1H-[1,2,4]triazol-3-il)-fenil]-3,6-dihidro-2H-piridin-1-il}-2-oxo-etil)-pirrolidin-3-carboxílico



A20

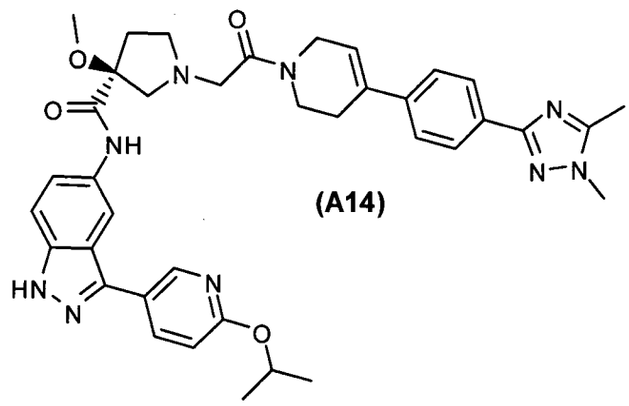
El compuesto aislado (**A20)** se aisló de la descomposición de la sal di-HCl de la [3-(6-isopropoxi-piridin-3-il)-1H-indazol-5-il]-amida del ácido 3-metoxi-1-(2-{4-[4-(1-metil-1H-[1,2,4]triazol-3-il)-fenil]-3,6-dihidro-2H-piridin-1-il}-2-oxo-etil)-pirrolidin-3-carboxílico.

LCMS M+1 634, tiempo de retención = 2,28 minutos. ^{1}H-RMN (400 MHz, DMSO-d_6):δ 13,09 (br, 1H), 11,84 (br, 1H), 10,02 (s, 1H), 8,51 (s, 1H), 8,37 (s, 1H), 8,02 (dd, 1H, J=9,5 Hz & 2,5 Hz), 7,95 (m, 2H), 7,82 (d, 1H, J=1,9 Hz), 7,71 (m, 1H), 7,51 (m, 3H), 6,52 (d, 1H, J=9,5 Hz), 6,27 (m, 1H), 4,08-4,34 (m,

2H), 3,92 (s, 3H), 3,70 (m, 2H), 3,49 (m, 2H), 3,24 (s, 3H), 3,16 (d, 1H, J=5,2 Hz), 2,84-3,13 (m, 3H), 2,55-2,76 (m, 2H), 2,36 (m, 1H), 2,05 (m, 1H).

Ejemplo 3

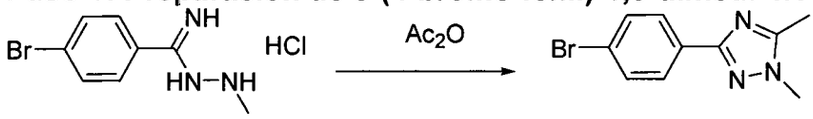
Síntesis de [3-(6-isopropoxi-piridin-3-il)-1H-indazol-5-il]-amida del ácido 1-(2-{4-[4-(1,5-dimetil-1H-[1,2,4]triazol-3-il)-fenil]-3,6-dihidro-2H-piridin-1-il}-2-oxo-etil)-3-Metoxi-pirrolidin-3-carboxílico



(A14)

Síntesis de (S)-1-(2-(4-(4-(1,5-dimetil-1*H*-1,2,4-triazol-3-il)fenil)-5,6-dihidropiridin-1(2*H*)-il)-2-oxoetil)-*N*-(3-(6-isopropoxipiridin-3-il)-1*H*-indazol-5-il)-3-metoxipirrolidin-3-carboxamida

Paso 1: Preparación de 3-(4-bromo-fenil)-1,5-dimetil-1*H*-[1,2,4]triazol

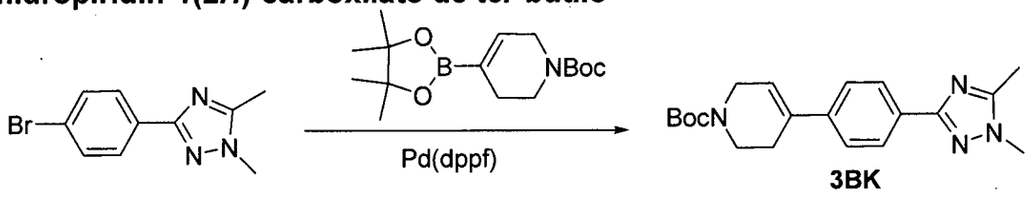


1BK **2BK**

Una mezcla de clorhidrato de 4-bromo-*N*'-metilbencimidohidrazida **1** (1,7 g) (preparada de acuerdo con un procedimiento de la Síntesis de Sch-1499895) en anhídrido acético (10 ml) se calentó a 100°C durante 0,5 horas. Luego del enfriamiento y concentración a presión reducida, el residuo se disolvió en EtOAc, se lavó dos veces con $NaHCO_3$ saturado, salmuera y se secó ($MgSO_4$). Luego de la evaporación del solvente, el residuo se purificó sobre gel de sílice.

La elución con EtOAc dio 3-(4-bromofenil)-1, 5-dimetil-1*H*-[1,2,4]-triazol **2BK** (1,04 g).

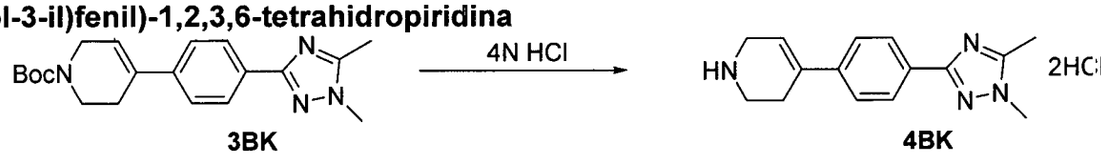
Paso 2: Preparación de 4-(4-(1, 5-dimetil-1*H*-1,2,4-triazol-3-il)fenil)-5,6-dihidropiridin-1(2*H*)-carboxilato de *ter*-butilo



2BK **3BK**

Se cargó a un tubo de presión el compuesto **2BK** (252 mg, 1 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 (403 mg, 1,3 mmol), [1,1'-bis(difenilfosfino)-ferrocene]dicloropaladio (II), complejo con diclorometano (1:1) (41 mg, 0,05 mmol), K_2CO_3 (410 mg, 3 mmol) y DME/agua (5:1, 6 ml). La mezcla se desgasificó brevemente con Ar durante ~0.5 minutos, se tapó y agitó a 100°C hasta el día siguiente. Luego del enfriamiento, la mezcla de reacción se diluyó con EtOAc y salmuera. La capa orgánica se aisló y secó ($MgSO_4$). Luego de la concentración, el residuo se purificó sobre gel de sílice. La elución con MeOH/EtOAc (0-10%) dio el producto deseado **3BK** (332 mg).

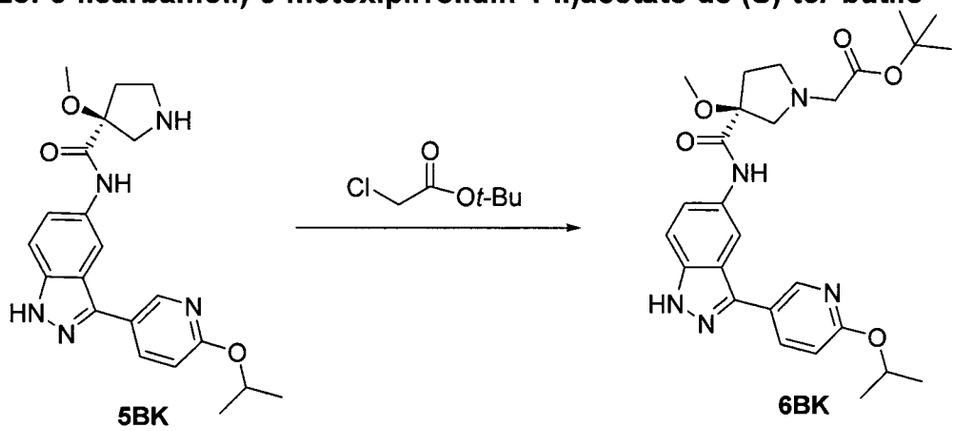
Paso 3: Preparación de diclorhidrato de 4-(4-(1,5-dimetil-1*H*-1,2,4-triazol-3-il)fenil)-1,2,3,6-tetrahidropiridina



3BK **4BK**

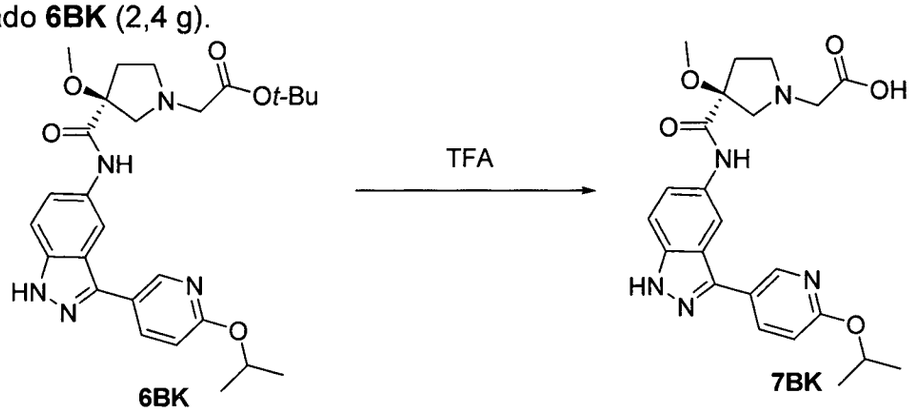
El grupo Boc puede retirarse tratando el compuesto **3BK** con HCl 4N en dioxano a ta durante dos horas. El retiro del solvente al vacío dio el compuesto **4BK**.

Paso 4: Preparación de 2-(3-(3-(6-isopropoxipiridin-3-il)-1*H*-imidazol-5-ilcarbamoil)-3-metoxipirrolidin-1-il)acetato de (S)-*ter*-butilo



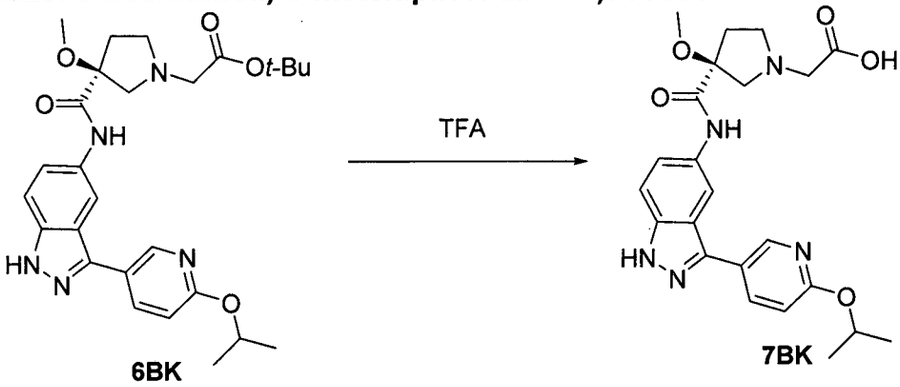
5BK **6BK**

En una solución del compuesto **5BK** (3,5 g, 6.6 mmol) (preparada de acuerdo con un procedimiento de la Síntesis de Sch-1499895) in acetonitrilo (26 ml) se agregó DIEA (5,7 ml, 32,9 mmol). Se enfrió a 0ºC y se agregó gota a gota 0,47 ml (3,29 mmol) de cloroacetato de ter-butilo. Luego de agitación durante 4 horas a 0ºC, se agregó nuevamente 0,47 ml (3,29 mmol) de cloroacetato de ter-butilo. Esta se agitó en forma adicional durante 1hora a 0ºC y luego se calentó a ta. Luego de agitación a temperatura ambiente hasta el día siguiente, se disolvió en EtOAc (200 ml) y se lavó con $NaHCO_3$ (1 x 50ml), agua (1x 50ml) y salmuera (1 x 50ml). Los extractos orgánicos se secaron sobre $MgSO_4$ y se retiró el solvente. El producto bruto se purificó mediante cromatografía en columna utilizando MeOH/EtOAC 20% para dar el producto deseado **6BK** (2,4 g).



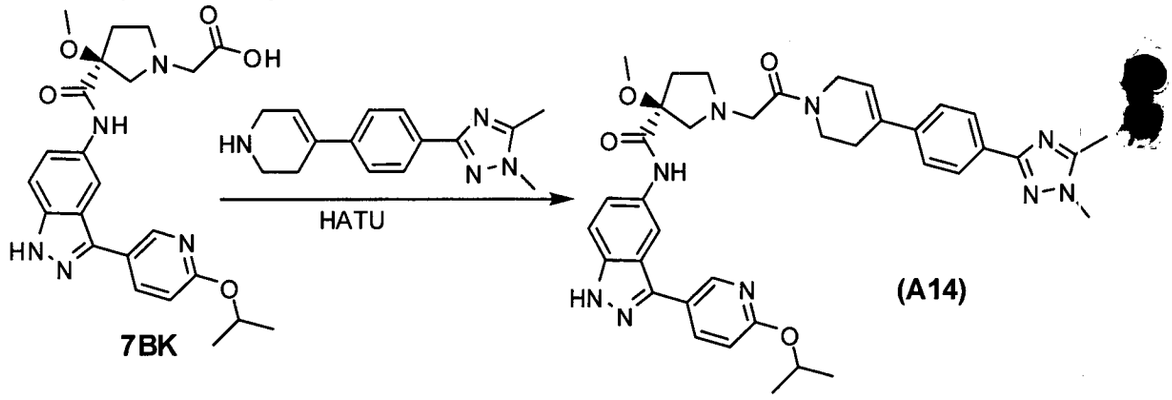
6BK **7BK**

Paso 5: Preparación del ácido (S)-2-(3-(3-(6-isopropoxipiridin-3-il)-1*H*-indazol-5-ilcarbamoil)-3-metoxipirrolidin-1-il)acético



El compuesto **6BK** (2.4 g) se trató con 40 ml de TFA durante 45 minutos a temperatura ambiente. Se retiró el TFA a presión reducida y el sólido se lavó con éter para obtener el compuesto **7BK** como una sal de TFA (4,4 g, 95%).

Paso 6: Preparación de (S)-1-(2-(4-(4-(1,5-dimetil-1*H*-1,2,4-triazol-3-il)fenil)-5,6-dihidropiridin-1(2*H*)-il)-2-oxoetil)-*N*-(3-(6-isopropoxipiridin-3-il)-1*H*-indazol-5-il)-3-metoxipirrolidin-3-carboxamida



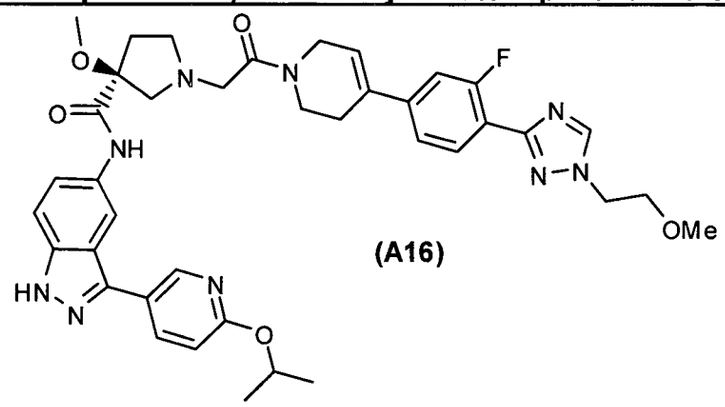
A una mezcla del compuesto **7BK** (0,12 mmol), HATU (46 mg, 0,12 mmol) en DMF (2 ml) se agregó el compuesto **4BK** (39 mg, 0,12 mmol) y DIEA (0,063 ml). La mezcla se agitó durante 20 minutos y se purificó directamente mediante HPLC para dar el compuesto **A14**. Espectro de masa: LCMS M+1= 690, tiempo de retención = 3,25 minutos;

^{1}H RMN de sal de HCl **A14** (400 MHz, DMSO-d_6):δ10,5 (br, 1H), 10,23 (d, J = 17,6 Hz, 1H), 8,7 (m, 1H), 8,45 (d, J = 1,2 Hz, 1H), 8,18 (m, 1H), 7,94

(m, 2H), 7,75 (dd, J = 8,8, 2,0 Hz, 1H), 7,56 (m, 3H), 6,93 (m, 1H), 6,3 (m, 1H), 5,3 (m, 1H), 4,6-4,53 (m, 2H), 4,2-4,0 (m, 3H), 3,82 (s, 3H), 3,7-3,5 (m, 5H), 3,3 (s, 3H), 2,67-2,54 (m, 3H), 2,44 (s, 3H), 2,4(m, 1H), 1,33 (d, J = 6,4 Hz, 6H).

Ejemplo 4

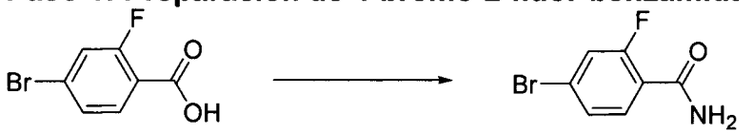
Síntesis de [3-(6-isopropoxi-piridin-3-il)-1H-indazol-5-il]-amida del ácido 1-[2-(4-{3-flúor-4-[1-(2-metoxi-etil)-1H-[1,2,4]triazol-3-il]-fenil}-3,6-dihidro-2H-piridin-1-il)-2-oxo-etil]-3-Metoxi-pirrolidin-3-carboxílico



(A16)

Síntesis de [3-(6-isopropoxi-piridin-3-il)-1*H*-indazol-5-il]-amida del ácido (S)-1-[2-(4-{3-flúor-4-[1-(2-metoxi-etil)-1*H*-[1,2,4]triazol-3-il]-fenil}-3,6-dihidro-2*H*-piridin-1-il)-2-oxo-etil]-3-Metoxi-pirrolidin-3-carboxílico

Paso 1: Preparación de 4-bromo-2-flúor-benzamida

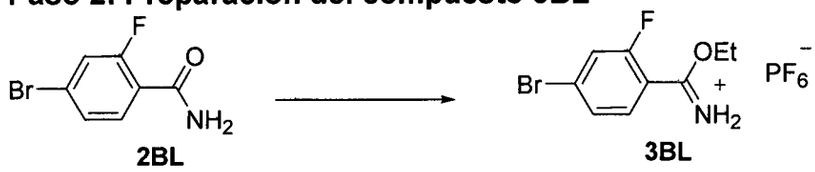


1BL **2BL**

A 0°C, se agregó 1,1'-carbonildiimidazol (8,8 g, 54,3 mmol) en porciones una mezcla agitada de ácido 4-bromo-2-fluorbenzoico (6 g, 27,3 mmol) en diclorometano (100 ml). Luego de 20 minutos, se obtuvo una solución clara. Se agregó hidróxido de amonio (28%, 30 ml) y la mezcla se agitó hasta el día siguiente. Se aisló la capa acuosa, se extrajo con diclorometano dos veces. Los extractos orgánicos combinados se lavaron con agua, dos veces con HCl

1N, agua, salmuera y se secaron ($MgSO_4$). El solvente se retiró al vacío, y el sólido se lavó con hexano para dar 4-bromo-2-flúor-benzamida **2BL** (5,56 g).

Paso 2: Preparación del compuesto 3BL



2BL **3BL**

Una mezcla del compuesto **2BL** (4,66 g, 21,48 mmol), Et_3OPF_6 (6,4 g, 25,77 mmol) en dicloroetano (86 ml) se calentó a reflujo durante 1 hora. El solvente se retiró a presión reducida. El producto bruto se enfrió a 0°C, se trituró con éter y se filtró para dar el producto deseado **3BL** (7,5 g).

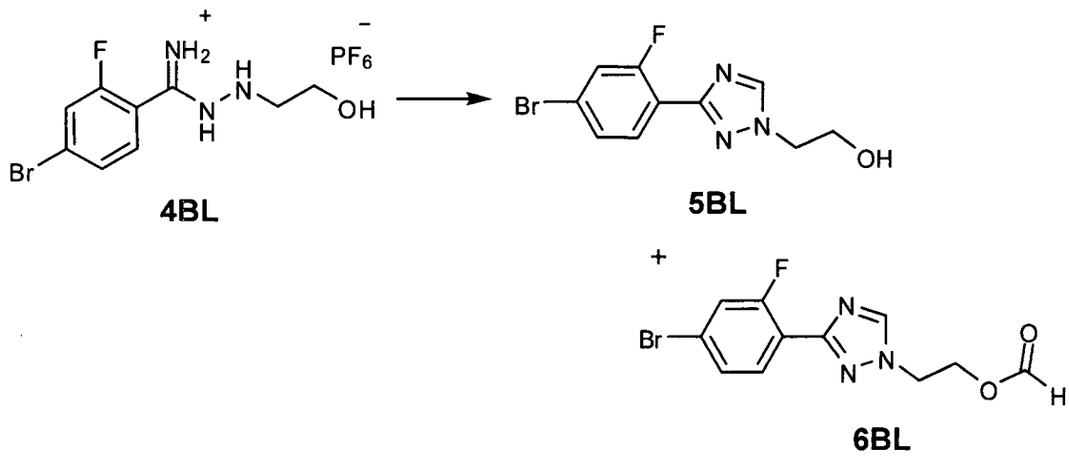
Paso 3: Preparación del compuesto 4BL



3BL **4BL**

El compuesto **3BL** (1,96 g) se disolvió en piridina (10 ml). Se agregó hidroxietilhidrazina (0,51 ml) con agitación y la mezcla resultante se dejó agitar hasta el día siguiente. La mezcla de reacción se concentró a presión reducida para dar un **4BL** bruto como una goma amarilla que se utilizó directamente en el próximo paso de síntesis sin purificación adicional.

Paso 4: Preparación del compuesto 5BL

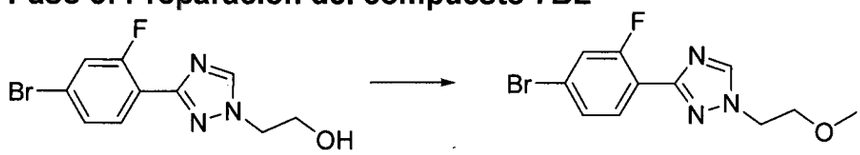


4BL **5BL** **6BL**

Una mezcla del **4BL** bruto del paso previo en ácido fórmico (30 ml) se calentó a reflujo hasta el día siguiente y se concentró a presión reducida. El residuo se trató con $NaHCO_3$ saturado, y se extrajo con EtOAc tres veces. Los orgánicos combinados se secaron sobre $MgSO_4$. Luego de la concentración, el residuo del compuesto se purificó sobre gel de sílice. La elución con EtOAc dio el compuesto **6BL** (1,1 g), luego **5BL** (183 mg).

El compuesto **6BL** puede convertirse fácilmente en **5BL** mediante hidrólisis básica acuosa.

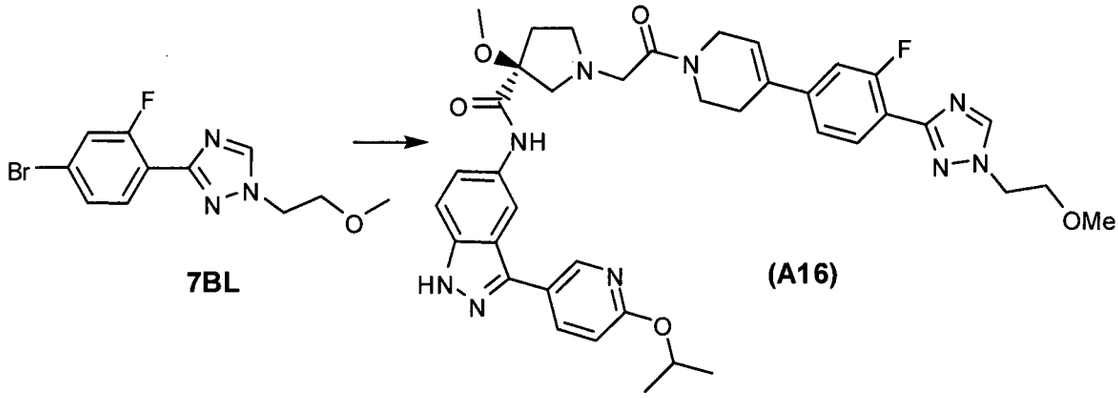
Paso 5: Preparación del compuesto 7BL



5BL **7BL**

Una solución de **5BL** (429 mg, 1.5 mmol) en DMF (3 ml) se agregó con agitación en un matraz que contiene NaH (60%, 66 mg, 1,65 mmol). Luego de agitación durante 30 minutos, se agregó MeI (0,103 ml, 1,65 mmol) lentamente. Luego de 30 minutos, la mezcla de reacción se diluyó con EtOAc, se lavó con agua tres veces, salmuera y se secó ($MgSO_4$). Luego de la concentración, el residuo se purificó sobre gel de sílice. La elución con MeOH/EtOAc 10% dio el compuesto **7BL** (88 mg).

Paso 6: Preparación del compuesto A16



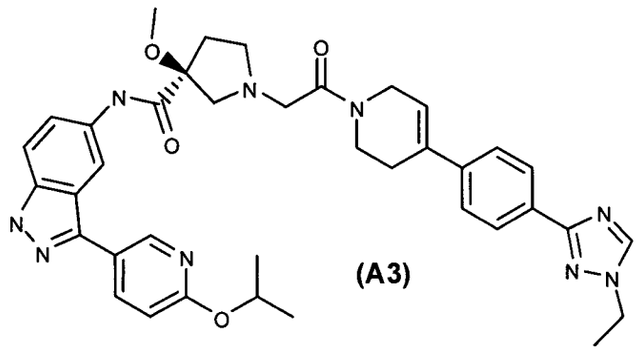
7BL **(A16)**

El compuesto **A16** se preparó a partir de **7BL** siguiendo procedimientos similares a aquellos de la Síntesis de (S)-1-(2-(4-(4-(1,5-dimetil-1*H*-1,2,4-triazol-3-il)fenil)-5,6-dihidropiridin-1(2*H*)-il)-2-oxoetil)-*N*-(3-(6-isopropoxipiridin-3-il)-1*H*-indazol-5-il)-3-metoxipirrolidin-3-carboxamida (**A14**, Ejemplo 3).

Espectro de masa: LCMS M+1= 738, tiempo de retención= 4 minutos. ^{1}H RMN de sal de HCl **A16** (400 MHz, DMSO-d_6):δ10,45 (br, 1H), 10,23 (d, J = 16,8 Hz, 1H), 8,7 (m, 1H), 8,6 (m, 1H), 8,46 (m, 1H), 8,18 (m, 1H), 8,0 (m, 1H), 7,74 (d, J = 8 Hz, 1H), 7,57 (d, J = 8 Hz, 1H), 7,42 (m, 1H), 6,93 (m, 1H), 6,43 (m, 1H), 5,3 (m, 1H), 4,6-4,5 (m, 2H), 4,41 (m, 2H), 4,21-4,01(m, 4H), 3,8-3,6 (br, 7H), 3,33 (m, 3H), 3,25 (m, 2H), 2,67-2,54 (m, 3H), 2,4(m, 1H), 1,33 (d, J = 6,4 Hz, 6H).

Ejemplo 5

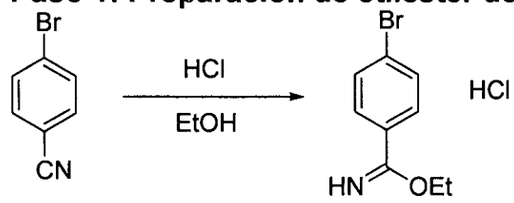
Síntesis de [3-(6-isopropoxi-piridin-3-il)-1H-indazol-5-il]-amida del ácido 1-(2-{4-[4-(1-etil-1H-[1,2,4]triazol-3-il)-fenil]-3,6-dihidro-2H-piridin-1-il}-2-oxo-etil)-3-Metoxi-pirrolidin-3-carboxílico



(A3)

Síntesis de clorhidrato de 4-[4-(1-etil-1*H*-[1,2,4]triazol-3-il)-fenil]-1,2,3,6-tetrahidro-piridina

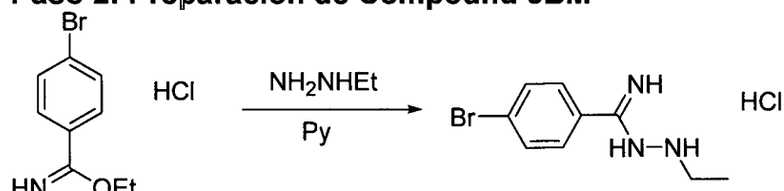
Paso 1: Preparación de etiléster del ácido 4-bromo-bencimídico



1BM **2BM**

Se suspendió 4-bromo-benzonitrilo (5 g) en EtOH absoluto (100 ml) y se enfrió a 0-5°C. Se burbujeó gas de HCl a través del mismo, en un principio en forma vigorosa durante varios minutos y luego lentamente durante 5 horas. La solución resultante se dejó agitar hasta el día siguiente. La mayor parte del solvente se retiró y el precipitado se filtró, se lavó dos veces con EtOH y se secó para dar el compuesto **2BM** (4,1 g) como un sólido blanco.

Paso 2: Preparación de Compound 3BM

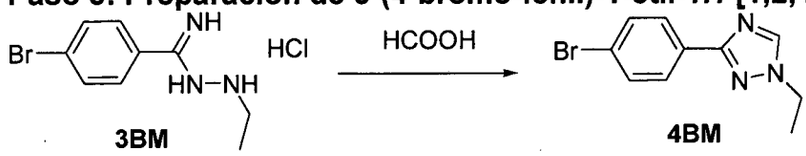


2BM **3BM**

El etiléster del ácido 4-bromo-bencimídico (1 g) se disolvió en piridina (20 ml). Se agregó etilhidrazina (550 mg) con agitación y la mezcla resultante se dejó agitar hasta el día siguiente. La mezcla de reacción se concentró bajo

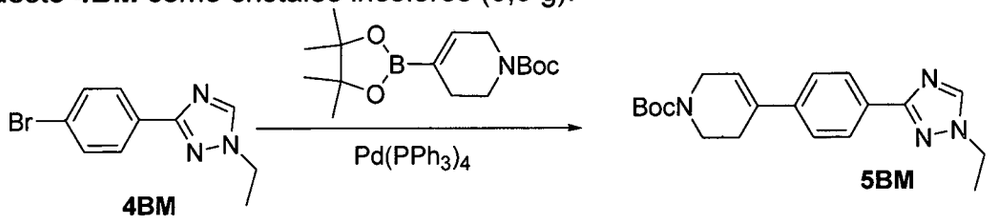
presión reducida, y se agregó éter, se filtró y lavó tres veces con éter y se secó para proveer el compuesto **3BM** (1 g).

Paso 3: Preparación de 3-(4-bromo-fenil)-1-etil-*1H*-[1,2,4]triazol



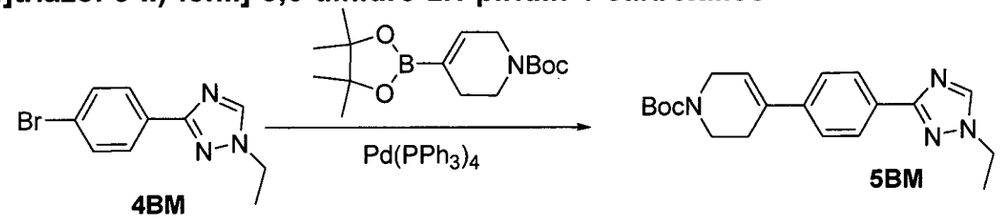
3BM **4BM**

Una mezcla del compuesto **3BM** (1 g) en ácido fórmico (10 ml) se calentó a reflujo hasta el día siguiente y se concentró. El residuo se trató con NaHCO3 saturado, y se extrajo tres veces con EtOAc. Los orgánicos combinados se secaron sobre $MgSO_4$. Luego de la concentración, se obtuvo el compuesto **4BM** como cristales incoloros (0,9 g).



4BM **5BM**

Paso 4: Preparación de ter-butil éster del ácido 4-[4-(1-etil-*1H*-[1,2,4]triazol-3-il)-fenil]-3,6-dihidro-*2H*-piridin-1-carboxílico

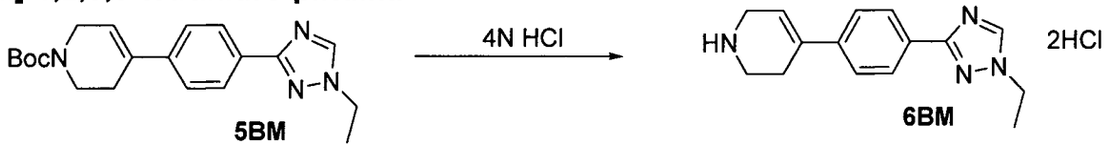


4BM **5BM**

Se cargaron en un matraz de alta presión, el compuesto **4BM** (400 mg), 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 (540 mg), $Pd(PPh_3)_4$ (180 mg), Na_2CO_3 2N (3 ml) y Dioxano/EtOH/agua (7:3:2, 10 ml). La mezcla se desgasificó brevemente con Ar durante ~0,5 minutos, se tapó y se sometió a microondas a 120°C durante 20 minutos. Luego del enfriamiento, la mezcla de reacción se diluyó con EtOAc y salmuera. La capa orgánica se aisló y secó ($MgSO_4$). Luego de la

concentración, el residuo se purificó sobre gel de sílice. La elución con MeOH/EtOAc (0-10%) dio el producto deseado **5BM** (310 mg).

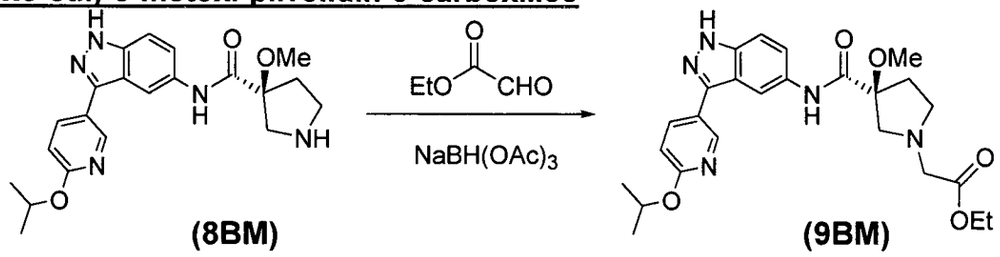
Paso 5: Preparación de clorhidrato de 4-[4-(1-etil-1*H*-[1,2,4]triazol-3-il)-fenil]-1,2,3,6-tetrahidro-piridina



5BM **6BM**

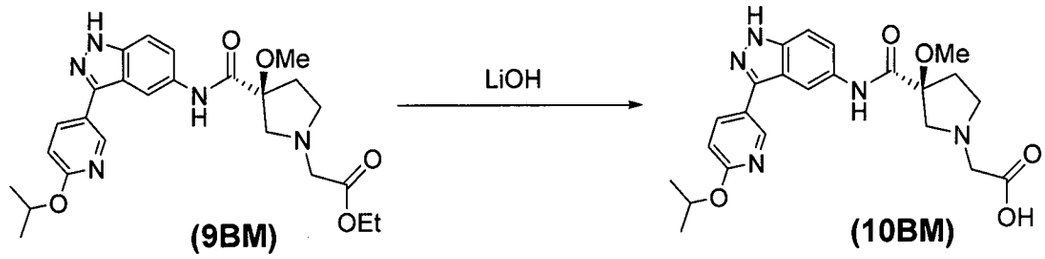
El grupo Boc puede retirarse tratando el compuesto **5BM** con HCl 4N en dioxano a ta durante dos horas. El retiro del solvente al vacío dio el compuesto **6BM**.

<u>Síntesis de [3-(6-isopropoxi-piridin-3-il)-1H-indazol-5-il]-amida del ácido 1-(2-{4-[4-(1-etil-1H-[1,2,4]triazol-3-il)-fenil]-3,6-dihidro-2H-piridin-1-il}-2-oxo-etil)-3-metoxi-pirrolidin-3-carboxílico</u>

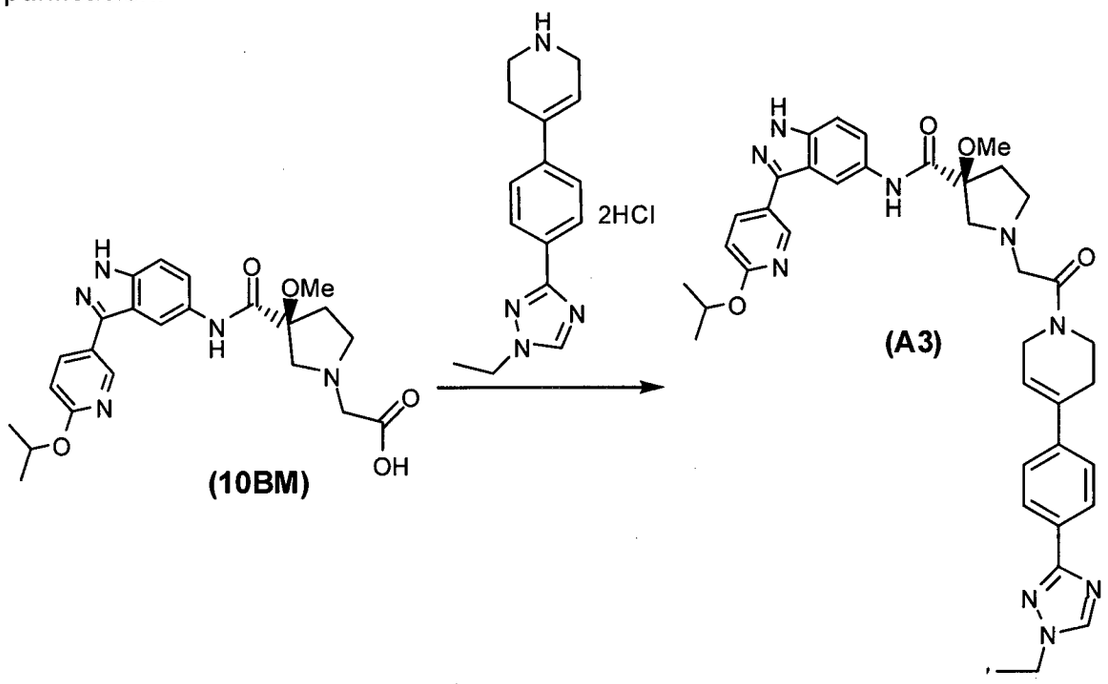


(8BM) **(9BM)**

El **8BM** bruto (5,9 mmol) se agitó en una mezcla de diclorometano/MeOH (1:1, 20 ml), etil éster del ácido oxoacético (10 ml, 50%) y NaBH(OAc)3 (10 ml) a ta hasta el día siguiente. La mezcla se desactivó con bicarbonato de sodio saturado acuoso. Los solventes se retiraron al vacío. Se diluyeron con agua y acetato de etilo. Se separaron las capas y la capa acuosa separada se extrajo con acetato de etilo (X3). Las capas orgánicas combinadas se secaron ($MgSO_4$), se filtraron y los solventes se retiraron al vacío. La purificación en columna dio **8BM** como un aceite amarillo.

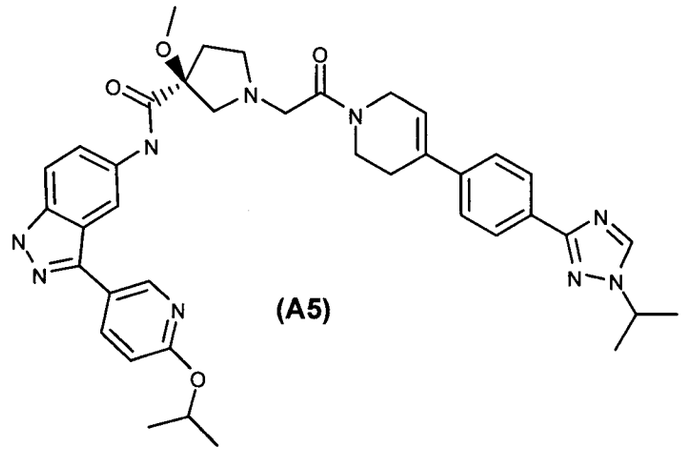


El **9BM** bruto (2,35 g) se agitó en una solución de LiOH (1M, 10 ml) y THF (10 ml) a ta hasta el día siguiente. La mezcla se ajustó a pH 3. Los solventes se retiraron al vacío. El producto se utilizó en el próximo paso sin purificación.



El **10BM** bruto (49 mg), 4-[4-(1-etil-1H-[1,2,4]triazol-3-il)-fenil]-1,2,3,6-tetrahidro-piridina (25,4 mg), HATU (45 mg) y trietil amina (0.1 ml) se agitaron en DMF (1 ml) a ta hasta el día siguiente. La mezcla se purificó mediante HPLC para dar **A3** como un aceite amarillo. Espectro de masa: LCMS M+1= 690, tiempo de retención = 3,47 minutos

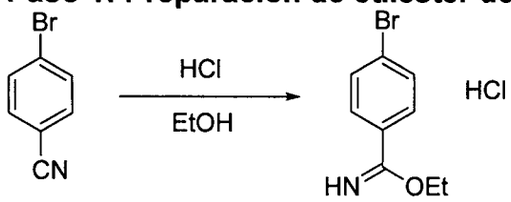
Ejemplo 6



(A5)

Síntesis de clorhidrato de 4-[4-(1-isopropil-1*H*-[1,2,4]triazol-3-il)-fenil]-1,2,3,6-tetrahidro-piridina

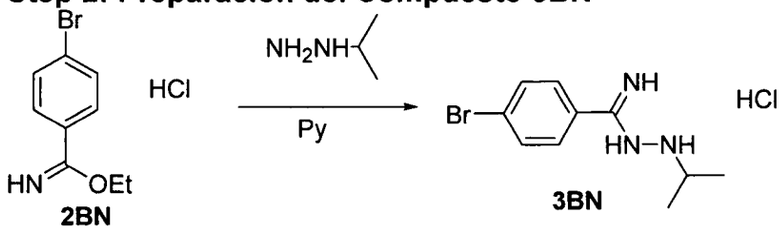
Paso 1: Preparación de etiléster del ácido 4-bromo-bencimídico



1BN **2BN**

Se suspendió 4-bromo-benzonitrilo (5 g) en EtOH absoluto (100 ml) y se enfrió a 0-5°C. Se burbujeó gas de HCl a través del mismo, en un principio en forma vigorosa durante varios minutos y luego lentamente durante 5 horas. La solución resultante se dejó agitar hasta el día siguiente. La mayor parte del solvente se retiró y el precipitado se filtró, se lavó dos veces con EtOH y se secó para dar el compuesto **2BN** (4,1 g) como un sólido blanco. (Nota: una síntesis a gran escala puede demorar más tiempo en obtener una reacción completa. Se prefiere observar la desaparación del material de inicio para determinar el fin de la reacción).

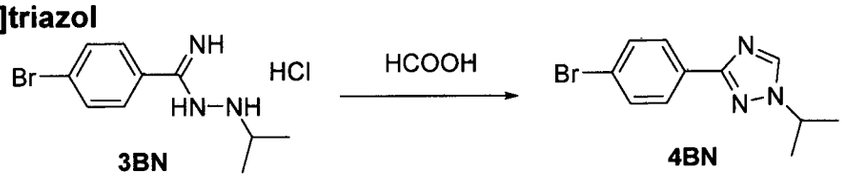
Step 2: Preparación del Compuesto 3BN



2BN **3BN**

El etiléster del ácido 4-bromo-bencimídico (1 g) se disolvió en piridina (20 ml). Se agregó isopropilhidrazina (550 mg) con agitación y la mezcla resultante se dejó agitar hasta el día siguiente. La mezcla de reacción se concentró bajo presión reducida, y se agregó éter, se filtró y lavó tres veces con éter y se secó para proveer el compuesto **3BN** (0.9 g).

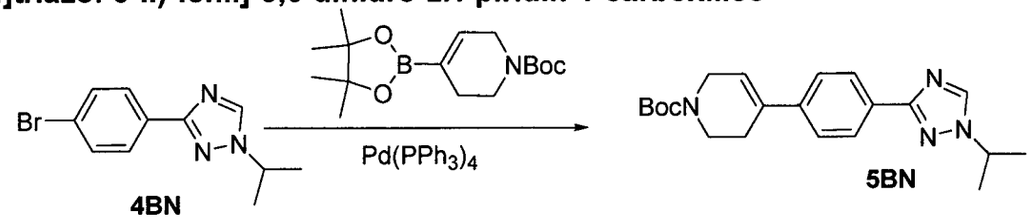
Paso 3: Preparación de 3-(4-bromo-fenil)-1-isopropil-*1H*-[1,2,4]triazol



3BN **4BN**

Una mezcla del compuesto **3BN** (1 g) en ácido fórmico (10 ml) se calentó a reflujo hasta el día siguiente y se concentró. El residuo se trató con NaHCO3 saturado, y se extrajo tres veces con EtOAc. Los orgánicos combinados se secaron sobre $MgSO_4$. Luego de la concentración, se obtuvo el compuesto **4BN** como cristales incoloros (0.9 g).

Paso 4: Preparación de ter-butil éster del ácido 4-[4-(1-isopropil-*1H*-[1,2,4]triazol-3-il)-fenil]-3,6-dihidro-*2H*-piridin-1-carboxílico

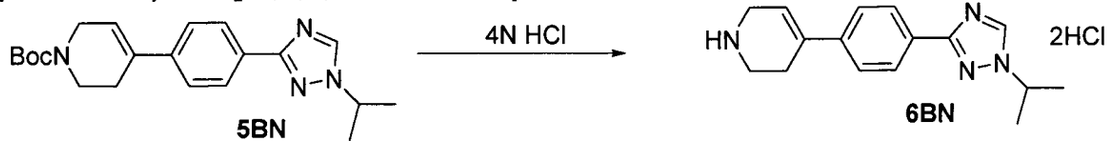


4BN **5BN**

Se cargó a un matraz de presión, el compuesto **4BN** (500 mg), 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 (583 mg), $Pd(PPh_3)_4$ (112 mg), Na_2CO_3 2N (3 ml) y Dioxano (10 ml). La mezcla se desgasificó brevemente con Ar durante ~0,5 minutos, se tapó y agitó a 100°C hasta el día siguiente. Luego del enfriamiento, la mezcla de reacción se diluyó con EtOAc y salmuera. La capa orgánica se aisló y secó ($MgSO_4$). Luego de la concentración, el residuo se purificó sobre

gel de sílice. La elución con MeOH/EtOAc (0-10%) dio el producto deseado **5BN** (410 mg).

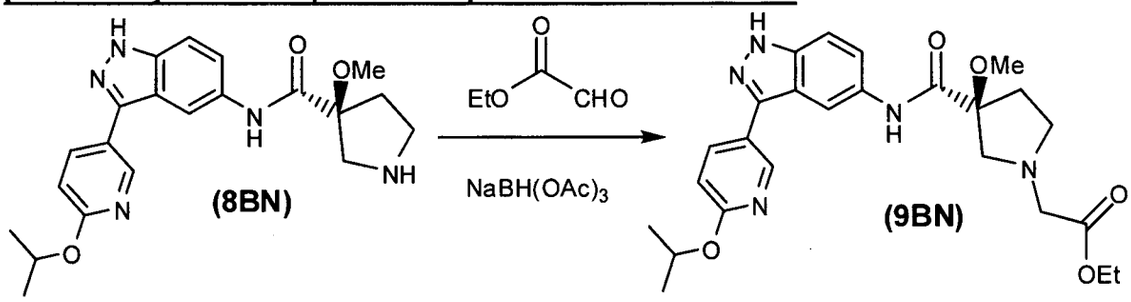
Paso 5: Preparación de clorhidrato de 4-[4-(1-isopropil-1*H*-[1,2,4]triazol-3-il)-fenil]-1,2,3,6-tetrahidro-piridina



5BN **6BN**

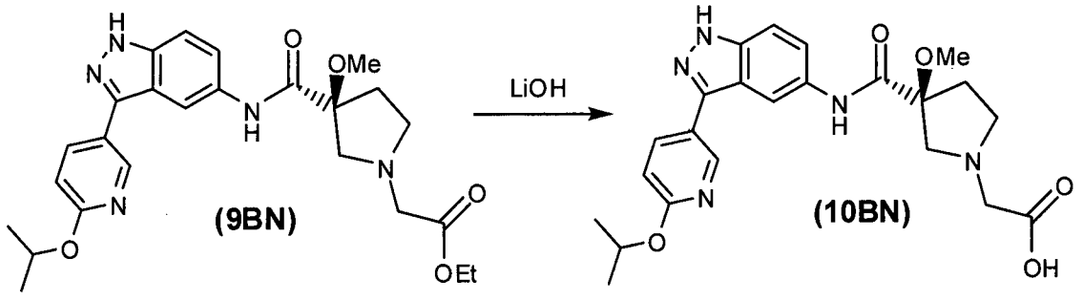
El grupo Boc puede retirarse tratando el compuesto **5BN** con HCl 4N en dioxano a ta durante dos horas. El retiro del solvente al vacío dio el compuesto **6BN**.

Síntesis de [3-(6-isopropoxi-piridin-3-il)-1H-indazol-5-il]-amida del ácido 1-(2-{4-[4-(1-isopropil-1H-[1,2,4]triazol-3-il)-fenil]-3,6-dihidro-2H-piridin-1-il}-2-oxo-etil)-3-metoxi-pirrolidin-3-carboxílico

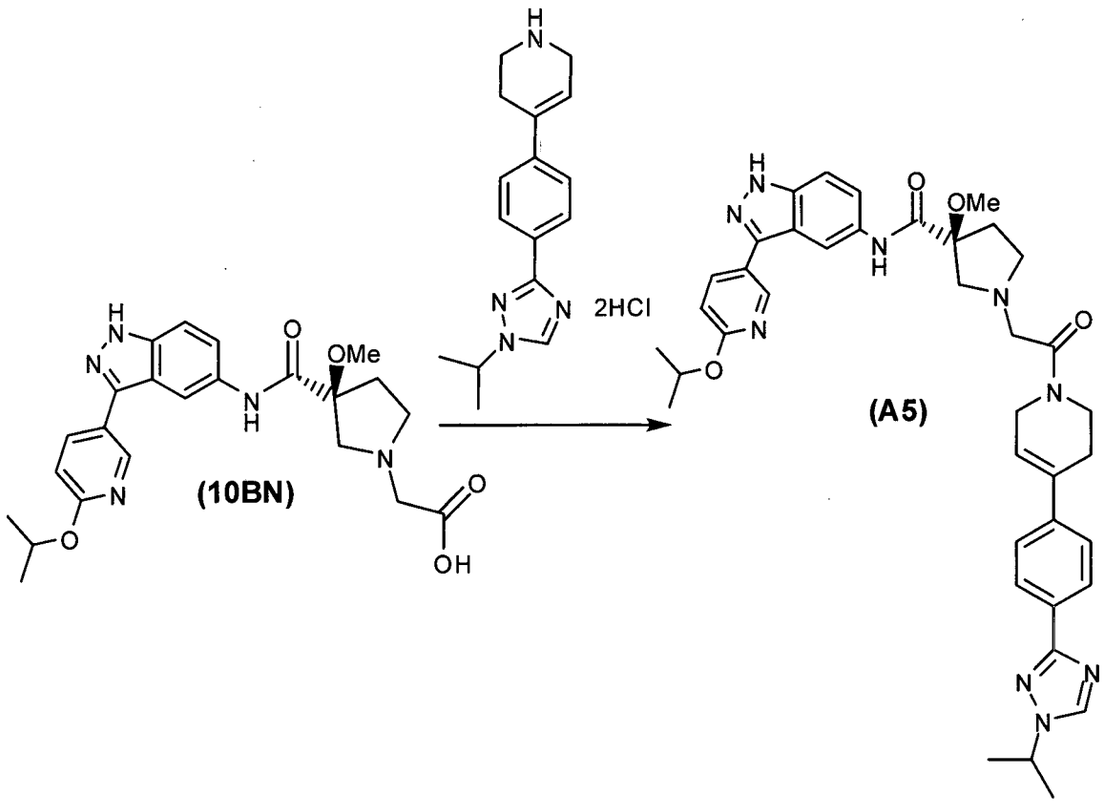


(8BN) **(9BN)**

El **8BN** bruto (5,9 mmol) se agitó en una mezcla de diclorometano/MeOH (1:1, 20 ml), etiléster del ácido oxoacético (10 ml, 50%) y NaBH(OAc)3 (10 ml) a ta hasta el día siguiente. La mezcla se desactivó con saturado acuoso bicarbonato de sodio. Los solventes se retiraron al vacío. Se diluyeron con agua y acetato de etilo. Se separaron las capas y la capa acuosa separada se extrajo con acetato de etilo (X3). Las capas orgánicas combinadas se secaron ($MgSO_4$), se filtraron y los solventes se retiraron al vacío. La purificación en columna dio **9BN** como un aceite amarillo con un rendimiento de 65%.



El **9 BN** bruto (2,35 g) se agitó en una solución de LiOH (1M, 10 ml) y THF (10 ml) a ta hasta el día siguiente. La mezcla se ajustó a pH 3. Los solventes se retiraron al vacío. El producto se utilizó en el próximo paso sin purificación, rendimiento cuantitativo.

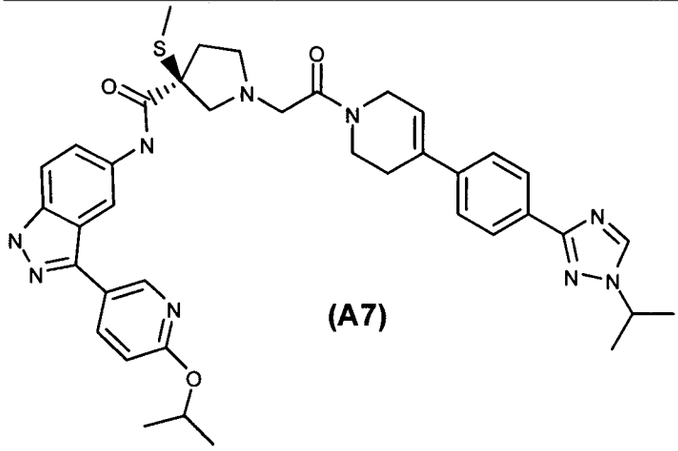


El **10BN** bruto (60 mg), 4-[4-(1-isopropil-1H-[1,2,4]triazol-3-il)-fenil]-1,2,3,6-tetrahidro-piridina (35 mg), HATU (52 mg) y trietilamina (0,1 ml) se agitaron en DMF (1 ml) a ta hasta el día siguiente. La mezcla se purificó

mediante HPLC para dio **A5** como un aceite amarillo. Espectro de masa: LCMS M+1= 704, tiempo de retención = 3,56 minutos

Ejemplo 7

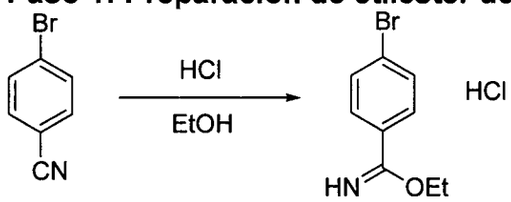
Síntesis de [3-(6-isopropoxi-piridin-3-il)-1H-indazol-5-il]-amida del ácido 1-(2-{4-[4-(1-Isopropil-1H-[1,2,4]triazol-3-il)-fenil]-3,6-dihidro-2H-piridin-1-il}-2-oxo-etil)-3-Metoxi-pirrolidin-3-carboxílico



(A7)

Síntesis de clorhidrato de 4-[4-(1-isopropil-1*H*-[1,2,4]triazol-3-il)-fenil]-1,2,3,6-tetrahidro-piridina

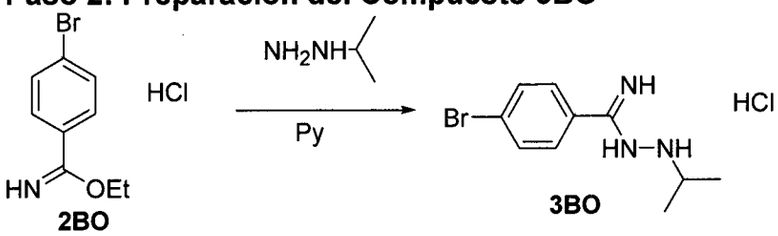
Paso 1: Preparación de etiléster del ácido 4-bromo-bencimídico



1BO **2BO**

Se suspendió 4-bromo-benzonitrilo (5 g) en EtOH absoluto (100 ml) y se enfrió a 0-5°C. Se burbujeó gas de HCl a través del mismo, en un principio en forma vigorosa durante varios minutos y luego lentamente durante 5 horas. La solución resultante se dejó agitar hasta el día siguiente. La mayor parte del solvente se retiró y el precipitado se filtró, se lavó dos veces con EtOH y se secó para dar el compuesto **2BO** (4,1 g) como un sólido blanco.

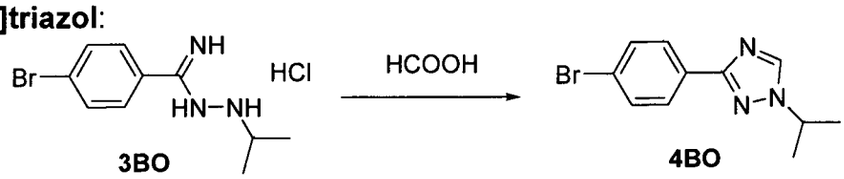
Paso 2: Preparación del Compuesto 3BO



2BO **3BO**

El etiléster del ácido 4-bromo-bencimídico (1 g) se disolvió en piridina (20 ml). Se agregó isopropilhidrazina (550 mg) con agitación y la mezcla resultante se dejó agitar hasta el día siguiente. La mezcla de reacción se concentró bajo presión reducida, y se agregó éter, se filtró y lavó tres veces con éter y se secó para proveer el compuesto **3BO** (0,9 g).

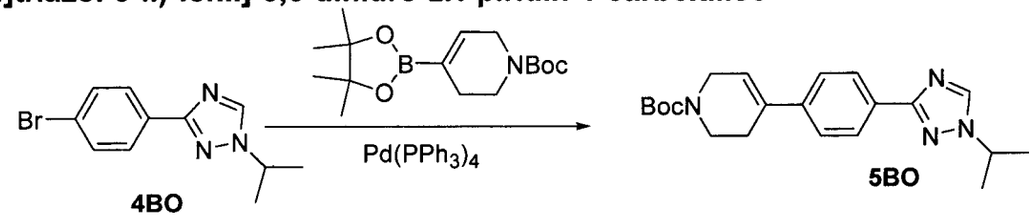
Paso 3: Preparación de 3-(4-bromo-phenil)-1-isopropil-*1H*-[1,2,4]triazol:



3BO **4BO**

Una mezcla del compuesto **3BO** (1 g) en ácido fórmico (10 ml) se calentó a reflujo hasta el día siguiente y se concentró. El residuo se trató con NaHCO3 saturado, y se extrajo tres veces con EtOAc. Los orgánicos combinados se secaron sobre $MgSO_4$. Luego de la concentración, se obtuvo el compuesto **4BO** como cristales incoloros (0,9 g). (Nota: se ha descubierto que la reacción puede llevarse a cabo en sólo dos horas. En síntesis a gran escala, utilizar NaOH 10% para reemplazar NaHCO3).

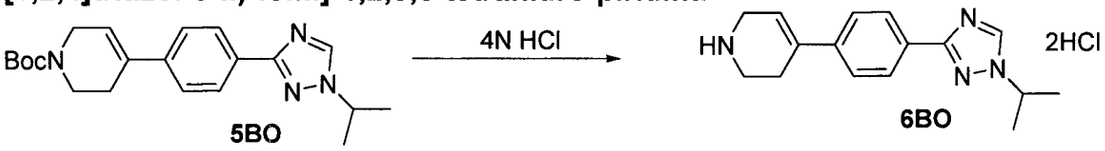
Paso 4: Preparación de ter-butil éster del ácido 4-[4-(1-isopropil-*1H*-[1,2,4]triazol-3-il)-fenil]-3,6-dihidro-*2H*-piridin-1-carboxílico



4BO **5BO**

Se cargaron en un matraz de alta presión, el compuesto **4BO** (500 mg), 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 (583 mg), $Pd(PPh_3)_4$ (112 mg), Na_2CO_3 2N (3 ml) y Dioxano (10 ml). La mezcla se desgasificó brevemente con Ar durante ~0,5 minutos, se tapó y agitó a 100°C hasta el día siguiente. Luego del enfriamiento, la mezcla de reacción se diluyó con EtOAc y salmuera. La capa orgánica se aisló y secó ($MgSO_4$). Luego de la concentración, el residuo se purificó sobre gel de sílice. La elución con MeOH/EtOAc (0-10%) dio el producto deseado **5BO** (410 mg).

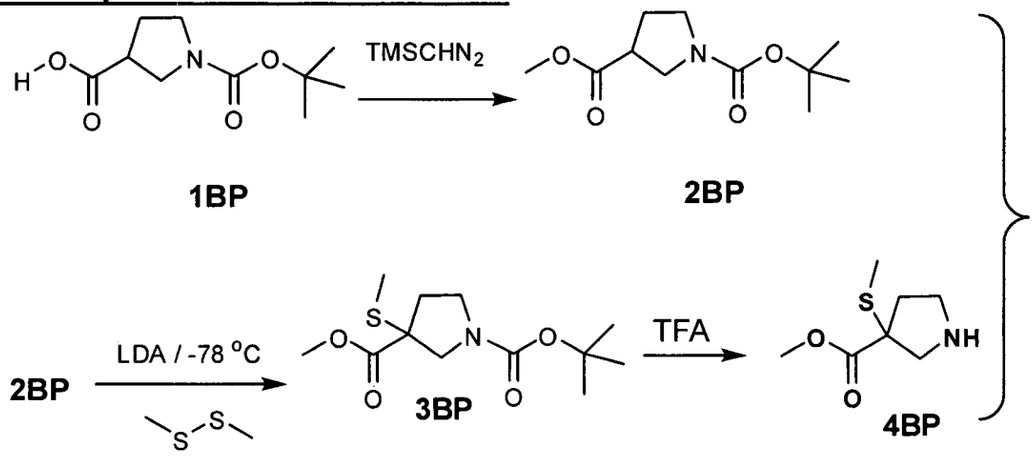
Paso 5: Preparación de clorhidrato de 4-[4-(1-isopropil-1*H*-[1,2,4]triazol-3-il)-fenil]-1,2,3,6-tetrahidro-piridina



5BO **6BO**

El grupo Boc puede retirarse tratando el compuesto **5BO** con HCl 4N en dioxano a ta durante dos horas. El retiro del solvente al vacío dio el compuesto **6BO**.

<u>Preparación y resolución quiral de metiléster del ácido 3-metilsulfanil-pirrolidin-3-carboxílico 4BP</u>



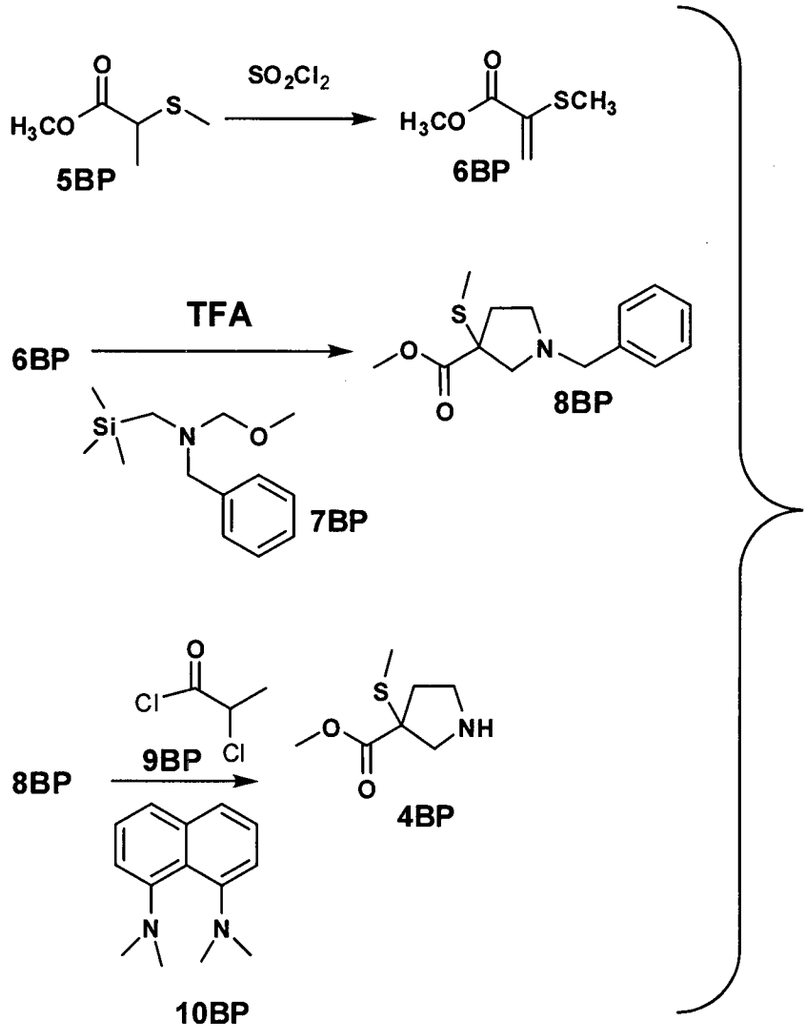
1BP **2BP**

1-ter-butil éster del ácido pirrolidin-1,3-dicarboxílico **1BP** (4,3 gm, 20 mmol) se disolvió en 28 ml de tolueno y 3,5 ml de metanol. Se agregó gota a gota una solución 2N de trimetilsilildiazometano en hexanos (13 ml, 26 mmol) a 0°C y la mezcla de reacción se agitó durante 10 minutos a temperatura ambiente. La mezcla se evaporó para obtener 4,3 gm de aceite.

Al aceite **2BP** (0,5 gm, 2,1 mmol) disuelto en tetrahidrofurano (15 ml) se agregó gota a gota 1,2 ml de una solución 2N de diisopropilamida de litio en hexanos y la mezcla de reacción se agitó durante 1 hora a -78°C. Se agregó dimetildisulfuro (0,48 ml, 5,4 mmol) lentamente y se dejó calendar gradualmente a temperatura ambiente. La mezcla de reacción se agitó durante 18 horas. Se agregó una solución saturada de cloruro de amonio (25 ml) y la mezcla de reacción se agitó durante 5 minutos. La mezcla de reacción se extrajo con acetato de etilo tres veces (3x25 ml), se secó sobre sulfato de magnesio, se filtró y evaporó para dar 0,386 g del producto del título **3BP** luego de cromatografía en columna.

Se disolvió 1-ter-butil éster 3-metil éster del ácido 3-metilsulfanil-pirrolidin-1,3-dicarboxílico (2,15 gm, 8,8 mmol) en 20 ml de ácido trifluoracético/diclorometano 50% y se agitó durante 2 horas. La mezcla de reacción se evaporó para dar 3,35 g de metiléster del ácido 3-metilsulfanil-pirrolidin-3-carboxílico **4BP** como un sólido gomoso.

<u>Alternativamente, 4BP puede prepararse como sigue:</u>



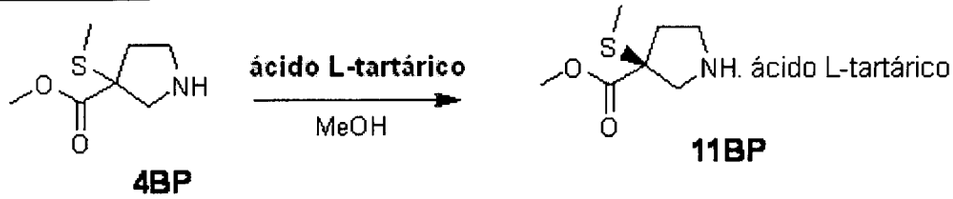
A metiléster del ácido 2-metilsulfanil-propiónico **5BP** (25 g, 0,1 mol) disuelto en cloroformo se agregó cloruro de sulfurilo (15,1 ml, 0,1 mol) lentamente a 0°C. La mezcla de reacción se agitó a 0°C durante 30 minutos y luego se calentó a reflujo a 65°C durante 30 minutos. Luego, la mezcla de reacción se concentró a sequedad para dar 23,75 g de metiléster del ácido 2-metilsulfanil-acrílico **6BP** como un líquido.

A una solución agitada de metiléster del ácido 2-etoxiacrilato 2-metilsulfanil-acrílico **6BP** (136 g, 1,03 mol) y bencil-metoximetil-trimetilsilanilmetil-amina **7BP** (290 g, 1,22 mol) en diclorometano (2,7 ml), se agregó a 0°C una solución de ácido trifluroacético (26 ml, 0,3 mol). La solución resultante se calentó a temperatura ambiente y se agitó durante una nocha. El

producto se purificó mediante cromatografía en columna sobre gel de sílice eluyendo con una solución de acetato de etilo en hexano (1:4) para dar metiléster del ácido 1-bencil-3-metilsulfanil-pirrolidin-3-carboxílico **8BP** (131 g, 47%).

A metiléster del ácido 1-bencil-3-metilsulfanil-pirrolidin-3-carboxílico **8BP** (131 g, 493,7 mmol) disuelto en dicloroetano (2,6 l) a 0°C se agregó N,N,N',N'-tetrametil-naftalen-1,8-diamina **9BP** (31,8 g, 0,144 mmol) y luego cloruro de 2-cloro-propionilo **10BP** (64 ml, 593,1 mmol) secuencialmente. La mezcla de reacción se agitó durante una noche a temperatura ambiente y luego se concentró a sequedad. El residuo se disolvió en 2,8 l de metanol y se calentó a reflujo a 65°C durante 3,5 horas. Luego, la mezcla de reacción se concentró a sequedad y el residuo se purificó mediante cromatografía en columna sobre gel de sílice eluyendo con una solución de metanol en diclorometano (1:9) para dar metiléster del ácido 3-metilsulfanil-pirrolidin-3-carboxílico **4BP** (75 g, 86%).

Resolución quiral de metiléster del ácido 3-metilsulfanil-pirrolidin-3-carboxílico 4BP



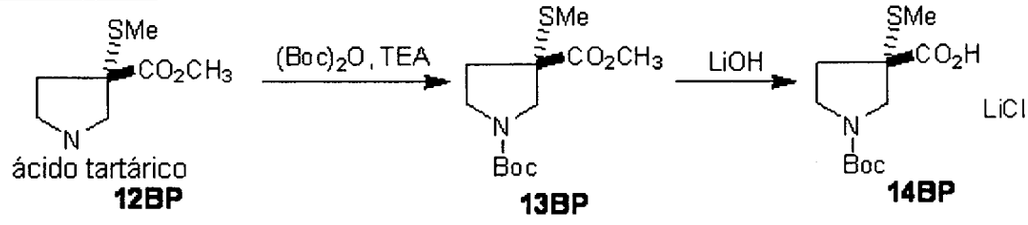
4BP **11BP**

Se colocaron metiléster del ácido 3-metilsulfanil-pirrolidin-3-carboxílico **4BP** (42,9 g, 244,8 mmol) y ácido L-tartárico (36,7 g, 244,8 mmol) en un matraz de fondo redondo de 1L y se disolvieron con 250 ml de metanol. Luego, el matraz se adjuntó a un rotavapor a 75°C. Se dejó rotar a la mezcla cuidadosamente a esta temperatura durante aproximadamente 20 minutos para asegurar una disolución completa. Luego de la formación de una solución clara, se agregaron aproximadamente 10 mg de cristales auténticos de metiléster del

ácido 3-metilsulfanil-pirrolidin-3-carboxílico **11BP** (para sembrar y auxilar a la formación de cristales) al que se permitió asentarse cuidadosamente para la formación de cristales. Luego de 3 días, se filtró 19,4 g de cristales que luego se lavaron con metanol frío (20 -30 ml) para dar 18,2 g de metiléster del ácido 3-metilsulfanil-pirrolidin-3-carboxílico cristalino **11BP**.

La pureza quiral de los cristales del metiléster del ácido 3-metilsulfanil-pirrolidin-3-carboxílico **11BP** se determinó por derivatización con cloroformato de 4-nitrobencilo y sujeción a HPLC analítica (columna AD Chiracel) bajo las condiciones de un sistema solvente de isopropanol/hexane 20% con un caudal de flujo de 1ml/min. La pureza era de >99,9% con un tiempo de retención de 16,58 minutos.

Preparación de 1-ter-butil éster del ácido 3-metilsulfanil-pirrolidin-1,3-dicarboxílico

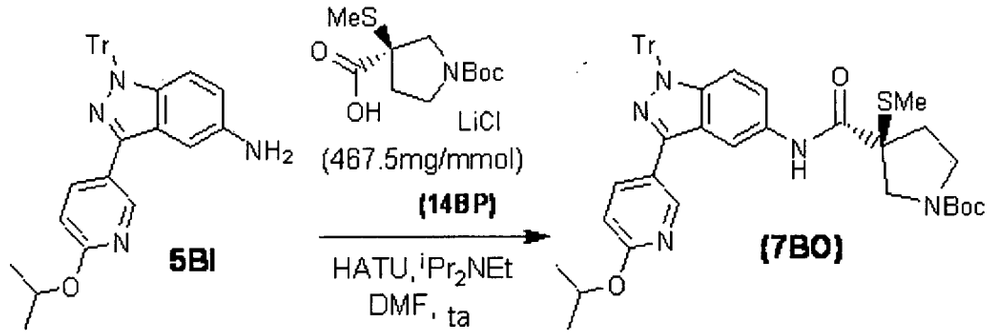


A una solución fría (0°C) de **12BP** (28 g, 90,52 mmol) en CH_2Cl_2 seco (250 ml) se agregó trietilamina (31,5 ml, 226,32 mmol, 2,5 equiv.) seguido por $(Boc)_2O$ (25,7 g, 117,68 mmol, 1,3 equiv.). La mezcla resultante se agitó de 0°C a ta durante toda la noche, luego se diluyó con CH_2Cl_2, que se lavó con una solución saturada acuosa de NaHCO3 y salmuera, se secó ($MgSO_4$) y concentró. La cromatografía sobre gel de sílice (hexanos/acetato de etilo, 4:1) dio **13BP** (23,5 mg, 90,52 mmol, 100%) como un aceite incoloro.

A una solución agitada de **13BP** (23,5 mg, 90,52 mmol) en THF/MeOH (175 ml/175 ml) se agregó 135 ml de LiOH (1M en H_2O, 135 mmol, 1,5 equiv.). La mezcla de reacción se agitó a ta hasta el día siguiente, a la que se agregó

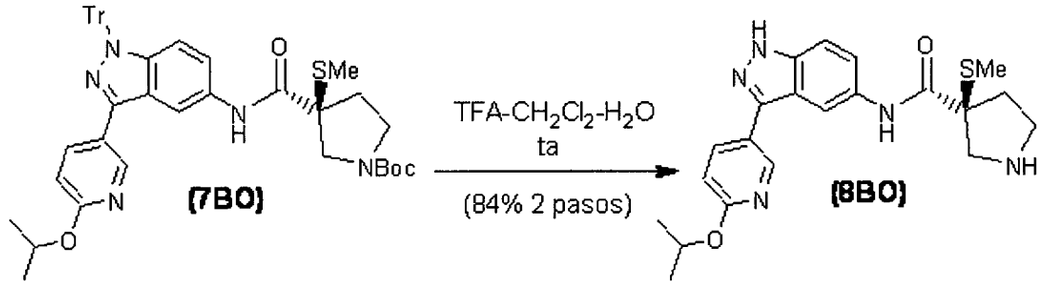
135 ml de HCl 1N. La mezcla resultante se agitó durante 15 minutos adicionales y concentró para dar **14BP**.

Paso 1:



Se disolvieron aminoindazol **5BI** (39 g, 0,076 mol) y ácido pirrolidincarboxílico **14BP** (32 g, 0,069 mol) en DMF (300 ml) a ta. Se agregó HATU (29 g, 0,076 mol) seguido por $^{i}Pr_2NEt$ (14,5ml, 0,083 mol) . La mezcla se agitó a ta hasta el día siguiente y se diluyó con acetato de etilo y agua. Se separaron las capas. La capa orgánica separada se lavó con agua (X2), se secó ($MgSO_4$) y filtró. La concentración al vacío seguida por la purificación en columna [hexanos – acetato de etilo = 4:1 (v/v)] dio **7BO** bruto como una espuma blancuzca.

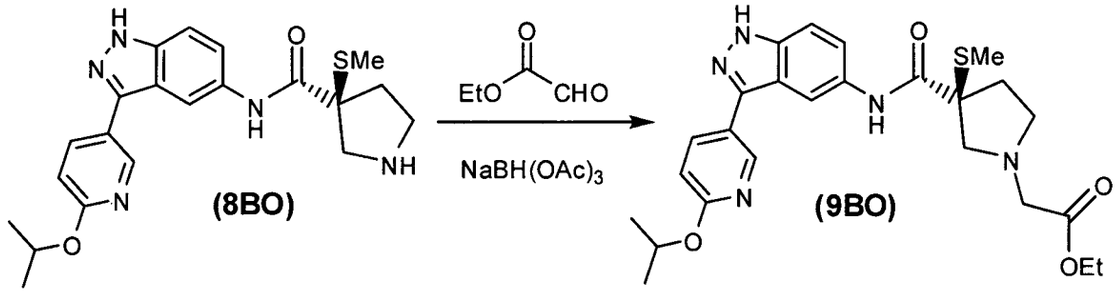
Paso 2:



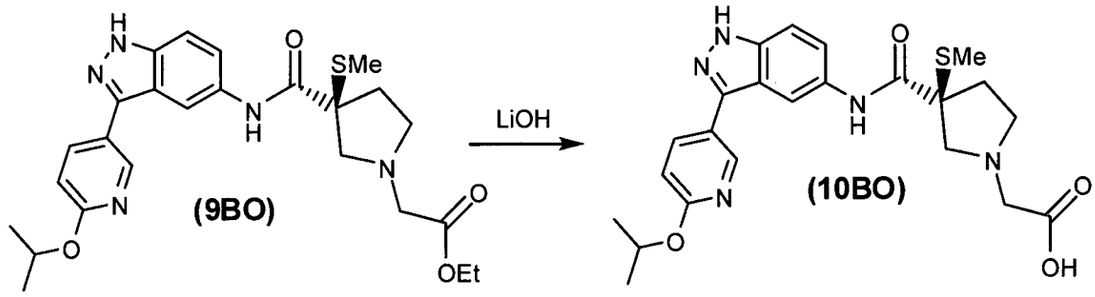
El **7BO** bruto se agitó en una mezcla de diclorometHane (300ml), ácido trifluoracético (100ml) y agua (50ml) a ta hasta el día siguiente. La mezcla se enfrió a 0°C y se desactivó cuidadosamente con bicarbonato de sodio saturado acuoso. Los solventes se retiraron al vacío. Se diluyeron con agua y acetato de

etilo. Se separaron las capas y la capa acuosa separada se extrajo con acetato de etilo (X3). Las capas orgánicas combinadas se secaron ($MgSO_4$), se filtraron y los solventes se retiraron al vacío. La purificación en columna [MeOH 5 a 10% (amoníaco 7N) en diclorometano] dio pirrolidina **8BO** (23g, 84%) como un sólido blancuzco.

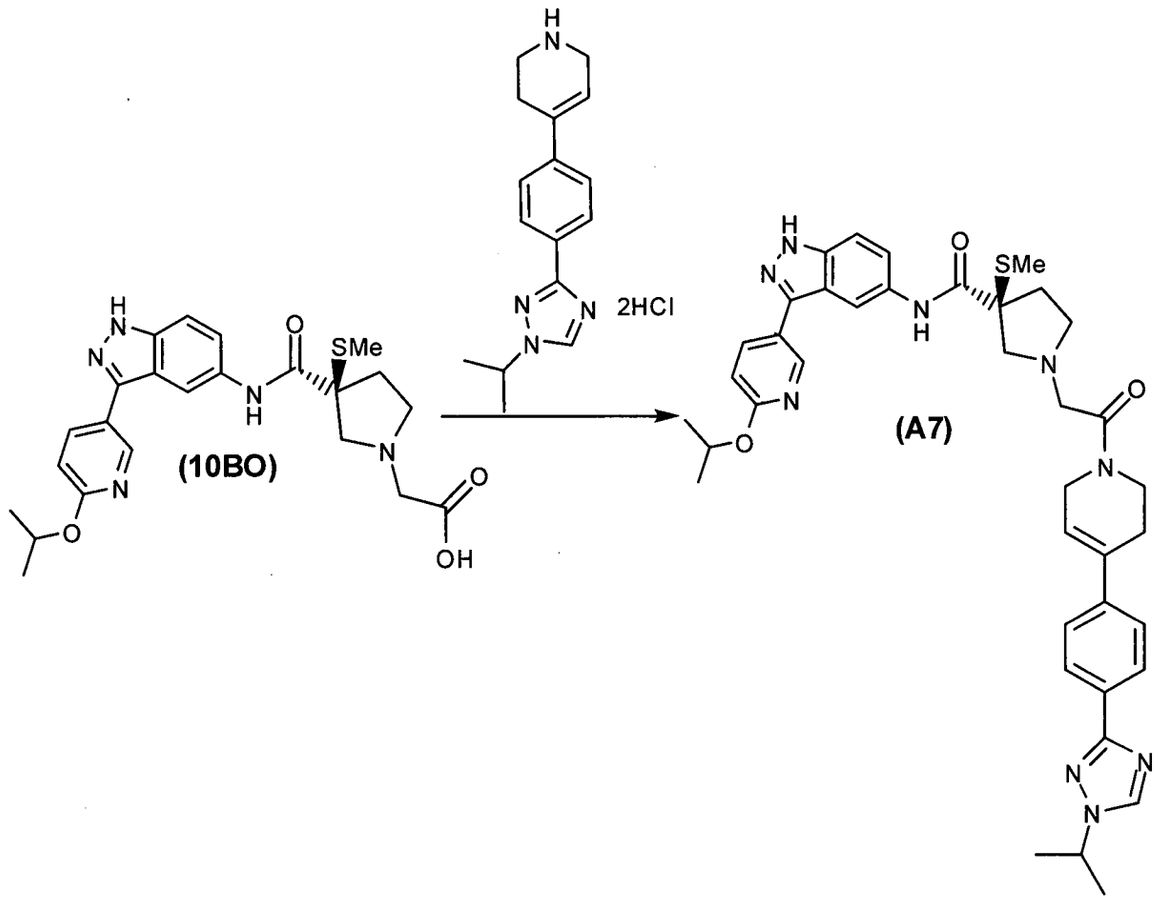
Síntesis de [3-(6-isopropoxi-piridin-3-il)-1H-indazol-5-il]-amida del ácido 1-(2-{4-[4-(1-isopropil-1H-[1,2,4]triazol-3-il)-fenil]-3,6-dihidro-2H-piridin-1-il}-2-oxo-etil)-3-metilsulfanil-pirrolidin-3-carboxílico



El **8BO** bruto (5,9 mmol) se agitó en una mezcla de diclorometano/MeOH (1:1, 20 ml), etiléster del ácido oxoacético (10 ml, 50%) y NaBH(OAc)3 (10 ml) a ta hasta el día siguiente. La mezcla se desactivó con saturado acuoso bicarbonato de sodio. Los solventes se retiraron al vacío. Se diluyeron con agua y acetato de etilo. Se separaron las capas y la capa acuosa separada se extrajo con acetato de etilo (X3). Las capas orgánicas combinadas se secaron ($MgSO_4$), se filtraron y los solventes se retiraron al vacío. La purificación en columna dio **9BO** como un aceite amarillo.



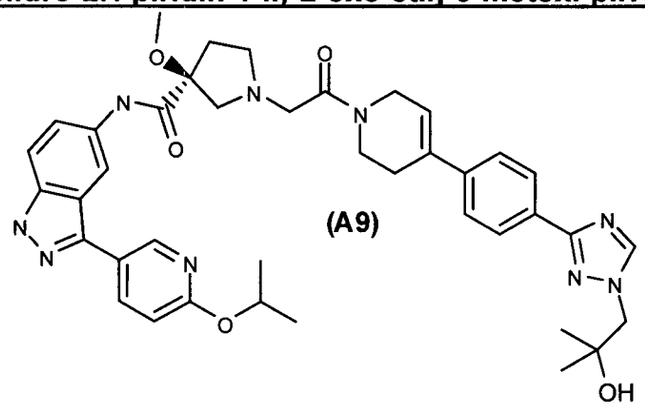
El **9BO** bruto (2,35 g) se agitó en una solución de LiOH (1M, 10 ml) y THF (10 ml) a ta hasta el día siguiente. La mezcla se ajustó a pH 3. Los solventes se retiraron al vacío. El producto se utilizó en el próximo paso sin purificación.



El **10BO** bruto (60 mg), 4-[4-(1-Isopropil-1H-[1,2,4]triazol-3-il)-fenil]-1,2,3,6-tetrahidro-piridina (35 mg), HATU (52 mg) y trietilamina (0,1 ml) se agitaron en DMF (1 ml) a ta hasta el día siguiente. La mezcla se purificó mediante HPLC para dar **11BO** como un aceite amarillo. Espectro de masa: LCMS M+1= 720, tiempo de retención = 3,68 minutos.

Example 8

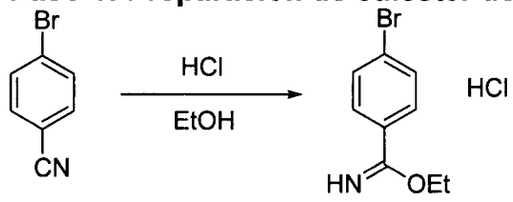
Preparación de [3-(6-isopropoxi-piridin-3-il)-1H-indazol-5-il]-amida del ácido 1-[2-(4-{4-[1-(2-hidroxi-2-metil-propil)-1H-[1,2,4]triazol-3-il]-fenil}-3,6-dihidro-2H-piridin-1-il)-2-oxo-etil]-3-metoxi-pirrolidin-3-carboxílico



(A9)

Síntesis de 2-cloro-1-{4-[4-(1-ethyl-1*H*-[1,2,4]triazol-3-il)-fenil]-3,6-dihidro-2*H*-piridin-1-il}-etanona

Paso 1: Preparación de etiléster del ácido 4-bromo-bencimídico

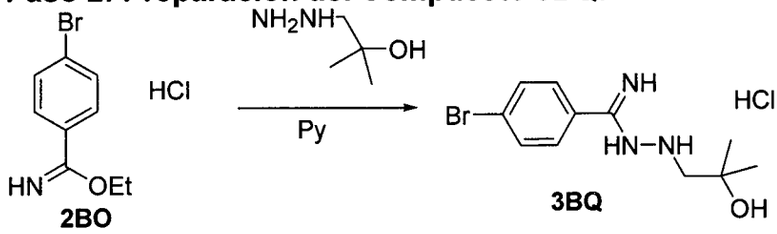


1BO **2BO**

Se suspendió 4-bromo-benzonitrilo (5 g) en EtOH absoluto (100 ml) y se enfrió a 0-5ºC. Se burbujeó gas de HCl a través del mismo, en un principio en forma vigorosa durante varios minutos y luego lentamente durante 5 horas. La solución resultante se dejó agitar hasta el día siguiente. La mayor parte del

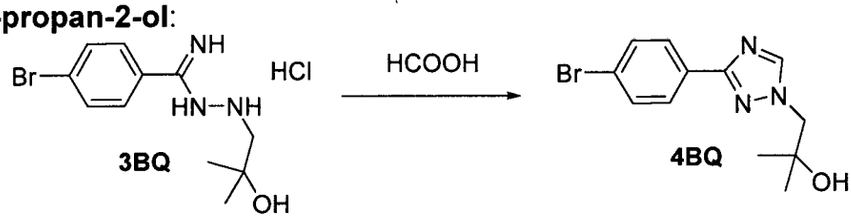
solvente se retiró y el precipitado se filtró, se lavó dos veces con EtOH y se secó para dar el compuesto **2BO** (4,1 g) como un sólido blanco.

Paso 2: Preparación del Compuesto 3BQ:



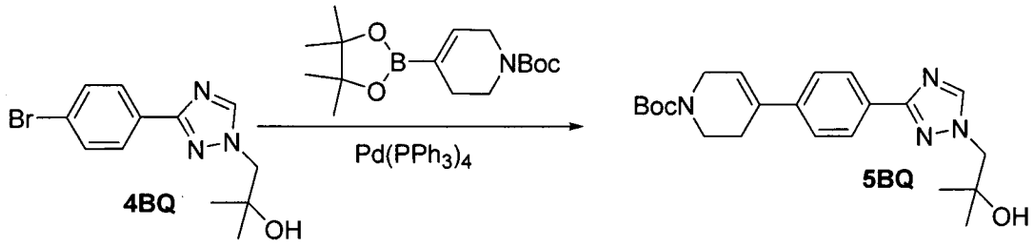
El etiléster del ácido 4-bromo-bencimídico (1,68 g) se disolvió en piridina (10 ml). Se agregó 1-hidrazino-2-metil-propan-2-ol (1 g) con agitación y la mezcla resultante se dejó agitar hasta el día siguiente. La mezcla de reacción se concentró a presión reducida, y se agregó éter, se filtró, se lavó con éter tres veces y se secó para dar el compuesto **3BQ** (1 g).

Paso 3: Preparación de 1-[3-(4-Bromo-fenil)-[1,2,4]triazol-1-il]-2-metil-propan-2-ol:



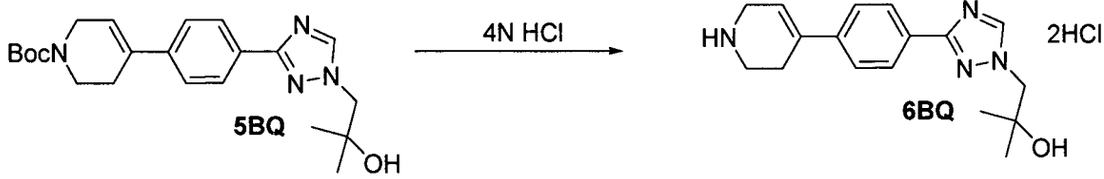
Una mezcla del compuesto **3BQ** (1 g) en ácido fórmico (10 ml) se calentó a reflujo hasta el día siguiente y se concentró. El residuo se trató con NaHCO3 saturado, y se extrajo tres veces con EtOAc. Los orgánicos combinados se secaron sobre $MgSO_4$. Luego de la concentración, se obtuvo el compuesto **4BQ** como cristales incoloros (0,9 g).

Paso 4: Preparación de ter-butil éster del ácido 4-{4-[1-(2-hidroxi-2-metil-propil)-1H-[1,2,4]triazol-3-il]-fenil}-3,6-dihidro-2H-piridin-1-carboxílico



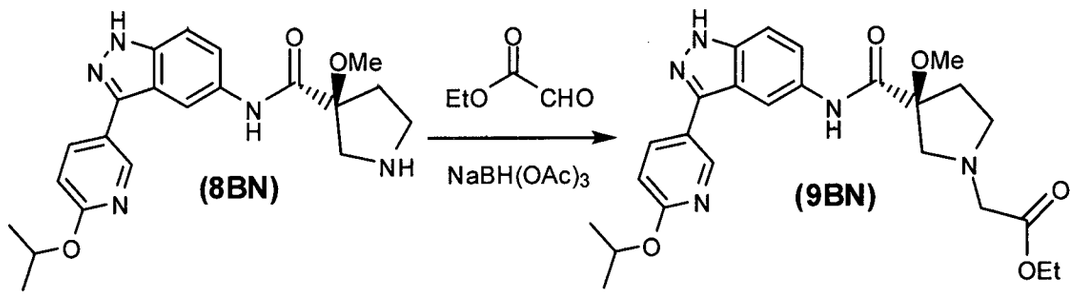
Se cargaron en un matraz de alta presión, el compuesto **4BQ** (400 mg), ter-butil éster del ácido 4-(4,4,5,5-tetrametil-[1,3,2]dioxaborolan-2-il)-3,6-dihidro-2*H*-piridin-1-carboxílico (540 mg), $Pd(PPh_3)_4$ (180 mg), Na_2CO_3 2N (3 ml) y Dioxano/EtOH/agua (7:3:2, 10 ml). La mezcla se desgasificó brevemente con Ar durante ~0,5 minutos, se tapó y se sometió a microondas a 120°C durante 20 minutos. Luego del enfriamiento, la mezcla de reacción se diluyó con EtOAc y salmuera. La capa orgánica se aisló y secó ($MgSO_4$). Luego de la concentración, el residuo se purificó sobre gel de sílice. La elución con MeOH/EtOAc (0-10%) dio el producto deseado **5BQ** (310 mg).

Step 5: Preparación de 2-metil-1-{3-[4-(1,2,3,6-tetrahidro-piridin-4-il)-fenil]-[1,2,4]triazol-1-il}-propan-2-ol

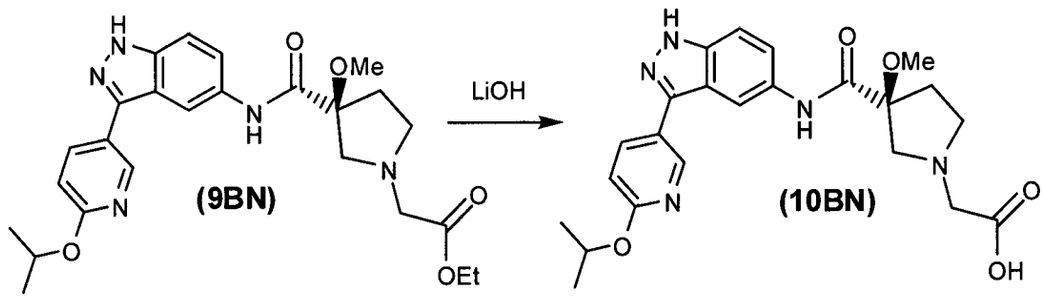


El grupo Boc puede retirarse tratando el compuesto **5BQ** con HCl 4N en dioxano a ta durante dos horas. El retiro del solvente al vacío dio el compuesto **6BQ**.

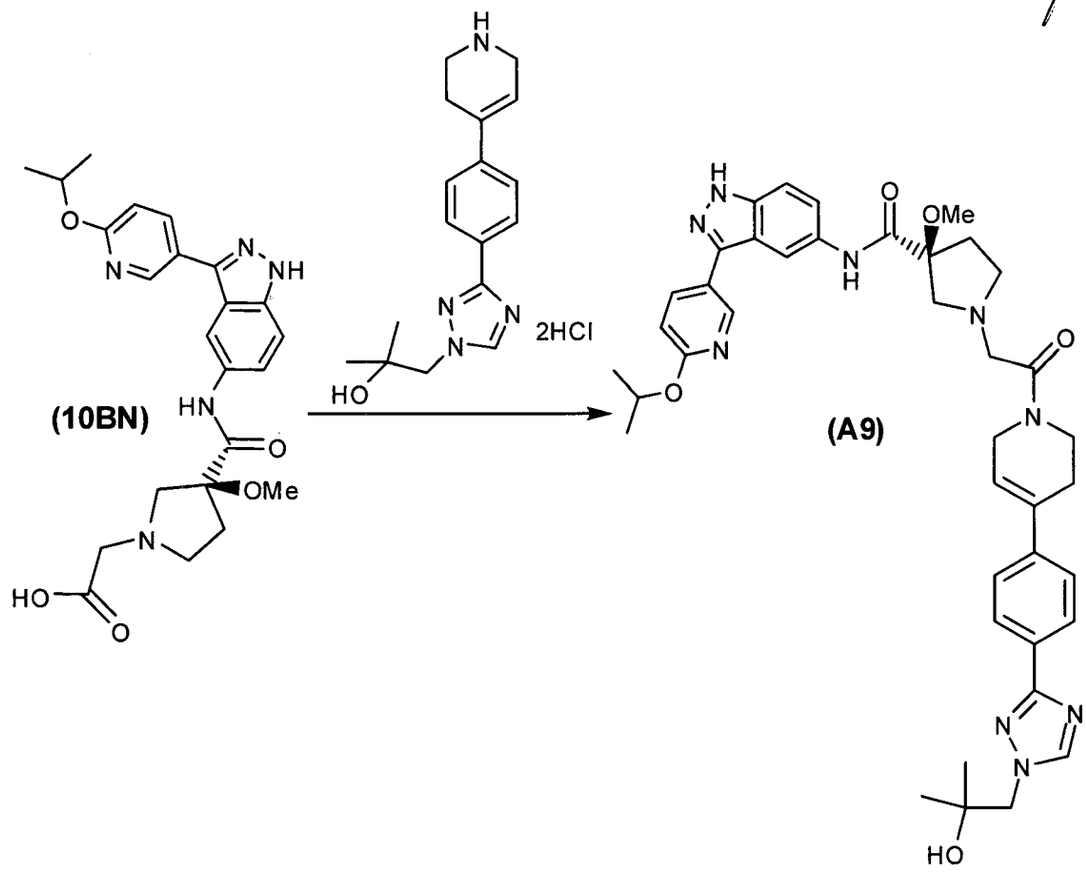
Síntesis de [3-(6-isopropoxi-piridin-3-il)-1H-indazol-5-il]-amida del ácido 1-[2-(4-{4-[1-(2-hidroxi-2-metil-propil)-1H-[1,2,4]triazol-3-il]-fenil}-3,6-dihidro-2H-piridin-1-il)-2-oxo-etil]-3-metoxi-pirrolidin-3-carboxílico



El **8BN** bruto (5,9 mmol) se agitó en una mezcla de diclorometano/MeOH (1:1, 20 ml), etiléster del ácido oxoacético (10 ml, 50%) y NaBH(OAc)3 (10 ml) a ta hasta el día siguiente. La mezcla se desactivó con saturado acuoso bicarbonato de sodio. Los solventes se retiraron al vacío. Se diluyeron con agua y acetato de etilo. Se separaron las capas y la capa acuosa separada se extrajo con acetato de etilo (X3). Las capas orgánicas combinadas se secaron ($MgSO_4$), se filtraron y los solventes se retiraron al vacío. La purificación en columna dio **9BN** como un aceite amarillo.



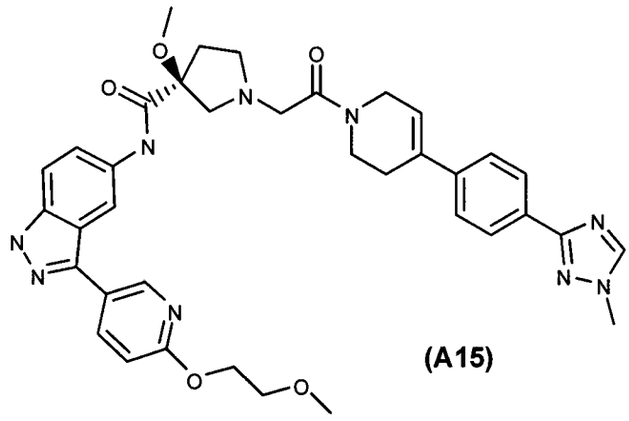
El **9BN** bruto (2,35 g) se agitó en una solución de LiOH (1M, 10 ml) y THF (10 ml) a ta hasta el día siguiente. La mezcla se ajustó a pH 3. Los solventes se retiraron al vacío. El producto se utilizó en el próximo paso sin purificación.



El **10BN** bruto (60 mg), 2-metil-1-{3-[4-(1,2,3,6-tetrahidro-piridin-4-il)-fenil]-[1,2,4]triazol-1-il}-propan-2-ol (38 mg), HATU (50 mg) y trietilamina (0.1 ml) se agitaron en DMF (1 ml) a ta hasta el día siguiente. La mezcla se purificó mediante HPLC para dar **A9** como un aceite amarillo, 50%. Espectro de masa: LCMS M+1= 734, tiempo de retención = 3,32 minutos.

Ejemplo 9

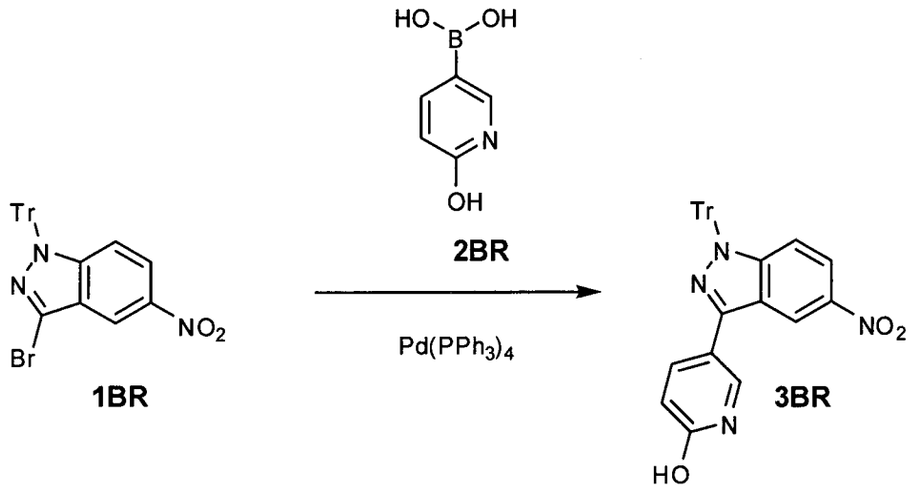
Preparación de {3-[6-(2-Metoxi-etoxi)-piridin-3-il]-1H-indazol-5-il}-amida del ácido 3-metoxi-1-(2-{4-[4-(1-metil-1H-[1,2,4]triazol-3-il)-fenil]-3,6-dihidro-2H-piridin-1-il}-2-oxo-etil)-pirrolidin-3-carboxílico



(A15)

Síntesis de {3-[6-(2-Metoxi-etoxi)-piridin-3-il]-1H-indazol-5-il}-amida del ácido 3-metoxi-pirrolidin-3-carboxílico

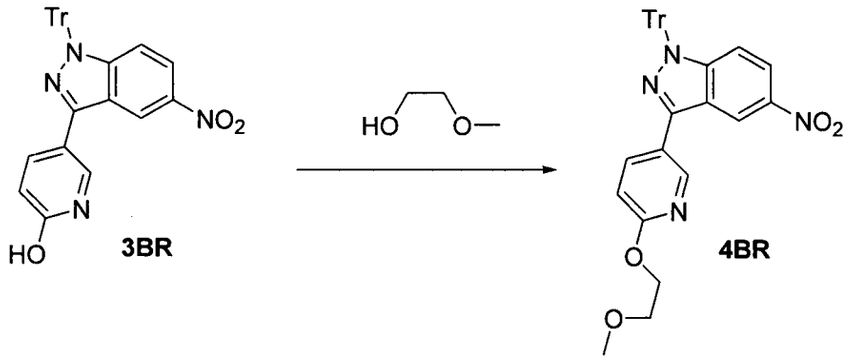
Paso 1:



1BR **2BR** **3BR**

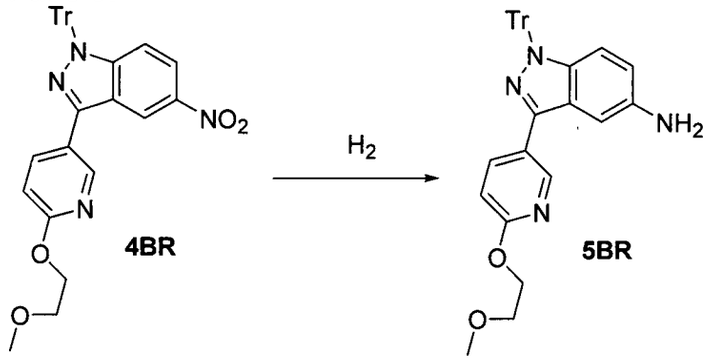
Se cargó en un matraz de presión, el compuesto **1BR** (1,75 g), **2BR** (0,5 g), $Pd(PPh_3)_4$ (210 mg), Na_2CO_3 2N (10 ml) y Dioxano (10 ml). La mezcla se desgasificó brevemente con Ar durante ~0,5 minutos, se tapó y agitó a 100°C hasta el día siguiente. Luego del enfriamiento, la mezcla de reacción se diluyó con EtOAc y salmuera. La capa orgánica se aisló y secó ($MgSO_4$). Luego de la concentración, el residuo se purificó sobre gel de sílice. La elución dio el producto deseado **3BR** (0,8 g).

Paso 2:



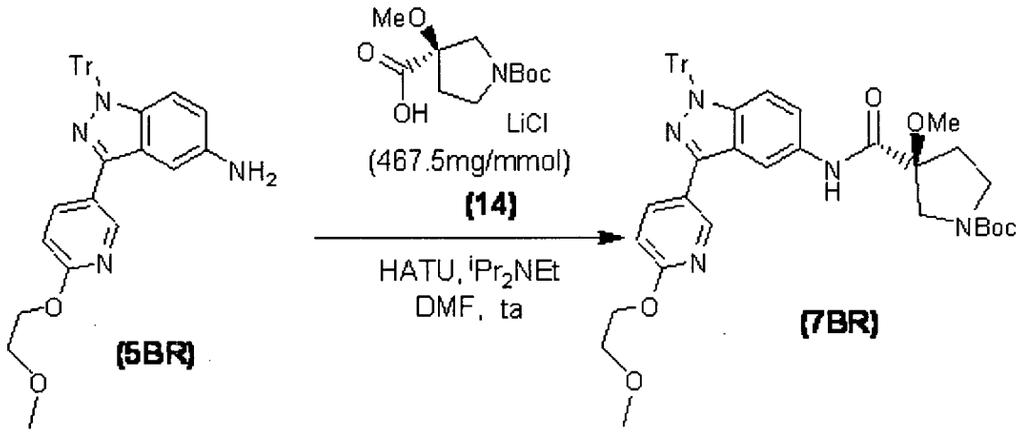
Una mezcla del compuesto **3BR** (1,8 g), 2-metoxi-etanol (1 g), DEAD (0,8 g) y PPh_3 (1,2 g) en THF (10 ml) se agitó hasta el día siguiente a ta y se concentró. El residuo se purificó mediante gel de sílice para dar el producto deseado **4BR** (0,8 g).

Paso 3:



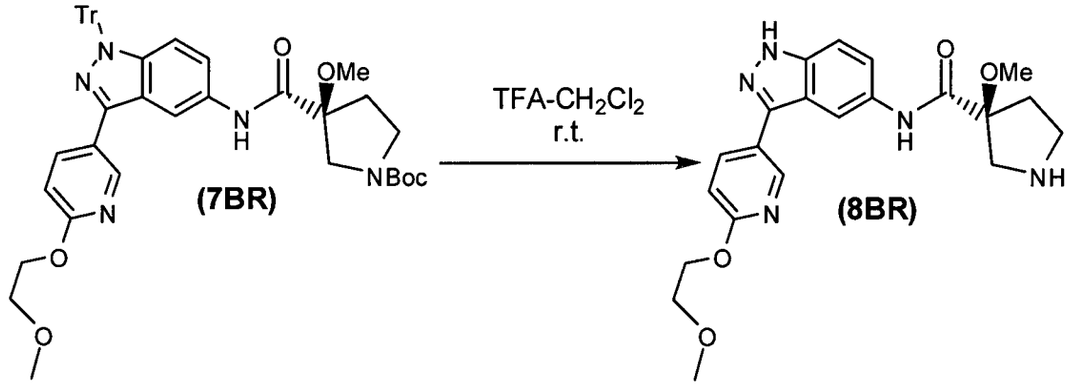
4BR (0,5 g) en MeOH (20 ml) se redujo mediante H-cube con una columna Pd/C (10%).

Paso 4:



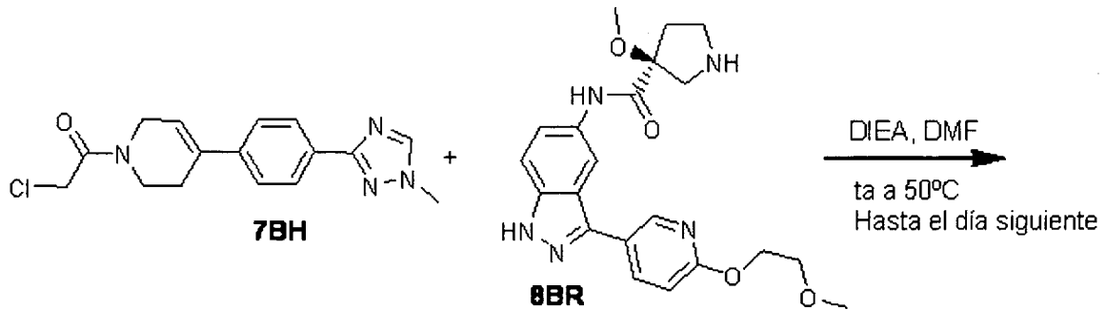
Se disolvieron aminoindazol **5BR** (80 mg) y ácido pirrolidincarboxílico **14BH** (38 mg) en DMF (1 ml) a ta. Se agregó HATU (69 mg) seguido por $^{i}Pr_2NEt$ (0,1 ml). La mezcla se agitó a ta hasta el día siguiente y se diluyó con acetato de etilo y agua. Se separaron las capas. La capa orgánica separada se lavó con agua (X2), dried ($MgSO_4$) y filtró. La concentración al vacío dio **7BR** bruto como una espuma blancuzca.

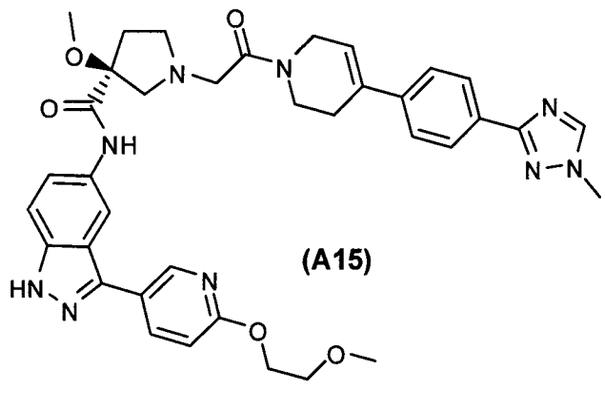
Paso 5:



El **7BR** bruto se agitó en una mezcla de dicloromethane (1 ml), ácido trifluoracético (1 ml) a ta durante 1 hora. La mezcla se enfrió a 0°C y se desactivó cuidadosamente con bicarbonato de sodio saturado acuoso. Los solventes se retiraron al vacío. Se diluyeron con agua y acetato de etilo. Se separaron las capas y la capa acuosa separada se extrajo con acetato de etilo (X3). Las capas orgánicas combinadas se secaron ($MgSO_4$), se filtraron y los solventes se retiraron al vacío para dar pirrolidina **8BR** como un sólido blancuzco.

Síntesis de {3-[6-(2-Metoxi-etoxi)-piridin-3-il]-1H-indazol-5-il}-amida del ácido 3-metoxi-1-(2-{4-[4-(1-metil-1H-[1,2,4]triazol-3-il)-fenil]-3,6-dihidro-2H-piridin-1-il}-2-oxo-etil)-pirrolidin-3-carboxílico

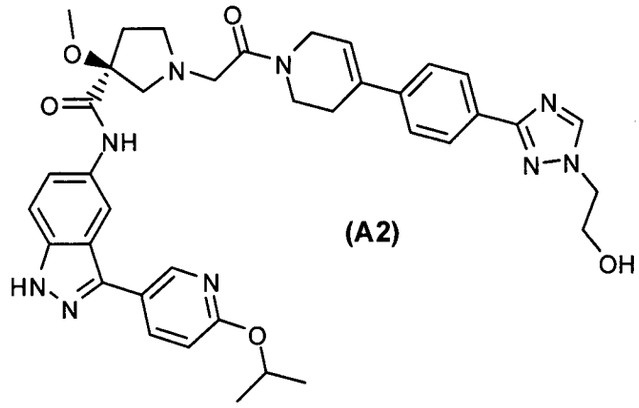




Una mezcla del compuesto **7BH** (52 mg), compuesto **8BR** (62 mg), y DIEA (0,3 ml) en DMF (1,5 ml) se agitó a temperatura ambiente hasta el día siguiente. LCMS muestra que la reacción estaba completa. El DMF se retiró a presión reducida. El bruto se purificó mediante HPLC. (LCMS M+1= 692, tiempo de retención = 3,00 minutos.) 1H RMN (400 MHz, CDCl3):δ11,92 (S, 1H), 11,11 (S, 1H), 9,14 (S, 1H), 8,58 (S, 1H), 8,03 (S, 1H), 7,99 (d, 1H, J= 8,4 Hz), 7,90 (t, 2H, J= 6,8), 7,39 (S, 2H), 7,20 (S, 3H), 6,76 (d, 1H, J=8,0 Hz), 5,85 (d, 1H, J= 20 Hz), 4,4 (S, 4H), 4,05 (q, 4H, J= 7,2 Hz), 3,8 (S, 3H), 3,50-3,56 (m, 6H), 2,34-2,62 (m, 5H), 2,0 (S, 2H), 1,64-1,49 (m, 3H).

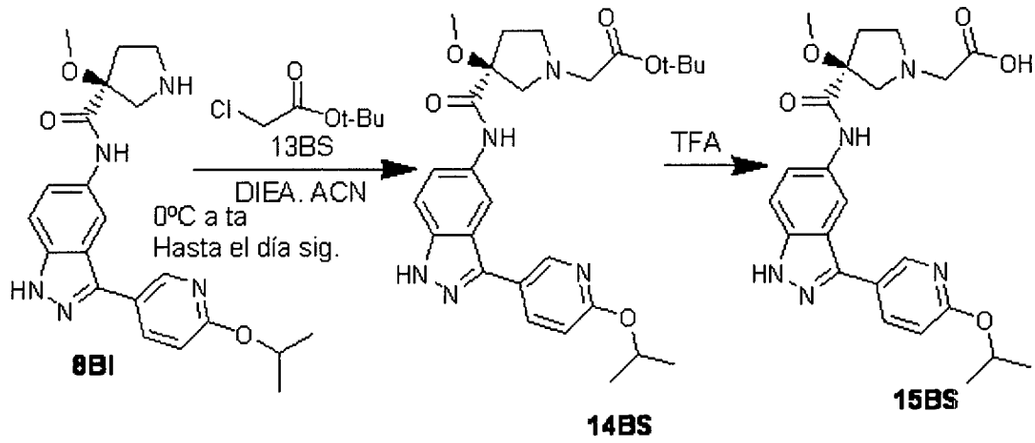
Ejemplo 10

Preparación de [3-(6-isopropoxi-piridin-3-il)-1H-indazol-5-il]-amida del ácido 1-[2-(4-{4-[1-(2-Hidroxi-etil)-1H-[1,2,4]triazol-3-il]-fenil}-3,6-dihidro-2H-piridin-1-il)-2-oxo-etil]-3-metoxi-pirrolidin-3-carboxílico



(A2)

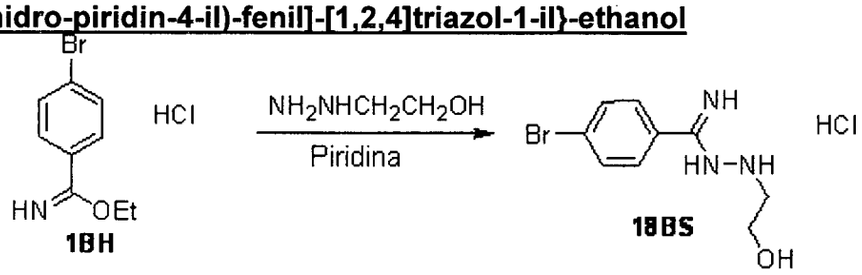
Preparación del ácido {3-[3-(6-Isopropoxi-piridin-3-il)-1*H*-inxazol-5-ilcarbamoil]-3-metoxi-pirrolidin-1-il}-acético



En una solución del compuesto **8BI** (3,5 g, 6,6 mmol) en acetonitrilo (26 ml) se agregó DIEA (5,7 ml, 32,9 mmol). Se enfrió a 0°C y se agregó gota a gota 0,47ml (3,29 mmol) del compuesto **13BS**. Luego de agitación durante 4 horas a 0ºC, se agregó nuevamente 0,47ml (3,29 mmol) del compuesto **13BS**. Esta se agitó en forma adicional durante 1 hora a 0ºC y luego se calentó a ta. Luego de agitación a temperatura ambiente hasta el día siguiente, se disolvió en EtOAc (200ml) y se lavó con $NaHCO_3$ (1 x 50ml), agua (1x 50ml) y salmuera (1 x 50ml). Los extractos orgánicos se secaron sobre $MgSO_4$ y se retiró el solvente. El producto bruto se purificó mediante cromatografía en columna utilizando MeOH/EtOAC 20% para dar el producto deseado **14BS** (2,4g).

El compuesto **14BS** (2.4g) se trató con 40 ml de TFA durante 45 minutos a temperatura ambiente. Se retiró el TFA a presión reducida y el sólido se lavó con éter para dar el compuesto deseado **15BS** como una sal de TFA (4,4gm, 95%). El compuesto **15BS** se convirtió en la sal de HCl mediante la adición de HCl 4N en agua.

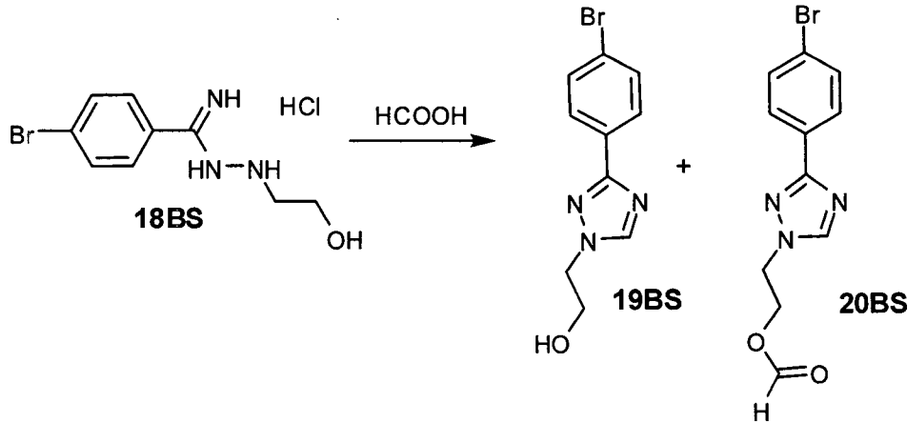
Síntesis de la preparación de clorhidrato de 2-{3-[[4[(1,2,3,6-tetrahidro-piridin-4-il)-fenil]-[1,2,4]triazol-1-il}-ethanol



1BH **18BS**

Preparación de clorhidrato de 4-bromo-*N'*-(2-hidroxietil)bencimidohidrazida

El etiléster del ácido 4-bromo-bencimídico **1BH** (5g) se disolvió en piridina (100 ml). Se agregó hidroxietilhidrazina (1,92 ml) con agitación y la mezcla resultante se dejó agitar hasta el día siguiente. El precipitado se recolectó por filtración y el líquido madre se concentró casi a sequedad y se agregó éter. El sólido se recolectó por filtración. El sólido combinado se lavó dos veces con éter para dar **18BS** (5,1g).

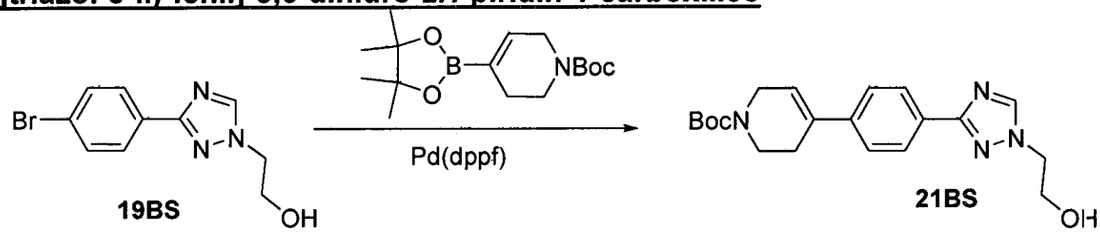


Preparación de 2-(3-(4-bromofenil)-1*H*-1,2,4-triazol-1-il)etanol

Una mezcla del compuesto **18BS** (3g) en ácido fórmico (50ml) se agitó a temperatura ambiente durante 30 minutos, a 100°C durante 1,5 horas y se concentró. El residuo se trató con $NaHCO_3$ saturado, y se extrajo con EtOAc tres veces. Los extractos orgánicos combinados se secaron sobre $MgSO_4$. Luego de la concentración, el bruto se purificó sobre gel de sílice. La elución con EtOAc dio el compuesto **20BS** (2g), y el compuesto **19BS** (262mg).

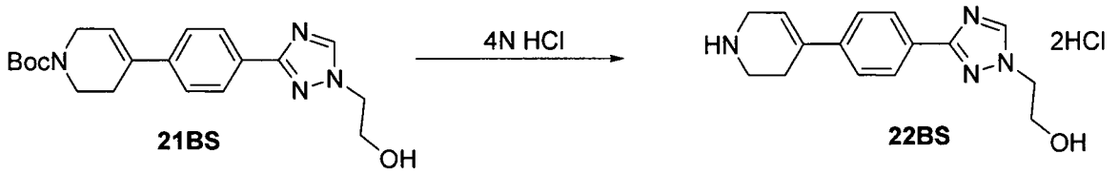
El compuesto **20BS** puede convertirse fácilmente en **19BS** mediante hidrólisis acuosa.

Preparación de ter-butil éster del ácido 4-[4-(1-(2-hidroxi-etil)-*1H*-[1,2,4]triazol-3-il)-fenil]-3,6-dihidro-*2H*-piridin-1-carboxílico



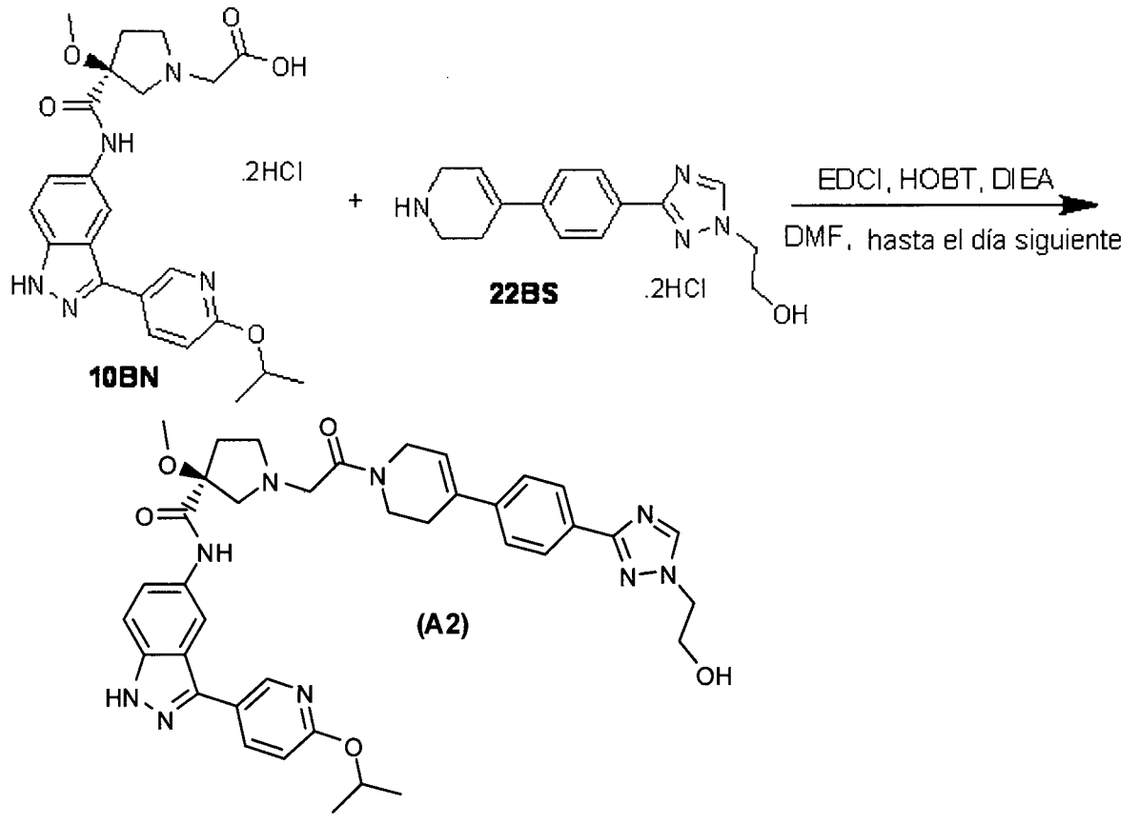
Se cargaron en un matraz de alta presión, el compuesto **19BS** (1,5 g, 5,6 mmoles), ter-butil éster del ácido 4-(4,4,5,5-tetrametil-[1,3,2]dioxaborolan-2-il)-3,6-dihidro-2*H*-piridin-1-carboxílico (1,9 g, 6,2 mmoles), [1,1'-bis(difenilfosfino)-ferroceno]dicloropaladio (II), complejo con diclorometano (1:1) (0,22g, 0,28 mmoles), K_2CO_3 (2.32g, 16,8 mmoles) y DME/agua (5:1, 12 ml). La mezcla se desgasificó brevemente con Ar durante ~0,5 minutos, se tapó y agitó a 80°C hasta el día siguiente. Luego del enfriamiento, la mezcla de reacción se diluyó con EtOAc y se lavó con agua (1X) y salmuera (1x). La capa orgánica se aisló y secó sobre $MgSO_4$. Luego de la concentración, el residuo se purificó sobre gel de sílice. La elución con MeOH/EtOAc (0-10%) dio el producto deseado **21BS** (1,4 g, 73%).

Preparación de clorhidrato de 2-{3-[[4[(1,2,3,6-tetrahidro-piridin-4-il)-fenil]-[1,2,4]triazol-1-il}-etanol



El grupo Boc puede retirarse tratando el compuesto **21BS** con HCl 4N en dioxano a ta durante dos horas. El retiro del solvente al vacío dio el compuesto **22BS**.

Preparación de [3-(6-isopropoxi-pyrididn-3-il)-1*H*-inxazol-5-il]-amida del ácido 1-[2-(4-{4-[1-(2-hidroxi-etil)-1*H*-[1,2,4]triazol-3-il]-fenil}-3,6-dihidro-2*H*-piridin-1-il)-2-oxo-etil]-3-metoxi-pirrolidin-3-carboxílico

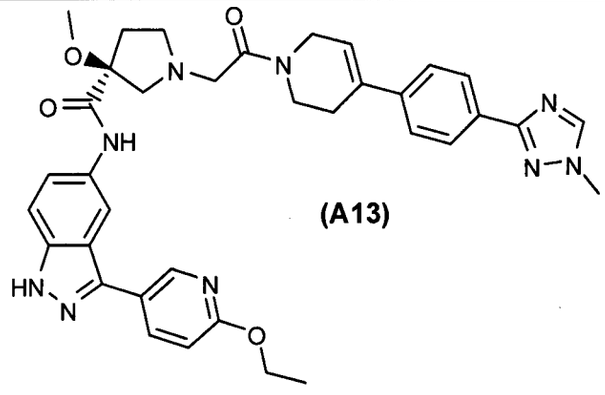


Una mezcla del compuesto **10BN** (0,49g, 1mmol), clorhidrato de 1-(3-dimetil-aminopropil)-3-etilcarboxiimida (0,38 g, 2 mmol), y 1-hidroxibenzotriazol (0,14g, 1 mmol) se disolvió en DMF (3 ml). Luego de agitación durante 20 minutos a temperatura ambiente, se agregaron el compuesto **16BS** (0,34g,

1mmol) y DIEA (0,7ml, 4mmol). Luego de agitación durante toda la noche a temperatura ambiente, esta se diluyó con DCM (45ml) y se lavó con $NaHCO_3$ (1 X 7ml), agua (3 x 7ml) y salmuera (1X10ml). La capa orgánica se secó sobre $MgSO_4$. Luego de la concentración, el residuo se purificó sobre gel de sílice. La elución con NH_3 2% en MeOH/EtOAc 20% dio el producto deseado **A2** (0,3 g). Este compuesto se convirtió en una sal de HCl mediante la adición de HCl 4N en 1,4-dixoano. (LCMS: M+1= 706, tiempo de retención = 3,13 minutos), ^1H RMN (400 MHz, DMSO-*d*6): □□□□□(m, 1H), 10,25 (d, 1H, J = 19,2Hz), 8,60 - 8,75 (m, 2H), 8,43 (m, 1H), 8,18 (m, 1H), 7,98 (m, 2H), 7,78 (d, 2H, J = 20Hz), 7,5 - 7,6 (m, 4H), 6,9 (m, 2H), 6,3 (m, 1H), 5,3 (m, 1H), 4,5 - 4,6 (m, 2H), 4,15 - 4,3 (m, 4H), 4,0 - 4,15 (m, 2H), 3,75 (t, 4H, 5,2 Hz), 3,5 - 3,6 (m, 2H), 3,4 - 3,3 (m, 1H), 3,29 (s, 2H), 2,5 - 2,7 (m, 3H), 2,3 - 2,4 (m, 1H), 1,3 (d, 6H, J = 6,4Hz).

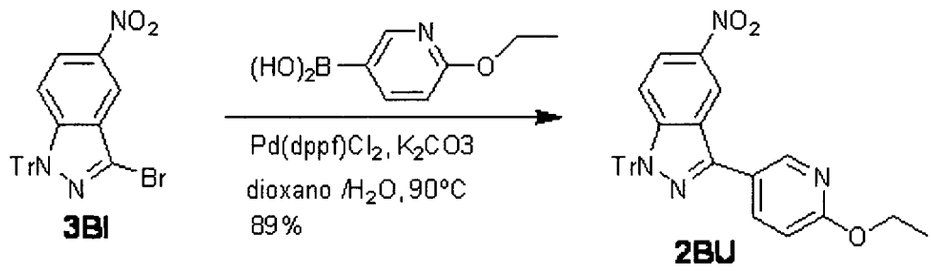
Ejemplo 11

Síntesis de [3-(6-etoxi-piridin-3-il)-1H-indazol-5-il]-amida del ácido 3-metoxi-1-(2-{4-[4-(1-metil-1H-[1,2,4]triazol-3-il)-fenil]-3,6-dihidro-2H-piridin-1-il}-2-oxo-etil)-pirrolidin-3-carboxílico (Ejemplo 1)



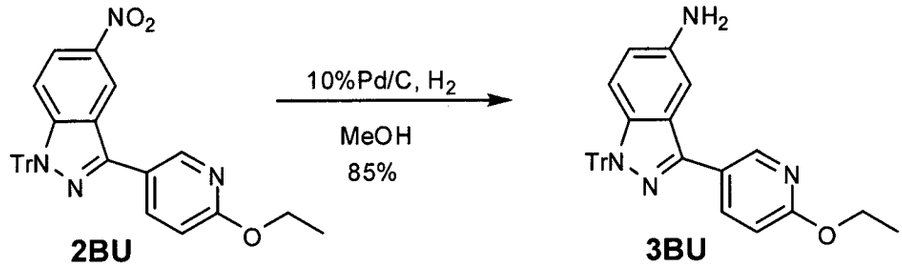
(A13)

Paso 1:



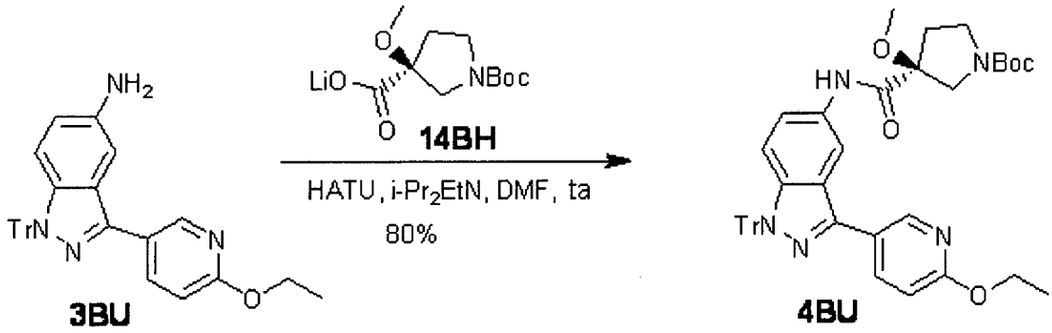
Una mezcla de ácido 6-etoxipiridin-3-borónico (2,5 g, 14,97 mmol), bromoindazol **3BI** (7,25 g, 14,97 mmol), carbonato de potasio (6,2 g, 44,91 mmol), $PdCl_2(dppf)_2.CH_2Cl_2$ (1,22 g, 1,497 mmol), 1,4-dioxano (40 ml) y agua (10 ml), se purgó con nitrógeno durante 15 minutos a ta y luego se calentó a 90°C durante 18 horas y se enfrió a ta. Se agregaron agua (100 ml) y acetato de etilo (300 ml). Los sólidos se filtraron a través de Celite. Se separaron las capas y la capa orgánica separada se lavó con agua (100 ml). Las capas orgánicas combinadas se secaron (Na_2SO_4), se filtraron y los solventes se retiraron al vacío. La purificación en columna [Hexanos-acetato de etilo = 9:1 (v/v)] dio el compuesto **2BU** (7 g, 89%).

Paso 2:



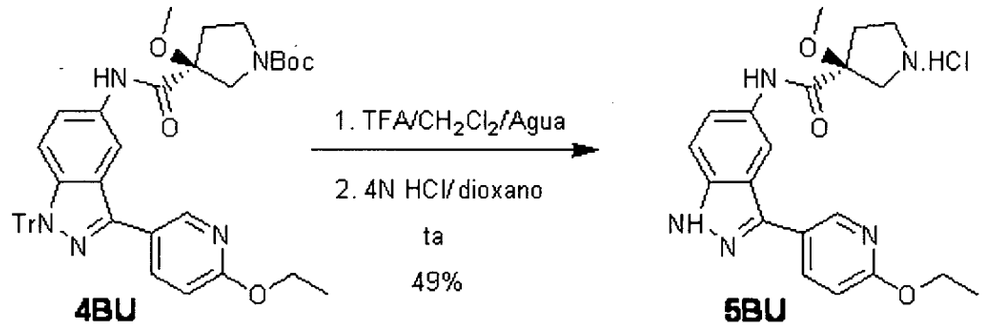
El compuesto **2BU** (2 g, 3,8 mmol) y Pd/C (10%, húmedo 50%, 0,7 g) se agitaron en tolueno (30 ml) y MeOH (15 ml) bajo H_2 (globo) a ta durante 18 horas. El catalizador sólido se filtró a través de Celite y los solventes se eliminaron al vacío. La purificación en columna utlizando MeOH/CH_2Cl_2 4% dio el compuesto **3BU** (1,6 g, 85%).

Paso 3:



El compuesto **3BU** (1,46 g, 3,22 mmol) y ácido pirrolidincarboxílico **14BH** (0,56 g, 3,22 mmol) se disolvieron en DMF (300ml) a ta. Se agregó HATU (1,68 g, 4,83 mmol) seguido por $^{i}Pr_2NEt$ (0,78 ml, 4,83 mmol). La mezcla se agitó a ta hasta el día siguiente y se diluyó con acetato de etilo (200 ml) y agua (100 ml). Se separaron las capas. La capa orgánica separada se lavó con agua (100 ml), se secó (Na_2SO_4) y filtró. La concentración al vacío seguida por la purificación en columna [hexanos – acetato de etilo = 9:1 (v/v)] dio el producto **4BU**.

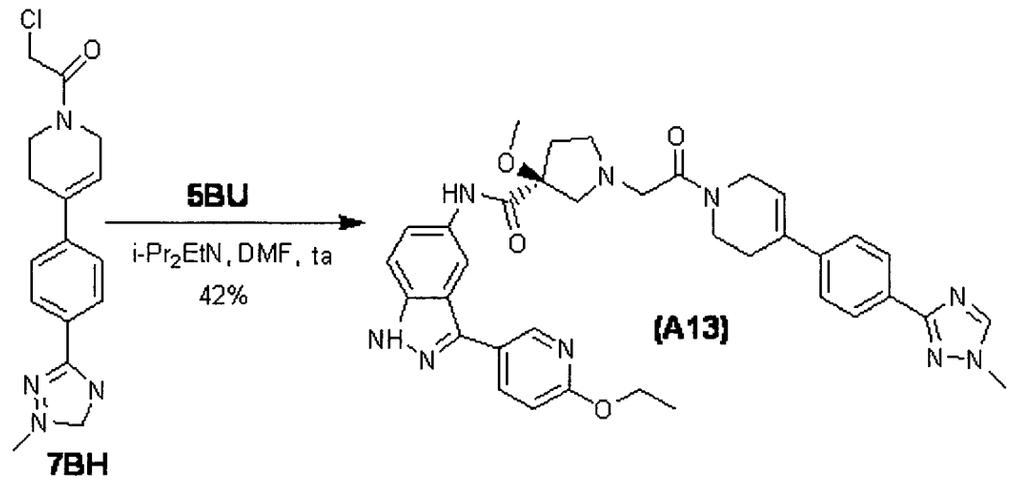
Paso 4:



4BU **5BU**

El compuesto **4BU** (1,6 g) se agitó en una mezcla de diclorometano (30 ml), ácido trifluoracético (4 ml) y unas pocas gotas de agua a ta hasta el día siguiente. La mezcla se enfrió a 0°C y se desactivó con cuidado con MeOH 7% (NH_3)/CH_2Cl_2. Los solventes se retiraron al vacío. La mezcla se diluyó con agua (100 ml) y acetato de etilo (200 ml). Se separaron las capas. La capa orgánica se secó (Na_2SO_4), se filtró y los solventes se retiraron al vacío. La purificación en columna [7% MeOH (amoníaco 7N) en diclorometano] dio el compuesto **5BU** (0,44 g, 49%) que se convirtió en una sal mono HCl por tratamiento con HCl/dioxano 4N y evaporación de la solución a sequedad.

Paso 5:



7BH

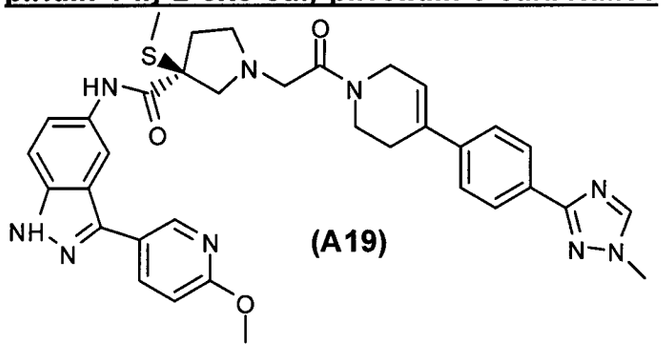
Una mezcla del compuesto **7BH** (46 mg, 0,144 mmol), compuesto **5BU** (60 mg, 0,144 mmol), DMF (2 ml) y N,N-diisopropiletilamina (0,076 ml, 0,432 mmol) se agitó a temperatura ambiente durante 18 horas. Se diluyó con EtOAc

(100 ml) y se lavó con agua (2 x 100 ml). La capa orgánica se secó sobre Na_2SO_4, se filtró y concentró. El residuo se purificó sobre gel de sílice eluyendo con MeOH 4% (NH_3)/ CH_2Cl_2 para dar el producto deseado **6BU** (40 mg, 42%).

LC Espectro de Masa M+1en tiempo de retención = 662 en 2,57 minutos

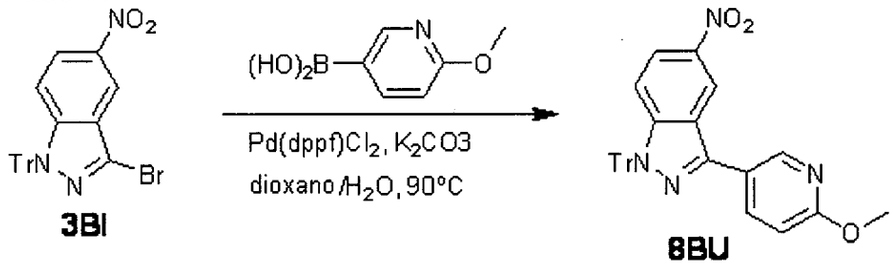
Ejemplo 12

Síntesis de [3-(6-Metoxi-piridin-3-il)-1H-indazol-5-il]-amida del ácido 3-metilsulfanil-1-(2-{4-[4-(1-metil-1H-[1,2,4]triazol-3-il)-fenil]-3,6-dihidro-2H-piridin-1-il}-2-oxo-etil)-pirrolidin-3-carboxílico



(A19)

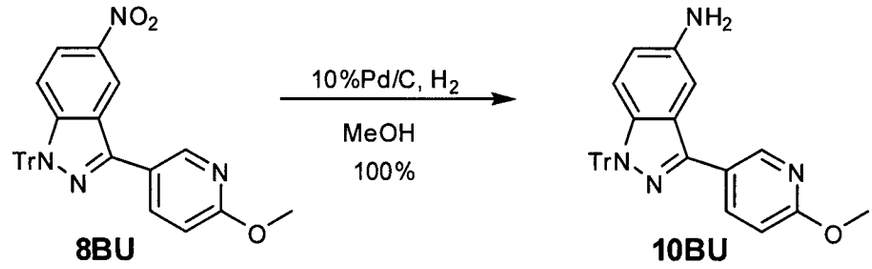
Paso 1:



3BI **8BU**

El compuesto **8BU** se preparó a partir del compuesto **3BI** utilizando esencialmente el mismo procedimiento descripto para la preparación del Compuesto **2BU** a partir del Compuesto **3BI** (Ejemplo 11, Paso 1), utilizando ácido 6-metoxipiridin-3-borónico en lugar de ácido 6-etoxipiridin-3-borónico.

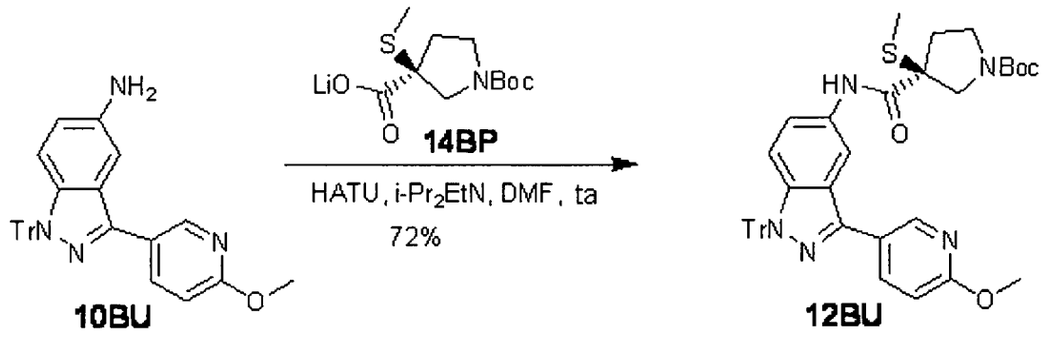
Paso 2:



8BU **10BU**

El compuesto **8BU** (3 g, 3,8 mmol) y Pd/C (10%, húmedo 50%, 1,2 g) se agitaron en tolueno (30 ml) y MeOH (15 ml) bajo H_2 (globo) a ta durante 18 horas. El catalizador sólido se filtró a través de Celite y los solventes se eliminaron al vacío para dar el compuesto **10BU** (2,8 g, 100%).

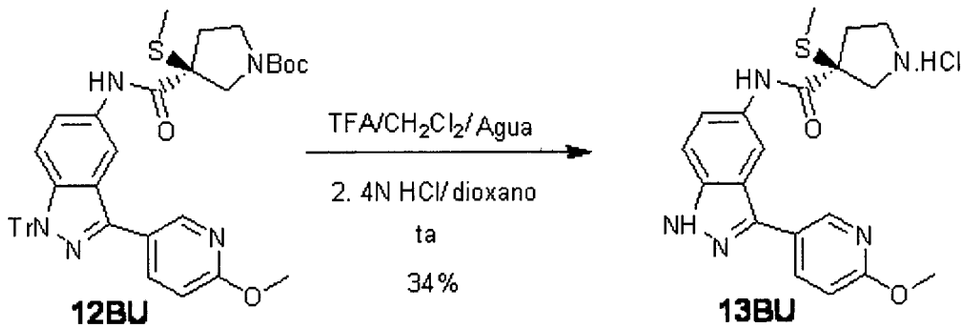
Paso 3:



10BU **12BU**

El compuesto **10BU** (0,6 g, 1,24 mmol) y ácido pirrolidincarboxílico **14BP** (0,33 g, 1,24 mmol) se disolvieron en DMF (5 ml) a ta. Se agregó HATU (0,71 g, 1,86 mmol) seguido por $^{i}Pr_2NEt$ (00,66 ml, 3,72 mmol). La mezcla se agitó a ta hasta el día siguiente y se diluyó con acetato de etilo (200 ml) y agua (100 ml). Se separaron las capas. La capa orgánica separada se lavó con agua (100 ml), se secó (Na_2SO_4) y filtró. La concentración al vacío seguida por la purificación en columna [hexanos – acetato de etilo = 9:1 (v/v)] dio el producto **12BU** (0,65 g, 72%).

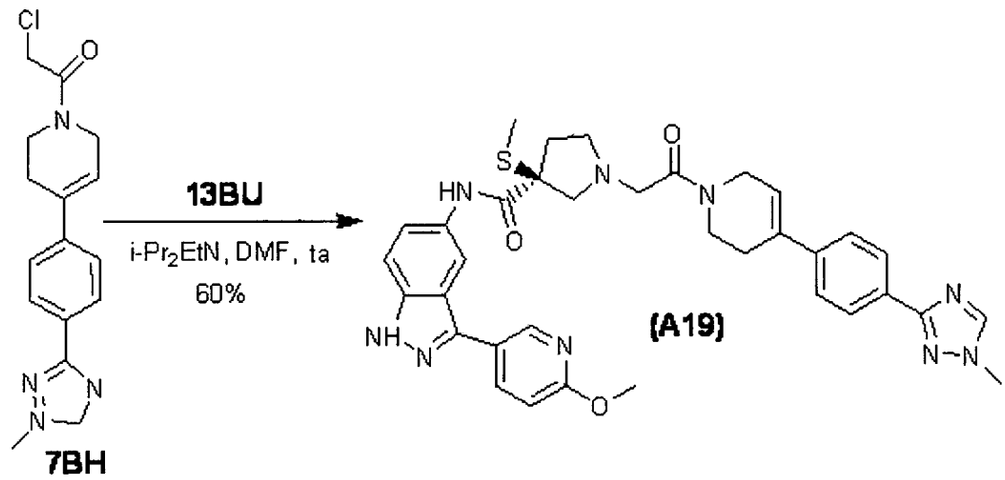
Paso 4:



12BU **13BU**

El compuesto **12BU** (0,65 g) se agitó en una mezcla de diclorometano (30 ml), ácido trifluoracético (4 ml) y unas pocas gotas de agua a ta hasta el día siguiente. La mezcla se enfrió a 0°C y se desactivó cuidadosamente con MeOH 7% (NH_3)/CH_2Cl_2. Los solventes se retiraron al vacío. Se diluyó con agua (100 ml) y acetato de etilo (200 ml). Se separaron las capas. La capa orgánica se secó (Na_2SO_4), se filtró y los solventes se retiraron al vacío. La purificación en columna [15% MeOH (amoníaco 7N) en diclorometano] dio el compuesto **13BU** (0,22 g, 34%).

Paso 5:



7BH

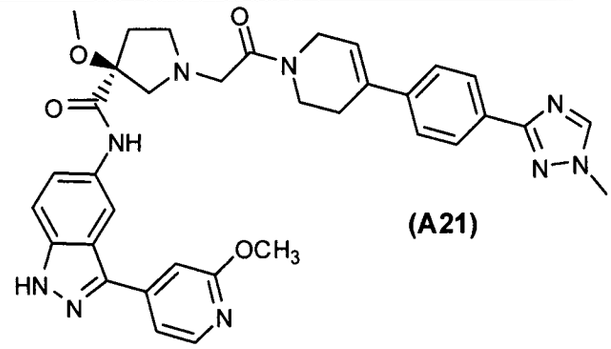
Una mezcla del compuesto **7BH** (40 mg, 0,126 mmol), compuesto **13BU** (50 mg, 0,126 mmol), DMF (2 ml) y N,N-diisopropiletilamina (0,045 ml, 0,25 mmol) se agitó a temperatura ambiente durante 18 horas. Se diluyó con EtOAc

(100 ml) y se lavó con agua (2 x 100 ml). La capa orgánica se secó sobre Na_2SO_4, se filtró y concentró. El residuo se purificó sobre gel de sílice eluyendo con MeOH 3% (NH_3)/ CH_2Cl_2 para dar el producto deseado **A19** (50 mg, 60%).

LC Espectro de Masa M+1 en tiempo de retención = 664 en 2,88 minutos

Ejemplo 13

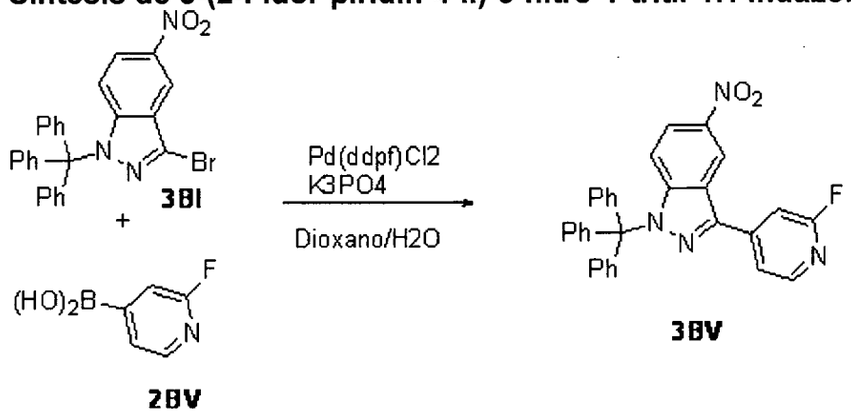
Síntesis de [3-(2-Metoxi-piridin-4-il)-1H-indazol-5-il]-amida del ácido 3-metoxi-1-(2-{4-[4-(1-metil-1H-[1,2,4]triazol-3-il)-fenil]-3,6-dihidro-2H-piridin-1-il}-2-oxo-etil)-pirrolidin-3-carboxílico



(A21)

Paso 1:

Síntesis de 3-(2-Flúor-piridin-4-il)-5-nitro-1-tritil-1H-indazol

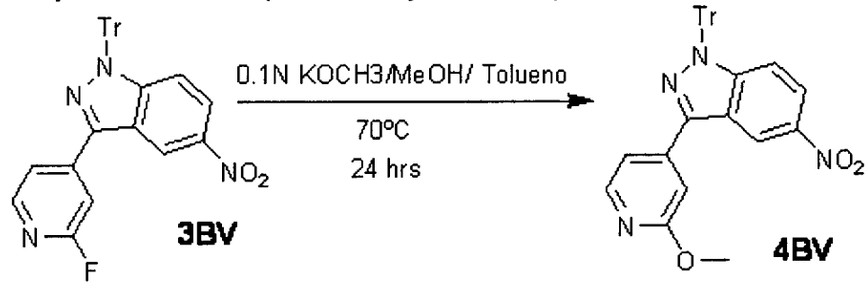


3-Bromo-5-nitro-1-tritil-1H-indazol **3BI** (15,64 g, 32,3 mmol), ácido 2-flúor-4-piridin borónico **2BV** (5,0 g, 35,5 mmol), K_3PO_4 (17,1 g, 80,7 mmol) y $Pd(dppf)Cl_2$ (2,64g, 3,23 mmol) se mezcló en dioxano/H_2O (240 ml/60 ml) a ta y se calentó a 80°C hasta el día siguiente. La mezcla de reacción se enfrió a ta y

se concentró a un volumen pequeño. El residuo se dividió entre acetato de etilo (200 ml) y salmuera (150 ml). La capa orgánica se lavó con salmuera, se secó ($MgSO_4$) y filtró. El filtrado resultante se concentró y el residuo se purificó sobre una columna de gel de sílice eluyendo con hexanos, acetato de etilo 5% en hexanos, 10% acetato de etilo en hexanos, en forma secuencial para dar un sólido amarillo **3BV** (3,33 g, 64%).

Paso 2:

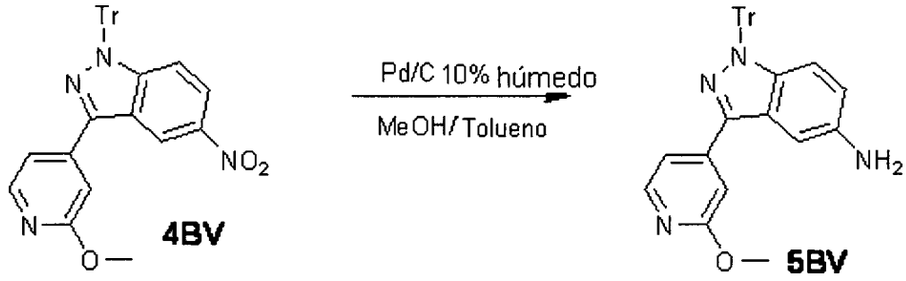
Preparación de 3-(2-metoxi-piridin-4-il)-5-nitro-1-tritil-1H-indazol



En un recipiente a presión de 250 ml, 3-(2-Flúor-piridin-4-il)-5-nitro-1-tritil-1H-indazol **3BV** (5,005 g, 10,0 mmoles) se disolvió en $KOCH_3$/MeOH/Tolueno 0,1N (Acros, 150 ml, 15,0 mmoles) con gas N_2 seco. El recipiente a presión se selló firmemente y se calentó bajo agitación a 70°C durante 24 horas. El recipiente a presión se enfrió a 0°C en un baño de hielo antes de la abertura. Los contenidos de los recipientes de presión se transfirieron RBF 500 ml y se evaporaron a sequedad. El sólido resultante se disolvió en CH_2Cl_2 y se lavó con una solución saturada de NaCl y se secaron sobre $MgSO_4$. El solvente se evaporó a sequedad y se secó en alto vacío para dar **4BV** como un sólido marrón (5,12 g, 100%).

Paso 3:

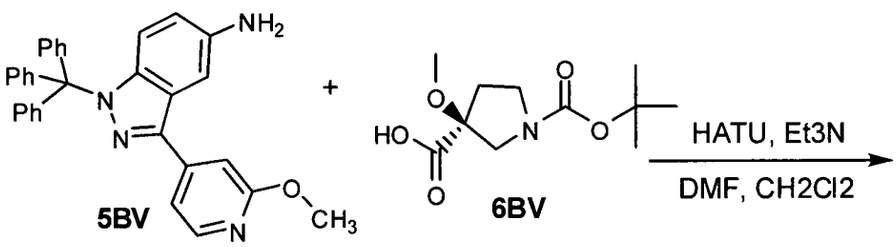
Preparación de 3-(2-Metoxi-piridin-4-il)-1-tritil-1H-indazol-5-ilamina

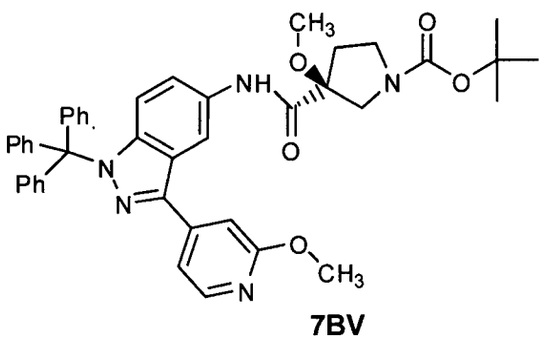


A la suspensión agitada de 3-(2-Metoxi-piridin-4-il)-5-nitro-1-tritil-1H-indazol **4BV** (5,125 g ,10,0 mmoles) en MeOH/tolueno (50 ml/50 ml) se agregó Pd/C 10% (tipo Degussa, 0,5 g) a ta con gas N_2 seco. La mezcla se desgasificó y se agitó bajo un globo inflado con gas de H2 hasta el día siguiente. El catalizador se filtró a través de un filtro de microfibra y se lavó con MeOH y CH_2Cl_2. El filtrado se evaporó a sequedad y se obtuvo un sólido marrón **5BV** (5,0 g).

Paso 4

Preparación de ter-butil éster del ácido 3-metoxi-3-[3-(2-metoxi-piridin-4-il)-1-tritil-1H-indazol-5-ilcarbamoil]-pirrolidin-1-carboxílico



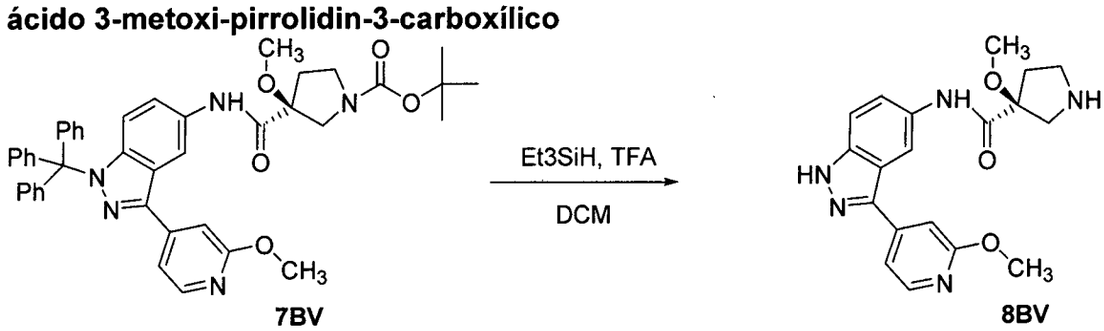


7BV

A la suspensión agitada de 1-ter-butil éster del ácido 3-metoxi-pirrolidin-1,3-dicarboxílico **6BV** (4,16 mmoles, bruto) en DMF/DCM (25 ml/25 ml), se agregaron 3-(2-metoxi-piridin-4-il)-1-tritil-1H-indazol-5-ilamina **5BV** (2,008 g, 4,16 mmole) y Et_3N (2,9 ml, 21 mmole) a ta con gas N_2 seco seguido por HATU (3,16 g, 8,32 mmole). La mezcla se agitó a ta bajo gas N_2 seco hasta el día siguiente. La mezcla se dividió entre 1:1 EtOAc y una solución saturada de $NaHCO_3$. La fase orgánica se separó, se lavó con salmuera, se secó sobre MgSO4 y se evaporó a sequedad. El sólido bruto se purificó sobre un cartucho RediSep 120g eluyendo con EtOAc/Hexanos 10-25% para dar un sólido marrón **7BV** (2,95 g, 100%).

Paso 5

Preparación de [3-(2-metoxi-piridin-4-il)-1H-indazol-5-il]-amida del ácido 3-metoxi-pirrolidin-3-carboxílico

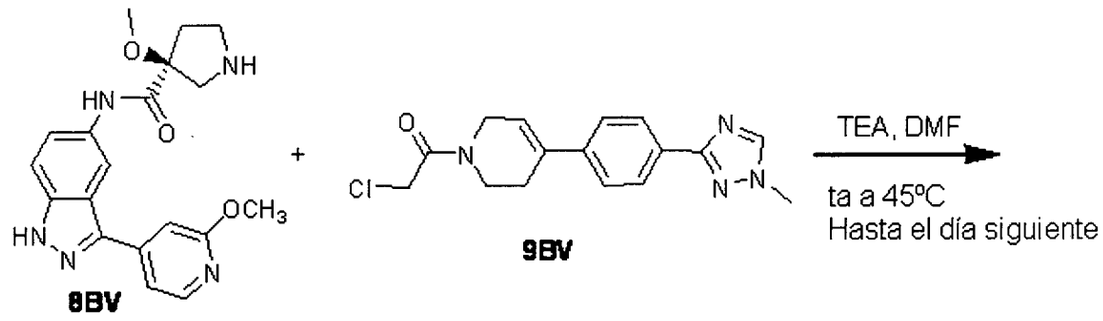


7BV **8BV**

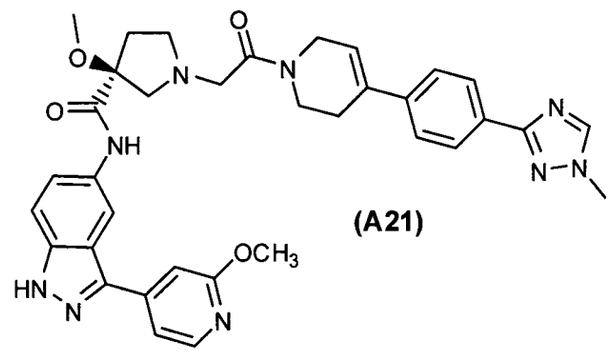
A la solución agitada de ter-butil éster del ácido 3-metoxi-3-[3-(2-metoxi-piridin-4-il)-1-tritil-1H-indazol-5-ilcarbamoil]-pirrolidin-1-carboxílico **7BV** (2,95 g, 4,16 mmole) en DCM (50 ml) a ta, se agregó trietilsilana (1,00 ml, 6,24 mmole) seguido por TFA (10 ml). La mezcla se agitó a ta con gas N_2 seco durante 4-5 horas. La mezcla se evaporó a sequedad y se co-evaporó con tolueno seco (2x75 ml). El sólido bruto resultante se purificó sobre un cartucho RediSep de 120 g eluyendo con NH_3-MeOH/CH_2Cl_2 2,5%-6% 2M para dar un sólido blancuzco **8BV** (1,23 g, 80%).

Paso 6

Síntesis de [3-(2-Metoxi-piridin-4-il)-1H-indazol-5-il]-amida del ácido 3-metoxi-1-(2-{4-[4-(1-metil-1H-[1,2,4]triazol-3-il)-fenil]-3,6-dihidro-2H-piridin-1-il}-2-oxo-etil)-pirrolidin-3-carboxílico



8BV + **9BV**



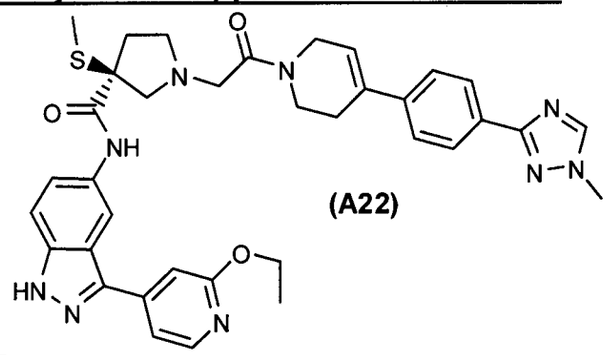
(A21)

Una mezcla del compuesto **8BV** (40 mg, 0,11 mmol), compuesto **9BV** (41,6 mg, 0,13 mmol) y trietilamina (0,1 ml) en DMF (3 ml) se calentó a 45°C con agitación hasta el día siguiente. Luego, la mezcla de reacción se concentró *in vacuo* y el bruto resultante se purificó sobre una columna de gel de sílice eluyendo con NH_3/MeOH 2N 2% y 4% en CH_2Cl_2 para aislar un sólido amarillo **A21** (39,6 mg, 55%). (LCMS M+1 = 648, tiempo de retención = 2,34 minutos). ^{1}H-RMN (400 MHz, $CDCl_3$): δ 10,54 (br, 1H), 9,51 & 9,44 (s, s, 1H), 8,46 (dd, 1H, J=8,2 Hz & 1,4 Hz), 8,27 (d, 1H, J=5,3 Hz), 8,07 (s, 1H), 8,05 (m, 2H), 7,76 (m, 1H), 7,54 (m, 1H), 7,44 (m, 3H), 7,37 (br, 1H), 6,20 & 6,11 (t, t, 1H, J=2,5 Hz), 4,27 (m, 2H), 4,00 & 3,98 (s, s, 6H), 3,96 & 3,86 (m, m, 1H), 3,74 (m, 1H), 3,47-3,60 (m, 2H), 3,453 & 3,446 (s, s, 3H), 3,32 (d, 1H, 9,9 Hz), 3,02 (m, 1H),

2,97 (dd, 1H, J=10,1 Hz & 1,0 Hz), 2,91 (m, 1H), 2,64 (m, 2H), 2,47 (m, 1H), 2,19 (m, 1H).

Ejemplo 14

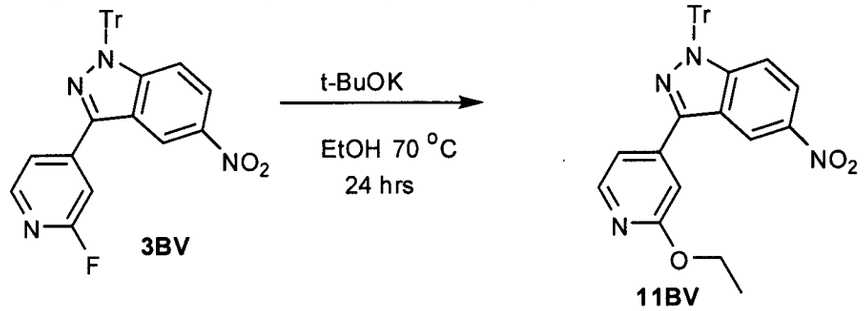
Síntesis de [3-(2-etoxi-piridin-4-il)-1H-indazol-5-il]-amida del ácido 3-metilsulfanil-1-(2-{4-[4-(1-metil-1H-[1,2,4]triazol-3-il)-fenil]-3,6-dihidro-2H-piridin-1-il}-2-oxo-etil)-pirrolidin-3-carboxílico



(A22)

Paso 1:

Preparación de 3-(2-Etoxi-piridin-4-il)-5-nitro-1-tritil-1H-indazol



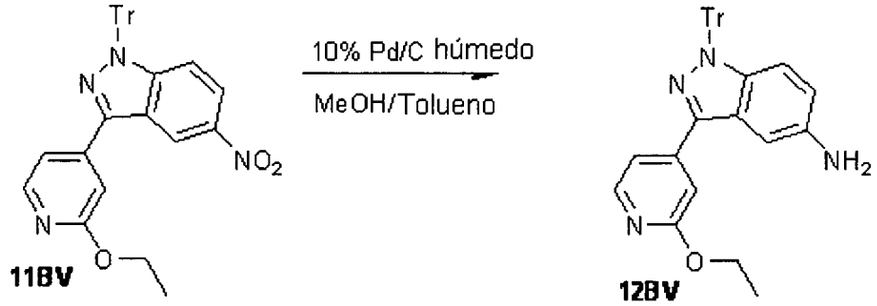
3BV **11BV**

En un recipiente a presión de 150 ml, a la solución agitada de 3-(2-Flúor-piridin-4-il)-5-nitro-1-tritil-1H-indazol **3BV** (2,0 g, 4,0 mmole) en EtOH anhidro (40 ml), se agregó ter-butóxido de potasio sólido (12 g, 10,0 mmole) bajo gas N_2 seco. El recipiente a presión se selló firmemente y se calentó a 80°C durante 24 horas. El recipiente a presión se enfrió a 0°C en un baño de hielo antes de la abertura. Los contenidos del recipiente a presión se transfirieron a RBF de 250 ml y se concentraron a un volumen pequeño. La mezcla resultante se dividió entre EtOAc y H_2O. La fase orgánica se separó, se lavó con una

solución saturada de NaCl y se secó sobre $MgSO_4$. El solvente se evaporó a sequedad para dar un sólido bruto **11BV** (1,5 g, 71%).

Paso 2:

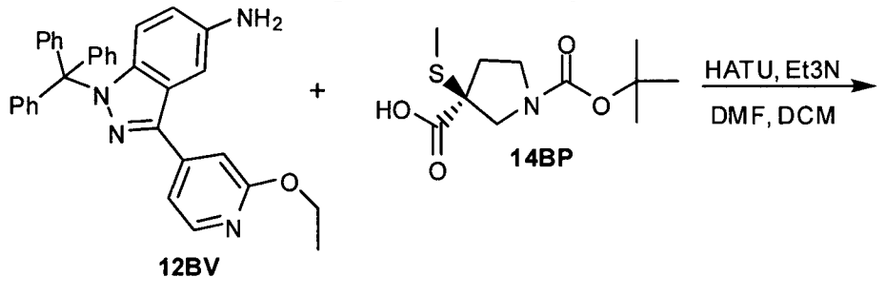
Preparación de 3-(2-etoxi-piridin-4-il)-1-tritil-1H-indazol-5-ilamina

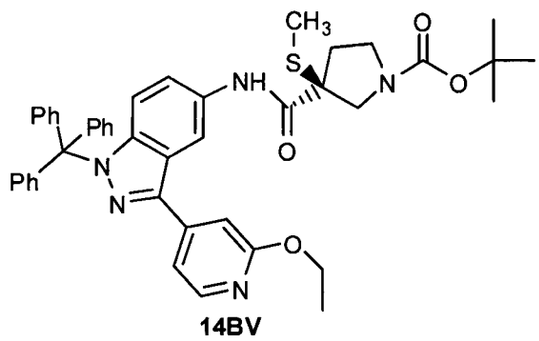


12BV se preparó utilizando esencialmente el mismo procedimiento del Ejemplo 13, Paso 3, con la excepción de que se utilizó **11BV** en lugar de **4BV.**

Paso 3:

Preparación de ter-butil éster del ácido 3-[3-(2-Etoxi-piridin-4-il)-1-tritil-1H-indazol-5-ilcarbamoil]-3-metilsulfanil-pirrolidin-1-carboxílico

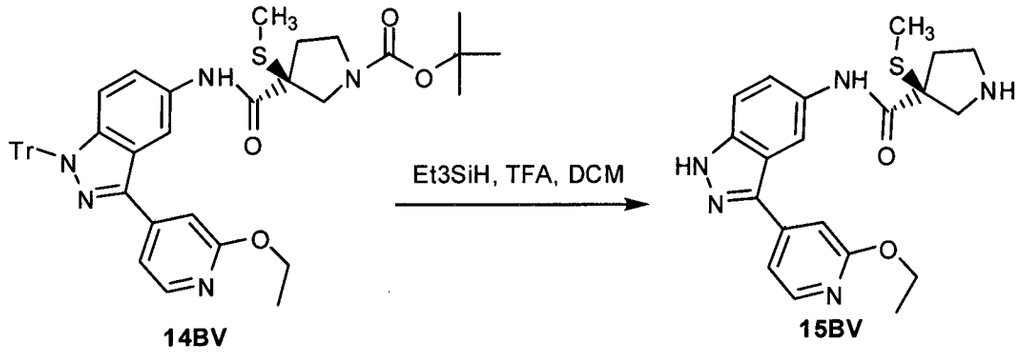




14BV, con un rendimiento de 88%, se preparó utilizando esencialmente el mismo procedimiento del Ejemplo 13, Paso 4, con la excepción de que se utilizó **12BV** y **14BP** en lugar de **5BV** y **6BV**.

Paso 4:

Preparación de [3-(2-etoxi-piridin-4-il)-1H-indazol-5-il]-amida del ácido 3-metilsulfanil-pirrolidin-3-carboxílico

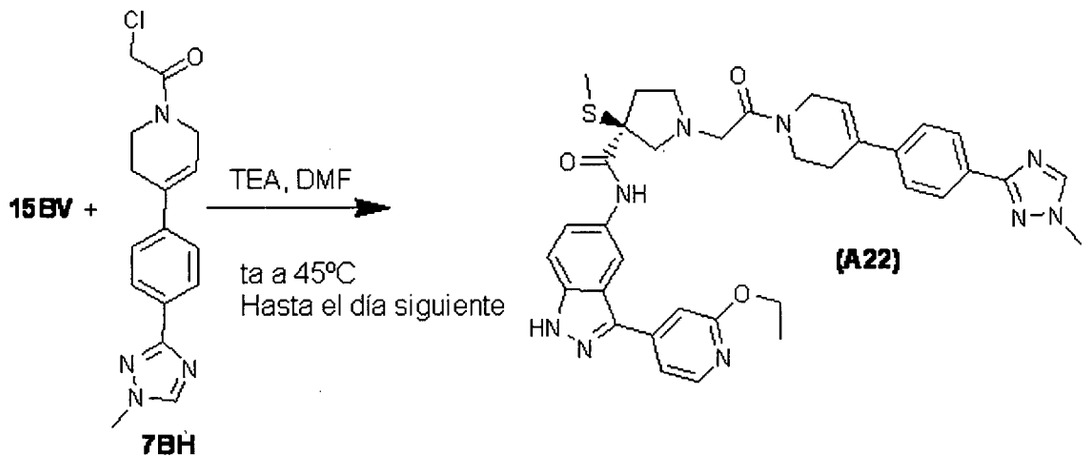


14BV **15BV**

15BV, con un rendimiento de 80%, se preparó utilizando esencialmente el mismo procedimiento del Ejemplo 13, Paso 5, con la excepción de que se utilizó **14BV** en lugar de **7BV**.

Paso 5:

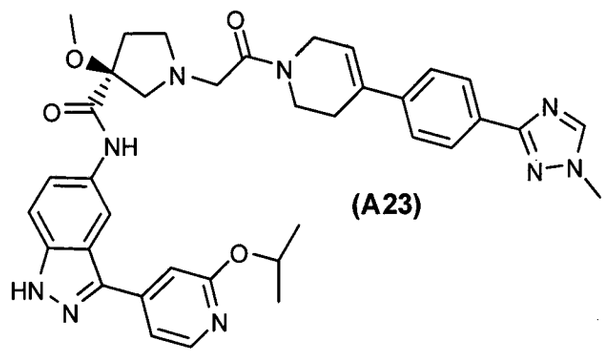
Preparación de [3-(2-etoxi-piridin-4-il)-1H-indazol-5-il]-amida del ácido 3-metilsulfanil-1-(2-{4-[4-(1-metil-1H-[1,2,4]triazol-3-il)-fenil]-3,6-dihidro-2H-piridin-1-il}-2-oxo-etil)-pirrolidin-3-carboxílico



Una mezcla del compuesto **15BV** (40 mg, 0,10 mmol), compuesto **7BH** (41,6 mg, 0,13 mmol) y trietilamina (0,1 ml) en DMF (3 ml) se calentó a 45°C con agitación hasta el día siguiente. Luego, la mezcla de reacción se concentró *in vacuo* y el producto bruto resultante se purificó sobre una columna de gel eluyendo con NH_3/MeOH 2N 2% y 4% en CH_2Cl_2 para aislar un sólido amarillo **A22** (36,0 mg, 53%). (LCMS M+1 = 678, tiempo de retención = 2,41 minutos) ^{1}H-RMN (400 MHz), $CDCl_3$): δ 10,55 (br, 1H), 10,01 & 9,84 (s, s, 1H), 8,50 & 8,44 (d, d, 1H, J=1 Hz), 8,25 (d, 1H, J=5,2 Hz), 8,08 (s, 1H), 8,04 (d, 1H, J=8,2 Hz), 8,00 (d, 1H, J=8,2 Hz), 7,75 (m, 1H), 7,53 (m, 1H), 7,43 (d, 1H, J=8,2 Hz), 7,39 (m, 2H), 7,34 (d, 1H, J=5,2 Hz), 6,18 & 6,11 (t, t, 1H, J=2,5 Hz), 4,42 (q, 2H, J=7,0 Hz), 4,35 & 4,30 (m, m, 1H), 4,22 (m, 1H), 3,99 (s, 3H), 3,92 (t, 1H, J=5,6 Hz), 3,72 (m, 3H), 3,42 (m, 1H), 3,12 (m, 1H), 2,84 (q, 1H, J=7,9 Hz), 2,76 (d, 1H, J=9,9 Hz), 2,70 (m, 1H), 2,63 (m, 2H), 2,15 (s, 3H), 2,11 (m, 1H), 1,44 (t, 3H, J=7,0 Hz).

Ejemplo 15

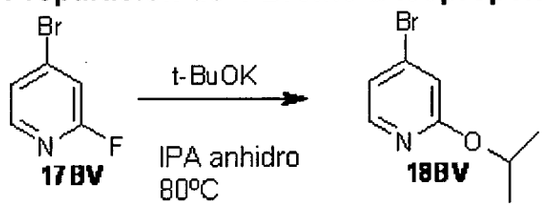
Síntesis de [3-(2-isopropoxi-piridin-4-il)-1H-indazol-5-il]-amida del ácido 3-metoxi-1-(2-{4-[4-(1-metil-1H-[1,2,4]triazol-3-il)-fenil]-3,6-dihidro-2H-piridin-1-il}-2-oxo-etil)-pirrolidin-3-carboxílico



(A23)

Paso 1:

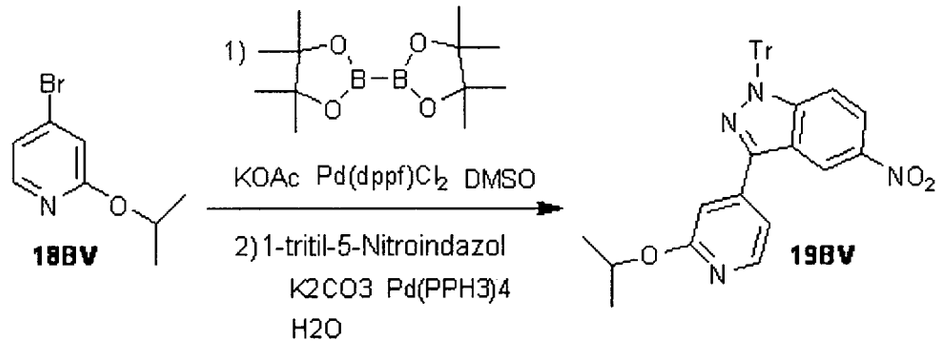
Preparación de 4-Bromo-2-isopropoxi-piridina



A la solución agitada de 4-bromo-2-flúor-piridina **17BV** (4,12 g, 23,41 mmoles) en IPA anhidro 50 ml en un recipiente a presión de 150 ml, se agregó 2,627 g (23,41 mmoles) de de ter-butóxido de potasio sólido bajo gas N_2 seco. El recipiente a presión se selló firmemente y se calentó a 80°C durante 3 horas. El recipiente a presión se enfrió a 0°C en un baño de hielo antes de la abertura. Los contenidos del recipiente a presión se transfirieron a RBF de 250 ml y se concentraron a un volumen pequeño. La mezcla resultante se dividió entre EtOAc y H_2O. La fase orgánica se separó, se lavó con una solución saturada de NaCl y se secó sobre $MgSO_4$. El solvente se evaporó y el aceite claro resultante se purificó sobre un cartucho de RediSep de 80 g eluyendo con Hexanos/EtOAc 20:1 para dar un aceite claro **18BV** (4,2 g, 83%).

Paso 2

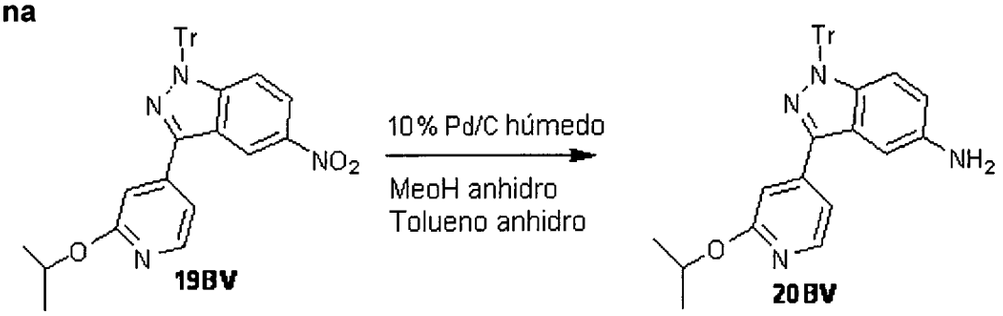
Preparación de 3-(2-Isopropoxi-piridin-4-il)-5-nitro-1-tritil-1H-indazol



A la solución agitada de 4,20 g (19,4 mmoles) de 4-bromo-2-isopropoxi-piridina **18BV** en DMSO anhidro 150 ml, se agregaron 7,39 g (29,1 mmoles) de bis(pinacolato)diboro, 5,704 g (58,2 mmoles) de acetato de potasio, y 1,584 g (1,94 mmoles) de $Pd(dppf)Cl_2$ a ta bajo gas N_2 seco. La mezcla se desgasificó un par de veces con gas N_2 seco. La mezcla anaranjada oscura se calentó a 100°C durante 2 horas. La mezcla de color oscuro se dejó enfriar a ta. Se agregaron 75 ml de H_2O seguido por 9,396 g (19,4 mmoles) de 1-tritil-5-Nitroindazol, 13,401 g (96,96 mmoles) de carbonato de potasio, y se agregaron 2,246 g (1,94 mmoles) de PdTetrakis(Trifenilfosfina) a ta con gas N_2 seco. La mezcla se desgasificó un par de veces con gas N_2 seco. La mezcla de color oscuro se calentó a 100°C hasta el día siguiente. La mezcla se dejó enfriar a ta y se diluyó con una mezcla 1:1 de H_2O/EtOAc. La mezcla diluida se filtró a través de un lecho de Celite, dicho lecho se lavó generosamente con EtOAc. Los contenidos se transfirieron a un embudo de separación y se agitaron bien. La fase orgánica se separó y se lavó un par de veces con una solución saturada de NaCl, se secó sobre $MgSO_4$ y se evaporó a sequedad. La goma de color oscuro se purificó sobre un cartucho de RediSep de 330 g eluyendo con Hexanos, EtOAc/Hexanop 5% y EtOAc/Hexanos 10%, y dio 3,24 g (31%) de un sólido amarillo pálido **19BV**.

Paso 3

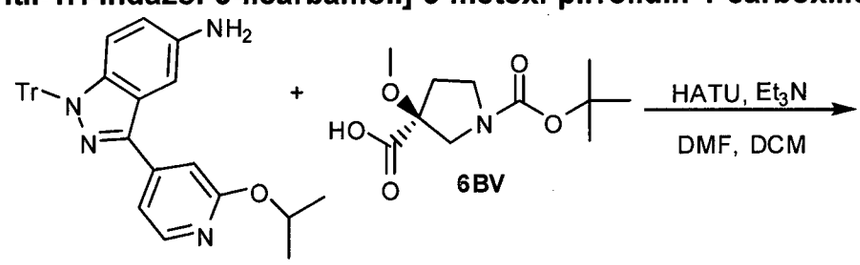
Preparación de 3-(2-Isopropoxi-piridin-4-il)-1-tritil-1H-indazol-5-ilamina

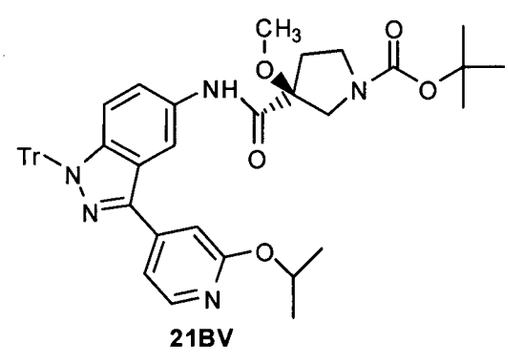


20BV se preparó, con un rendimiento bruto de 100%, utilizando esencialmente el mismo procedimiento del Ejemplo 13, Paso 3, con la excepción de que se utilizó **19BV** en lugar de **4BV**.

Paso 4:

Preparación de ter-butil éster del ácido 3-[3-(2-isopropoxi-piridin-4-il)-1-tritil-1H-indazol-5-ilcarbamoil]-3-metoxi-pirrolidin-1-carboxílico

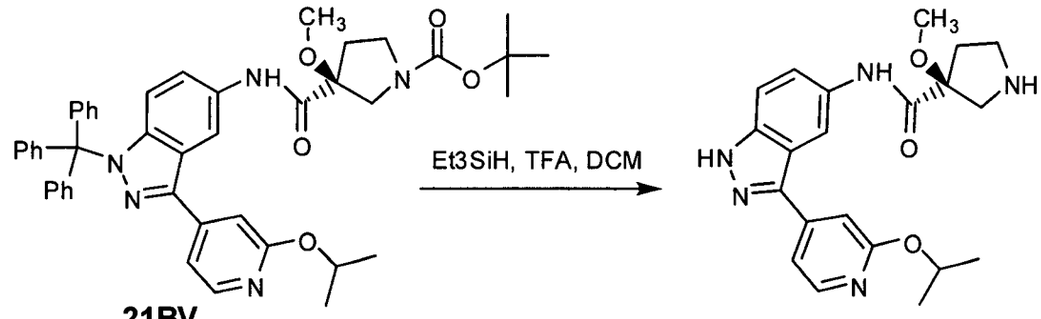




21BV se preparó utilizando esencialmente el mismo procedimiento del Ejemplo 13, Paso 4, comenzando con **20BV** en lugar de **5BV**.

Paso 5:

Preparación de [3-(2-isopropoxi-piridin-4-il)-1H-indazol-5-il]-amida del ácido 3-metoxi-pirrolidin-3-carboxílico

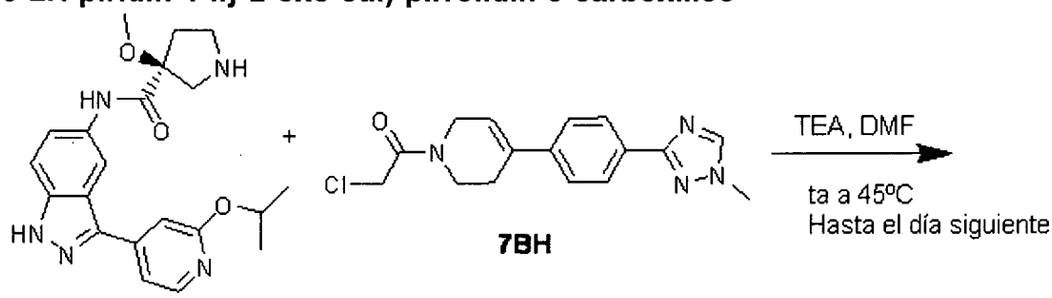


21BV **22BV**

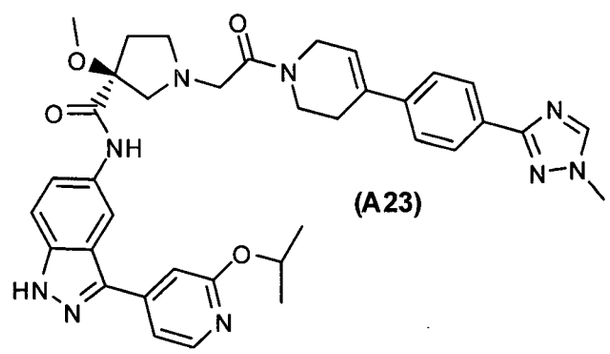
22BV se preparó utilizando esencialmente el mismo procedimiento del Ejemplo 13, Paso 5, utilizando **21BV** en lugar de **7BV**.

Paso 6:

Preparación de [3-(2-isopropoxi-piridin-4-il)-1H-indazol-5-il]-amida del ácido 3-metoxi-1-(2-{4-[4-(1-metil-1H-[1,2,4]triazol-3-il)-fenil]-3,6-dihidro-2H-piridin-1-il}-2-oxo-etil)-pirrolidin-3-carboxílico



22BV **7BH**

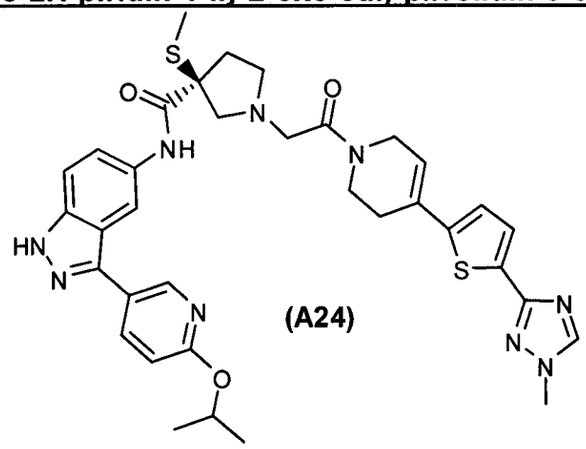


(A23)

Una mezcla del compuesto **22BV** (40 mg, 0,10 mmol), compuesto **7BH** (41,6 mg, 0,13 mmol) y trietilamina (0,1 ml) en DMF (3 ml) se calentó a 45°C con agitación hasta el día siguiente. La mezcla de reacción se concentró *in vacuo* y el producto bruto resultante se purificó sobre una columna de gel eluyendo con NH_3/MeOH 2N 2% y 4% en CH_2Cl_2 para aislar un sólido amarillo **23BV** (35,0 mg, 52%). LCMS M+1 = 676, tiempo de retención = 2,45 minutos. ^{1}H-RMN (400 MHz, $CDCl_3$): δ 10,42 (br, 1H), 9,41 & 9,34 (s, s,1H), 8,43 (dd, 1H, J=10,7 Hz & 1,2 Hz), 8,25 (d, 1H, J=5,2 Hz), 8,07 (s, 1H), 8,05 (m, 2H), 7,74 (m, 1H), 7,49 (m,1H), 7,44 (m, 3H), 7,29 (br, 1H), 6,20 & 6,11 (t, t, 1H, J=2,5 Hz), 5,37 (m, 1H), 4,27 (m, 2H), 3,98 (s, 3H), 3,80-3,98 (m, 1H), 3,74 (m, 1H), 3,53 (d, 1H, J=6,6 Hz), 3,49 (br, 1H), 3,47 & 3,46 (s, s, 3H), 3,28 (d, 1H, J=10 Hz), 3,02 (m, 2H), 2,88 (m, 1H), 2,64 (m, 2H), 2,47 (m, 1H), 2,19 (m, 1H), 1,40 (d, 6H, J=6,1 Hz).

Ejemplo 16

Síntesis de [3-(6-isopropoxi-piridin-3-il)-1H-indazol-5-il]-amida del ácido 3-metilsulfanil-1-(2-{4-[5-(1-metil-1H-[1,2,4]triazol-3-il)-tiofen-2-il]-3,6-dihidro-2H-piridin-1-il}-2-oxo-etil)-pirrolidin-3-carboxílico

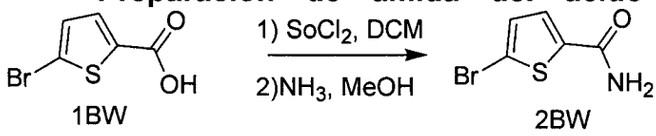


(A24)

Síntesis de 2-Cloro-1-{4-[5-(1-metil-1*H*-[1,2,4]triazol-3-il)-tiofen-2-il]-3,6-dihidro-2*H*-piridin-1-il}-etanona

Paso 1:

Preparación de amida del ácido 5-bromo-tiofen-2-carboxílico

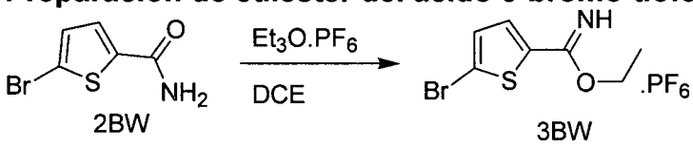


1BW 2BW

Se suspendió ácido 5-bromo-tiofen 2-carboxílico (**1BW)** (6g) en diclorometano (30 ml) y tionil cloruro (30 ml). La solución resultante se dejó calentar a reflujo hasta el día siguiente a 80°C. El solvente se retiró a presión reducida y el precipitado se disolvió en diclorometano que se agregó gota a gota a la solución enfriada de amoníaco en metanol (100 ml). La reacción se observó mediante TLC y LC-MS. El solvente se retiró a presión reducida para dar la amida del ácido 5-bromo-tiofen-2-carboxílico (**2BW)**.

Paso 2:

Preparación de etiléster del ácido 5-bromo-tiofen-2-carboximídico

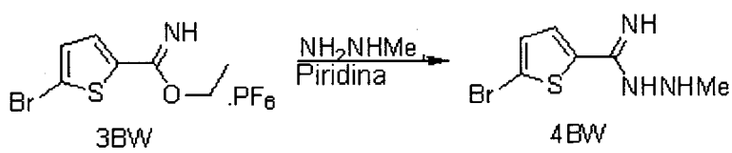


2BW 3BW

La amida del ácido 5-bromo-tiofen-2-carboxílico **(2BW)** (7g, 34,1 mmoles) se disolvió en dicloroetano (170 ml). Se agregó hexafluorfosfato de trietiloxonio (10,16g, 40,97 mmoles) y la mezcla resultante se calentó a reflujo durante 1 hora a 90°C. La mezcla de reacción se concentró a presión reducida, y se tomó directamente en el próximo paso.

Paso 3:

Preparación de N'-metil-hidrazida-2-carboximídica de 5-bromo-tiofeno

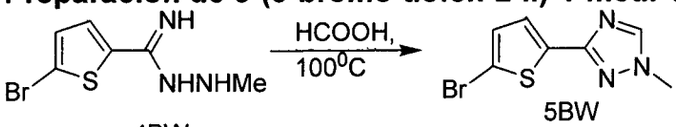


3BW 4BW

El etiléster del ácido 5-bromo-tiofen-2-carboximídico **(3BW)** (13g, 34,3 mmoles) se disolvió en piridina (100 ml). Se agregó metilhidrazina (2,7, 51,45 mmoles) con agitación y la mezcla resultante se dejó agitar hasta el día siguiente. La mezcla de reacción se concentró a presión reducida, y se agregó éter, se filtró, se lavó con éter tres veces y se secó para dar el compuesto del título (**4BW)** (13 g).

Paso 4:

Preparación de 3-(5-bromo-tiofen-2-il)-1-metil-*1H*-[1,2, 4]triazol

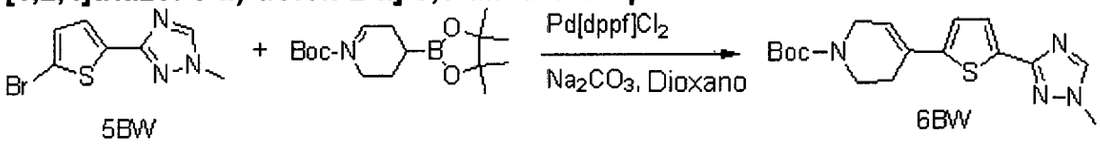


4BW 5BW

Una mezcla del compuesto N'-metil-hidrazida-2-carboximídica de 5-bromo-tiofen **(4BW)** (13 g) en ácido fórmico (100 ml) se calentó a reflujo hasta el día siguiente y se concentró. El residuo se trató con $NaHCO_3$ saturado, y se extrajo tres veces con EtOAc. Los orgánicos combinados se secaron sobre $MgSO_4$. Luego de la concentración, el compuesto **5BW** se purificó en columna utilizando EtoAc/hexano 80% para dar un sólido de color amarillo claro.

Paso 5:

Preparación de ter-butil éster del ácido 4-[5-(1-metil-*1H*-[1,2,4]triazol-3-il)-tiofen-2-il]-3,6-dihidro-*2H*-piridin-1-carboxílico



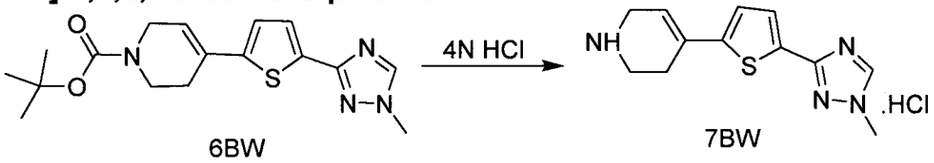
5BW 6BW

Se cargaron en un matraz de alta presión, el compuesto 3-(5-bromo-thiophen-2-il)-1-metil-1H-[1,2, 4]triazol (3,1 g, 12,8 mmoles) **(5BW)**, 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 (3,6 g, 11,65 mmoles), [1,1'-bis(difenilfosfino)-ferroceno]dicloro-paladio (II), complejo con diclorometano (1:1) (0,475 g, 0,89

mmoles), Na_2CO_3 (8,5 ml) y dioxano (40 ml). La mezcla se desgasificó brevemente con Ar durante ~0,5 minutos, se tapó y agitó a 80°C hasta el día siguiente. Luego del enfriamiento, la mezcla de reacción se diluyó con EtOAc y salmuera. La capa orgánica se aisló y secó $MgSO_4$. Luego de la concentración, el residuo se purificó sobre gel de sílice. La elución con EtOAc (100%) dio el producto deseado **(6BW)** (3,5 g).

Paso 6:

Preparación de clorhidrato de 4-[5-(1-metil-1*H*-[1,2,4]triazol-3-il)-tiofen-2-il]-1,2,3,6-tetrahidro-piridina

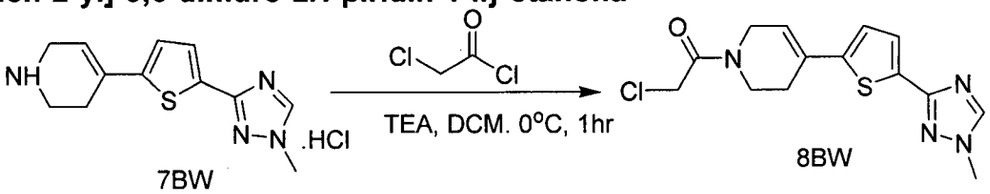


6BW 7BW

El grupo Boc de **6BW** puede retirarse tratando el compuesto ter-butil éster del ácido 4-[5-(1-metil-1H-[1,2,4]triazol-3-il)-tiofen-2-il]-3,6-dihidro-2H-piridin-1-carboxílico con HCl 4N en dioxano a temperatura ambiente durante dos horas. El retiro del solvente al vacío seguido por lavado con éter dio el compuesto deseado **(7BW)**.

Paso 7:

Preparación de 2-cloro-1-{4-[5-(1-metil-1*H*-[1,2,4]triazol-3-il)-thiophen-2-yl]-3,6-dihidro-2*H*-piridin-1-il}-etanona



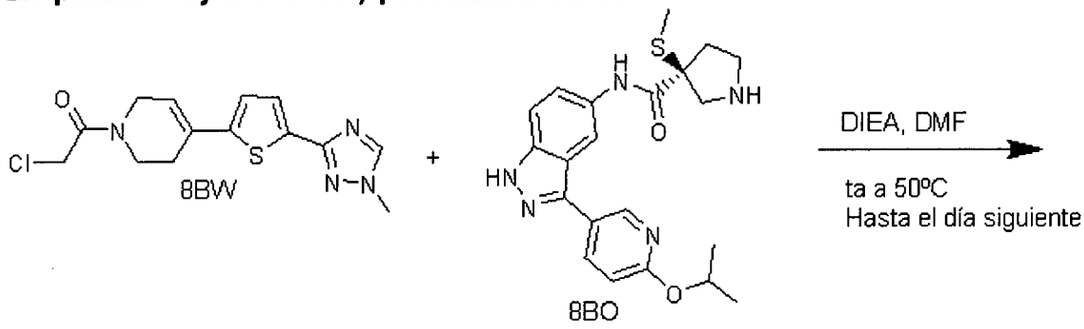
7BW 8BW

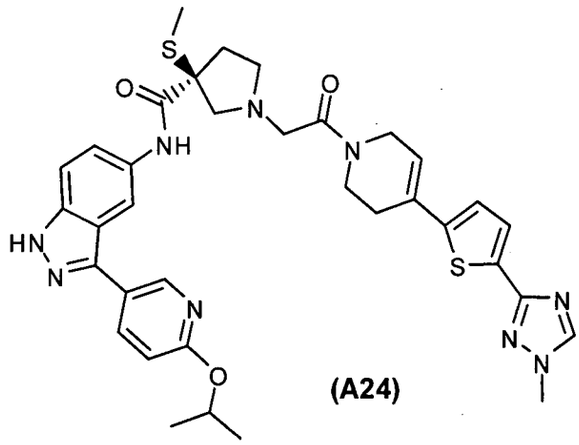
A una solución fría (0°C) de 4-[5-(1-metil-1*H*-[1,2,4]triazol-3-il)-tiofen-2-il]-1,2,3,6-tetrahidro-piridina **(7BW)** (1,5 g, 4,72 mmol) en diclorometano (50 ml) se agregó TEA (4,5 ml, 28,32 mmol) gota a gota. Luego de agitación a 0°C durante 10 minutos, se agregó cloroacetil cloruro (1,12 ml, 14,2 mmol) a la mezcla de reacción. La mezcla resultante se agitó a 0°C durante 1 hora, y se desactivó

con agua (15,6 ml). La mezcla de reacción se diluyó con diclorometano (200 ml). La capa orgánica se separó y lavó con salmuera, se secó sobre $MgSO_4$. La mezcla de reacción se concentró a ~50 ml, se agregó éter y el sólido se filtró para obtener el producto deseado **(8BW)**.

Paso 8:

Síntesis de [3-(6-isopropoxi-piridin-3-il)-1H-indazol-5-il]-amida del ácido 3-metoxi-1-(2-{4-[4-(1-metil-1H-[1,2,4]triazol-3-il)-fenil]-3,6-dihidro-2H-piridin-1-il}-2-oxo-etil)-pirrolidin-3-carboxílico





(A24)

Una mezcla de 2-cloro-1-{4-[5-(1-metil-1H-[1,2,4]triazol-3-il)-tiofen-2-il]-3,6-dihidro-2H-piridin-1-il}-etanona **(8BW)** (0.522gm, 0.863mmol), [3-(6-isopropoxi-piridin-3-il)-1H-indazol-5-il]-amida del ácido 3-metilsulfanil-pirrolidin-3-carboxílico **(8BO)** (0,463 gm, 0,95 mmol), y DIEA (0,9 ml, 5,2 mmol) en DMF (10 ml) se agitó a temperatura ambiente durante toda la noche. El DMF se retiró a presión reducida. La mezcla de reacción bruta se precipitó en agua

helada 30 ml, se filtró, secó, y purificó mediante cromatografía en columna utilizando MeOH/EtOAc 10% para obtener el producto deseado **A24** como un sólido amarillo (70%). (LCMS M+1= 698, tiempo de retención= 3,6 minutos) 1H RMN (400 MHz, DMSO): δ 8,67 (S, 1H), 8,64(S,1H), 8,36 (S, 1H), 8,15 (S, 1H), 7,64(d, 1H, J= 8,8Hz), 7,52 (S, 1H), 7,49 (d, 1H J= 5,2Hz), 7,40(d, 1H J=8,8Hz), 7,02 (m, 1H), 6,18 (d, 1H, J= 18,8 Hz), 5,08 (m, 1H), 4,41 (d, 2H, J=7,6Hz), 4,34 (d, 1H, J=6,4Hz)), 4,12(S, 1H), 3,96 (s, 2H), 3,84 (S, 3H), 3,76 (S, 2H), 3,52(S, 2H), 2,76 (S, 1H), 2,58 (d, 2H J = 20,4Hz), 2,13 (S, 3H), 1,94 (t, 2H J= 2,8Hz), 1,39 (d, 6H, J=4,8 Hz).

Ejemplos 17 a 25

Los ejemplos A4, A6, A8, A10-A12, A18, A25 y A26 se prepararon siguiendo los procedimientos indicados en la Tabla 1 a continuación.

Tabla 1

Ej.	Compuesto preparado	Procedimiento seguido
17	A4	Esencialmente el mismo procedimiento del Ejemplo 4 con la excepción de que se sustituye hidrazina por hidroxietilhidrazina en la preparación de 4BL
18	A6	Esencialmente el mismo procedimiento del Ejemplo 1 con la excepción de que se sustituye 11BP por 14BH
19	A8	Esencialmente el mismo procedimiento del Ejemplo 10 con la excepción de que se sustituye 8BO por 8BN en la preparación de 10BN
20	A10	Esencialmente el mismo procedimiento del Ejemplo 8 con la excepción de que se sustituye 8BO por 8BN en la preparación de 10BN
21	A11	Esencialmente el mismo procedimiento del Ejemplo 4 con la excepción de que se sustituye hidroxietilhidrazina por metoxietilhidrazina
22	A12	Esencialmente el mismo procedimiento del Ejemplo 21 con la excepción de que se sustituye con la excepción de que se sustituye 8BO por 8BN en la preparación de 10BN
23	A18	Esencialmente el mismo procedimiento del Ejemplo 7 utilizando 5-(4-Bromo-fenil)-2H-[1,2,4]triazol-3-ilamina comercialmente disponible por 4BN.
24	A25	Esencialmente el mismo procedimiento del Ejemplo 14 con la excepción de que se sustituye 4BV por 11BV
25	A26	Esencialmente el mismo procedimiento del Ejemplo 14 con la excepción de que se sustituye 20BV por 11BV

Los datos de LCMS para los compuestos de la Tabla 1 se dan en la Tabla 2 a continuación.

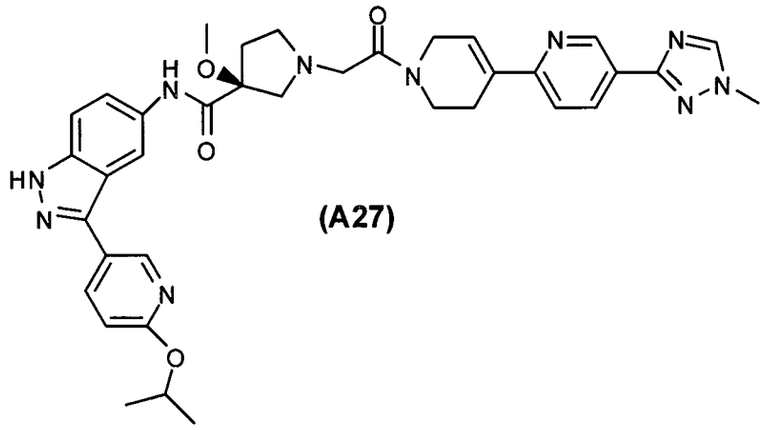
Tabla 2

Compuesto	LCMS Tiempo de retención (Minutos)	LCMS M + 1
A4	3,08	680
A6	3,36	692
A8	3,16	722
A10	3,41	750
A11	3,23	724
A12	3,19	740

A18	3,21	693
A25	2,24	664
A26	2,49	692

Ejemplo 26

Preparación de (S)-N-(3-(6-isopropoxipiridin-3-il)-1H-indazol-5-il)-3-metoxi-1-(2-(4-(5-(1-metil-1H-1,2,4-triazol-3-il)piridin-2-il)-5,6-dihidropiridin-1(2H)-il)-2-oxoetil)pirrolidina-3-carboxamida:



(A27)

Paso 1: 6-cloronicotinimidato de metilo (1BX)

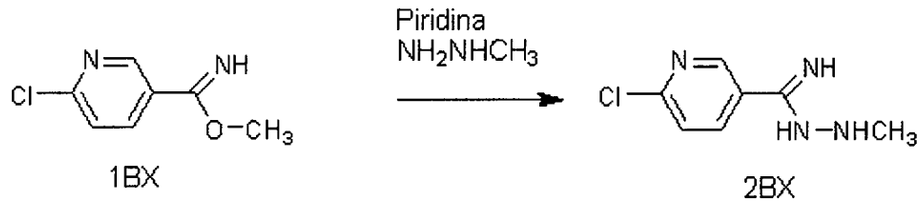


6-cloronicotinonitrilo

6-cloronicotinimidato de metilo
1BX

Se agregó metóxido de sodio (725 mg, 13,42 mmol) a una solución de 2-cloro piridin-5-carbonitrilo (1,8 g,13,04 mmol) en MeOH:dioxano (40 ml,1:1) a 0°C, luego se agitó durante 30 minutos a 0°C, y 1 hora a temperatura ambiente. La reacción se diluyó con EtOAc (200 ml) y H_2O (100 ml), se separó la capa orgánica, se secó sobre Na_2SO_4, se filtró y se evaporó el solvente para dar el compuesto del título **1BX** como un sólido blanco (2,6 g,100%) MS (MH 171).

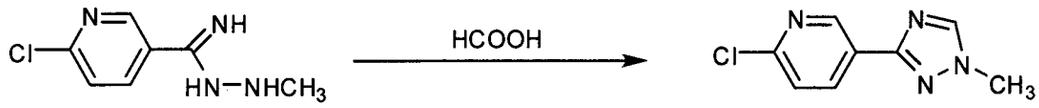
Paso 2: 6-cloro-N'-metilnicotinimidohidrazida (2BX)



1BX 2BX

Se agregó metil hidrazina (750 mg, 16,30 mmol) a una solución de 6-cloronicotinimidato de metilo (**1BX**) (2,6 g, 15,29 mmol) en Piridina (10 ml) a temperatura ambiente, luego se agitó durante 1 hora. El solvente se evaporó, y el sólido residual se trituró con éter frío (2 x 10ml) dando el producto del título **2BX** como un polvo amarillo (2,4 g, 85%) MS (MH, 185)

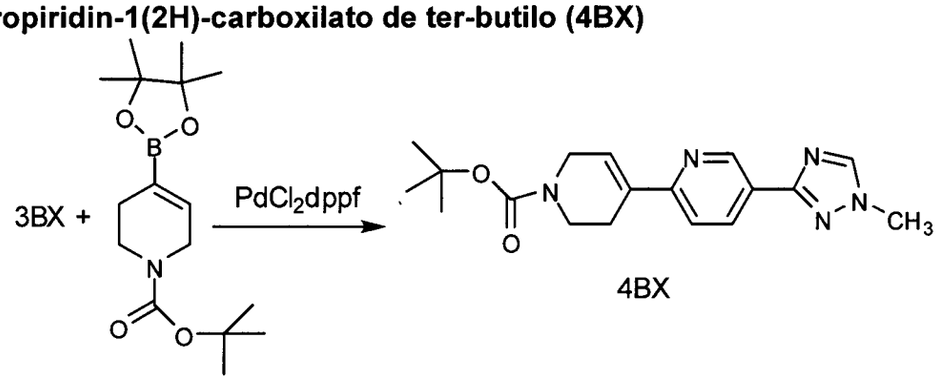
Paso 3: 2-cloro-5-(1-metil-1H-1,2,4-triazol-3-il)piridina (3BX)



2BX 3BX

Una solución de 6-cloro-N'-metilnicotinimidohidrazida (**2BX**) (2,4 g, 13 mmol) en ácido fórmico (99%,10 ml) se agitó a temperatura de reflujo durante 1 hora. La reacción se enfrió y se evaporó el solvente. El residuo se extrajo con EtOAc (100 ml) y $NaHCO_3$ acuoso (50 ml), se separó la capa orgánica, se secó sobre Na_2SO_4, se filtró y se evaporó el solvente. El residuo se sometió a cromatografía sobre gel de sílice eluyendo con MeOH:CH_2Cl_2 10% dando el producto como un sólido (1,8 g, 72%) MS (MH, 195).

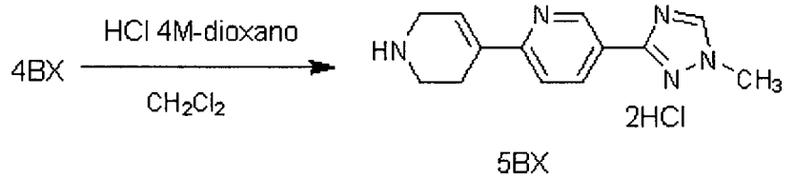
Paso 4: 4-(5-(1-metil-1H-1,2,4-triazol-3-il)piridin-2-il)-5,6-dihidropiridin-1(2H)-carboxilato de ter-butilo (4BX)



4BX

Una mezcla de 2-cloro-5-(1-metil-1H-1,2,4-triazol-3-il)piridina (**3BX**) (400 mg, 2,06 mmol); pinacol éster del ácido N-ter-butoxicarbonil-1,2,3,6-tetrahidropiridin-4-borónico (1,4 g, 4,53 mmol); carbonato de cesio (2,3 g, 7,07 mmol) y $PdCl_2$dppf (100 mg) en dioxano/H_2O (v/v 10:1, 20 ml) se agitó a 100ºC durante 2 horas. La reacción se enfrió, se diluyó con CH_2Cl_2 (300 ml) y H_2O (100 ml), se separó la capa orgánica, se secó sobre Na_2SO_4, se filtró y se evaporó el solvente dando un residuo que se sometió a cromatografía sobre gel de sílice eluyendo con EtOAc dando el producto del título **4BX** como un sólido (400 mg, 57%) MS (MH,342).

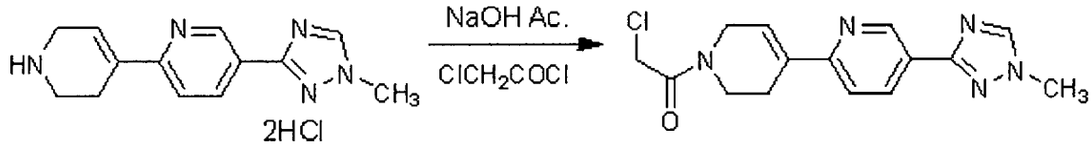
Paso 5: diclorhidrato de 5-(1-metil-1H-1,2,4-triazol-3-il)-2-(1,2,3,6-tetrahidropiridin-4-il)piridina (5BX)



5BX

Se agregó HCl 4M en dioxano (20 ml) a una solución de 4-(5-(1-metil-1H-1,2,4-triazol-3-il)piridin-2-il)-5,6-dihidropiridin-1(2H)-carboxilato de ter-butilo (**4BX**) (4 g, 11,67 mmol) en CH_2Cl_2 (50 ml) a temperatura ambiente. La mezcla se agitó durante 3 horas, luego se evaporó el solvente dando el producto del título como un sólido blanco (3,8 g).

Paso 6: 2-cloro-1-(4-(5-(1-metil-1H-1,2,4-triazol-3-il)piridin-2-il)-5,6-dihidropiridin-1(2H)-il)etanona (6BX)

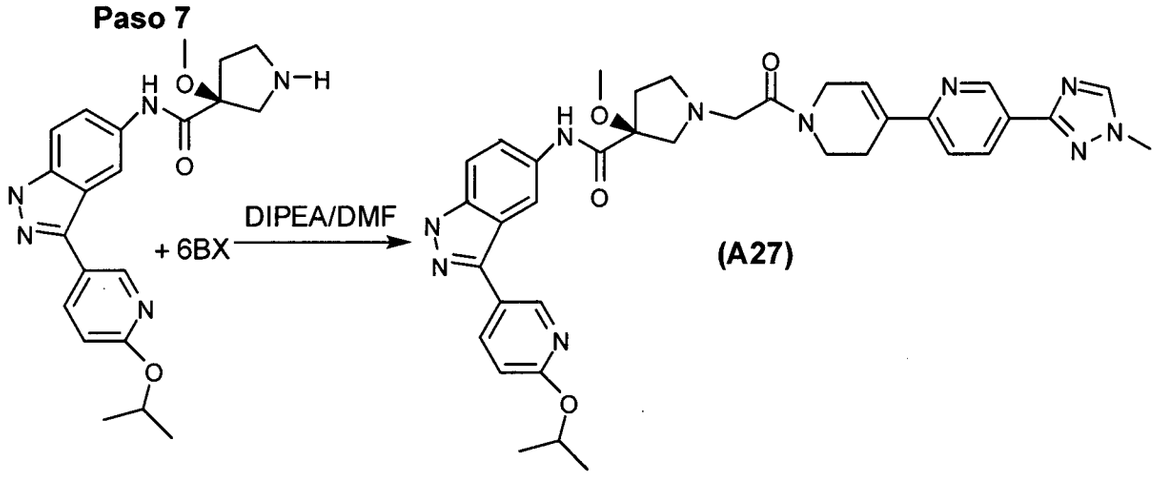


5BX

6BX

Se agregó gota a gota NaOH 1N (50 ml, 50 mmol) y cloroacetil cloruro (3 ml, 37,7 mmol) en CH_2Cl_2 (50 ml) a una solución de diclorhidrato de 5-(1-metil-1H-1,2,4-triazol-3-il)-2-(1,2,3,6-tetrahidropiridin-4-il)piridina (**5BX**) (1 g, 3,60 mmol) en CH_2Cl_2 (50 ml a 0°C, manteniendo el pH a >12. La mezcla se agitó durante 2 horas a 0°C, luego la reacción se diluyó con CH_2Cl_2 (200 ml) y H_2O (100 ml). Se separó la capa orgánica, se lavó con H_2O (50 ml), se secó (Na_2SO_4), se filtró y se evaporó el solvente dando el producto del título como un sólido blanco (1,1 g, 100%) MS (MH, 318)

Paso 7

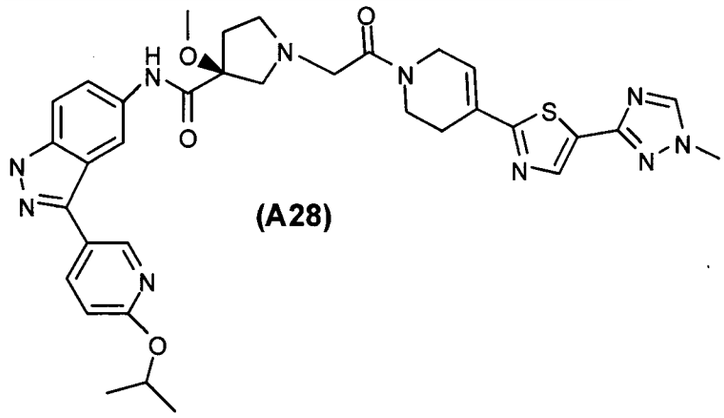


Se agregó una solución de 2-cloro-1-(4-(5-(1-metil-1H-1,2,4-triazol-3-il)piridin-2-il)-5,6-dihidropiridin-1(2H)-il)etanona (**6BX**) (0,85 g, 2,68 mmol) en CH_2Cl_2 (10 ml) a una solución del Indazol (1 g, 2,53 mmol) en DMF (10 ml) a temperatura ambiente, luego se agitó a 50°C durante 3 horas. La reacción se diluyó con EtOAc (300ml) y H_20 (100ml), luego se separó la capa orgánica, se secó sobre Na_2SO_4, se filtró y se evaporó el solvente. El residuo se sometió a cromatografía sobre gel de sílice eluyendo con MeOH/CH_2Cl_2/NH_4OH 10% v/v dando el producto **A27** como un sólido blanco (1,3 g,76%) MS (MH,677)

LCMS Tiempo de elución = 2,61minutos

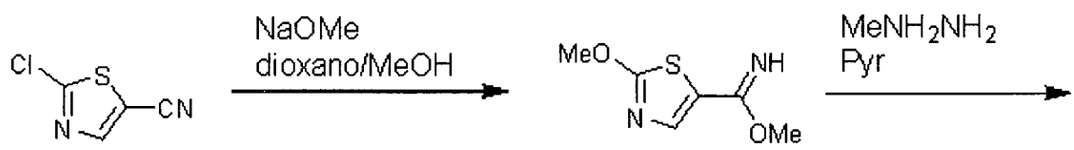
Ejemplo 27

Preparación de (S)-N-(3-(6-isopropoxipiridin-3-il)-1H-indazol-5-il)-3-metoxi-1-(2-(4-(5-(1-metil-1H-1,2,4-triazol-3-il)tiazol-2-il)-5,6-dihidropiridin-1(2H)-il)-2-oxoetil)pirrolidin-3-carboxamida:

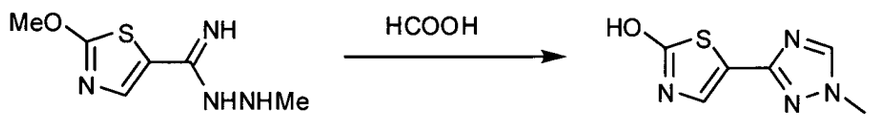


(A28)

Paso 1



1BY **2BY**

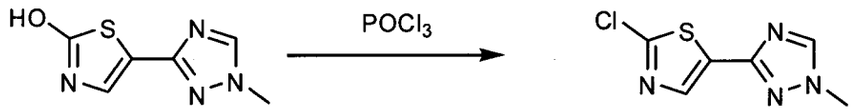


3BY **4BY**

A una mezcla agitada de 2-clorotiazol-carbonitrilo (1 g, 6,92 mmol) en MeOH se agregó NaOMe (745 mg, 13,8 mmol, 2 equiv.) y la mezcla de reacción se agitó a 0ºC durante 15 minutos y se calentó a ta durante otros 15 minutos, se desactivó con agua, se extrajo con EtOAc. La capa orgánica combinada se lavó con salmuera, se secó sobre Na_2SO_4 y concentró para dar **2BY** bruto (1,2 g) como un aceite amarillo. A la solución agitada de **2BY** bruto en piridina (1 ml) se agregó metil hidrazina (363 µl, 6,9 mmol, 1 equiv.), la

mezcla resultante se agitó a 0°C durante 15 minutos y se desactivó con HCOOH (5 ml). Luego, la mezcla resultante se transfirió a un tubo sellado y se agitó a 110°C hasta el día siguiente, se enfrió a ta, a lo que se agregó agua. La mezcla resultante se extrajo con CH_2Cl_2. La capa orgánica combinada se lavó con salmuera, se secó y concentró para dar un sólido amarillo, que se filtró y lavó con CH_2Cl_2. El sólido amarillo resultante (375 mg) es el producto deseado **4BY**. El filtrado se concentró y puede purificarse en columna para proveer más producto.

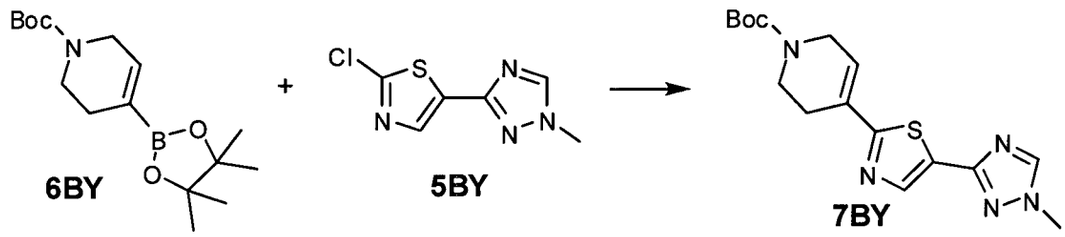
Paso 2



4BY **5BY**

Se agitó una mezcla de **4BY** (130 mg) en $POCl_3$ con N_2 a 120°C durante 2 días. La mezcla heterogénea inicial se tornó una solución marrón claro, que se concentró y purificó sobre gel de sílice (CH_2Cl_2/MeOH, 50/1) para dar **5BY** (143 mg) como un sólido amarillo.

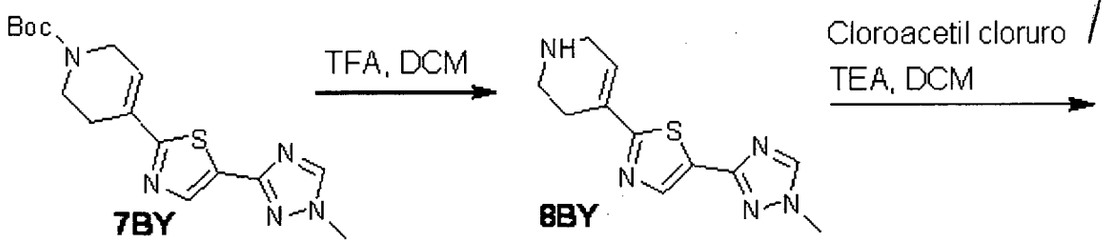
Paso 3

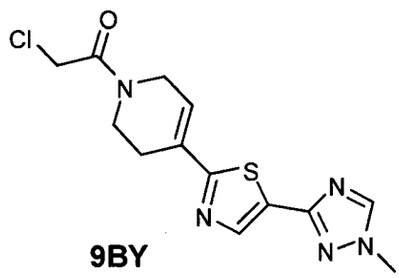


6BY **5BY** **7BY**

Una mezcla de **5BY** (118 mg, 0,59 mmol), **6BY** (274 mg, 0,89 mmol, 1,5 equiv.), Na_2CO_3 2M (590 µl, 1,18 mmol, 2 equiv.) y $Pd(PPh_3)_4$ (34 mg, 0,05 equiv.) en benceno/MeOH (5 ml, 4/1) se desgasificó y agitó con N_2 at 80°C hasta el día siguiente. La mezcla de reacción se concentró y purificó sobre gel de sílice (CH_2Cl_2/MeOH, 30/1) para dar **7BY** (150 mg) como un sólido amarillo.

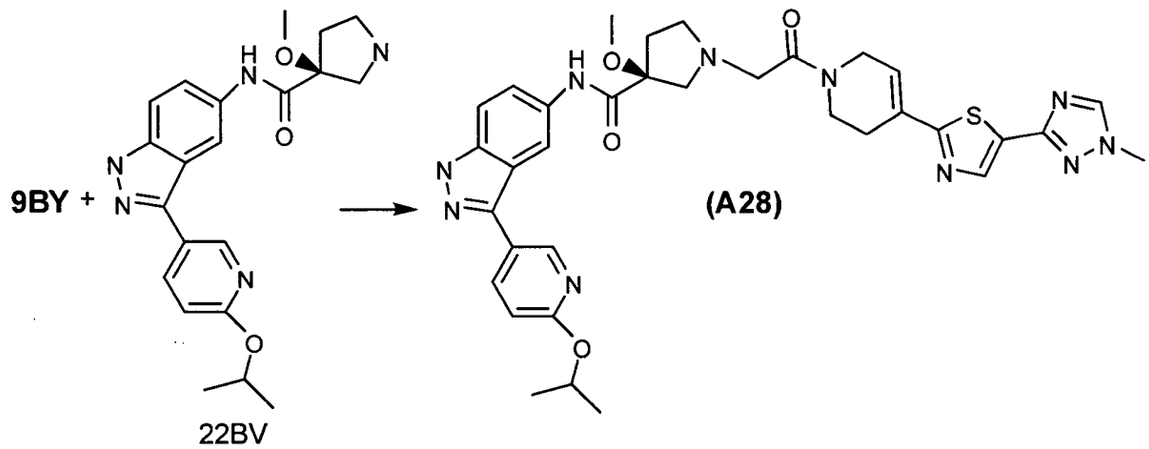
Paso 4





Una mezcla de **7BY** (150 mg, 0,43 mmol) y TFA (1,5 ml) se agitó a ta durante 1 hora y se concentró. La cromatografía sobre gel de sílice (CH_2Cl_2/MeOH, 15/1) dio el **8BY** (98 mg). A una mezcla agitada de **8BY** (98 mg, 0,4 mmol) y trietilamina (335 µl, 2,4 mmol, 6 equiv.) en CH_2Cl_2/MeOH (6 ml, 2/1) a 0°C se agregó cloroacetil cloruro (126 µl, 1,6 mmol, 4 equiv.). La mezcla de reacción se agitó a 0°C durante 1 hora y se concentró. La cromatografía sobre gel de sílice (CH_2Cl_2/MeOH, 25/1) dio el **9BY** (103 mg) como un sólido blanco.

Paso 5

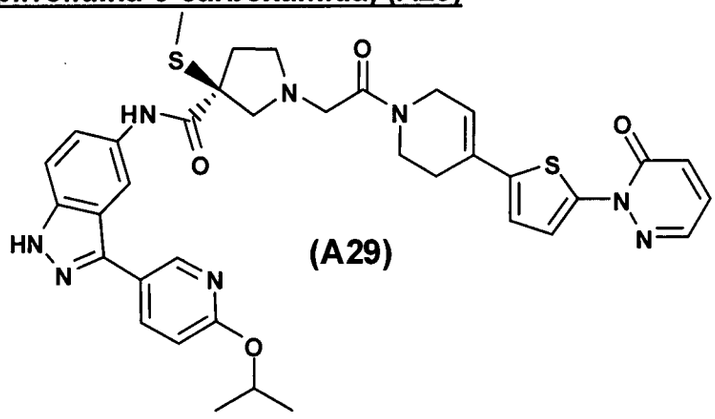


El compuesto **9BY** se sustituyó por el compuesto **7BH** en el Ejemplo 15 Paso 6 para obtener **A28**. LCMS MH = 683,4, Tiempo de retención = 2,77

minutos

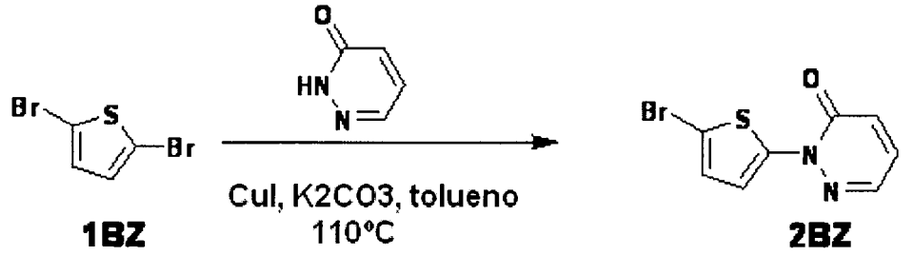
Ejemplo 28

Preparación de (*S*)-N-(3-(6-isopropoxipiridin-3-il)-1H-indaol-5-il)-3-(metiltio)-1-(2-oxo-2-(4-(5-(6-oxopiridazin-1(6H)-il)-5,6-dihidropiridin-1(2H)-il)etil)pirrolidina-3-carboxamida) (A29)



(A29)

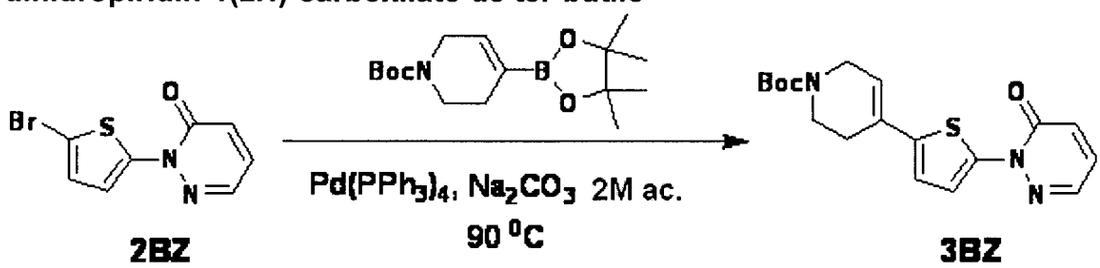
Paso 1: Preparación de 2-(5-bromotiofen-2-il)piridazin-3(2*H*)-ona



1BZ **2BZ**

Una mezcla de 2,5-dibromotiofeno (1,5 g, 6,2 mmol), piridazin-3(2*H*)-ona (0,4 g, 4,1 mmol), yoduro de cobre (I) (0,24 g, 1,2 mmol), carbonato de potasio (1,7 g, 12,4 mmol), trans-N,N'-dimetilciclohexan-1,2-diamina (0,2 ml, 1,2 mmol) y tolueno (15 ml) se desgasificó durante 15 minutos y luego se calentó en un tubo sellado a 110°C durante 18 horas. Se enfrió a temperatura ambiente, se filtró a través de celite y se lavó con EtOAc. El filtrado se lavó con agua (100 ml x 2). La capa orgánica se secó sobre Na_2SO_4, se filtró y concentró para dar el producto deseado **2BZ** (0,9 g, 90%). El residuo se purificó sobre gel de sílice eluyendo con EtOAc/ hexano 80% para dar el producto deseado **2BZ** (0,7 g, 67%).

Paso 2: Preparación de 4-(5-(6-oxopiridazin-1(6H)-il)tiofen-2-il)-5,6-dihidropiridin-1(2*H*)-carboxilato de ter-butilo

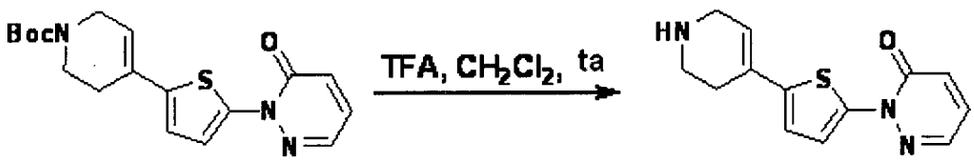


2BZ **3BZ**

Una mezcla del compuesto **2BZ** (0,7 g, 2,7 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 (0,84 g, 2,7 mmol), solución acuosa 2M de carbonato de sodio (6,8

ml, 13,6 mmol), $Pd(PPh_3)_4$ (0.31g, 0.27 mmol) y tolueno/etanol 1/1 (20 ml) se desgasificó durante 15 minutes. Luego, se calentó a 90°C hasta el día siguiente. Se enfrió a temperatura ambiente y se diluyó con EtOAc (200 ml). La capa orgánica se lavó con agua (100 ml), se secó sobre Na_2SO_4, se filtró y concentró. El residuo se purificó sobre gel de sílice eluyendo con 60% EtOAc/hexano para dar el producto deseado **3BZ** (0.63 g, 65%).

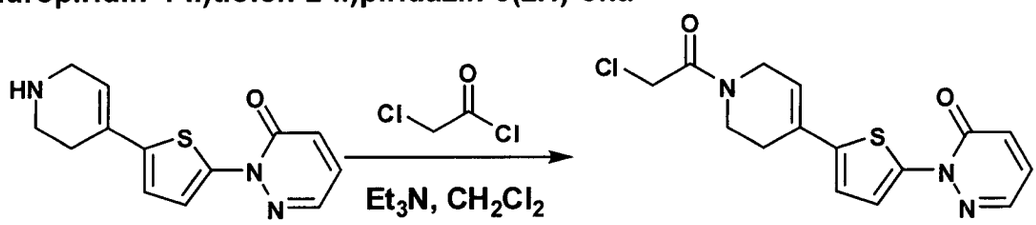
Paso 4: Preparación de 2-(5-(1,2,3,6-tetrahidropiridin-4-il)tiofen-2-il)piridazin-3(2*H*)-ona



3BZ **4BZ**

Una mezcla del compuesto **3BZ** (0,63 g, 1,75 mmol), CH_2Cl_2 (20 ml) y TFA (23mL) se agitó a temperatura ambiente durante 18 horas. Se concentró y purificó sobre gel de sílice eluyendo con MeOH (NH_3)/ CH_2Cl_2 5% para dar el producto deseado **4BZ** (0,4 g, 89%).

Paso 5: Preparación de 2-(5-(1-(2-cloroacetil)-1,2,3,6-tetrahidropiridin-4-il)tiofen-2-il)piridazin-3(2*H*)-ona

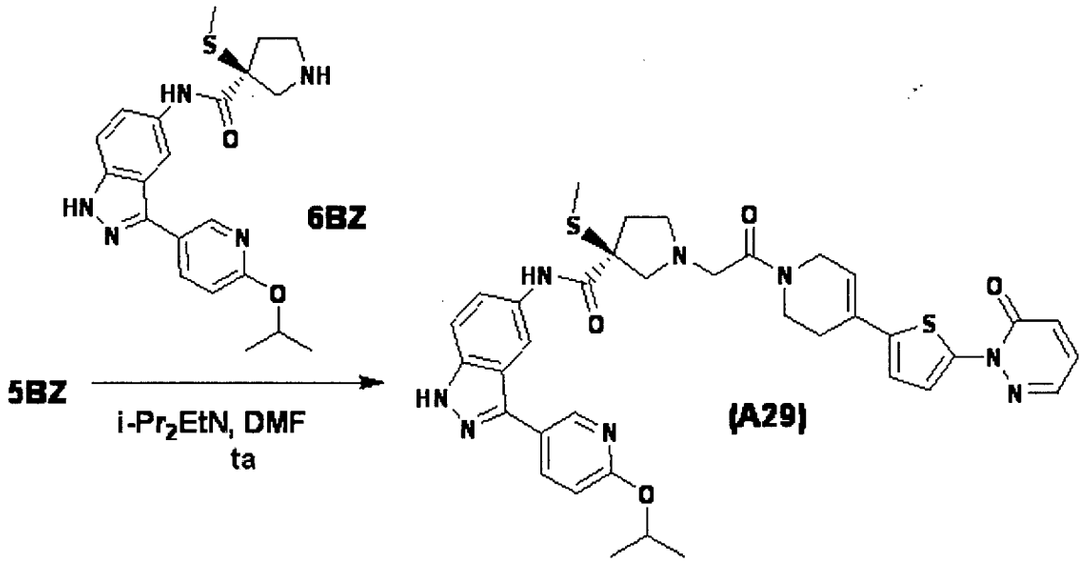


4BZ **5BZ**

A una mezcla del compuesto **4BZ** (0,62 g, 2,39 mmol), CH_2Cl_2 (10 ml), MeOH (3 ml) y trietil amina (0,67 ml, 4,78 mmol) a -78°C se agregó cloroacetil cloruro (0,19 ml, 2,39 mmol). La mezcla de reacción se agitó a -78°C durante

10 minutos, luego se calentó a 0°C y se agitó durante 1 hora. Se diluyó con CH_2Cl_2 (100 ml) y se lavó con $NaHCO_3$ saturado acuoso (100 ml). La capa orgánica se secó sobre Na_2SO_4, se filtró y concentró. El residuo se tomó en CH_2Cl_2 y se agregó éter. El sólido resultante se filtró y se lavó con éter y se secó para dar el producto deseado **5BZ** (0,56 g, 70%).

Paso 6

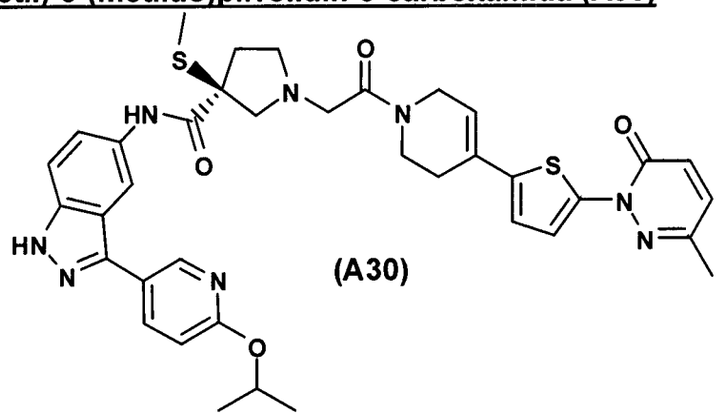


Una mezcla del compuesto **5BZ** (0,04 g, 0,12 mmol), compuesto **6BZ** (0,05 g, 0,12 mmol), DMF (2 ml) y N,N-diisopropiletilamina (0,042 ml, 0,24 mmol) se agitó a temperatura ambiente durante 18 horas. Se diluyó con EtOAc (100 ml) y se lavó con agua (2 x 100 ml). La capa orgánica se secó sobre Na_2SO_4, se filtró y concentró. El residuo se purificó sobre gel de sílice eluyendo con MeOH (NH_3)/ CH_2Cl_2 3% para dar el producto deseado **A29** (0,083 g, 97%).

LCMS MH = 711, Tiempo de retención = 3,26 minutos.

Ejemplo 29

Preparación de (*S*)-N-(3-(6-isopropoxipiridin-3-il)-1*H*-indaol-5-il)-1-(2-(4-(5-(3-metil-6-oxopiridazin-1(6*H*)-il)tiofen-2-il)-5,6-dihidropiridin-1(2*H*)-il)-2-oxoetil)-3-(metiltio)pirrolidin-3-carboxamida (A30)

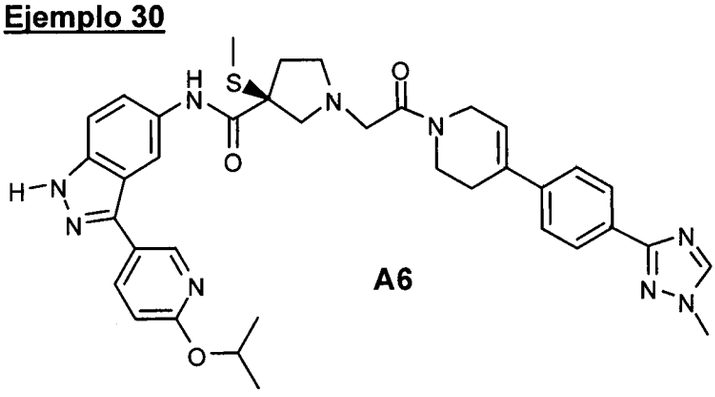


(A30)

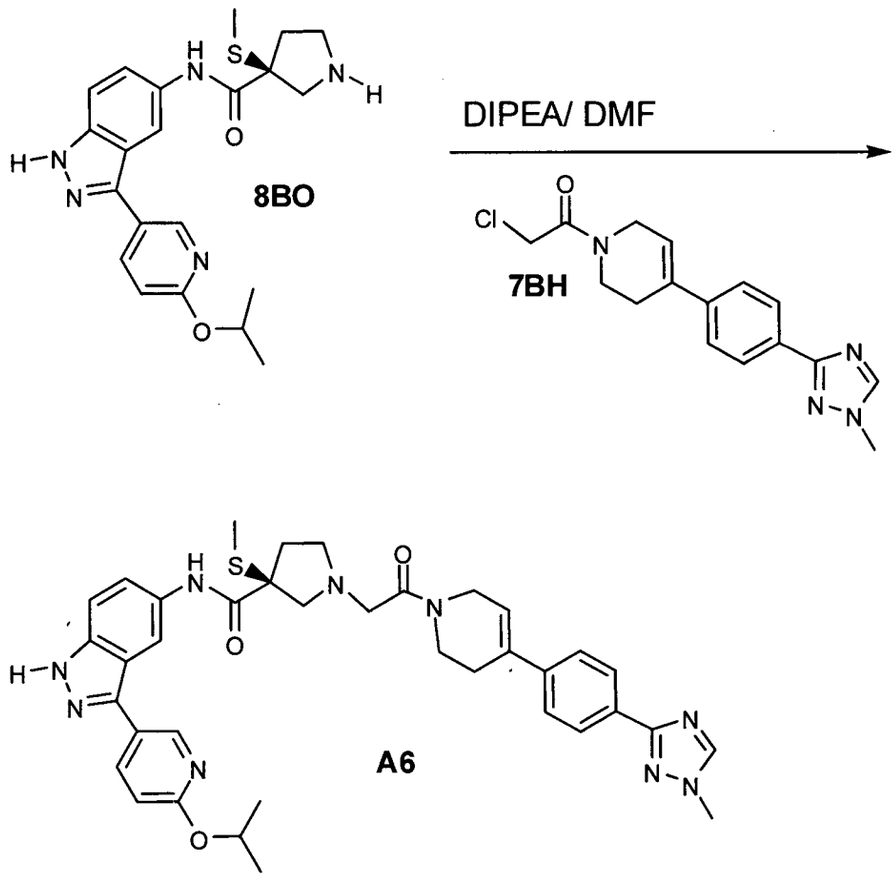
El compuesto **A30** se preparó utilizando un procedimiento similar al del Ejemplo 28 con la excepción de que se utilizó 6-metilpiridazin-3(2*H*)-ona en lugar de piridazin-3(2*H*)-ona en el Paso 1.

LCMS MH = 725, Tiempo de retención = 3,21 minutos.

Ejemplo 30

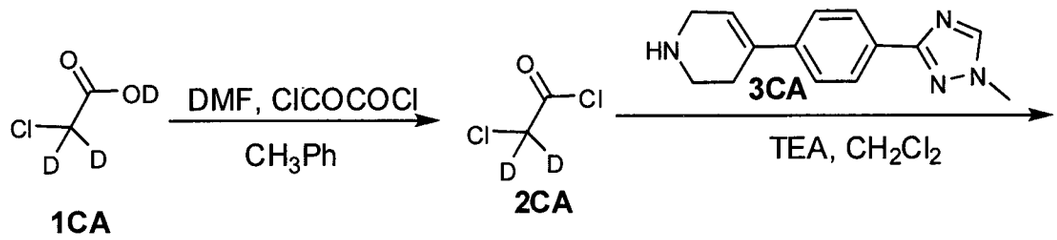


A6

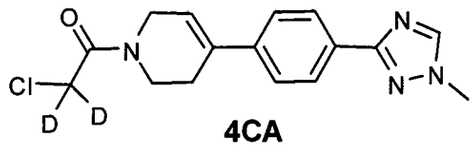


Se disolvió **8BO** (4,25 g, 10,33 mmol) en N,N-dimetilformamida (40 ml) a temperatura ambiente. Se agregó diisopropiletilamina (5,1 ml, 30,99 mmol) seguido por **7BH** (3,27 g, 10,33 mmol). La mezcla de reacción se agitó durante 1 hora a temperatura ambiente hasta el día siguiente. Se agregó salmuera a la mezcla de reacción que luego se extrajo con etilacetato (3 x 100 ml). Los extractos de etilacetato se secaron sobre sulfato de magnesio, se filtraron y evaporaron para obtener el producto del título bruto. El producto bruto se sometió a cromatografía para obtener 4,95 g (69%) del producto del título (**A6**) (NH_3 2N 10% en MeOH:CH_2Cl_2).

Ejemplo 31



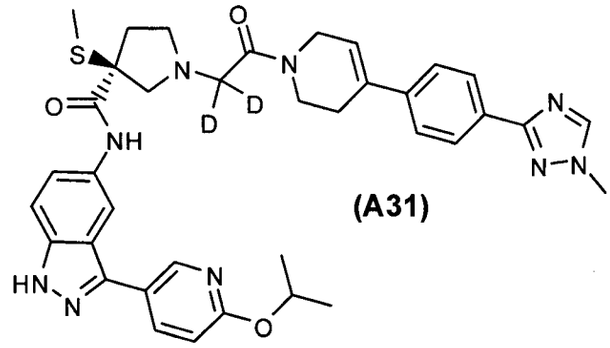
1CA **2CA**



4CA

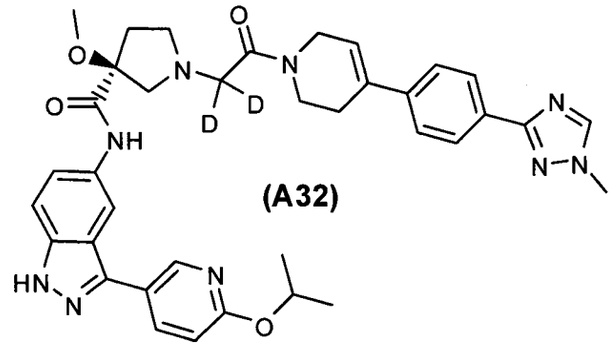
A una solución CH_3Ph (3 ml) de **1CA** (140 mg, 1,4 mmol) se agregó una gota de DMF seguido por la adición de cloruro de oxalilo (0,14 ml, 1,6 mmol) a ta. Luego de 30 minutos, la solución clara resultante se agregó a una solución CH_2Cl_2 de **3CA** (240 mg, 1 mmol) y trietil amina (0,5 ml). Luego de agitación a ta durante 30 minutos, esta se desactivó con $NaHCO_3$ saturado, se extrajo con CH_2Cl_2 y se concentró para obtener un sólido blancuzco como un **4CA** bruto (312 mg) que se utilizó directamente en las próximas reacciones. En **1CA**, **2CA**, y **4CA** "D" representa deuterio.

Los compuestos **A31** y **A32,** se prepararon mediante un método similar al método para preparar el Compuesto **A1** y **A6** sustituyendo **4CA** por **7BH**. Los compuestos **A45** y **A48** se prepararon mediante un método similar al método para preparar **A23** y **A25** sustituyendo **4CA** por **7BH**. En **A31**, **A32**, **A45** y **A48** "D" representa deuterio.



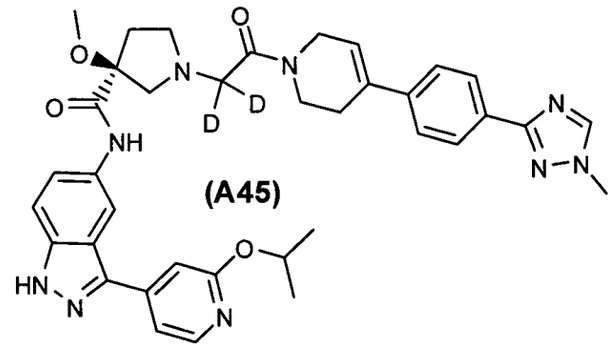
(A31)

LCMS 3,95 minutos M+1 = 694,4



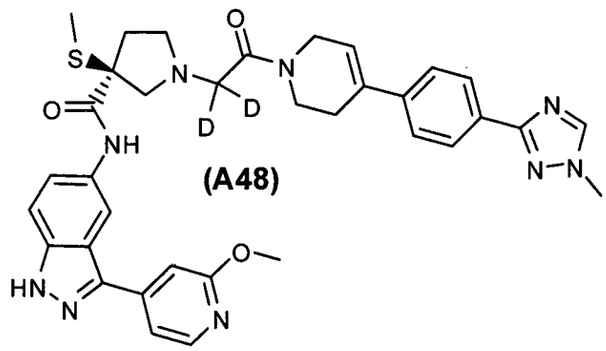
(A32)

LCMS 4,24 minutos M+1 = 678,4



(A45)

LCMS 3,94 minutos M+1 = 674

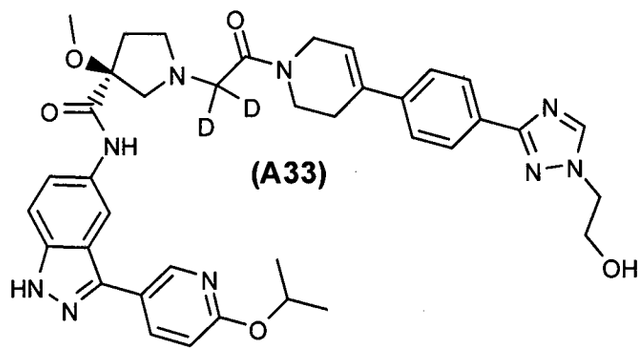


(A48)

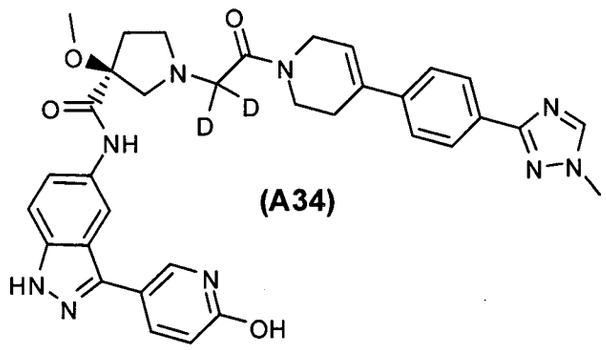
LCMS 3,61 minutos M+1 = 664

Ejemplo 32

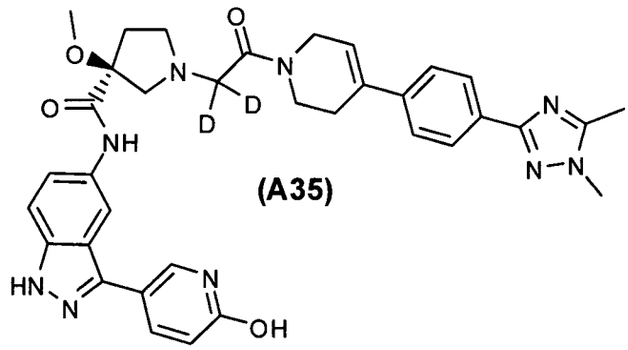
En caso de seguirse un procedimiento similar al procedimiento del Ejemplo 31, se obtendrían los Compuestos **A33** a **A44**, **A46**, y **A47** a continuación. En **A33** a **A44**, **A46**, y **A47** "D" representa deuterio.



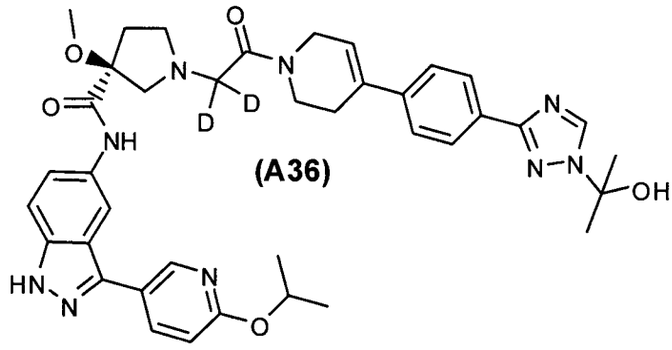
(A33)



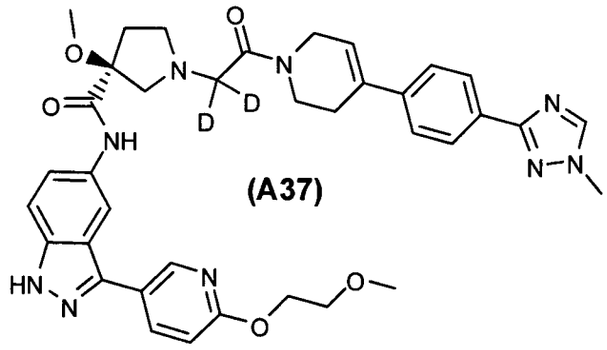
(A34)



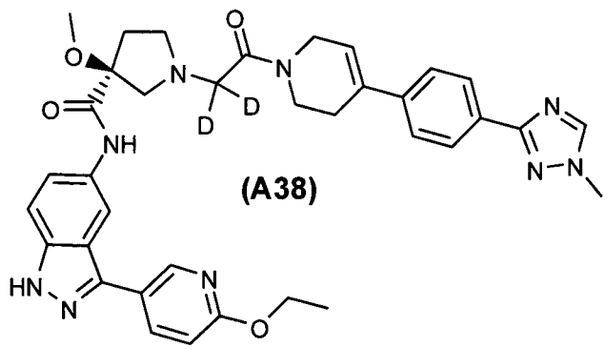
(A35)



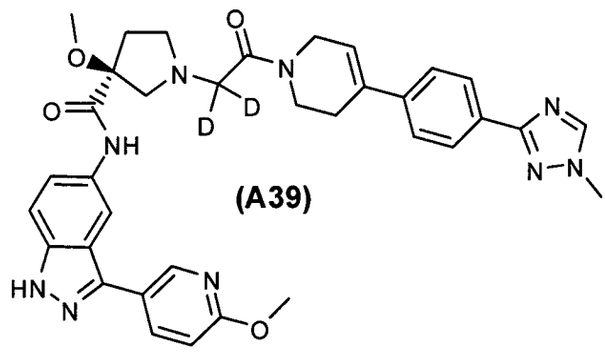
(A36)



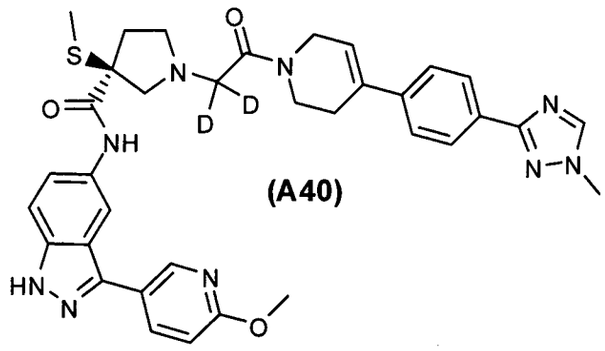
(A37)



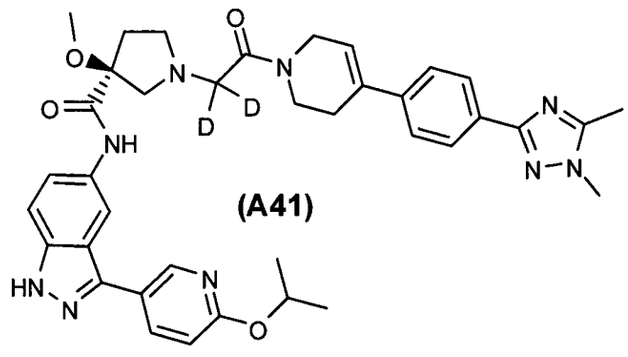
(A38)



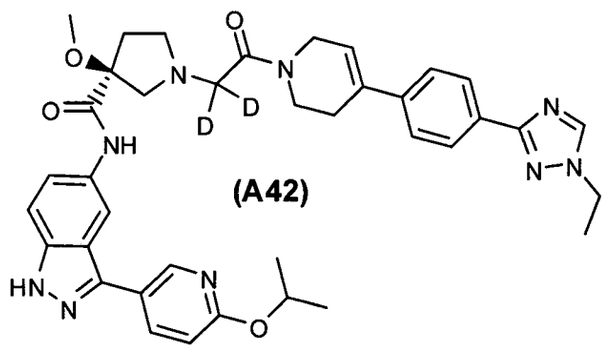
(A39)



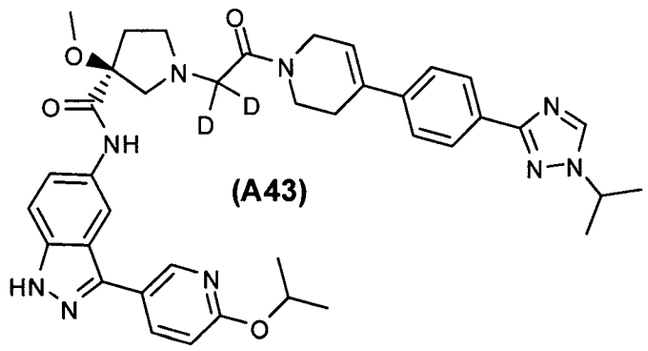
(A40)



(A41)

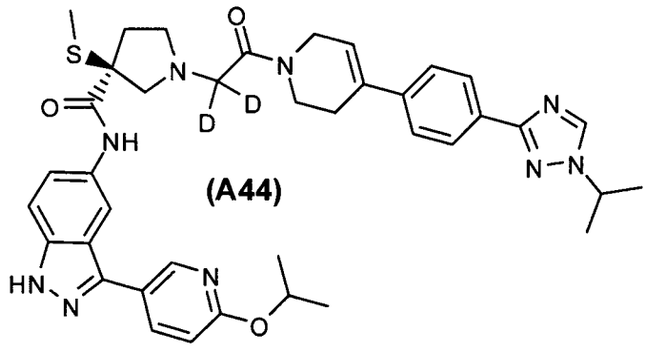


(A42)



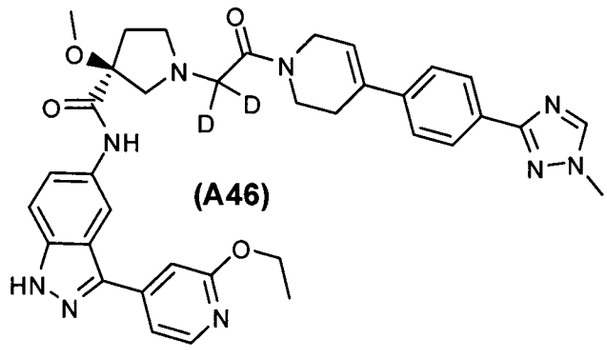
(A43)

,



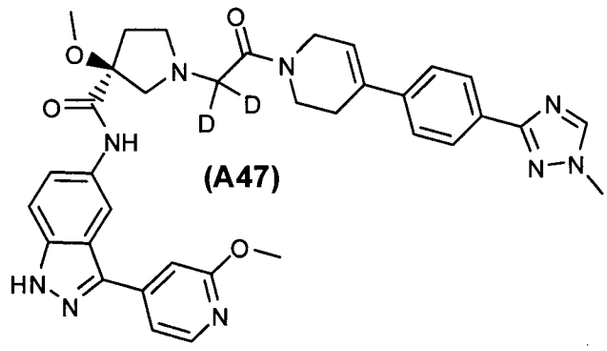
(A44)

,



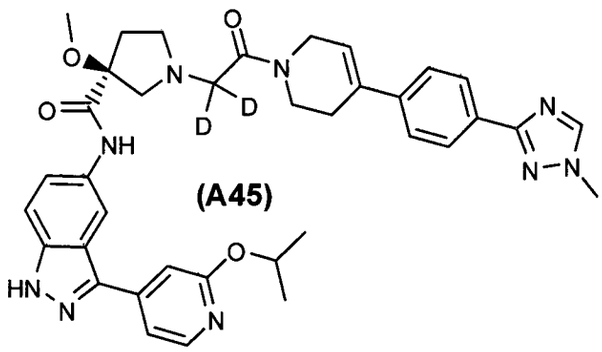
(A46)

y



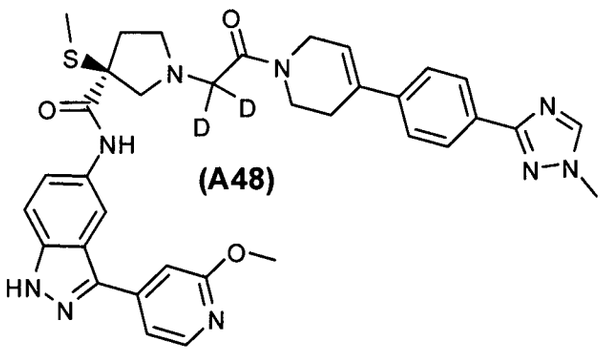
(A47)

.



(A45)

y



(A48)

En **A33** a **A44**, **A46**, y **A47** "D" representa deuterio.

Ensayos

Ensayo de ERK2 Acoplada:

La actividad de los compuetos contra la ERK2 inactiva puede ensayarse en en ensayo IMAP MEK1/ERK2 acoplado, como sigue: Los compuestos pueden diluirse a una concentración de ensayo final 25x en DMSO 100%. Puede agregarse 14µl de buffer quinasa (Tris.HCl 10mM pH 7,2, $MgCl_2$ 10mM, Tween-20, 0,01% DTT 1mM) que contiene proteína ERK2 no fosforilada de ratón 0,4ng a cada pocillo de una placa de ensayo negra de 384 pocillos. Puede agregarse 1µl de compuesto 25x a cada pocillo e incubarse a temperatura ambiente durante 30 minutos para dar una oportunidad al compuesto de unirse a la enzima inactiva. La concentración de DMSO durante la incubación inicial es de 6,7%. La actividad de ERK2 puede determinarse "no sensible" en concentraciones de DMSO de hasta 20%. Luego, puede activarse la ERK2 y su actividad de quinasa puede calcularse mediante la adición de buffer quinasa

10µl con los siguientes componentes (concentración final por reacción): proteína MEK1 humana active (fosforilada) 2ng y péptidos de sustrado de IMAP 4µM (total) (IPTTPITTTYFFFK-$CONH_2$ no marcado 3,9µM y IPTTPITTTYFFFK(5-carboxifluoresceína)-$CONH_2$ 100nM) y ATP 30µM. La concentración de DMSO durante la activación de ERK puede ser del 4%. Luego de una hora, pueden terminarse las reacciones con la adición de perlas de detección IMAP 60µl en buffer de unión (Molecular Devices). Puede permitirse el equilibrio de la unión durante 30 minutos antes de la lectura de la placa con un lector de placa LJL Analyst Fluorescence Polarization. La inhibición del compuesto puede calcularse con relación a DMSO y a estándares completamente inhibidores. Los compuestos activos pueden reconfirmarse en un ensayo independiente.

Ensayo de ERK2 Activa:

La actividad de ERK2 activada también se determinó con el formato de ensayo IMAP utilizado en procedimiento esbozado con anterioridad. Se agregó 1µl de compuesto 25x a buffer de quinasa 14µl que contiene proteína ERK2 activa de ratón completa fosforilada 0,25ng. Luego de incubación durante 30 minutos, se iniciaron las reacciones con la adición de buffer quinasa 10µl que contiene péptido de sustrato IMAP ERK2 1µM (IPTTPITTTYFFFK-$CONH_2$ no marcada 0,9µM y IPTTPITTTYFFFK(5-carboxifluoresceína)-$CONH_2$ 100nM) y ATP 30µM. Las reacciones continuaron durante 30 minutos antes de la terminación con la adición de perlas de detección IMAP 60µl en buffer de unión. Las placas se leyeron como con anterioridad luego de una equilibración de unión de 30 minutos. Los compuestos activos se reconfirmaron en un ensayo independiente.

Ensayo de Agar Suave:

El crecimiento independiente de anclaje es una característica de las líneas celulares tumorigénicas. Pueden suspenderse células tumorales humanas en medio de crecimieto que contiene agarosa 0,3% y una concentración indicada de un inhibidor de la farnesil transferasa. La solución puede recubrir el medio de crecimiento solidificado con agarosa 0,6% que contiene la misma concentración de inhibidor de ERK1 y ERK2 que la capa superior. Una vez solidificada la capa superior, pueden incubarse placas durante 10-16 días a 37°C con CO_2 5% para permitir la excrecencia de la colonia. Luego de la incubación, las colonias pueden mancharse recubriendo el agar con una solución de MTT (bromuro de 3-[4,5-dimetil-tiazol-2-il]-2,5-difeniltetrazolio, azul de Tiazolilo) (1 mg/ml en PBS). Luego, pueden contarse las colonias y determinarse los IC_{50}.

La AUC (área bajo la curva concentración-tiempo durante las primeras 6 horas (AUC_{6hr}) se determinó utilizando el Protocolo de Observación Rápida de Ratas de Aceleración por Cinta (CARRS)

Dosificación a animales y recolección de muestras

Se pre-canularon (arteria femoral) ratas Sprague-Dawley macho (Charles River, Co.) con el fin de facilitar tiempos precisos de muestreo de sangre, y para reducir el estrés en los animales causado por los sangrados seriales. Luego de una noche de ayuno, se dosificó en forma oral a dos ratas con un compuesto en una dosis de 10 mg/kg en un volumen de dosis de 5-ml/kg. Se recolectó sangre de cada animal (en forma serial) en tubos que contienen heparina a las 0,5, 1, 2, 3, 4 y 6 horas post-dosificación, dicha sangre se centrifugó para generar plasma. Aproximadamente se recolectaron 100 µl de plasma en los tiempos individuales. Las muestras de plasma se conservaron a -20°C hasta el análisis.

Muestra de plasma y preparación de curva estándar

Se generó un grupo de 12 muestras de plasma de rata para cada NCE (es decir, 6 momentos y n = 2 ratas). Estas 12 muestras de las dos ratas se combinaron en cada momento para proveer 6 muestras combinadas (una muestra por momento de extracción) para cada NCE. Las muestras combinadas se ensayaron como cintas de seis (36 muestras totales) para proveer datos de 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. Se seleccionó un compuesto adicional (a menudo un análogo estructural de los compuestos de ensayo) como el estándar interno. Se preparó una mini-curva de calibración (tres puntos más un cero) para cada compuesto ensayado. Se midió el plasma de ratas libres de drogas en alícuotas de 1 ml y cada alícuota se fortaleció con concentraciones conocidas de los compuestos para generar estándares de las concentraciones deseadas. Las concentraciones de los estándares se seleccionaron para separar la concentración esperada de las muestras combinadas con base en datos históricos de estudios previos de otros compuestos. Para este ensayo, los estándares se ajustaron para contener concentraciones de plasma NCE/ml de 25, 250 y 2500 ng. Los estándares de plasma se precipitaron en duplicado junto con las muestras. La precipitación de proteína ocurrió luego de la adición de 150 µl de acetonitrilo que contiene el estándar interno a una concentración de 1 ng/ml en cada pocillo de muestra utilizando el sistema Tomtec Quadra 96. Las muestras y estándares precipitados se agitaron con vórtex y centrifugaron en la placa de 96 pocillos. Aproximadamente, se retiraron 50-100 µl del sobrenadante y se colocaron en una placa fresca de 96 pocillos utilizando el sistema Tomtec Quadra 96. Se utilizó un volumen de 5-10 µl del sobrenadante para análisis mediante HPLC-MS/MS. La mini-curva estándar se llevó en duplicado, una vez antes y después de las muestras. De este modo, se

analizaron un total de 14 muestras de estudio más estándares por compuesto. Más aún, se inyectaron controles de solvente antes y después de cada grupo de 14 y después del estándar de calibración más elevado para cada compuesto; por lo tanto, se realizaron un total de 103 inyecciones en cada sistema de HPLC para cada grupo de seis compuestos. Pueden realizarse inyecciones de control de solvente múltiples a partir de un solo pocillo. Se designaron doce pocillos de control de solvente en cada placa de 96 pocillos. De este modo, se preparó y ensayó un lote (cinta) de seis NCE, utilizando un formato de placa de 96 pocillos.

Análisis de HPLC-MS/MS

Todos los compuestos se analizaron utilizando métodos de observación de reacciones seleccionados (SRM) con instrumentos LC/MS/MS. Una vez completo el desarrollo del método, el ensayo se preparaba rápidamente utilizando una plantilla de secuencia de inyección estándar para el ensayo CARRS.

Los compuestos A1 a A16, A18, A20, A21, A23, A25, A26, y A27 a A30 presentaron un IC_{50} de AERK2 en el rango de 1,2 a 50 nM.

Los compuestos A1-A3, A6, A8-A11, A13-A16, A20-A24, A26 y A27 a A30 presentaron un AUC en el rango de 36 a 50,999 nM.hr en el ensayo CARRS.

Para preparar composiciones farmacéuticas a partir de los compuestos descriptos por esta invención, los vehículos inertes aceptables para uso farmacéutico pueden ser sólidos o líquidos. Las preparaciones en forma sólida incluyen polvos, comprimidos, gránulos dispersables, cápsulas, sellos y supositorios. Los polvos y comprimidos pueden comprender de aproximadamente 5 a aproximadamente 95% de componente activo. Los vehículos sólidos adecuados son conocidos en la técnica, por ej., carbonato de

magnesio, estearato de magnesio, talco, azúcar o lactosa. Los comprimidos, polvos, sellos y cápsulas pueden utilizarse como formas sólidas de dosificación adecuadas para administración oral. Pueden hallarse ejemplos de vehículos aceptables para uso farmacéutico y métodos de manufacturación de varias composiciones en: A. Gennaro (ed.), Remington: The Science and Practice of Pharmacy, 20 Ed., (2000), Lippincott Williams & Wilkins, Baltimore, MD.

Las preparaciones en forma líquida incluyen soluciones, suspensiones y emulsiones. Pueden mencionarse a modo de ejemplo agua o soluciones de agua-propilen glicol para inyección parenteral o la adición de edulcorantes y opacantes para soluciones, supensiones y emulsiones orales. Las preparaciones en forma líquida también pueden incluir soluciones para administración intranasal.

Las preparaciones en aerosol adecuadas para inhalación pueden incluir soluciones y sólidas en forma de polvo, que pueden estar en combinación con un vehículo aceptable para uso farmacéutico, tal como un gas comprimido inerte, por ej., nitrógeno.

También se incluyen preparaciones en forma sólida con la intención de convertirlas, inmediatamente antes del uso, en preparaciones en forma líquida para administración oral o parenteral. Tales formas líquidas incluyen soluciones, suspensiones y emulsiones.

Los compuestos de la invención también pueden administrarse en forma transdérmica. Las composiciones transdérmicas pueden tomar la forma de cremas, lociones, aerosoles y/o emulsiones y pueden incluirse en un parche transdérmico de tipo matriz o reservorio de uso convencional en la técnica para este propósito.

Preferentemente, el compuesto se administra en forma oral.

Preferentemente, la composición farmacéutica está en una forma de dosificación unitaria. En una forma tal, las preparaciones se subdividen en dosis unitarias con tamaños adecuados que contienen cantidades apropiadas del componente activo, por ej., una cantidad efectiva para lograr el propósito deseado.

La cantidad de compuesto activo en una preparación de dosis unitaria puede variar o ajustarse entre, de aproximadamente 0,01 mg a aproximadamente 1000 mg, preferentemente de aproximadamente 0,01 mg a aproximadamente 750 mg, con más preferencia de aproximadamente 0,01 mg a aproximadamente 500 mg, y con la mayor preferencia de aproximadamente 0,01 mg a aproximadamente 250 mg de acuerdo con la aplicación particular.

La dosis real empleada puede variar dependiendo de los requerimientos del paciente y de la severidad de la afección bajo tratamiento. La determinación del régimen de dosificación adecuado para una situación particular es parte de los conocimientos de aquellos con experiencia en la técnica. Por conveniencia, la dosis diaria total puede dividirse y administrarse en porciones durante el día según sea requerido.

La cantidad y frecuencia de administración de los compuestos de la invención y/o sales aceptables para uso farmacéutico de los mismos se regulará de acuerdo con el juicio del profesional a cargo en consideración de factores tales como la edad, condición y tamaño del paciente, así como la severidad de los síntomas bajo tratamiento. Un régimen típico de dosificación diario recomendado para administración oral puede oscilar entre aproximadamente 0,04 mg/día y aproximadamente 4000 mg/día, en dos a cuatro dosis divididas.

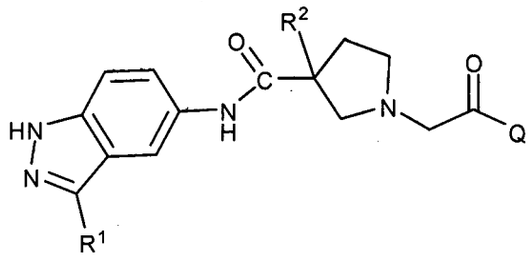
Aunque la presente invención se ha descripto junto con las realizaciones específicas expuestas con anterioridad, numerorasas alternativas,

modificaciones y variaciones de las mismas serán aparentes a aquellos con experiencia en la técnica. Todas las tales alternativas, modificaciones y variaciones forman parte del espíritu y alcance de la presente invención.

REIVINDICACIONES

Habiendo así especialmente descripto 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.

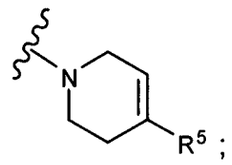
1. Un compuesto de fórmula 1.0:



(1.0)

o una sal farmacéuticamente aceptable o solvato de la misma donde R^1, R^2 y Q se seleccionan independientemente, y donde:

Q es:



R^1 se selecciona del grupo que consiste en: heteroarilo y heteroarilo sustituido, donde dicho heteroarilo sustituido se sustituye con 1 a 3 sustituyentes seleccionados en forma independiente del grupo que consiste en: -OH, alcoxi, y –O-alquilen-O-alquilo;

R^2 se selecciona del grupo que consiste en: -O-alquilo y -S-alquilo; y

R^5 se selecciona del grupo que consiste en:

(a) triazolil-fenil-,

(b) triazolil-fenil- donde dicho fenilo se sustituye en forma opcional con 1 a 3 sustituyentes seleccionados en forma independiente del grupo que consiste en: halo y alcoxi,

(c) triazolil-fenil- sustituido donde dicho fenilo se sustituye en forma opcional con 1 a 3 sustituyentes seleccionados en forma independiente del

grupo que consiste en: halo y alcoxi, y dicho grupo triazolilo se sustituye con uno o dos sustituyentes seleccionados en forma independiente del grupo que consiste en: alquilo, alquilo sustituido con hidroxi, -alquilen-O-alquilo, y amino,

(d) triazolil-tienil-,

(e) triazolil-tienil- donde dicho tienilo se sustituye en forma opcional con 1 a 2 sustituyentes seleccionados en forma independiente del grupo que consiste en: halo y alcoxi,

(f) triazolil-tienil- sustituido donde dicho tienilo se sustituye en forma opcional con 1 a 2 sustituyentes seleccionados en forma independiente del grupo que consiste en: halo y alcoxi, y dicho grupo triazolilo se sustituye con uno o dos sustituyentes seleccionados en forma independiente del grupo que consiste en: alquilo, alquilo sustituido con hidroxi, -alquilen-O-alquilo, y amino,

(g) triazolil-piridil-,

(h) triazolil-piridil- donde dicho piridilo se sustituye en forma opcional con 1 a 3 sustituyentes seleccionados en forma independiente del grupo que consiste en: halo, alquilo, y alcoxi, con la condición que los átomos de carbono adyacentes al átomo de nitrógeno en dicho piridilo no estén sustituidos con halo, y

(i) triazolil-piridil- sustituido donde: (1) dicho piridilo se sustituye en forma opcional con 1 a 3 sustituyentes seleccionados en forma independiente del grupo que consiste en: halo, alquilo, y alcoxi, con la condición que los átomos de carbono adyacentes al átomo de nitrógeno en dicho piridilo no estén sustituidos con halo, y (2) dicho grupo triazolilo se sustituye con uno o dos sustituyentes seleccionados en forma independiente del grupo que consiste en: alquilo, alquilo sustituido con hidroxi,-alquilen-O-alquilo, y amino,

(j) triazolil-tiazolil-,

(k) triazolil-tiazolil- donde dicho tiazolilo se sustituye en forma opcional con 1 sustituyente seleccionado en forma independiente del grupo que consiste en: halo, alquilo, y alcoxi, amino, alquilamino, y dialquilamino donde cada alquilo se selecciona en forma independiente, y

(l) triazolil-tiazolil- sustituido donde (1) dicho tiazolilo se sustituye en forma opcional con 1 sustituyente seleccionado en forma independiente del grupo que consiste en: halo, alquilo, y alcoxi, amino, alquilamino, y dialquilamino donde cada alquilo se selecciona en forma independiente, y (2) dicho triazolilo se sustituye con uno o dos sustituyentes seleccionados en forma independiente del grupo que consiste en: alquilo, alquilo sustituido con hidroxi,-alquilen-O-alquilo, y amino,

(m) piridazinil-tienil-,

(n) piridazinil-tienil- donde dicho tienilo se sustituye en forma opcional con 1 a 2 sustituyentes seleccionados en forma independiente del grupo que consiste en: halo y alcoxi, y

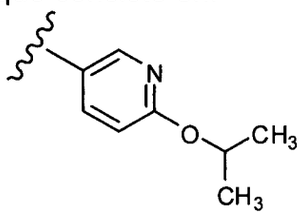
(o) piridazinil-tienil- sustituido donde (1) dicho tienilo se sustituye en forma opcional con 1 a 2 sustituyentes seleccionados en forma independiente del grupo que consiste en: halo y alcoxi, y (2) dicho grupo piridazinilo se sustituye con 1 a 3 sustituyentes seleccionados en forma independiente del grupo que consiste en: =O, alquilo, amino, alquilamino, dialquilamino donde cada alquilo se selecciona en forma independiente, y halo, con la condición que los átomos de carbono adyacentes a los átomos de nitrógeno en dicho piridazinilo no estén sustituidos con halo, y

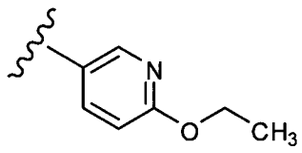
con la condición de que cuando dicho grupo -alquilen-O-alquilo esté unido al nitrógeno de dicho triazolilo en (c), (f), (i) y (l) de R^5 el resto alquileno de dicho grupo -alquilen-O-alquilo no sea $-CH_2-$.

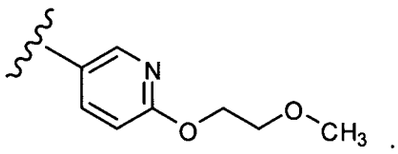
2. El compuesto de la reivindicación 1 donde R^1 es un piridilo sustituido con un sustituyente seleccionado del grupo que consiste en: -OH, alcoxi, y –O-alquilen-O-alquilo.

3. El compuesto de la reivindicación 2 donde dicho sustituyente se selecciona del grupo que consiste en: -O-CH_3, -O-C_2H_5, –O-$CH(CH_3)_2$, y –O-$(CH_2)_2$-O-CH_3.

4. El compuesto de la reivindicación 1 donde R^1 se selecciona del grupo que consiste en:



,


, y


.

5. El compuesto de la reivindicación 1 donde R^2 se selecciona del grupo que consiste en: -OCH_3 y –SCH_3.

6. El compuesto de la reivindicación 1 donde R^5 se selecciona del grupo que consiste en:

(a) un triazolil-fenil- sustituido donde el resto triazolilo se sustituye con uno o dos grupos alquilo seleccionados del grupo que consiste en: alquilo-C1-C6, alquilo-C1-C4, alquilo-C1-C2, y –CH_3;

(b) un triazolil-fenil- sustituido donde el resto triazolilo se sustituye con uno o dos grupos alquilo seleccionados del grupo que consiste en: alquilo-C_1-C_4, alquilo-C_1-C_2, y –CH_3;

(c) un triazolil-fenil- sustituido donde el resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo seleccionado del grupo que consiste en :

alquilo-C_1-C_4, alquilo-C_1-C_2, y $-CH_3$;

(d) un triazolil-fenil- sustituido donde el resto triazolilo se sustituye sobre el nitrógeno con un grupo -alquilen-O-alquilo seleccionado del grupo que consiste en: alquilen-C_2-C_4-alquil-O-C_1-C_6, alquilen-C_2 alquil-O-C_1-C_2, alquilen-C_2-C_4-O-CH_3, y $-CH_2CH_2OCH_3$;

(e) un triazolil-fenil- sustituido donde el resto triazolilo se sustituye sobre el nitrógeno con un grupo -alquilen-O-alquilo seleccionado del grupo que consiste en: alquilen-C_2O alquil-C_1-C_2, y $-CH_2CH_2OCH_3$;

(f) un triazolil-fenil- sustituido donde el resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo sustituido con hidroxi seleccionado del grupo que consiste en: alquilo-C_1-C_4 sustituido con hidroxi, alquilo-C_1-C_2 sustituido con hidroxi, y -CH_3 sustituido con hidroxi; y

(g) un triazolil-fenil- sustituido donde el resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo sustituido con hidroxi seleccionado del grupo que consiste en: $CH_2COH(CH_3)_2$, y -CH_2CH_2OH.

7. El compuesto de la reivindicación 1 donde los sustituyentes halo opcionales para el resto fenilo de R^5 son F.

8. El compuesto de la reivindicación 1 donde R^5 es un grupo triazolil-fenil- sustituido donde:

(1)

(a) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un sustituyente seleccionado del grupo que consiste en: $-CH_2COH(CH_3)_2$, y -CH_2CH_2OH,

(b) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con

un grupo alquilo, (c) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo alquilo, y sobre el carbono con un grupo alquilo, (d) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo $-CH_3$, (e) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo $-CH_3$, y sobre el carbono con un grupo $-CH_3$, (f) dicho resto triazolilo se sustituye en forma opcional sobre el carbono con un grupo $-NH_2$, o (g) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo $-CH_2CH_2OCH_3$; y donde dicho resto fenilo se sustituye en forma opcional con halo; o

(2)

(a) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un sustituyente seleccionado del grupo que consiste en: $-CH_2COH(CH_3)_2$, y $-CH_2CH_2OH$,
(b) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo alquilo, (c) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo alquilo, y sobre el carbono con un grupo alquilo, (d) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo $-CH_3$, (e) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo $-CH_3$, y sobre el carbono con un grupo $-CH_3$, (f) dicho resto triazolilo se sustituye en forma opcional sobre el carbono con un grupo $-NH_2$, o (g) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo $-CH_2CH_2OCH_3$; y donde dicho resto fenilo se sustituye en forma opcional con alcoxi; o

(3)

(a) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un sustituyente seleccionado del grupo que consiste en: $-CH_2COH(CH_3)_2$, y $-CH_2CH_2OH$,

(b) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo alquilo, (c) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo alquilo, y sobre el carbono con un grupo alquilo, (d) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo $-CH_3$, (e) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo $-CH_3$, y sobre el carbono con un grupo $-CH_3$, (f) dicho resto triazolilo se sustituye en forma opcional sobre el carbono con un grupo $-NH_2$, o (g) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo $-CH_2CH_2OCH_3$; y donde dicho resto fenilo se sustituye con halo; o

(4)

(a) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un sustituyente seleccionado del grupo que consiste en: $-CH_2COH(CH_3)_2$, y $-CH_2CH_2OH$,
(b) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo alquilo, (c) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo alquilo, y sobre el carbono con un grupo alquilo, (d) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo $-CH_3$, (e) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo $-CH_3$, y sobre el carbono con un grupo $-CH_3$, (f) dicho resto triazolilo se sustituye en forma opcional sobre el carbono con un grupo $-NH_2$, o (g) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo $-CH_2CH_2OCH_3$; y donde dicho resto fenilo se sustituye con alcoxi; o

(5)

(a) dicho resto triazolilo se sustituye sobre el nitrógeno con un sustituyente seleccionado del grupo que consiste en: $-CH_2COH(CH_3)_2$, y -

CH_2CH_2OH, (b) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo, (c) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo, y sobre el carbono con un grupo alquilo, (d) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_3$, (e) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_3$, y sobre el carbono con un grupo $-CH_3$, (f) dicho resto triazolilo se sustituye sobre el carbono con un grupo $-NH_2$, o (g) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_2CH_2OCH_3$; y donde dicho resto fenilo se sustituye en forma opcional con halo; o

(6)

(a) dicho resto triazolilo se sustituye sobre el nitrógeno con un sustituyente seleccionado del grupo que consiste en: $-CH_2COH(CH_3)_2$, y $-CH_2CH_2OH$, (b) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo, (c) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo, y sobre el carbono con un grupo alquilo, (d) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_3$, (e) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_3$, y sobre el carbono con un grupo $-CH_3$, (f) dicho resto triazolilo se sustituye sobre el carbono con un grupo $-NH_2$, o (g) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_2CH_2OCH_3$; y donde dicho resto fenilo se sustituye en forma opcional con alcoxi; o

(7)

(a) dicho resto triazolilo se sustituye sobre el nitrógeno con un sustituyente seleccionado del grupo que consiste en: $-CH_2COH(CH_3)_2$, y $-CH_2CH_2OH$, (b) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo, (c) dicho resto triazolilo se sustituye sobre el nitrógeno con un

grupo alquilo, y sobre el carbono con un grupo alquilo, (d) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo -CH_3, (e) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo –CH_3, y sobre el carbono con un grupo –CH_3, (f) dicho resto triazolilo se sustituye sobre el carbono con un grupo –NH2, o (g) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo –$CH_2CH_2OCH_3$; y donde dicho resto fenilo se sustituye con halo; o

(8)

(a) dicho resto triazolilo se sustituye sobre el nitrógeno con un sustituyente seleccionado del grupo que consiste en: –$CH_2COH(CH_3)_2$, y -CH_2CH_2OH, (b) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo, (c) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo, y sobre el carbono con un grupo alquilo, (d) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo -CH_3, (e) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo –CH_3, y sobre el carbono con un grupo –CH_3, (f) dicho resto triazolilo se sustituye sobre el carbono con un grupo –NH_2, o (g) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo –$CH_2CH_2OCH_3$; y donde dicho resto fenilo se sustituye con alcoxi; o

(9)

(a) dicho resto triazolilo se sustituye sobre el nitrógeno con un sustituyente seleccionado del grupo que consiste en: –$CH_2COH(CH_3)_2$, y -CH_2CH_2OH, (b) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo, (c) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo, y sobre el carbono con un grupo alquilo, (d) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo -CH_3, (e) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo –CH_3, y sobre el carbono con un grupo –CH_3, (f) dicho resto triazolilo se sustituye sobre el carbono con un grupo

$-NH_2$, o (g) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_2CH_2OCH_3$; y donde dicho resto fenilo no está sustituido.

9. El compuesto de la reivindicación 1 donde R^5 es un grupo triazolil-fenilo sustituido donde dicho resto triazolilo se sustituye con: (a) un sustituyente seleccionado del grupo que consiste en: $-CH_2COH(CH_3)_2$, y $-CH_2CH_2OH$, (b) un grupo alquilo, (c) dos grupos alquilo, (d) un grupo $-CH_3$, (e) dos grupos $-CH_3$, (f) un grupo $-NH_2$, o (g) un grupo $-CH_2CH_2OCH_3$.

10. El compuesto de la reivindicación 1 donde los sustituyentes de alcoxi opcionales para el resto fenilo de R^5 son $-OCH_3$.

11. El compuesto de la reivindicación 1 donde R^5 se selecciona del grupo que consiste en:

(a) un triazolil-tienil- sustituido donde el resto triazolilo se sustituye con uno o dos grupos alquilo seleccionados del grupo que consiste en: alquilo-C_1-C_6, alquilo-C_1-C_4, alquilo-C_1-C_2, y $-CH_3$;

(b) un triazolil-tienil- sustituido donde el resto triazolilo se sustituye con uno o dos grupos alquilo seleccionados del grupo que consiste en: alquilo-C_1-C_4, alquilo-C_1-C_2, y $-CH_3$;

(c) un triazolil-tienil- sustituido donde el resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo seleccionado del grupo que consiste en: alquilo-C_1-C_4, alquilo-C_1-C_2, y $-CH_3$;

(d) un triazolil-tienil- sustituido donde el resto triazolilo se sustituye sobre el nitrógeno con un grupo -alquilen-O-alquilo seleccionado del grupo que consiste en: alquilen-C_2-C_4 -O-alquilC_1-C_6, alquilen-C_2-O- alquilC_1-C_2,

alquilen-C_2-C_4 -O-CH_3, y $-CH_2CH_2OCH_3$;

(e) un triazolil-tienil- sustituido donde el resto triazolilo se sustituye sobre el nitrógeno con un grupo -alquilen-O-alquilo seleccionado del grupo que consiste en: alquilen-C_2 -O-alquilC_1-C_2, y $-CH_2CH_2OCH_3$;

(f) un triazolil-tienil- sustituido donde el resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo sustituido con hidroxi seleccionado del grupo que consiste en: alquilo-C_1-C_4 sustituido con hidroxi, alquilo-C_1-C_2 sustituido con hidroxi, y -CH_3 sustituido con hidroxi; y

(g) un triazolil-tienil- sustituido donde el resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo sustituido con hidroxi seleccionado del grupo que consiste en: $CH_2COH(CH_3)_2$, y -CH_2CH_2OH.

12. El compuesto de la reivindicación 1 donde R^5 es un grupo triazolil-tienil- sustituido donde:

(A)

(a) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un sustituyente seleccionado del grupo que consiste en: $-CH_2COH(CH_3)_2$, y -CH_2CH_2OH,
(b) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo alquilo, (c) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo alquilo, y sobre el carbono con un grupo alquilo, (d) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo $-CH_3$, (e) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo -CH_3, y sobre el carbono con un grupo $-CH_3$, (f) dicho resto triazolilo se sustituye en forma opcional sobre el carbono con un grupo -NH_2, o (g) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo $-CH_2CH_2OCH_3$; y donde dicho resto tienilo se sustituye en forma opcional con halo; o

(B)

(a) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un sustituyente seleccionado del grupo que consiste en: $-CH_2COH(CH_3)_2$, y $-CH_2CH_2OH$, (b) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo alquilo, (c) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo alquilo, y sobre el carbono con un grupo alquilo, (d) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo $-CH_3$, (e) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo $-CH_3$, y sobre el carbono con un grupo $-CH_3$, (f) dicho resto triazolilo se sustituye en forma opcional sobre el carbono con un grupo $-NH_2$, o (g) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo $-CH_2CH_2OCH_3$; y donde dicho resto tienilo se sustituye en forma opcional con alcoxi; o

(C)

(a) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un sustituyente seleccionado del grupo que consiste en: $-CH_2COH(CH_3)_2$, y $-CH_2CH_2OH$, (b) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo alquilo, (c) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo alquilo, y sobre el carbono con un grupo alquilo, (d) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo $-CH_3$, (e) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo $-CH_3$, y sobre el carbono con un grupo $-CH_3$, (f) dicho resto triazolilo se sustituye en forma opcional sobre el carbono con un grupo $-NH_2$, o (g) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo $-CH_2CH_2OCH_3$; y donde dicho resto tienilo se sustituye con halo; o

(D)

(a) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un sustituyente seleccionado del grupo que consiste en: $-CH_2COH(CH_3)_2$, y $-CH_2CH_2OH$, (b) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo alquilo, (c) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo alquilo, y sobre el carbono con un grupo alquilo, (d) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo $-CH_3$, (e) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo $-CH_3$, y sobre el carbono con un grupo $-CH_3$, (f) dicho resto triazolilo se sustituye en forma opcional sobre el carbono con un grupo $-NH_2$, o (g) dicho resto triazolilo se sustituye en forma opcional sobre el nitrógeno con un grupo $-CH_2CH_2OCH_3$; y donde dicho resto tienilo se sustituye con alcoxi; o

(E)

(a) dicho resto triazolilo se sustituye sobre el nitrógeno con un sustituyente seleccionado del grupo que consiste en: $-CH_2COH(CH_3)_2$, y $-CH_2CH_2OH$, (b) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo, (c) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo, y sobre el carbono con un grupo alquilo, (d) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_3$, (e) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_3$, y sobre el carbono con un grupo $-CH_3$, (f) dicho resto triazolilo se sustituye sobre el carbono con un grupo $-NH_2$, o (g) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_2CH_2OCH_3$; y donde dicho resto tienilo se sustituye en forma opcional con halo; o

(F)

(a) dicho resto triazolilo se sustituye sobre el nitrógeno con un sustituyente seleccionado del grupo que consiste en: $-CH_2COH(CH_3)_2$, y $-CH_2CH_2OH$, (b) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo, (c) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo, y sobre el carbono con un grupo alquilo, (d) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_3$, (e) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_3$, y sobre el carbono con un grupo $-CH_3$, (f) dicho resto triazolilo se sustituye sobre el carbono con un grupo –NH2, o (g) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_2CH_2OCH_3$; y donde dicho resto tienilo se sustituye en forma opcional con alcoxi; o

(G)

(a) dicho resto triazolilo se sustituye sobre el nitrógeno con un sustituyente seleccionado del grupo que consiste en: $-CH_2COH(CH_3)_2$, y $-CH_2CH_2OH$, (b) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo, (c) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo, y sobre el carbono con un grupo alquilo, (d) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_3$, (e) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_3$, y sobre el carbono con un grupo $-CH_3$, (f) dicho resto triazolilo se sustituye sobre el carbono con un grupo $-NH_2$, o (g) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_2CH_2OCH_3$; y donde dicho resto tienilo se sustituye con halo; o

(H)

(a) dicho resto triazolilo se sustituye sobre el nitrógeno con un sustituyente seleccionado del grupo que consiste en: $-CH_2COH(CH_3)_2$, y $-CH_2CH_2OH$, (b) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo, (c) dicho resto triazolilo se sustituye sobre el nitrógeno con un

grupo alquilo, y sobre el carbono con un grupo alquilo, (d) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo -CH_3, (e) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo –CH_3, y sobre el carbono con un grupo –CH_3, (f) dicho resto triazolilo se sustituye sobre el carbono con un grupo –NH_2, o (g) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo –$CH_2CH_2OCH_3$; y donde dicho resto tienilo se sustituye con alcoxi; o

(l)

(a) dicho resto triazolilo se sustituye sobre el nitrógeno con un sustituyente seleccionado del grupo que consiste en: –$CH_2COH(CH_3)_2$, y -CH_2CH_2OH, (b) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo, (c) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo alquilo, y sobre el carbono con un grupo alquilo, (d) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo -CH_3, (e) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo –CH_3, y sobre el carbono con un grupo –CH_3, (f) dicho resto triazolilo se sustituye sobre el carbono con un grupo –NH_2, o (g) dicho resto triazolilo se sustituye sobre el nitrógeno con un grupo –$CH_2CH_2OCH_3$; y donde dicho resto tienilo no está sustituido.

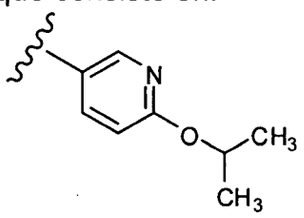
13. El compuesto de la reivindicación 1 donde R^5 es un grupo triazolil-tienilo sustituido donde dicho resto triazolilo se sustituye con: (a) un sustituyente seleccionado del grupo que consiste en:–$CH_2COH(CH_3)_2$ y -CH_2CH_2OH, (b) un grupo alquilo, (c) dos grupos alquilo, (d) un grupo –CH_3, (e) dos grupos –CH_3, (f) un grupo –NH_2, o (g) un grupo –$CH_2CH_2OCH_3$.

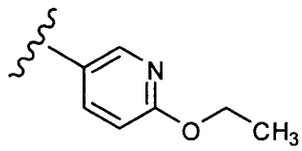
14. El compuesto de la reivindicación 1 donde los sustituyentes de alcoxi opcionales para el resto fenilo de R^5 son –OCH_3.

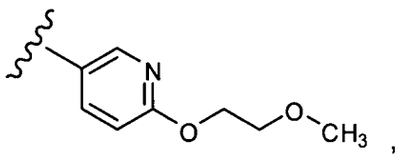
15. El compuesto de la reivindicación 8 donde R^1 es un piridilo sustituido con un sustituyente seleccionado del grupo que consiste en: -O-CH_3,

$-O-C_2H_5$, $-O-CH(CH_3)_2$, y $-O-(CH_2)_2-O-CH_3$, y R^2 se selecciona del grupo que consiste en: $-OCH_3$ y $-SCH_3$.

16. El compuesto de la reivindicación 8 donde R^1 se selecciona del grupo que consiste en:



,


, y


,

y R^2 se selecciona del grupo que consiste en: $-OCH_3$ y $-SCH_3$.

17. El compuesto de la reivindicación 1 donde:

(a) R^5 es un triazolil-piridil- sustituido donde dicho triazolilo está sustituido y dicho piridilo está sustituido; o

(b) R^5 es un triazolil-piridil- sustituido donde dicho triazolilo se sustituye sobre el nitrógeno y dicho piridilo está sustituido; o

(c) R^5 es un triazolil-piridil- sustituido donde dicho triazolilo se sustituye sobre el carbono y dicho piridilo está sustituido; o

(d) R^5 es un triazolil-piridil- sustituido donde dicho triazolilo se sustituye sobre el nitrógeno y sobre el carbono y dicho piridilo está sustituido; o

(e) R^5 es un triazolil-piridil- sustituido donde dicho triazolilo no está sustituido y dicho piridilo está sustituido.

18. El compuesto de la reivindicación 1 donde:

(a) R^5 es un triazolil-piridil- sustituido donde dicho triazolilo se sustituye sobre el nitrógeno con un grupo alquilo, y el piridilo no está sustituido; o

(b) R^5 es un triazolil-piridil- sustituido donde dicho triazolilo se sustituye sobre el nitrógeno y sobre el carbono con un grupo alquilo, donde cada grupo alquilo se selecciona en forma independiente, y el piridilo no está sustituido; o

(c) R^5 es un triazolil-piridil- sustituido donde dicho triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_3$, y el piridilo no está sustituido; o

(d) R^5 es un triazolil-piridil- sustituido donde dicho triazolilo se sustituye sobre el nitrógeno y sobre el carbono con un grupo $-CH_3$, y el piridilo no está sustituido.

19. El compuesto de la reivindicación 1 donde:

(a) R^5 es un triazolil-tiazolil- sustituido donde dicho triazolilo se sustituye y dicho tiazolilo no está sustituido; o

(b) R^5 es un triazolil-tiazolil- sustituido donde dicho triazolilo se sustituye sobre el nitrógeno y dicho tiazolilo no está sustituido; o

(c) R^5 es un triazolil-tiazolil- sustituido donde dicho triazolilo se sustituye sobre el carbono y dicho tiazolilo no está sustituido; o

(d) R^5 es un triazolil-tiazolil- sustituido donde dicho triazolilo se sustituye sobre el nitrógeno y sobre el carbono, y dicho tiazolilo no está sustituido; o

(e) R^5 es un triazolil-tiazolil- sustituido donde dicho triazolilo se sustituye y dicho tiazolilo está sustituido; o

(f) R^5 es un triazolil-tiazolil- sustituido donde dicho triazolilo se sustituye sobre el nitrógeno y dicho tiazolilo está sustituido; o

(g) R^5 es un triazolil-tiazolil- sustituido donde dicho triazolilo se sustituye sobre el carbono y dicho tiazolilo está sustituido; o

(f) R^5 es un triazolil-tiazolil- sustituido donde dicho triazolilo se sustituye sobre el nitrógeno y sobre el carbono, y dicho tiazolilo está sustituido; o

(h) R^5 es un triazolil-tiazolil- sustituido donde dicho triazolilo no está sustituido y dicho tiazolilo está sustituido.

20. El compuesto de la reivindicación 1 donde:

(a) R^5 es un triazolil-tiazolil- sustituido donde dicho triazolilo se sustituye sobre el nitrógeno con alquilo, y dicho tiazolilo no está sustituido; o

(b) R^5 es un triazolil-tiazolil- sustituido donde dicho triazolilo se sustituye sobre el nitrógeno y sobre el carbono con un grupo alquilo, donde dicho grupo alquilo se selecciona en forma independiente, y dicho tiazolilo no está sustituido; o

(c) R^5 es un triazolil-tiazolil- sustituido donde dicho triazolilo se sustituye sobre el nitrógeno con un grupo $-CH_3$, y dicho tiazolilo no está sustituido; o

(d) R^5 es un triazolil-tiazolil- sustituido donde dicho triazolilo se sustituye sobre el nitrógeno y sobre el carbono con un grupo $-CH_3$, y dicho tiazolilo no está sustituido.

21. El compuesto de la reivindicación 1 donde R^5 es un piridazinil-tienil- sustituido donde dicho piridazinilo se sustituye y dicho tienilo no está sustituido; o R^5 es un piridazinil-tienil- sustituido donde dicho piridazinilo no está sustituido y dicho tienilo está sustituido; o R^5 es un piridazinil-tienil- sustituido donde dicho piridazinilo se sustituye y dicho tienilo está sustituido.

22. El compuesto de la reivindicación 1 donde:

(a) R^5 es un piridazinil-tienil- sustituido donde dicho piridazinilo se sustituye con un grupo =O, y dicho tienilo no está sustituido; o

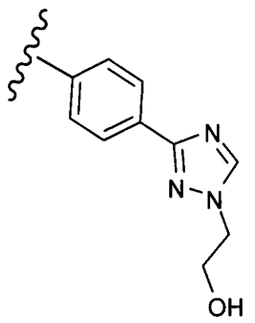
(b) R^5 es un piridazinil-tienil- sustituido donde dicho piridazinilo se sustituye con un grupo alquilo, y dicho tienilo no está sustituido; o

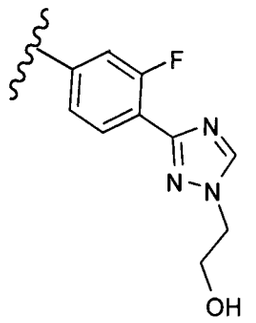
(c) R^5 es un piridazinil-tienil- sustituido donde dicho piridazinilo se sustituye con un grupo metilo, y dicho tienilo no está sustituido; o

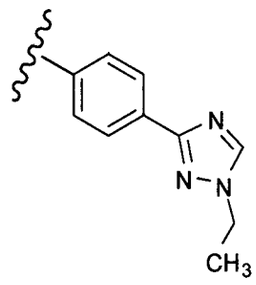
En otra realización de esta invención R^5 es un piridazinil-tienil- sustituido donde dicho piridazinilo se sustituye con un grupo =O, y con un grupo alquilo, y dicho tienilo no está sustituido.

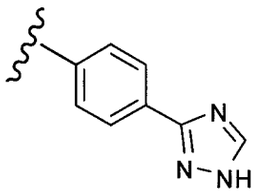
(d) $R^{5.}$ es un piridazinil-tienil- sustituido donde dicho piridazinilo se sustituye con un grupo =O, y con un grupo metilo, y dicho tienilo no está sustituido.

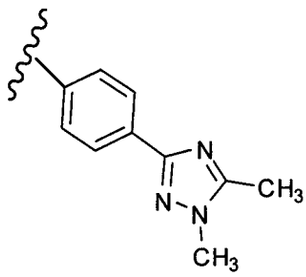
23. El compuesto de la reivindicación 1 donde:

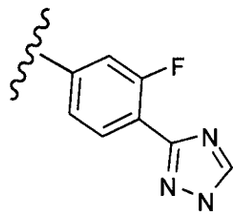


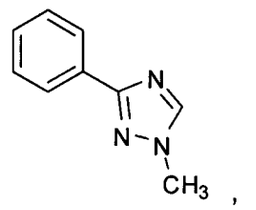
,


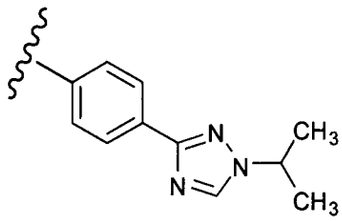
,


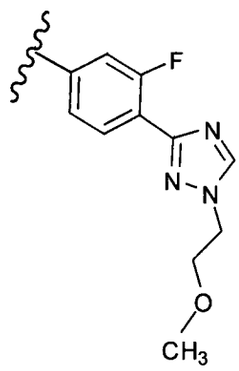
,


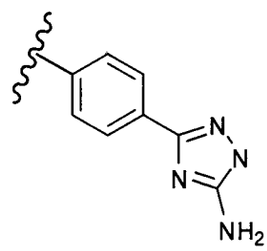
,


,


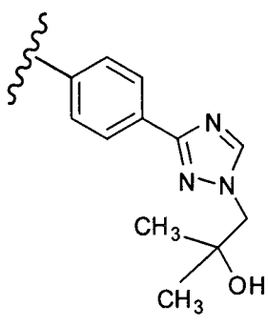
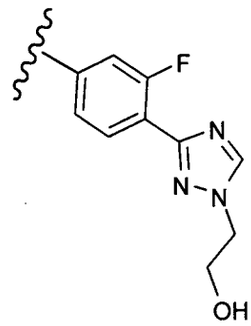
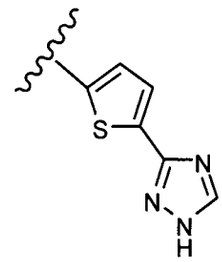
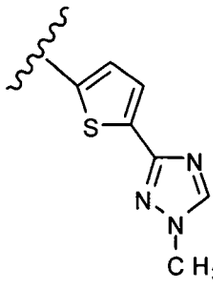
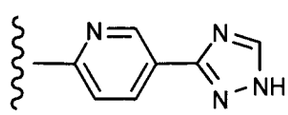
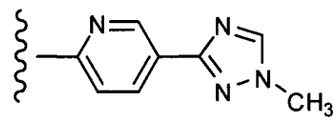
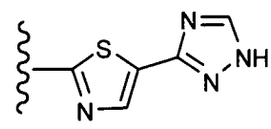
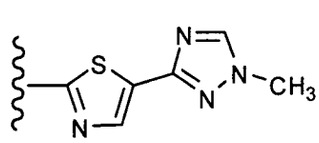
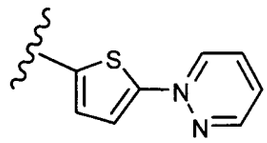
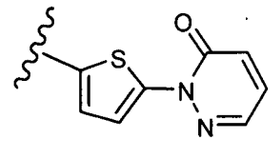
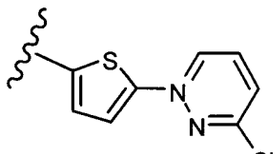
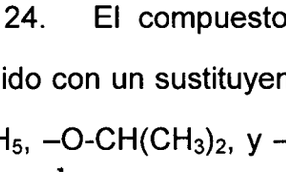
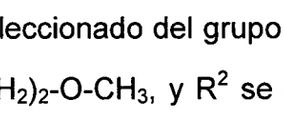
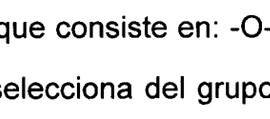
,


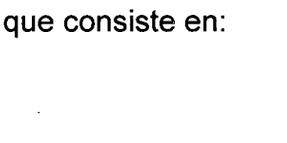
,


,


,


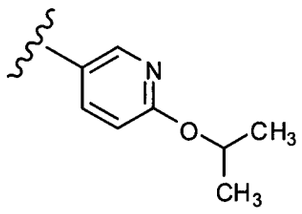
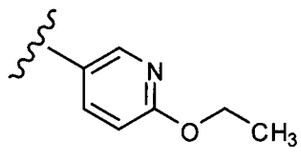
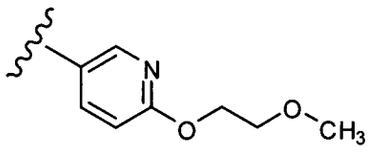
,



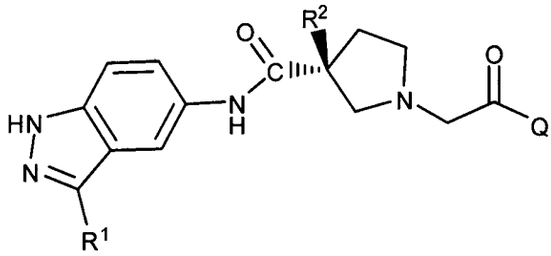
24. El compuesto de la reivindicación 23 donde R^1 es un piridilo sustituido con un sustituyente seleccionado del grupo que consiste en: -O-CH_3, -O-C_2H_5, –O-$CH(CH_3)_2$, y –O-$(CH_2)_2$-O-CH_3, y R^2 se selecciona del grupo que consiste en: -OCH_3 y –SCH_3.

25. El compuesto de la reivindicación 24 donde R^1 se selecciona del grupo que consiste en:

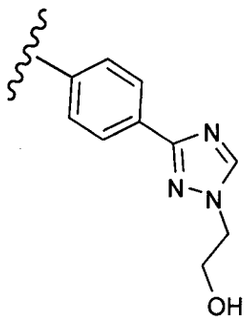
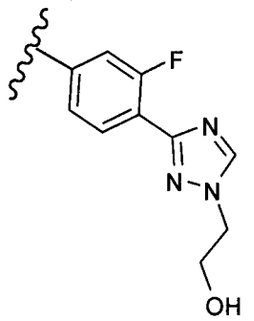
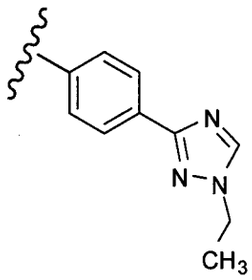
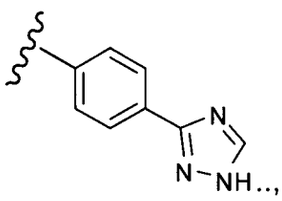


y

,

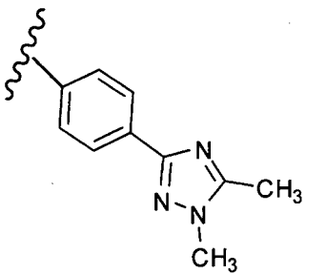
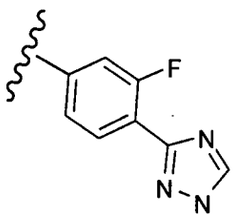
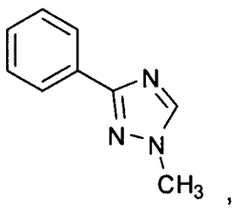
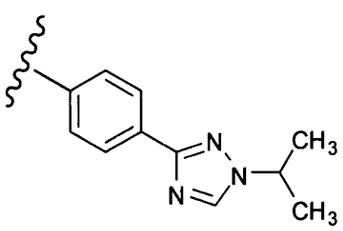
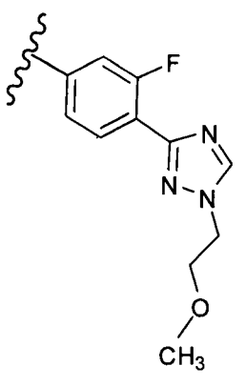
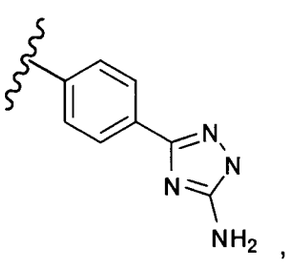
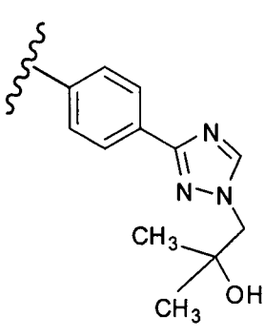
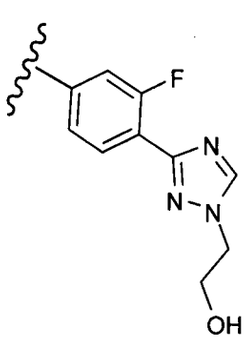
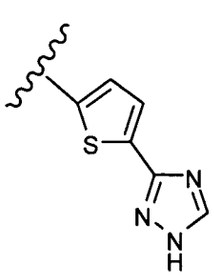
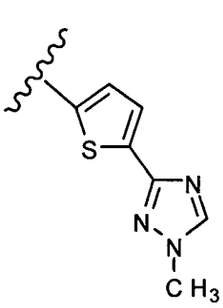
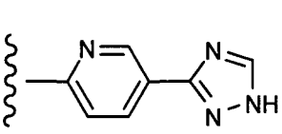
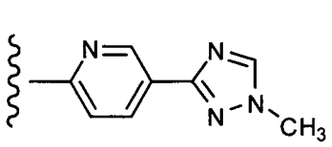
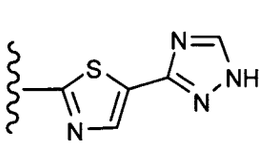
y R^2 se selecciona del grupo que consiste en: -OCH_3 y –SCH_3.

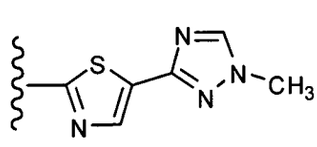
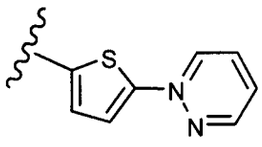
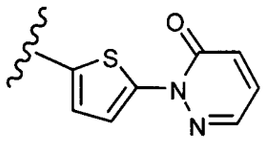
26. El compuesto de la reivindicación 11 donde el compuesto de fórmula 1.0 es un compuesto de fórmula 1.1:

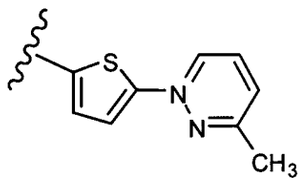
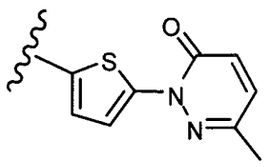

(1.1)

27. El compuesto de la reivindicación 26 donde R^5 se selecciona del grupo que consiste en:


,

,

,

,,

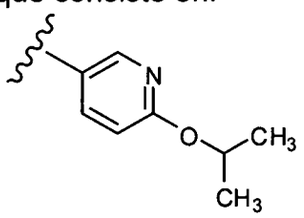
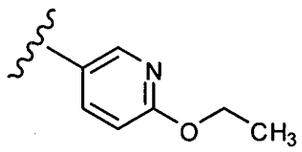
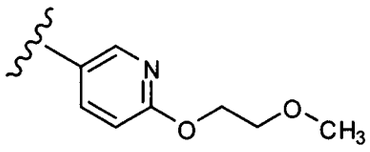

,

,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

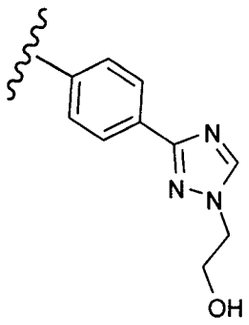
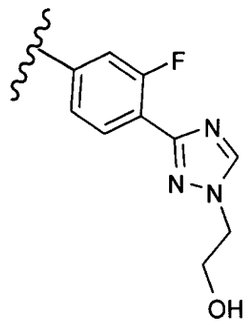
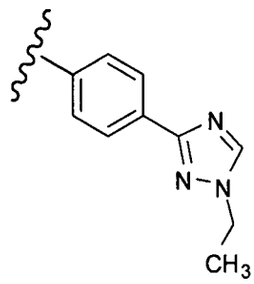
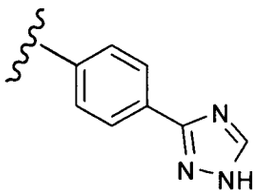
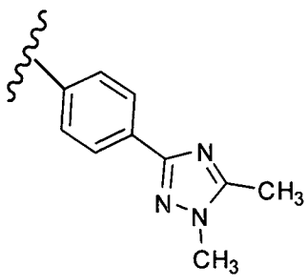
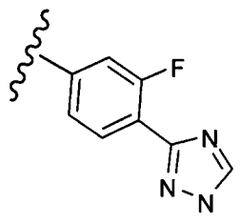
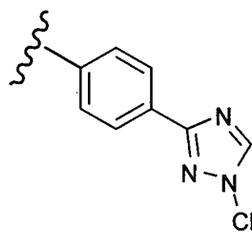
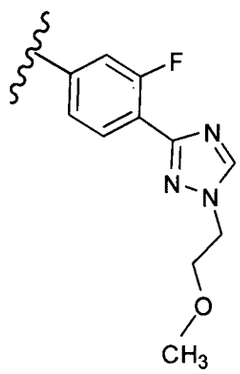
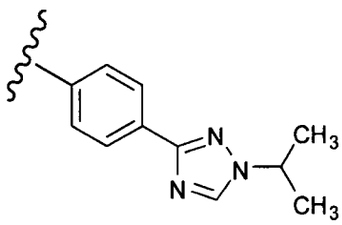
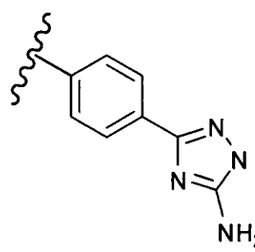
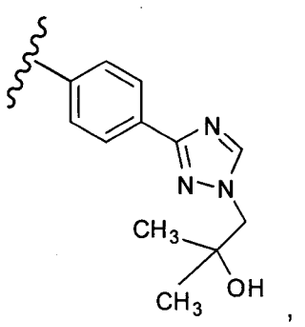
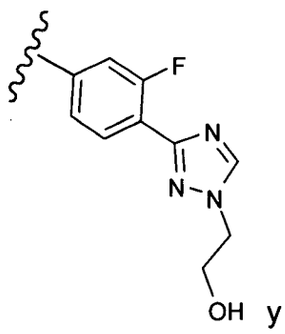
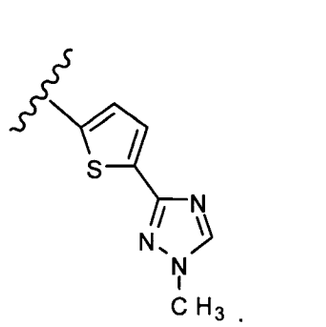

, y

.

28. El compuesto de la reivindicación 27 donde R^1 es un piridilo sustituido con un sustituyente seleccionado del grupo que consiste en: -O-CH_3, -O-C_2H_5, –O-$CH(CH_3)_2$, y –O-$(CH_2)_2$-O-CH_3, y R^2 se selecciona del grupo que consiste en: -OCH_3 y –SCH_3.

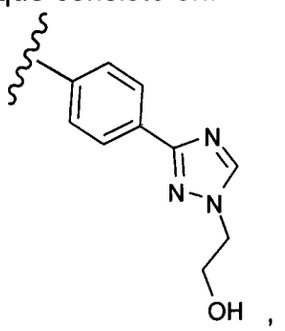
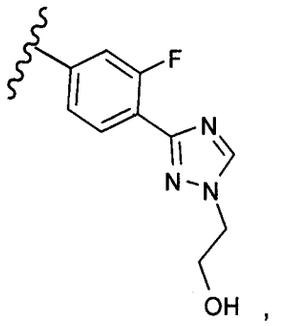
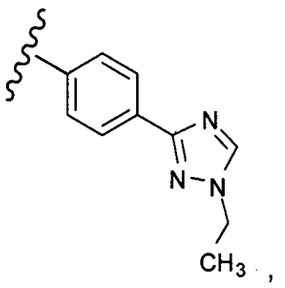
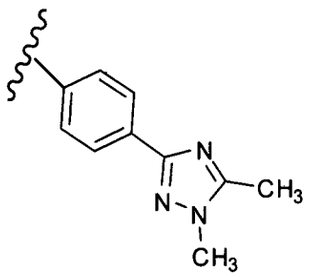
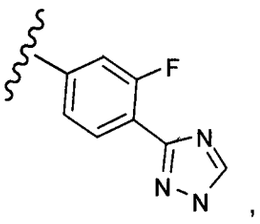
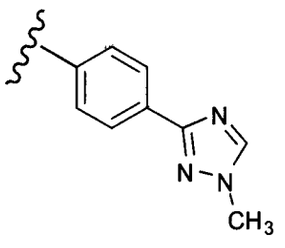
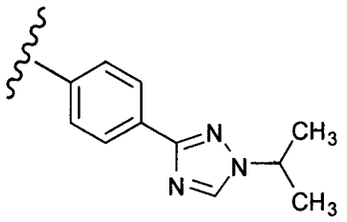
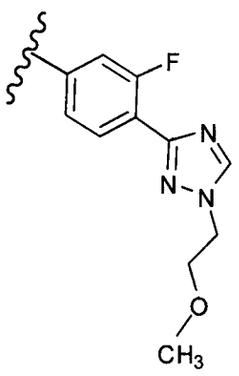
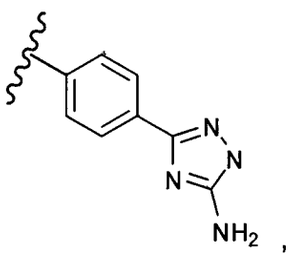
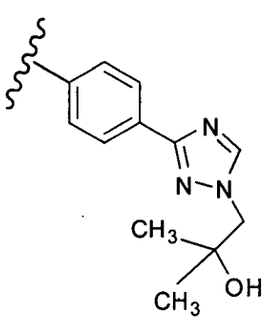
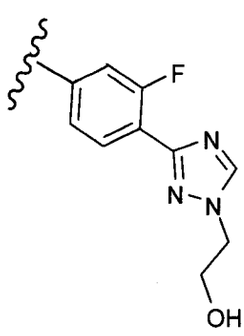
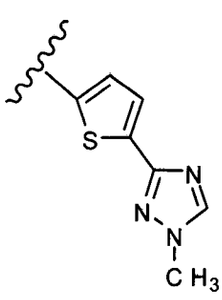
29. El compuesto de la reivindicación 28 donde R^1 se selecciona del grupo que consiste en:


,

, y

,

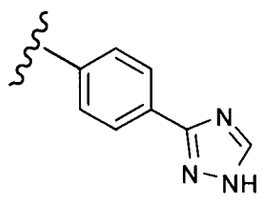
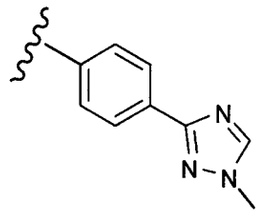
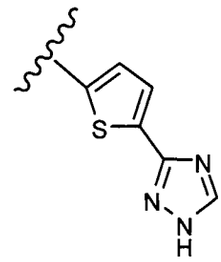
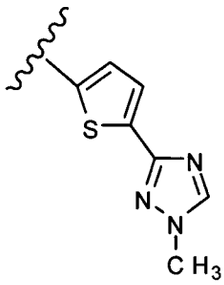
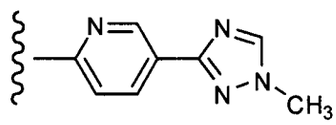
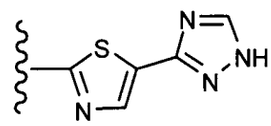
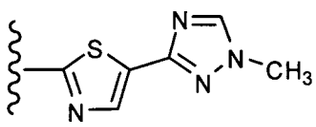
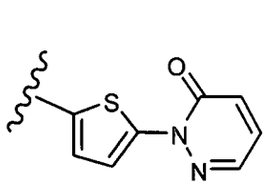
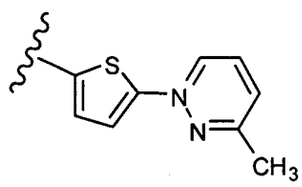
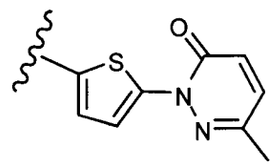
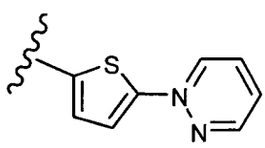
30. El compuesto de la reivindicación 1 donde R^5 se selecciona del grupo que consiste en:

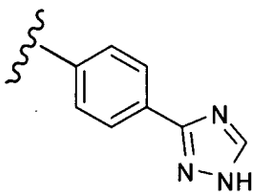
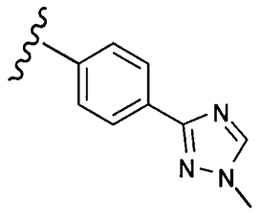
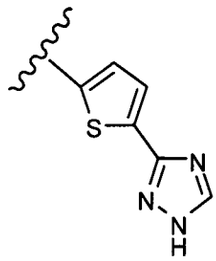
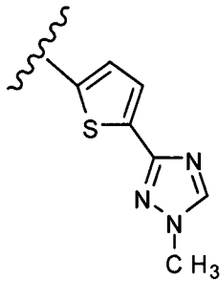
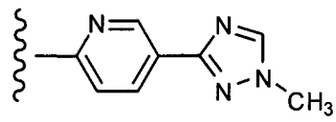
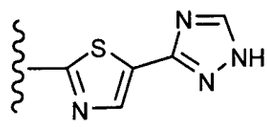
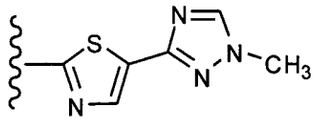
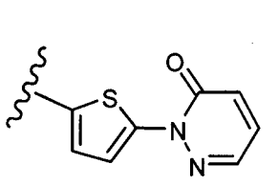
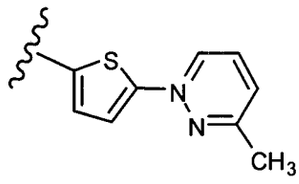
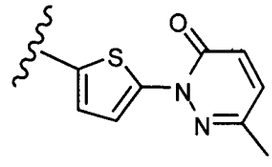
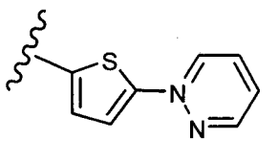
31. El compuesto de la reivindicación 29 donde R^5 se selecciona del grupo que consiste en:


,

,

,

,

,

,

,

,

,

,

y

.

32. El compuesto de la reivindicación 1 donde R^5 se selecciona del grupo que consiste en:


,

,

,

,

,

,

,

,

,

, y

.

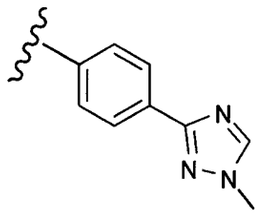
33. El compuesto de la reivindicación 29 donde R^5 se selecciona del grupo que consiste en:

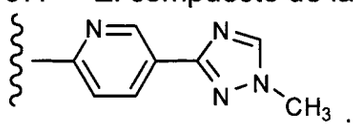
34. El compuesto de la reivindicación 1 donde R^5 es triazolil-fenil-.

35. El compuesto de la reivindicación 1 donde R^5 es triazolil-tienil-.

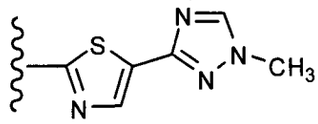
36. El compuesto de la reivindicación 1 donde R^5 es



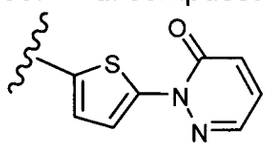
37. El compuesto de la reivindicación 1 donde R^5 es:



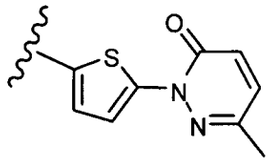
38. El compuesto de la reivindicación 1 donde R^5 es



39. El compuesto de la reivindicación 1 donde R^5 es



40. El compuesto de la reivindicación 1 donde R^5 es



41. Un compuesto seleccionado del grupo que consiste en los compuestos A1 a A16 y A18 a A30.

42. Un compuesto seleccionado del grupo que consiste en los compuestos A31 a A48.

43. El compuesto de la reivindicación 41 donde dicho compuesto es el compuesto A1.

44. El compuesto de la reivindicación 41 donde dicho compuesto es el compuesto A2.

45. El compuesto de la reivindicación 41 donde dicho compuesto es el compuesto A3.

46. El compuesto de la reivindicación 41 donde dicho compuesto es el compuesto A6.

47. El compuesto de la reivindicación 41 donde dicho compuesto es el compuesto A7.

48. El compuesto de la reivindicación 41 donde dicho compuesto es el compuesto A13.

49. El compuesto de la reivindicación 41 donde dicho compuesto es el compuesto A19.

50. El compuesto de la reivindicación 41 donde dicho compuesto es el compuesto A22.

51. El compuesto de la reivindicación 41 donde dicho compuesto es el compuesto A24.

52. El compuesto de la reivindicación 41 donde dicho compuesto es el compuesto A25.

53. El compuesto de la reivindicación 41 donde dicho compuesto es el compuesto A27.

54. El compuesto de la reivindicación 41 donde dicho compuesto es el compuesto A28.

55. El compuesto de la reivindicación 41 donde dicho compuesto es el compuesto A29.

56. El compuesto de la reivindicación 41 donde dicho compuesto es el compuesto A30.

57. Un solvato, o una sal aceptable para uso farmacéutico, de un compuesto seleccionado del grupo que consiste en los compuestos A1 a A16 y A18 a A48.

58. Una sal aceptable para uso farmacéutico de un compuesto de la reivindicación 41.

59. Un solvato de un compuesto de la reivindicación 41.

60. Un solvato, o una sal aceptable para uso farmacéutico, de un compuesto de la reivindicación 42.

61. El compuesto de la reivindicación 1 en forma pura y aislada.

62. El compuesto de la reivindicación 41 en forma pura y aislada.

63. El compuesto de la reivindicación 42 en forma pura y aislada.

64. Una sal aceptable para uso farmacéutico de un compuesto de la reivindicación 42.

65. Una composición farmacéutica que comprende al menos un compuesto de la reivindicación 1 y un vehículo aceptable para uso farmacéutico.

66. Una composición farmacéutica que comprende al menos un compuesto de la reivindicación 41 y un vehículo aceptable para uso farmacéutico.

67. Una composición farmacéutica que comprende al menos un compuesto de la reivindicación 42 y un vehículo aceptable para uso farmacéutico.

68. Un método para tratar el cáncer en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de al menos un compuesto de la reivindicación 1.

69. Un método para tratar el cáncer en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de al menos un compuesto de la reivindicación 1 en combinación con una cantidad efectiva de al menos un agente quimioterapéutico.

70. Un método para tratar el cáncer en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de al menos un compuesto de la reivindicación 1 en combinación con una cantidad efectiva de al menos un agente quimioterapéutico, y una cantidad efectiva de terapia con radiación.

71. Un método para tratar el cáncer en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de al menos un compuesto de la reivindicación 1, y cantidades efectivas para uso terapéutico de al menos un agente quimioterapéutico seleccionado del grupo que consiste en: (1) taxanos, (2) compuestos coordinadores de platino, (3) inhibidores del factor de crecimiento epidérmico (EGF) que son anticuerpos, (4) inhibidores de EGF que son pequeñas moléculas, (5) inhibidores del factor de crecimiento endotelial vascular (VEGF) que son anticuerpos, (6) Inhbidores de la quinasa VEGF que son pequeñas moléculas, (7) antagonistas del receptor de estrógenos o moduladores selectivos del receptor de estrógenos (SERM), (8) derivados nucleósidos antitumorales, (9) epotilonas, (10) inhibidores de la topoisomerasa, (11) vinca alcaloides, (12) anticuerpos que son inhibidores de αVβ3 integrinas, (13) antagonistas de folato, (14) inhibidores de la ribonucleótido reductasa, (15) antraciclinas, (16) biológicos; (17) inhibidores de angiogénesis y/o supresores de factor de necrosis tumoral alfa (TNF-alfa) tal como talidomida (o imida relacionada), (18) Inhibidores de la bcr/abl quinasa, (19) inhibidores de MEK1 y/o MEK 2 que son pequeñas moléculas, (20) inhibidores de IGF-1 y IGF-2 que son pequeñas moléculas, (21) inhibidores de pequeñas moléculas de las RAF y BRAF quinasas, (22) inhibidores de pequeñas moléculas de quinasas

dependientes de ciclos celulares tal como CDK1, CDK2, CDK4 y CDK6, (23) agentes alquilantes, e (24) inhibidores de la farnesil proteína transferasa.

72. Un método para tratar el cáncer en un paciente necesitado de dicho tratamiento, dicho método comprende administrar a dicho paciente una cantidad efectiva de:

(a) al menos un compuesto de la reivindicación 1 en combinación con al menos un inhibidor de la transducción de señales;

(b) al menos un compuesto de la reivindicación 1, dicho cáncer seleccionándose del grupo que consiste en: cáncer de pulmón, cáncer pancreático, cáncer de colon, leucemias mieloides, cáncer de tiroides, síndrome mielodisplásico, carcionoma de la vejiga, carcinoma epidérmico, melanoma, cáncer de mama, cáncer de próstata, cánceres de cabeza y cuello, cáncer de ovarios, cánceres cerebrales, cánceres de origen mesenquimal, sarcomas, tetracarcinomas, nuroblastomas, carcinomas renales, hepatomas, linfoma no Hodgkin, myeloma múltiple, y carcinoma anaplásico de tiroides;

(c) al menos un compuesto de la reivindicación 1, donde dicho cáncer se selecciona del grupo que consiste en: melanoma, cáncer pancreático, cáncer de tiroides, cáncer colorectal, cáncer de pulmón, cáncer de mama y cáncer de ovarios;

(d) al menos un compuesto de la reivindicación 1, en combinación con una cantidad efectiva de al menos un agente quimioterapéutico, donde dicho cáncer se selecciona del grupo que consiste en: melanoma, cáncer pancreático, cáncer de tiroides, cáncer colorectal, cáncer de pulmón, cáncer de mama y cáncer de ovarios;

(e) al menos un compuesto de la reivindicación 1, y dicho cáncer es melanoma;

(f) al menos un compuesto de la reivindicación 1, en combinación con una cantidad efectiva de al menos un agente quimioterapéutico, y dicho cáncer es melanoma;

(g) al menos un compuesto de la reivindicación 1, y dicho cáncer es cáncer pancreático;

(h) al menos un compuesto de la reivindicación 1, en combinación con una cantidad efectiva de al menos un agente quimioterapéutico, y dicho cáncer es cáncer pancreático;

(i) al menos un compuesto de la reivindicación 1, y dicho cáncer es cáncer de tiroides;

(j) al menos un compuesto de la reivindicación 1, en combinación con una cantidad efectiva de al menos un agente quimioterapéutico, y dicho cáncer es cáncer de tiroides;

(k) al menos un compuesto de la reivindicación 1, y dicho cáncer es cáncer colorectal;

(l) al menos un compuesto de la reivindicación 1, en combinación con una cantidad efectiva de al menos un agente quimioterapéutico, y dicho cáncer es cáncer colorectal;

(m) al menos un compuesto de la reivindicación 1, y dicho cáncer es cáncer de pulmón;

(n) al menos un compuesto de la reivindicación 1, en combinación con una cantidad efectiva de al menos un agente quimioterapéutico, donde dicho cáncer es cáncer de pulmón;

(o) al menos un compuesto de la reivindicación 1, y dicho cáncer es cáncer de mama;

(p) al menos un compuesto de la reivindicación 1, en combinación con una cantidad efectiva de al menos un agente quimioterapéutico, y dicho cáncer es cáncer de mama;

(q) al menos un compuesto de la reivindicación 1, y dicho cáncer es cáncer de ovarios;

(r) al menos un compuesto de la reivindicación 1, en combinación con una cantidad efectiva de al menos un agente quimioterapéutico, y dicho cáncer es cáncer de ovarios;

(s) al menos un compuesto de la reivindicación 1, en combinación con agentes antihormonales, donde dicho cáncer es cáncer de mama hormona-dependiente;

(t) al menos un compuesto de la reivindicación 1, en combinación con agentes antihormonales, y en combinación con una cantidad efectiva de al menos un agente quimioterapéutico donde dicho cáncer es cáncer de mama hormona-dependiente;

(u) al menos un compuesto de la reivindicación 1, y dicho cáncer es cáncer cerebral;

(v) al menos un compuesto de la reivindicación 1, en combinación con una cantidad efectiva de al menos un agente quimioterapéutico, y dicho cáncer es cáncer cerebral;

(w) al menos un compuesto de la reivindicación 1, en combinación con una cantidad efectiva de al menos un agente quimioterapéutico, y dicho agente quimioterapéutico es temozolomida, y donde dicho cáncer es cáncer cerebral;

(x) al menos un compuesto de la reivindicación 1, y dicho cáncer es cáncer de próstata;

(y) al menos un compuesto de la reivindicación 1, en combinación con una cantidad efectiva de al menos un agente quimioterapéutico, y dicho cáncer es cáncer de próstata;

(z) al menos un compuesto de la reivindicación 1, y dicho cáncer es síndrome mielodisplásico;

(aa) al menos un compuesto de la reivindicación 1, en combinación con una cantidad efectiva de al menos un agente quimioterapéutico, y dicho cáncer es síndrome mielodisplásico;

(ab) al menos un compuesto de la reivindicación 1, y dicho cáncer es una leucemia mieloide;

(ac) al menos un compuesto de la reivindicación 1, en combinación con una cantidad efectiva de al menos un agente quimioterapéutico, y dicho cáncer es una leucemia mieloide;

(ad) al menos un compuesto de la reivindicación 1, y dicho cáncer es leucemia mielógena aguda;

(ae) al menos un compuesto de la reivindicación 1, en combinación con una cantidad efectiva de al menos un agente quimioterapéutico, y dicho cáncer es leucemia mielógena aguda;

(af) al menos un compuesto de la reivindicación 1, y dicho cáncer es leucemia mielomonocítica crónica;

(ag) al menos un compuesto de la reivindicación 1, en combinación con una cantidad efectiva de al menos un agente quimioterapéutico, y dicho cáncer es leucemia mielomonocítica crónica;

(ah) al menos un compuesto de la reivindicación 1, y dicho cáncer es leucemia mielógena crónica;

(ai) al menos un compuesto de la reivindicación 1, en combinación con una cantidad efectiva de al menos un agente quimioterapéutico, y dicho cáncer es leucemia mielógena crónica;

(aj) al menos un compuesto de la reivindicación 1, y dicho cáncer es cáncer de vejiga;

(ak) al menos un compuesto de la reivindicación 1, en combinación con una cantidad efectiva de al menos un agente quimioterapéutico, y dicho cáncer es cáncer de vejiga;

(al) al menos un compuesto de la reivindicación 1, y dicho cáncer es linfoma no Hodgkin;

(am) al menos un compuesto de la reivindicación 1, en combinación con una cantidad efectiva de al menos un agente quimioterapéutico, y dicho cáncer es linfoma no Hodgkin;

(an) al menos un compuesto de la reivindicación 1, y dicho cáncer es mieloma múltiple; o

(ao) al menos un compuesto de la reivindicación 1, en combinación con una cantidad efectiva de al menos un agente quimioterapéutico, y dicho cáncer es mieloma múltiple;

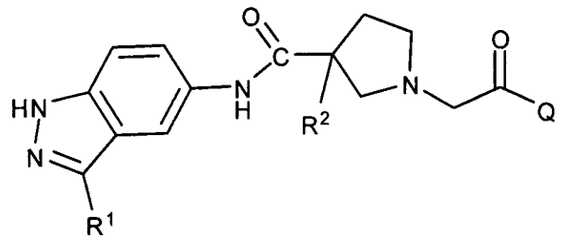
73. Un método para prevenir el cáncer de mama hormona-dependiente en un paciente necesitado de dicho tratamiento, dicho tratamiento comprende la administración de una cantidad efectiva de:

(a) al menos un compuesto de la reivindicación 1 en combinación con agentes antihormonales; o

(b) al menos un compuesto de la reivindicación 1 en combinación con agentes antihormonales, y en combinación con una cantidad efectiva de al menos un agente quimioterapéutico.

RESUMEN

Se describen inhibidores ERK de fórmula 1.0:



(1.0)

y las sales aceptables para uso farmacéutico, y solvatos de los mismos. Q es un anillo tetrahidopiridinilo. Todos los otros sustituyentes son lo definido en la presente. También se describen métodos para tratar el cáncer utilizando los compuestos de fórmula 1.0.

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 10-116702- -00000-0000

Fecha: 2010-09-21 15:26:51 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 392

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 D.C.,
2020

Doctor(a)
OLARTE GARCIA CARLOS REYNALDO
Apoderado(a) y/o Representante de
SCHERING CORPORATION

REFERENCIA	Radicación No.	10 116702
	Solicitud internacional	PCT/US2009/034447
	Fecha inicio fase nacional	21/09/2010
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	14078

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. 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.

ALIX CARMENZA CESPEDES DE VERGEL
Directora de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista de fecha 29 OCT. 2010
adpa11

Industria y Comercio
SUPERINTENDENCIA

Bogotá D.C.,
2020

Doctor(a)
OLARTE GARCIA CARLOS REYNALDO
Apoderado(a) y/o Representante de
SCHERING CORPORATION

REFERENCIA	Radicación No.	10 116702
	Solicitud internacional	PCT/US2009/034447
	Fecha inicio fase nacional	21/09/2010
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	№ 14079

Teniendo en cuenta que el capítulo reivindicatorio presentado excede de diez 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 N° 10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Directora de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista de fecha 29 OCT. 2010
adpa11