07

PCT

UOM RCF

Industria y Comercio

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENTAR

SUPERINTENDENCIA

10-9533

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIRECCIÓN DE NUEVAS CREACIONES

SOLICITUD DE PATENTE DE INVENCIÓN

TITULO: 6 COMBINACIÓN DE AGENTE ANTIMITÓTICO E INHIBIDOR DE AURORA QUINASA COMO TRATAMIENTO ANTICANCERÍGENO

SOLICITANTE: SCHERING CORPORATION

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

APODERADO: CARLOS R. OLARTE

BOGOTÁ 29 de Enero de 2010

Cuad. Titulo
Fs 01-03-2010
No. Exclusivo

P2010/000010

OLARTERAISBECK

OLARTE RAISBECK MOUR

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-009533- -00000-0000
Fecha: 2010-01-29 17:33:14 Dep: 2020 DIR.NUEVASCR
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 1281

PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2010/000010**

SOLICITUD DE:

(1)

[X] Patente de Invención. [ ] Patente de Modelo de Utilidad.

[X] Capítulo I. [ ] Capítulo II.

(2) **SOLICITANTE (71)**

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

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

REPRESENTANTE O APODERADO

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

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

INVENTOR (ES) (72)

Nombre: Andrea Dawn Basso
Dirección: 40 Lydia Drive Guttenberg, New Jersey 07093 E.U.A
Nacionalidad o Domicilio: Estadounidense

(5) **PCT (86)**

Solicitud Internacional No. PCT/US2008/009108 Fecha Julio 28, 2008

Publicación Internacional No. WO 2009/017701 Fecha Febrero 5, 2009

(6) **Título (54)** **6 COMBINACIÓN DE AGENTE ANTIMITÓTICO E INHIBIDOR DE AURORA QUINASA COMO TRATAMIENTO ANTICANCERÍGENO**

Ver folio 1286

Clasificación Internacional (51) A61K 45/06 A61P 35/00

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

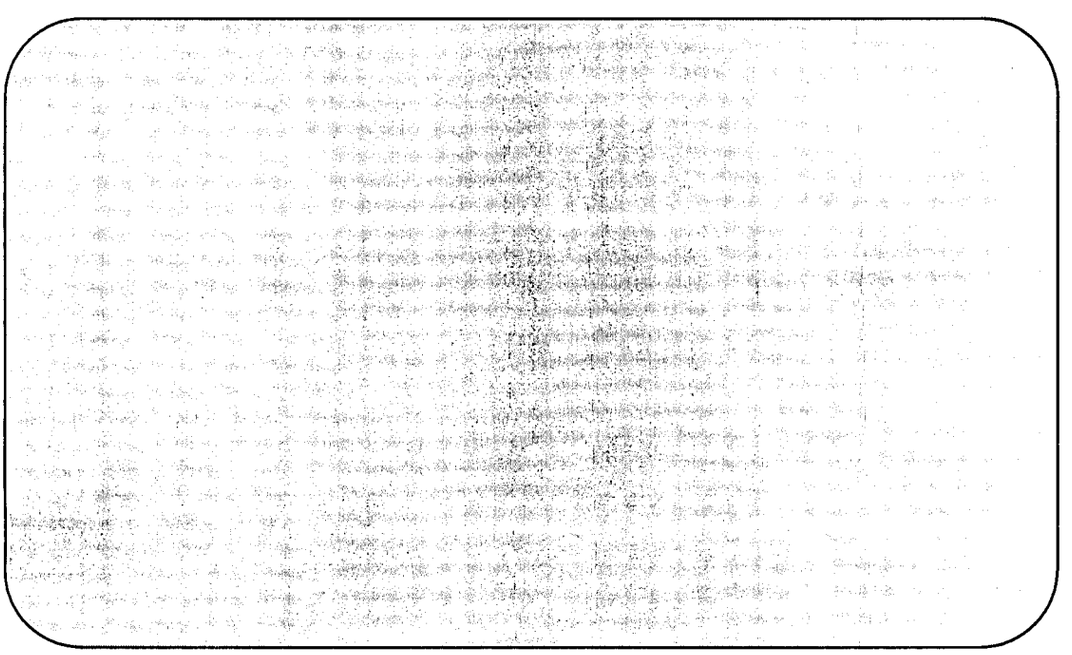
(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Julio 31, 2007	60/953.087
US	Enero 28 2008	61/023,985

(9) **Comprobante de pago No.** 10-6255 **Fecha** Enero 27, 2010

(10) **ANEXOS**

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

(11) **FIGURA CARACTERÍSTICA:**



(12) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE FIRMA: _____

C.C. 79.782.747 Btá T.P. 74.295

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

3

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 10 - 6,255
FECHA : ENERO 27 DE 2010

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-009533- -00000-0000
Fecha: 2010-01-29 17:33:14 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 1281

***** 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	105821940	27/01/2010	3,927,000.00

***** 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

APOSTILLA EN PODER DE REPRESENTACIÓN DE

SCHERING CORPORATION

APOSTILLA

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

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

CERTIFICADO

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

PODER DE REPRESENTACIÓN

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

CERTIFICADO NOTARIAL

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

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

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

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

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

APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA

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

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

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

CERTIFIED

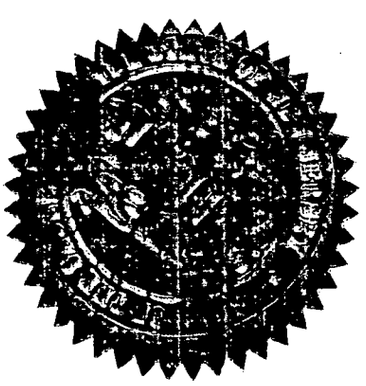
5. AT TRENTON, NEW JERSEY

6. THE 29TH DAY OF AUGUST 2003

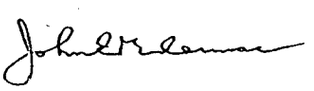
7. BY: John E McCormac, CPA, NEW JERSEY TREASURER

8. NO. A180345

9. SEAL/STAMP:



10. SIGNATURE



OLARTERAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

WORLD TRADE CENTER – TORRE C
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6

Power of Attorney

The undersigned,
SCHERING CORPORATION
domiciled in
2000 Galloping Hill Road, Kenilworth, New Jersey 07033-0532, U.S.A.

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

Poder

El suscrito,

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

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

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

Date/Fecha: August 7, 2003

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

OLARTERAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

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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

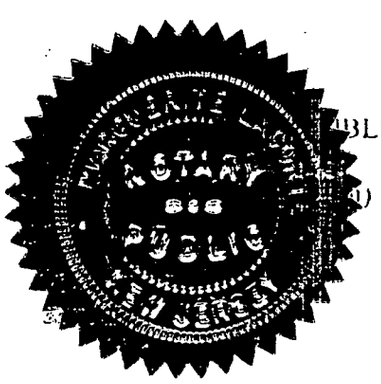
4. Que

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):



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
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60/953,087 31 July 2007 (31.07.2007) US
61/023,985 28 January 2008 (28.01.2008) US

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

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **BASSO, Andrea, Dawn** [US/US]; 9 Bush Court, New City, New York 10956 (US).

(74) Agent: **FARQUHARSON-TORRES, Serena**; 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, 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).

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

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

(54) **Title:** ANTI-MITOTIC AGENT AND AURORA KINASE INHIBITOR COMBINATION AS ANTI-CANCER TREATMENT

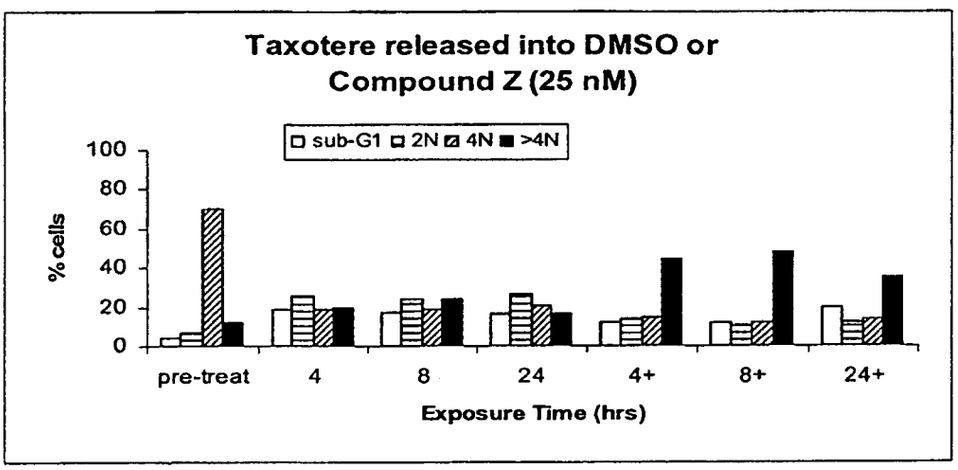


FIG. 11

(57) **Abstract:** The present invention relates to a method of treating cancer by pretreatment with anti-mitotic agents followed by at least one aurora kinase inhibitor. Extensive illustrations are provided for the antimitotic agents and aurora kinase inhibitors that are useful in the inventive treatment.

WO 2009/017701 A2

ANTI-MITOTIC AGENT AND AURORA KINASE INHIBITOR COMBINATION AS ANTI-CANCER TREATMENT

FIELD OF THE INVENTION

The present invention relates to a method of treating cancer by pretreatment with anti-mitotic agents followed by aurora kinase inhibitors. This application claims priority from U.S. provisional patent application, Serial No. 60/953,087 filed July 31, 2007.

BACKGROUND OF THE INVENTION

Taxanes such as paclitaxel and docetaxel and vinca alkaloids target microtubules, which are responsible for distribution of duplicated sister chromatids to each of the daughter cells. Disruption of microtubules can inhibit cell division and induce apoptosis.

KSP inhibitors interfere with function of mitotic kinesins and therefore disrupt normal mitosis and blocks cell division. Mitotic Kinesin-KSP, known as Eg5, is required for centrosome separation. Cells in which KSP function is inhibited, arrest in mitosis with un-separated centrosomes. (Blangy et al., *Cell* 1995, 83: 1159-1169, Heald, R., *Cell* 2000, 102, 399). Mitotic arrest leads to growth inhibition of tumor cells. (Kaiser et al., *J. Biol. Chem.* 1999, 274: 18925-18931).

Like KSP inhibitor, Cenp-E inhibitors inhibit centrosome separation by inhibiting centrosome associated protein E. resulting in cell cycle arrest with bipolar mitotic spindles and misaligned chromosomes.

Ispinesib and Monastrol are kinesin spindle protein inhibitors. They cause cell cycle arrest by disrupting a kinesin-related motor protein that is necessary for formation of a bipolar spindle. (Mayer et al, *Science* 1999, Vol. 286, No. 5441, 971-974).

Aurora kinases (Aurora-A, Aurora-B, Aurora-C) are serine/threonine protein kinases that have been implicated in human cancer, such as colon, breast and other solid tumors. In various human cancers over expression of Aurora A and/or Aurora B has been observed. In some cases this is a result of gene amplification. Over expression of Aurora kinases correlates with poor survival prognosis.

Aurora kinases are involved in phosphorylation events that regulate the cell cycle. Misregulation of the cell cycle can lead to cellular proliferation and other abnormalities. Aurora A regulates centromere maturation, mitotic entry, bipolar spindle assembly, and

chromosome alignment. Aurora B regulates chromatin remodeling, kinetochore-spindle attachment, and cytokinesis. Aurora C expression is limited and its function is thought to be similar to that of Aurora B.

Small molecules that inhibit Aurora kinases have been developed as potential anti-cancer agents. VX-680 (Harrington 2004) and AT9283 are dual Aurora A/B inhibitors. AZD1152 is an Aurora B selective inhibitor (Morlock 2006) and MLN8054 is a reported Aurora A specific inhibitor (Manfredi 2007). Compounds that inhibit Aurora B result in induction of endoreduplication, cells continue through the cell cycle without undergoing cytokinesis and accumulate DNA with >4N content (where 2N DNA represents cells in G1 and 4N represents cell in mitosis).

Reference is also made to R. R. Hoover. and M. W. Harding, *Journal of Clinical Oncology, 2007 American Society of Clinical Oncology Annual Meeting Proceedings Part I.* Vol. 25, No. 18S (June 20 Supplement), 2007: 14069, which discusses the in vitro use of a reversible kinase inhibitor (MK-0457) that targets Aurora A, B and C in sequential or simultaneous combination with the microtubule targeted agent, Taxotere, on cancer cell lines. It states that synergy occurs with sequential and not simultaneous exposure to both compounds in the short-term viability assays and synergy occurred with simultaneous exposure in the long-term survival assays.

Reference is made to Aurora inhibition in combination with taxanes in *Proceedings from the American Association for Cancer Research 2007 Annual Meeting* (April 18, 2007). P Phatak *et al.* (abstract No. 5746) discusses the schedule dependent synergy of a non-specific aurora kinase inhibitor (VE-465), which is similar to MK-0457, which is currently in clinical trials, and paclitaxel in non-small cell lung cancer. It states that VE-465 and paclitaxel exhibit schedule dependent synergy that results in enhanced cell kill with dependence on the cell line. Additionally, Abstract No. 4357 concluded VX-680 and taxotere combination showed enhanced cell growth inhibition and Abstract No. 1819 concluded VE-645 and taxol combination showed enhanced cell growth inhibition. Abstract No. 4359 and No. 3263 concluded AZD1152 in combination with taxol showed enhanced cell growth inhibition.

References have been made to selective Aurora A inhibition and taxanes. Tanaka et al. (*Clinical Cancer Research* 2007; 13:1331) showed Aurora A siRNA in combination with Taxotere resulted in enhanced apoptosis. Hata et al (*Cancer Research* 2005; 65: 2899) demonstrated Aurora A siRNA in combination with taxanes showed enhanced cytotoxicity.

Ohkubo M et al disclosed in a patent combination of novel aminopyridines having selective Aurora A inhibitory effects with Taxol had enhanced cell growth inhibition.

Yang et al (*International Journal of Cancer* 2006; 119:2304) found that ectopic expression of Aurora A rendered cells resistant to anti-cancer agents such as Taxol. Similarly, Anand et al (*Cancer Cell* 2003; 3:51) found elevated Aurora A expression causes resistance to apoptosis induced by Taxol. Anand et al (WO05/002571, filed January 13, 2005) disclosed that over-expression of Aurora A mediates resistance to anti-cancer agents and the resistance can be reduced by inhibiting Aurora kinases or predicted by measuring the expression or activity of Aurora kinases within the cell.

SUMMARY OF THE INVENTION

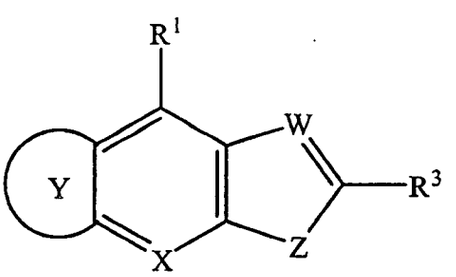
This invention provides a pharmaceutical composition for treating or ameliorating cancer comprising at least one first compound, which is an anti-mitotic agent and at least one second compound, which is an aurora kinase inhibitor.

This invention further provides a method of treating or ameliorating cancer comprising administration to a mammal in need of such treatment an amount of at least one first compound, which is an anti-mitotic agent followed by an amount of at least one second compound, which is an aurora kinase inhibitor. The following sections describe the antimitotic agent and the aurora kinase inhibitor in more details.

Non-limiting examples of anti-mitotic agents useful in this invention include:

Taxanes, paclitaxel, docetaxel, Cenp-E Inhibitor (such as for example GSK-923295), Abraxane, Epothilone, Monastrol, and KSP inhibitors. Non-limiting examples of useful KSP inhibitors include Ispinesib SB-715992 (Cytokinetics), as well as the compounds of Formulas A-D shown in paragraphs a-d below:

a. A compound represented by the structural Formula A:



Formula A

or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:

ring Y is a 5- to 6-membered aryl or a 5- or 6-membered heteroaryl fused as shown in Formula A, wherein in said aryl and heteroaryl each substitutable ring carbon is independently substituted with R^2 and each substitutable ring nitrogen is independently substituted with R^6;

W is N or $C(R^{12})$;

X is N or N-oxide;

Z is S, S(=O) or $S(=O)_2$;

R^1 is H, alkyl, alkoxy, hydroxy, halo, -CN, $-S(O)_m$-alkyl, $-C(O)NR^9R^{10}$, $-(CR^9R^{10})_{1-6}OH$, or $-NR^4(CR^9R^{10})_{1-2}OR^9$;

each R^2 is independently selected from the group consisting of H, halo, alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, $-(CR^{10}R^{11})_{0-6}$-OR^7, $-C(O)R^4$, $-C(S)R^4$, $-C(O)OR^7$, $-C(S)OR^7$, $-OC(O)R^7$, $-OC(S)R^7$, $-C(O)NR^4R^5$, $-C(S)NR^4R^5$, $-C(O)NR^4OR^7$, $-C(S)NR^4OR^7$, $-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, -CN, $-OCF_3$, $-SCF_3$, $-C(=NR^7)NR^4$, $-C(O)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}OR^7$, $-C(S)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(S)NR^7(CH_2)_{1-10}OR^7$, haloalkyl and alkylsilyl, wherein each of said alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl or heteroaralkyl is independently optionally substituted with 1-5 R^9 moieties;

each R^3 is independently selected from the group consisting of H, halo, alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, $-(CR^{10}R^{11})_{0-6}$-OR^7, $-C(O)R^4$, $-C(S)R^4$, $-C(O)OR^7$, $-C(S)OR^7$, $-OC(O)R^7$, $-OC(S)R^7$, $-C(O)NR^4R^5$, $-C(S)NR^4R^5$, $-C(O)NR^4OR^7$, $-C(S)NR^4OR^7$, $-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, -CN, $-OCF_3$, $-SCF_3$, $-C(=NR^7)NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}OR^7$, $-C(S)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(S)NR^7(CH_2)_{1-10}OR^7$, haloalkyl and alkylsilyl, wherein each of said alkyl, cycloalkyl,

cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl or heteroaralkyl is independently optionally substituted with 1-5 R^9 moieties;

each R^4 and R^5 is independently selected from the group consisting of H, alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, $-OR^7$, $-C(O)R^7$, and $-C(O)OR^7$, wherein each of said alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl is optionally substituted with 1-4 R^8 moieties;

or R^4 and R^5, when attached to the same nitrogen atom, are optionally taken together with the nitrogen atom to which they are attached to form a 3-6 membered heterocyclic ring having 0-2 additional heteroatoms selected from N, O or S;

each R^6 is independently selected from the group consisting of H, alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroaralkyl, $-(CH_2)_{1-6}CF_3$, $-C(O)R^7$, $-C(O)OR^7$ and $-SO_2R^7$;

each R^7 is independently selected from the group consisting of H, alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, and heteroaralkyl, wherein each member of R^7 except H is optionally substituted with 1-4 R^8 moieties;

each R^8 is independently selected from the group consisting of halo, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-NO_2$, $-OR^{10}$, $-(C_1\text{-}C_6$ alkyl$)\text{-}OR^{10}$, $-CN$, $-NR^{10}R^{11}$, $-C(O)R^{10}$, $-C(O)OR^{10}$, $-C(O)NR^{10}R^{11}$, $-CF_3$, $-OCF_3$, $-CF_2CF_3$, $-C(=NOH)R^{10}$, $-N(R^{10})C(O)R^{11}$, $-C(=NR^{10})NR^{10}R^{11}$, and $-NR^{10}C(O)OR^{11}$, wherein each of said alkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally independently substituted with 1-3 moieties selected from the group consisting of halo, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-NO_2$, $-OR^{10}$, $-(C_1\text{-}C_6$ alkyl$)\text{-}OR^{10}$, $-CN$, $-NR^{10}R^{11}$, $-C(O)OR^{10}$, $-C(O)NR^{10}R^{11}$, $-CF^3$, $-OCF_3$, $-NR^{10}C(O)OR^{11}$, and $-NR^{10}C(O)R^{40}$;

or two R^8 groups, when attached to the same carbon atom, are optionally taken together with the carbon atom to which they are attached to form a C=O or a C=S group;

each R^9 is independently selected from the group consisting of H, alkyl, alkoxy, OH, CN, halo, $-(CR^{10}R^{11})_{0-4}NR^4R^5$, haloalkyl, hydroxyalkyl, alkoxyalkyl, $-C(O)NR^4R^5$, $-C(O)OR^7$, $-OC(O)NR^4R^5$, $-NR^4C(O)R^5$, and $-NR^4C(O)NR^4R^5$;

each R^{10} is independently H or alkyl; or R^9 and R^{10}, when attached to the same nitrogen atom, are optionally taken together with the nitrogen atom to which they are attached to form a 3-6 membered heterocyclic ring having 0-2 additional heteroatoms selected from N, O or S;

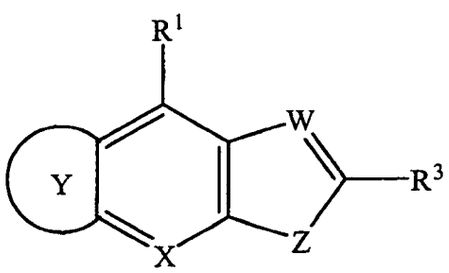
each R^{11} is independently H or alkyl; or R^{10} and R^{11}, when attached to the same nitrogen atom, are optionally taken together with the nitrogen atom to which they are attached to form a 3-6 membered heterocyclic ring having 0-2 additional heteroatoms selected from N, O or S;

each R^{12} is independently selected from the group consisting of H, halo, alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, $-(CR^{10}R^{11})_{0-6}-OR^7$, $-C(O)R^4$, $-C(S)R^4$, $-C(O)OR^7$, $-C(S)OR^7$, $-OC(O)R^7$, $-OC(S)R^7$, $-C(O)NR^4R^5$, $-C(S)NR^4R^5$, $-C(O)NR^4OR^7$, $-C(S)NR^4OR^7$, $-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, $-CN$, $-OCF_3$, $-SCF_3$, $-C(=NR^7)NR^4$, $-C(O)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}OR^7$, $-C(S)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(S)NR^7(CH_2)_{1-10}OR^7$, haloalkyl and alkylsilyl, wherein each of said alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl or heteroaralkyl is independently optionally substituted with 1-5 R^9 moieties; and

R^{40} is selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl, wherein each of said cycloalkyl, heterocyclyl, aryl and heteroaryl are optionally independently substituted with 1-3 moieties independently selected from the group consisting of -CN, -OH, halo, alkyl, haloalkyl, alkoxy, and $-NR^{10}R^{11}$.

Such compounds of Formula A in (a) are disclosed in WO 2006/098962, filed March 7, 2006, the content of which is incorporated herein by reference in its entirety;

b. A compound represented by the structural Formula B:



Formula B

or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:

ring Y is a 5- to 7-membered ring selected from the group consisting of cycloalkyl, cycloalkenyl, heterocyclyl or heterocyclenyl fused as shown in Formula B, wherein in each of said 5- to 7-membered ring, each substitutable ring carbon is independently substituted with 1-2 R^2 moieties and each substitutable ring heteroatom is independently substituted with R^6;

W is N or $C(R^{12})$;

X is N or N-oxide;

Z is S, S(=O) or $S(=O)_2$;

R^1 is H, alkyl, alkoxy, hydroxy, halo, -CN, $-S(O)_m$-alkyl, $-C(O)NR^9R^{10}$, $-(CR^9R^{10})_{1-6}OH$, or $-NR^4(CR^9R^{10})_{1-2}OR^9$; wherein m is 0 to 2;

each R^2 is independently selected from the group consisting of H, halo, alkyl, cycloalkyl, alkylsilyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, heteroaryl, $-(CR^{10}R^{11})_{0-6}-OR^7$, $-C(O)R^4$, $-C(S)R^4$, $-C(O)OR^7$, $-C(S)OR^7$, $-OC(O)R^7$, $-OC(S)R^7$, $-C(O)NR^4R^5$, $-C(S)NR^4R^5$, $-C(O)NR^4OR^7$, $-C(S)NR^4OR^7$, $-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, -CN, $-OCF_3$, $-SCF_3$, $-C(=NR^7)NR^4$, $-C(O)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}OR^7$, $-C(S)NR^7(CH_2)_{1-10}NR^4R^5$, and $-C(S)NR^7(CH_2)_{1-10}OR^7$, wherein each of said alkyl, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, and heteroaryl is independently optionally substituted with 1-5 R^9 moieties;

or two R^2s on the same carbon atom are optionally taken together with the carbon atom to which they are attached to form a C=O, a C=S or an ethylenedioxy group;

R^3 is independently selected from the group consisting of H, halo, alkyl, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, heteroaryl, $-(CR^{10}R^{11})_{0-6}-OR^7$, $-C(O)R^4$, $-C(S)R^4$, $-C(O)OR^7$, $-C(S)OR^7$, $-OC(O)R^7$, $-OC(S)R^7$, $-C(O)NR^4R^5$, $-C(S)NR^4R^5$, $-C(O)NR^4OR^7$, $-C(S)NR^4OR^7$, $-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, -CN, $-C(=NR^7)NR^4R^5$, $-C(O)N(R^7)-(CR^{40}R^{41})_{1-5}-C(=NR^7)NR^4R^5$, $-C(O)N(R^7)(CR^{40}R^{41})_{1-5}-NR^4R^5$,

$-C(O)N(R^7)(CR^{40}R^{41})_{1-5}-C(O)-NR^4R^5$,
$-C(O)N(R^7)(CR^{40}R^{41})_{1-5}-OR^7$, $-C(S)NR^7(CH_2)_{1-5}NR^4R^5$, and
$-C(S)NR^7(CH_2)_{1-5}OR^7$, wherein each of said alkyl, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, and heteroaryl is independently optionally substituted with 1-5 R^9 moieties;

each of R^4 and R^5 is independently selected from the group consisting of H, alkyl, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, heteroaryl, $-OR^7$, $-C(O)R^7$, and $-C(O)OR^7$, wherein each of said alkyl, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, and heteroaryl, is optionally substituted with 1-4 R^8 moieties;

or R^4 and R^5, when attached to the same nitrogen atom, are optionally taken together with the nitrogen atom to which they are attached to form a 3-6 membered heterocyclic ring having 0-2 additional heteroatoms selected from N, O or S;

each R^6 is independently selected from the group consisting of H, alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroaralkyl, $-(CH_2)_{1-6}CF_3$, $-C(O)R^7$, $-C(O)OR^7$ and $-SO_2R^7$;

each R^7 is independently selected from the group consisting of H, alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, and heteroaralkyl, wherein each member of R^7 except H is optionally substituted with 1-4 R^8 moieties;

each R^8 is independently selected from the group consisting of halo, alkyl, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, heteroaryl, $-NO_2$, $-OR^{10}$, $-(C_1-C_6$ alkyl$)-OR^{10}$, $-CN$, $-NR^{10}R^{11}$, $-C(O)R^{10}$, $-C(O)OR^{10}$, $-C(O)NR^{10}R^{11}$, $-CF_3$, $-OCF_3$, $-CF_2CF_3$, $-C(=NOH)R^{10}$, $-N(R^{10})C(O)R^{11}$, $-C(=NR^{10})NR^{10}R^{11}$, and $-NR^{10}C(O)OR^{11}$; wherein said each of said alkyl, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, and heteroaryl is independently optionally substituted with 1-4 R^{42} moieties; wherein when each of said cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, and heteroaryl contains two radicals on adjacent carbon atoms anywhere within said cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, and heteroaryl, such radicals may optionally and independently in each occurrence, be taken together with the carbon atoms to which they are attached, to form a five- or six-membered carbocyclic or heterocyclic ring;

or two R^8 groups, when attached to the same carbon, are optionally taken together with the carbon atom to which they are attached to form a C=O or a C=S group;

each R^9 is independently selected from the group consisting of H, alkyl, alkoxy, OH, CN, halo, $-(CR^{10}R^{11})_{0-4}NR^4R^5$, haloalkyl, hydroxyalkyl, alkoxyalkyl, $-C(O)NR^4R^5$, $-C(O)OR^7$, $-OC(O)NR^4R^5$, $-NR^4C(O)R^5$, and $-NR^4C(O)NR^4R^5$;

each R^{10} is independently H or alkyl; or R^9 and R^{10}, when attached to the same nitrogen atom, are optionally taken together with the nitrogen atom to which they are attached to form a 3-6 membered heterocyclic ring having 0-2 additional heteroatoms selected from N, O or S;

each R^{11} is independently H, alkyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heterocyclenyl, or heteroaryl; or R^{10} and R^{11}, when attached to the same nitrogen atom, are optionally taken together with the nitrogen atom to which they are attached to form a 3-6 membered heterocyclic ring having 0-2 additional heteroatoms selected from N, O or S; wherein each of said R^{11} alkyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heterocyclenyl, and heteroaryl is independently optionally substituted with 1-3 moieties selected from the group consisting of –CN, -OH, $-NH_2$, -N(H)alkyl, $-N(alkyl)_2$, halo, haloalkyl, CF_3, alkyl, hydroxyalkyl, alkoxy, aryl, aryloxy, and heteroaryl;

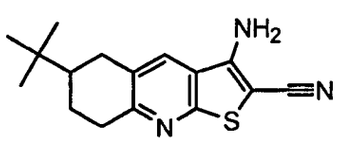
each R^{12} is independently selected from the group consisting of H, halo, alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, $-(CR^{10}R^{11})_{0-6}-OR^7$, $-C(O)R^4$, $-C(S)R^4$, $-C(O)OR^7$, $-C(S)OR^7$, $-OC(O)R^7$, $-OC(S)R^7$, $-C(O)NR^4R^5$, $-C(S)NR^4R^5$, $-C(O)NR^4OR^7$, $-C(S)NR^4OR^7$, $-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, -CN, $-OCF_3$, $-SCF_3$, $-C(=NR^7)NR^4$, $-C(O)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}OR^7$, $-C(S)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(S)NR^7(CH_2)_{1-10}OR^7$, haloalkyl and alkylsilyl, wherein each of said alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl or heteroaralkyl is independently optionally substituted with 1-5 R^9 moieties;

R^{40} and R^{41} can be the same or different, each being independently selected from the group consisting of H, alkyl, aryl, heteroaryl, heterocyclyl, heterocyclenyl, cycloalkyl and cycloalkenyl;

each R^{42} is independently selected from the group consisting of halo, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-NO_2$, $-OR^{10}$, $-(C_1-C_6$ alkyl$)-OR^{10}$, -CN, $–NR^{10}R^{11}$, $–C(O)R^{10}$, $-C(O)OR^{10}$, $-C(O)NR^{10}R^{11}$, $-CF_3$, $–OCF_3$,

$-N(R^{10})C(O)R^{11}$, and $-NR^{10}C(O)OR^{11}$;

with the proviso that when W is $C(R^{12})$, R^{12} and R^3 are optionally taken together, with the two ring carbon atoms to which they are attached to form a 6-membered ring selected from the group consisting of cycloalkenyl, aryl, heteroaryl, heterocyclyl and heterocyclenyl, wherein said 6-membered ring is optionally substituted with 1-3 moieties independently selected from oxo, thioxo, $-OR^{11}$, $-NR^{10}R^{11}$, $-C(O)R^{11}$, $-C(O)OR^{11}$, $-C(O)N(R^{10})(R^{11})$, or $-N(R^{10})C(O)R^{11}$. Such compounds of Formula B in (b) are disclosed in WO2006/098961, filed March 7, 2006, the content of which is incorporated herein by reference in its entirety;

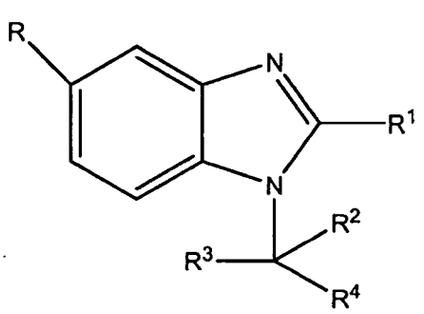
c. 

Formula C

or a pharmaceutically acceptable salt, solvate, or ester thereof.

Such compounds of Formula C in (c) are disclosed in U.S. Pub. No. 2006/0258699, filed March 7, 2006, the content of which is incorporated herein by reference in its entirety; and

d. A compound of Formula D



Formula D

or a pharmaceutically acceptable salt, solvate, or ester thereof, wherein:

R is selected from the group consisting of H, alkyl, cyano, haloalkyl, halo, —SH, -S-alkyl, -S-haloalkyl, $-S(=O)_2$alkyl, $-S(=O)_2OH$, $-S(=O)_2NH_2$, $-S(=O)_2NH$(alkyl), $S(=O)_2NH$(cycloalkyl), $-S(=O)_2N(alkyl)_2$, $-S(=O)_2$heterocyclyl, $-S(=O)_2$heteroaryl, cycloalkyl, aryl, heterocyclyl, heteroaryl, -NHC(=O)alkyl, $-C(=O)NH_2$, –C(=O)NH(alkyl), -C(=O)NH(cycloalkyl), $-C(=O)N(alkyl)_2$, –C(=O)OH, –C(=O)Oalkyl, -C(=O)heterocyclyl, -C(=O)NH(aryl), wherein when each of said cycloalkyl, aryl, heterocyclyl, heteroaryl, and the "heterocyclyl" and "aryl" portions of said R groups has two substituents on adjacent carbon atoms, said substituents, may

optionally be taken together with the carbon atoms to which they are attached to form a five- to six-membered cycloalkyl, aryl, heterocyclyl, heterocyclenyl, or heteroaryl ring; wherein each of the aforementioned R alkyl, aryl, cycloalkyl, heterocyclyl, and heteroaryl, and the "alkyl", "cycloalkyl", "heterocyclyl", and "aryl" portions of said R groups, optionally with said five- to six-membered aryl, heterocyclyl, heterocyclenyl, or heteroaryl ring, is optionally substituted with 1-3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, hydroxyl, cyano, halo, haloalkyl, haloalkoxy, -C(O)OH, -C(=O)Oalkyl, and -C(O)NH_2;

R^1 is selected from the group consisting of alkyl, heterocyclyl, -C(=O)aryl, -NH_2, -NH(alkyl), -NH(cycloalkyl), -N(alkyl)(cycloalkyl), -NH(heterocyclyl), -N(alkyl)(heterocyclyl), N(alkyl)$_2$, -NH(aryl), -N(alkyl)(aryl), -N(aryl)$_2$, -NH(heteroaryl), -N(alkyl)(heteroaryl), -NHC(=O)-alkyl, -N(alkyl)C(=O)-alkyl, -NHC(=O)Oalkyl, -N(alkyl)C(=O)O-alkyl, wherein each of the aforesaid alkyl, heterocyclyl, and the "alkyl", "cycloalkyl", "aryl", and "heteroaryl" portions of said R^1 groups is optionally substituted with 1-3 substituents independently selected from the group consisting of halo, heterocyclyl, aryl, heteroaryl, haloalkyl, haloalkoxy, aryloxy, cyano, –SH, -S-alkyl, -S-haloalkyl, -S(=O)$_2$alkyl, -S(=O)$_2$OH, -S(=O)$_2$$NH_2$, -S(=O)$_2$NH(alkyl), S(=O)$_2$NH(cycloalkyl), -S(=O)$_2$N(alkyl)$_2$, -S(=O)$_2$heterocyclyl, -S(=O)$_2$heteroaryl, hydroxy, alkyl, alkenyl, alkynyl, -NH_2, -NH(alkyl), -N(alkyl)$_2$, alkoxy, -NHC(=O)alkyl, -C(=O)H, -C(=O)alkyl, -C(=O)aryl, , -C(=O)heteroaryl, -C(=O)Oalkyl, -C(=O)NH_2, -C(O)NHalkyl, -C(=O)N(alkyl)$_2$; wherein when each of said heterocyclyl, aryl and heteroaryl has two substituents on adjacent carbon atoms, said substituents, may optionally be taken together with the carbon atoms to which they are attached to form a five to six-membered aryl, heterocyclyl, heterocyclenyl, or heteroaryl ring;

R^2 and R^3 independently are H or alkyl, or -C(R^2)(R^3)- is absent;

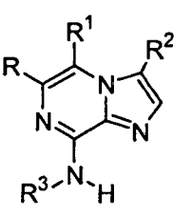
R^4 is selected from the group consisting of alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl, wherein when each of said cycloalkyl, heterocyclyl, aryl, and heteroaryl has two substituents on adjacent carbon atoms, said substituents, may optionally be taken together with the carbon atoms to which they are attached to form a five to six-membered aryl, heterocyclyl, heterocyclenyl, or heteroaryl ring; wherein each of the aforementioned R^4 alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl, optionally with

said five to six-membered aryl, heterocyclyl, heterocyclenyl, or heteroaryl ring is optionally substituted with 1-3 substituents independently selected from the group consisting of cyano, halo, haloalkyl, alkyl, alkoxy, hydroxyl, haloalkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-S(=O)_2$alkyl, $-S(=O)_2NH_2$, $-S(=O)_2NH$(alkyl), $-S(=O)_2N$(alkyl)$_2$, -S-alkyl, -S-haloalkyl, $-C(=O)OH$, $-NH_2$, -NH(alkyl), $-N(alkyl)_2$, and -C(=O)Oalkyl.

Compounds represented in the present application by Formula (d) are disclosed in PCT US2008/006472, filed May 21, 2008, the content of which is incorporated herein by reference in its entirety;

Non-limiting examples of suitable aurora kinase inhibitors useful in this invention include the compounds represented by Formulas E-K shown below in paragraphs e-k:

e. A compound represented by the structural Formula E:



Formula E

or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, wherein:

R is H, CN, $-NR^5R^6$, cycloalkyl, cycloalkenyl, heterocyclenyl, heteroaryl, $-C(O)NR^5R^6$, $-N(R^5)C(O)R^6$, heterocyclyl, heteroaryl substituted with $(CH_2)_{1-3}NR^5R^6$, unsubstituted alkyl, or alkyl substituted with one or more moieties which can be the same or different each moiety being independently selected from the group consisting of $-OR^5$, heterocyclyl, $-N(R^5)C(O)N(R^5R^6)$, $-N(R^5)-C(O)OR^6$, $-(CH_2)_{1-3}-N(R^5R^6)$ and $-NR^5R^6$;

R^1 is H, halo, aryl or heteroaryl, wherein each of said aryl and heteroaryl can be unsubstituted or substituted with one or more moieties which can be the same or different each moiety being independently selected from the group consisting of halo, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, $-CH_2OR^5$, $-C(O)NR^5R^6$, -C(O)OH, $-C(O)NH_2$, $-NR^5R^6$ (wherein the R^5 and R^6, together with the N of said $-NR^5R^6$, form a heterocyclyl ring), $-S(O)R^5$, $-S(O_2)R^5$, -CN, -CHO, $-SR^5$, $-C(O)OR^5$, $-C(O)R^5$ and $-OR^5$;

R^2 is H, halo, aryl, arylalkyl or heteroaryl, wherein each of said aryl, arylalkyl and heteroaryl can be unsubstituted or optionally independently be substituted with one or more moieties which can be the same or different each moiety being independently selected from the group consisting of halo, amide, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, -C(O)OH, $-C(O)NH_2$, $-NR^5R^6$ (wherein the R^5 and R^6, together with the N of said $-NR^5R^6$, form a heterocyclyl ring), -CN, arylalkyl, $-CH_2OR^5$, $-S(O)R^5$, $-S(O_2)R^5$, -CN, -CHO, $-SR^5$, $-C(O)OR^5$, $-C(O)R^5$, heteroaryl and heterocyclyl;

R^3 is H, alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl, wherein:

- said alkyl shown above for R^3 can be unsubstituted or substituted with one or more moieties which can be the same or different each moiety being independently selected from the group consisting of $-OR^5$, alkoxy, heteroaryl, and $-NR^5R^6$;
- said aryl shown above for R^3 is unsubstituted, or optionally substituted, or optionally fused, with halo, heteroaryl, heterocyclyl, cycloalkyl or heteroarylalkyl, wherein each of said heteroaryl, heterocyclyl, cycloalkyl and heteroarylalkyl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different each moiety being independently selected from alkyl, $-OR^5$, $-N(R^5R^6)$ and $-S(O_2)R^5$; and
- said heteroaryl shown above for R^3 can be unsubstituted or optionally substituted, or optionally fused, with one or more moieties which can be the same or different with each moiety being independently selected from the group consisting of halo, amino, alkoxycarbonyl, $-OR^5$, alkyl, -CHO, $-NR^5R^6$, $-S(O_2)N(R^5R^6)$, $-C(O)N(R^5R^6)$, $-SR^5$, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclenyl, and heterocyclyl;

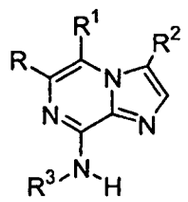
R^5 is H, alkyl, aminoalkyl, aryl, heteroaryl, heterocyclyl or cycloalkyl; and

R^6 is H, alkyl, aryl, arylalkyl, heteroaryl, heterocyclyl or cycloalkyl;

further wherein in any $-NR^5R^6$ in Formula I, said R^5 and R^6 can optionally be joined together with the N of said $-NR^5R^6$ to form a cyclic ring.

Such compounds of Formula E in (e) are disclosed in WO2007/058942 filed November 8, 2006, the content of which is incorporated herein by reference in its entirety;

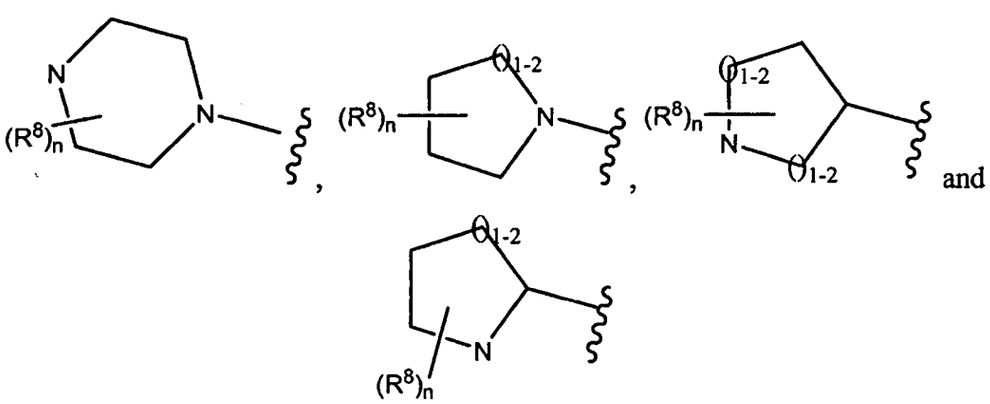
f. A compound represented by the structural formula:



Formula F

or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, wherein:

R is selected from the group consisting of H, halogen, aryl, heteroaryl, cycloalkyl, arylalkyl, heterocyclyl, heterocyclylalkyl, alkenyl, alkynyl, $-C(O)R^7$,

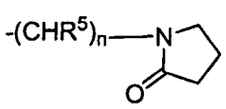


wherein each of said aryl, heteroaryl, cycloalkyl, arylalkyl, alkenyl, heterocyclyl and the heterocyclyl moieties whose structures are shown immediately above for R can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, cycloalkyl, CF_3, CN, $-OCF_3$, $-OR^6$, $-C(O)R^7$, $-NR^5R^6$, $-C(O_2)R^6$, $-C(O)NR^5R^6$, $-(CHR^5)_nOR^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ and $-N(R^5)C(O)NR^5R^6$;

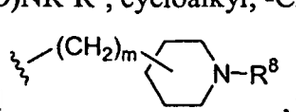
R^1 is H, halogen or alkyl;

R^2 is alkyl;

R^3 is selected from the group consisting of H, aryl, heteroaryl, heterocyclyl, $-(CHR^5)_n$-aryl, $-(CHR^5)_n$-heteroaryl, $-(CHR^5)_n-OR^6$, $-S(O_2)R^6$, $-C(O)R^6$, $-S(O_2)NR^5R^6$, $-C(O)OR^6$, $-C(O)NR^5R^6$, cycloalkyl, $-CH(aryl)_2$, $-(CH_2)_m-NR^8$, $-(CHR^5)_n-CH(aryl)_2$,



and



, wherein each of said aryl, heteroaryl and heterocyclyl can be

substituted or optionally substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl, cycloalkyl, CF_3, CN, $-OCF_3$, $-OR^5$, $-NR^5R^6$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^6$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ and $-N(R^5)C(O)NR^5R^6$;

R^5 is H or alkyl;

R^6 is selected from the group consisting of H, alkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, wherein each of said alkyl, heteroarylalkyl, aryl, heteroaryl and arylalkyl can be unsubstituted or optionally substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl, cycloalkyl, CF_3, OCF_3, CN, $-OR^5$, $-NR^5R^6$, $-CH_2OR^5$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ and $-N(R^5)C(O)NR^5R^6$;

R^7 is selected from the group consisting of alkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, wherein each of said alkyl, heteroarylalkyl, aryl, heteroaryl and arylalkyl can be unsubstituted or optionally substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl, cycloalkyl, CF_3, OCF_3, CN, $-OR^5$, $-NR^5R^6$, $-CH_2OR^5$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ and $-N(R^5)C(O)NR^5R^6$;

R^8 is selected from the group consisting of R^6, $-C(O)NR^5R^6$, $-S(O_2)NR^5R^6$, $-C(O)R^7$, $-C(O_2)R^6$, $-S(O_2)R^7$ and $-(CH_2)$-aryl;

R^9 is selected from the group consisting of halogen, CN, NR^5R^6, $-C(O_2)R^6$, $-C(O)NR^5R^6$, $-OR^6$, $-C(O)R^7$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$and $-N(R^5)C(O)NR^5R^6$;

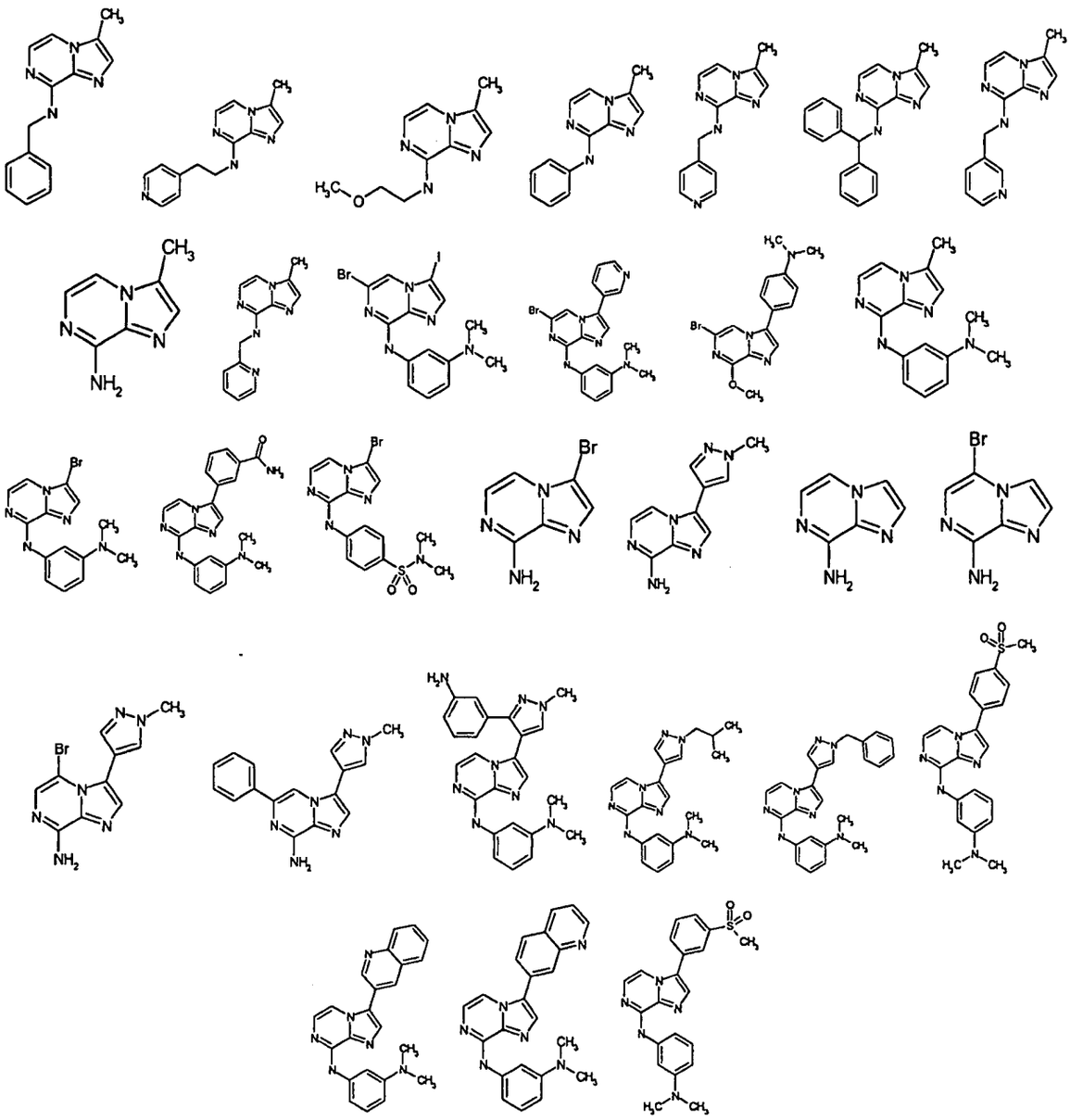
m is 0 to 4;

n is 1-4; and

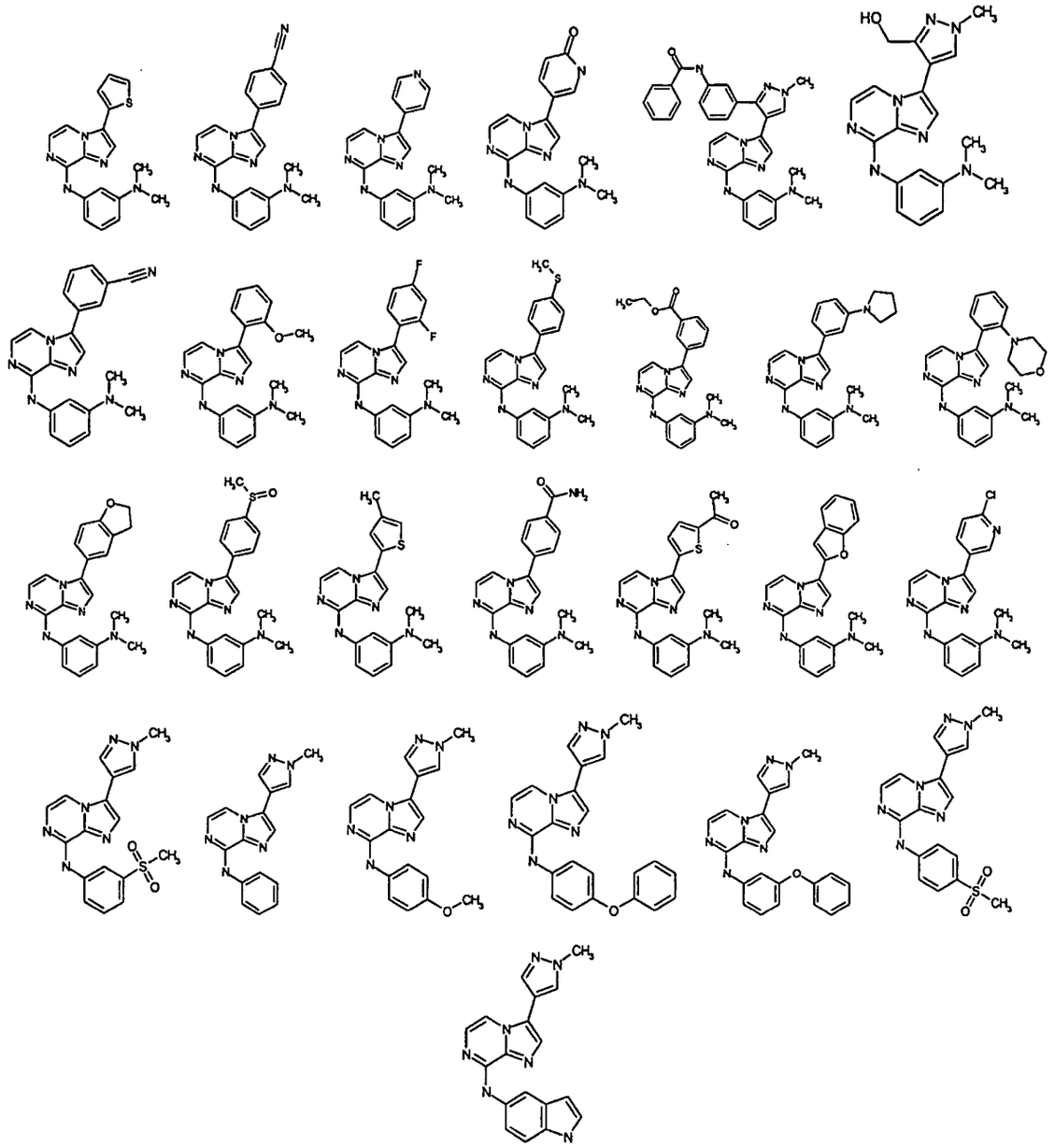
p is 0-3.

Such compounds of Formula F in (f) are disclosed in WO2004/026877, filed September 19, 2003, the content of which is incorporated herein by reference in its entirety;

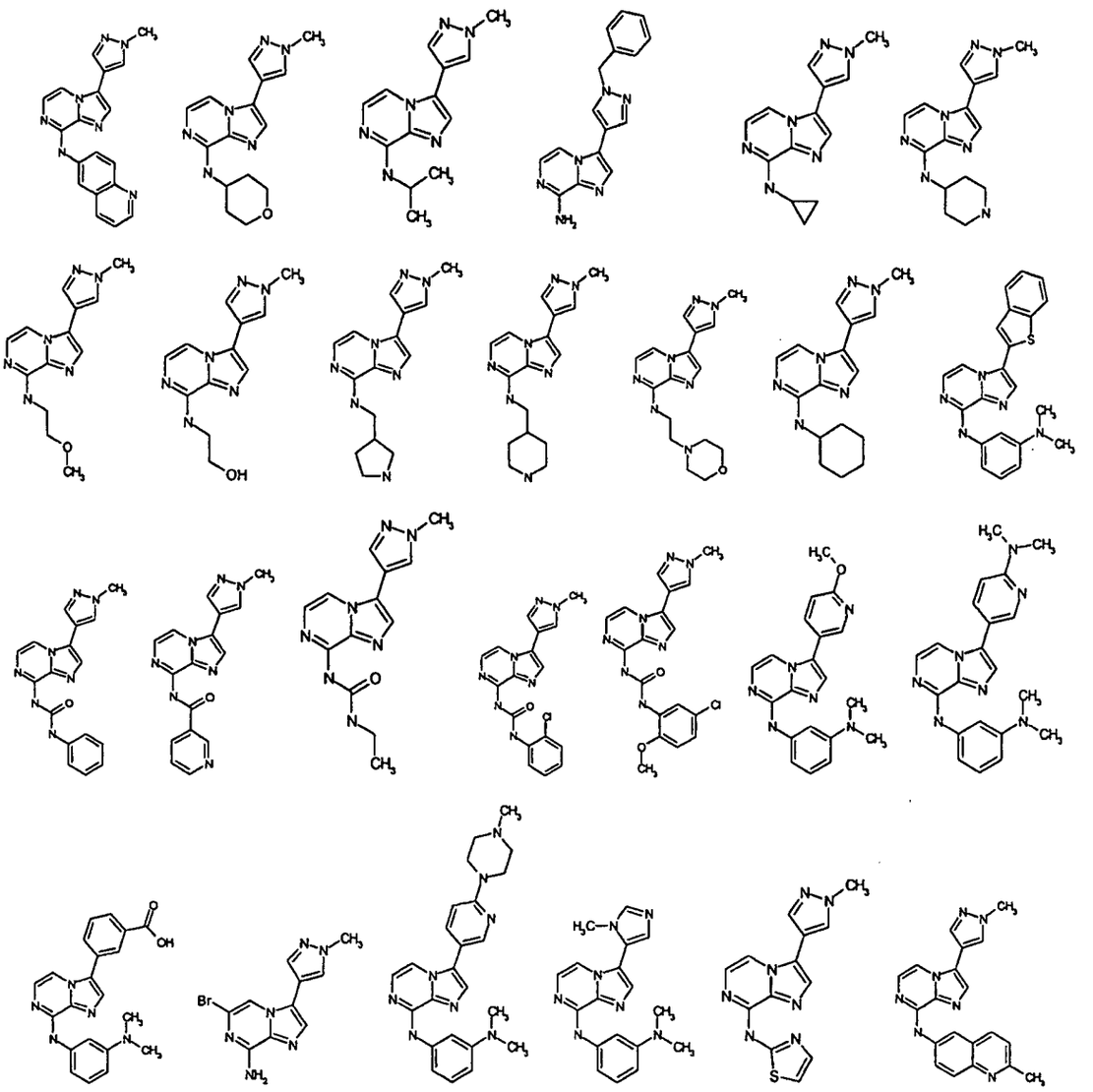
g. A compound selected from the compounds of the formulas:



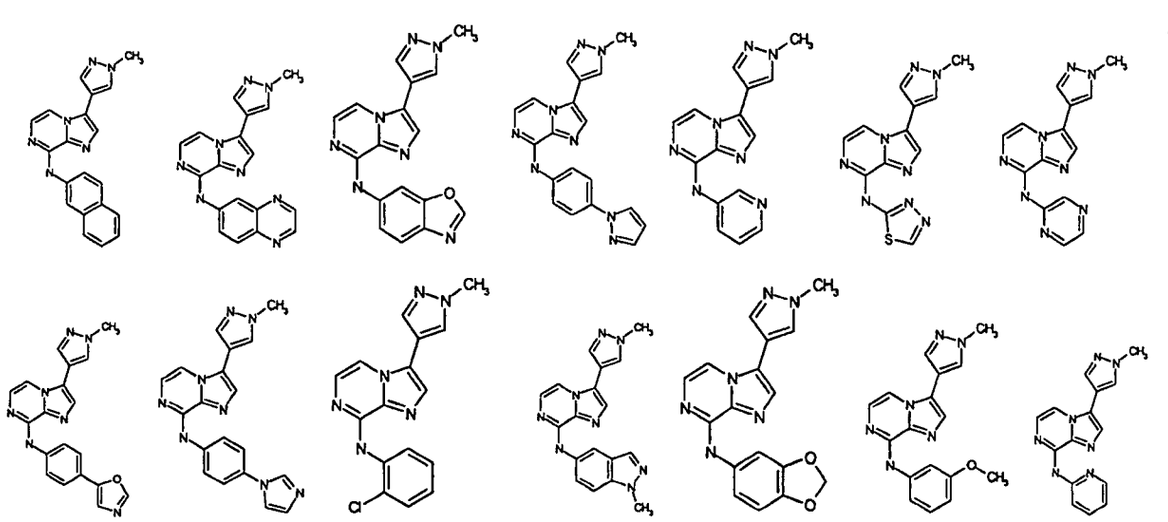
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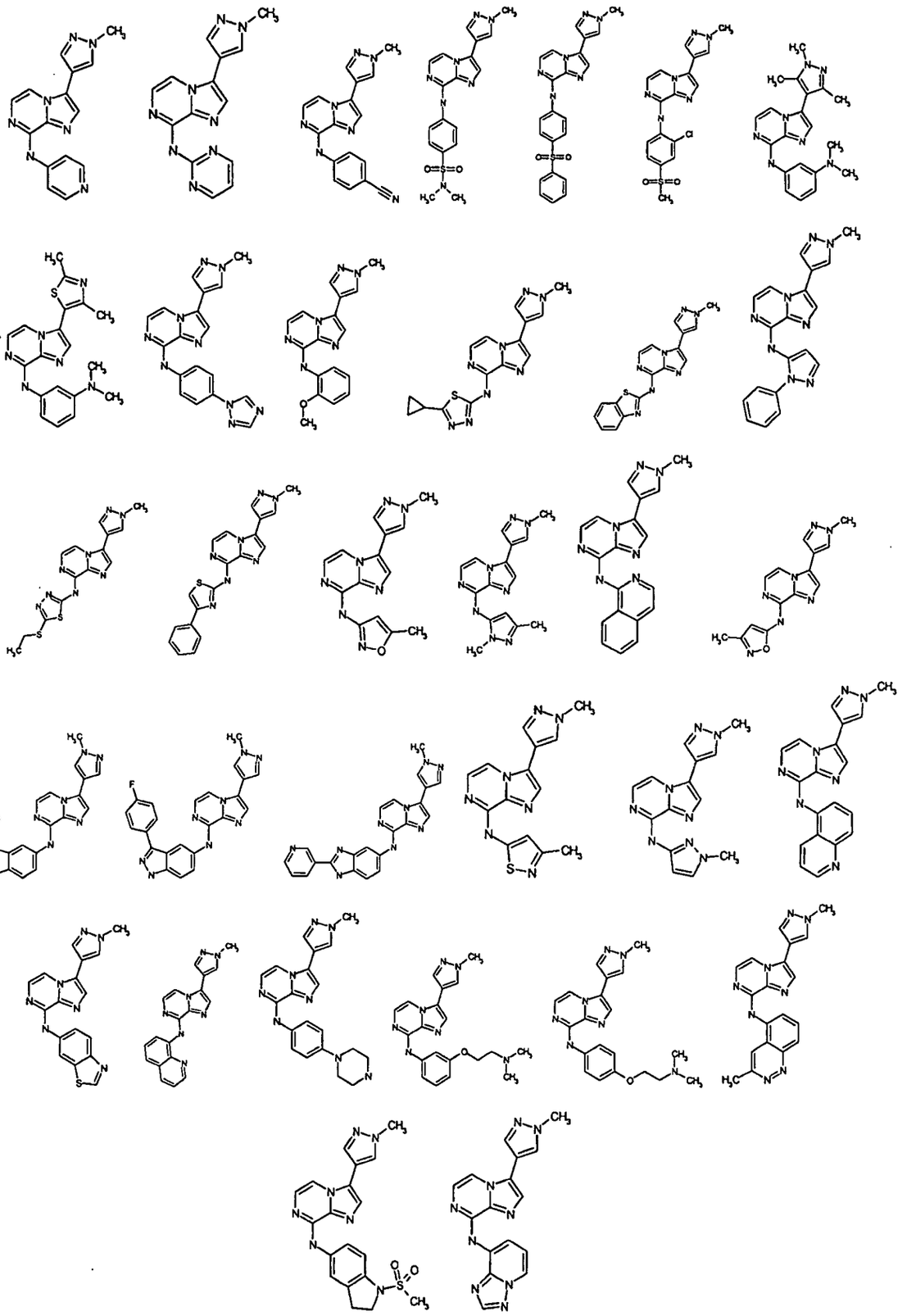


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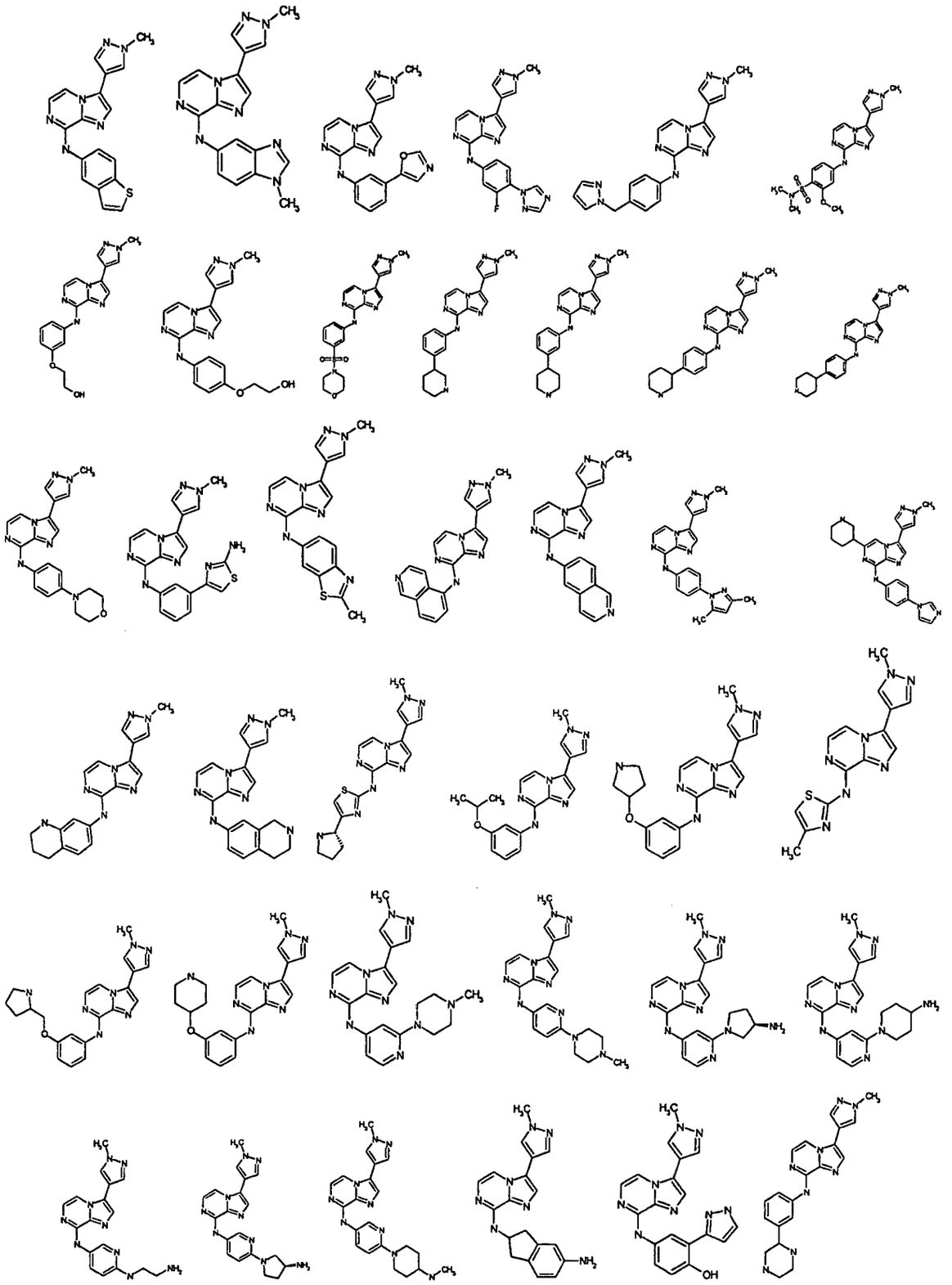


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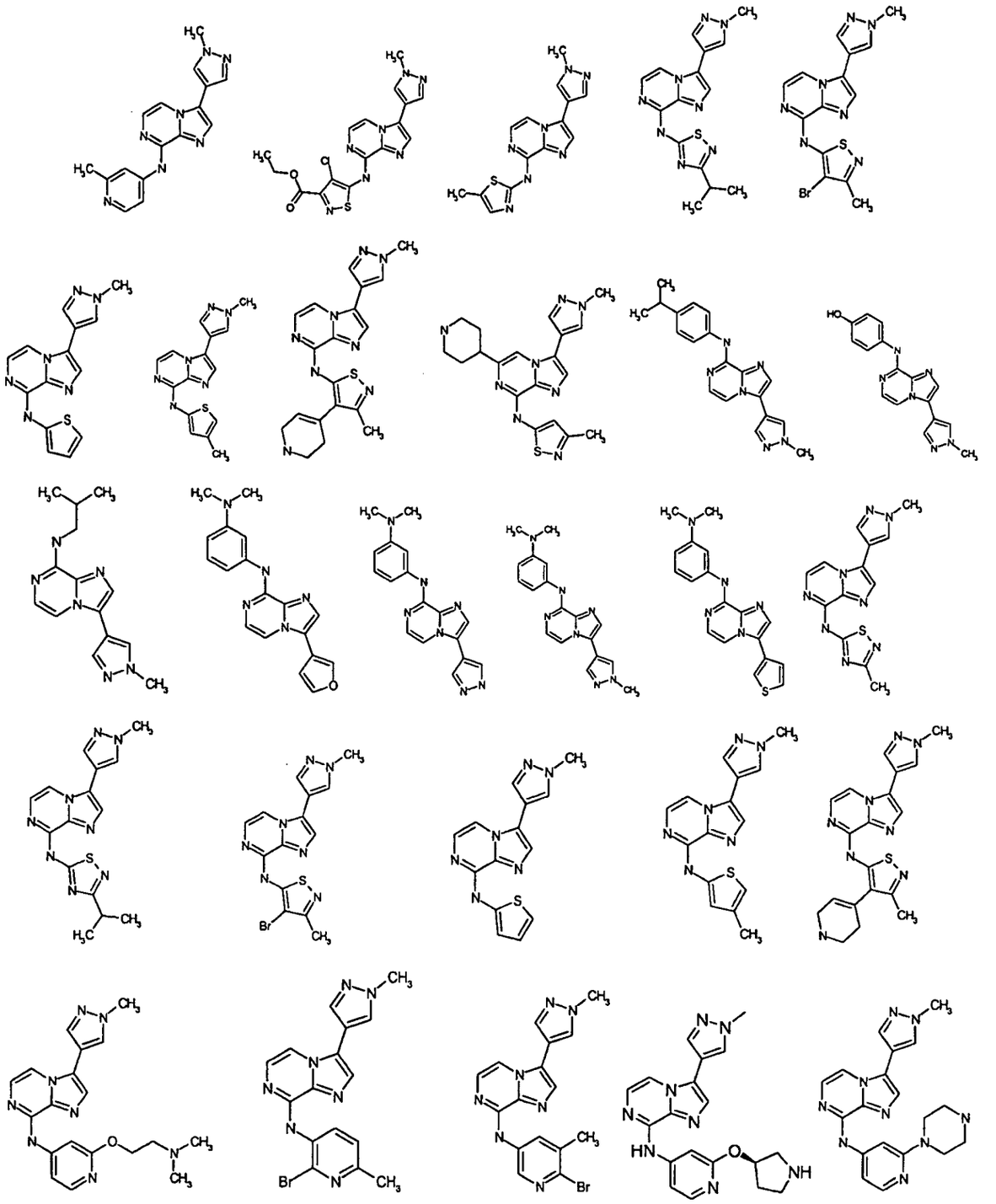




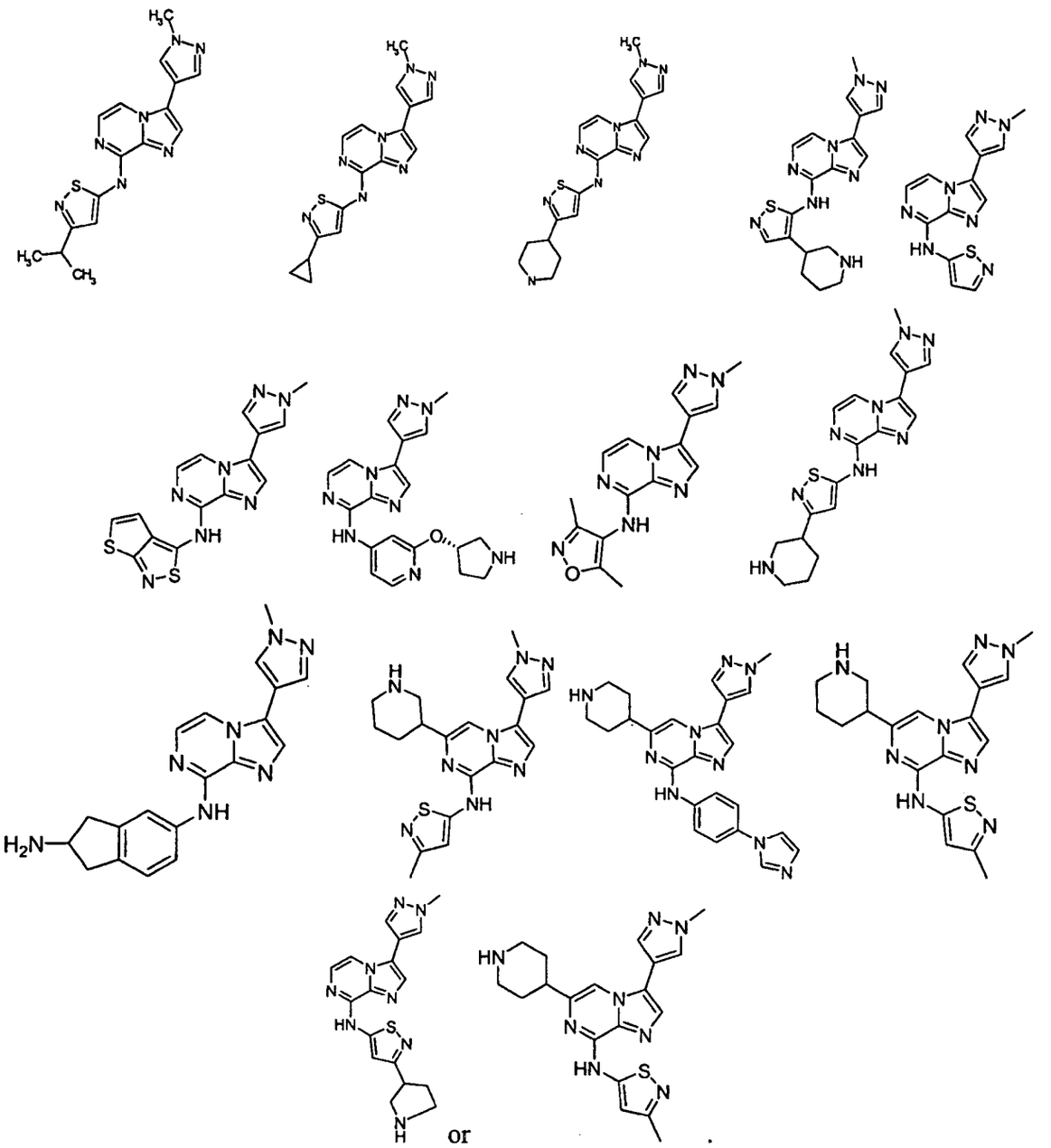
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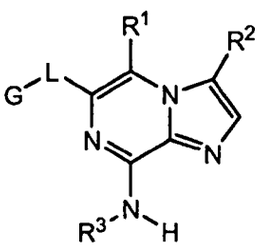
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or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof.

Such compounds of Formula G in (g) are disclosed in WO2007/058873, filed November 8, 2006, the content of which is incorporated herein by reference in its entirety;

h. A compound of the formula:



Formula H

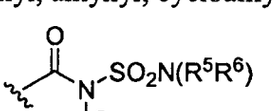
or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, wherein:

L is selected from the group consisting of S, S(O) and $S(O_2)$;

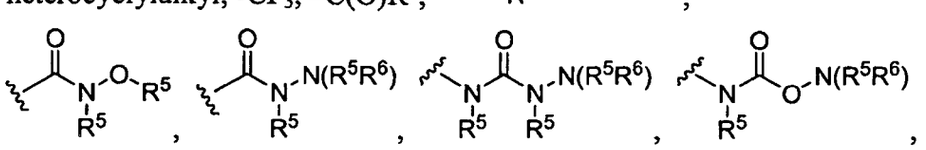
G is alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclenyl or heterocyclyl, wherein each of said alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclenyl or heterocyclyl can be unsubstituted or optionally independently substituted with one or more moieties which are independently selected from the group consisting of $-OR^5$, halo, -CN, $-C(O)NR^5R^6$, $-N(H)-C(O)R^5$, $-N(H)-C(O)-NR^5R^6$, $-S(O_2)NR^5R^6$, $-NR^5R^6$, $-C(O)R^5$, $-C(O_2)R^5$, $-SR^5$, $-S(O)R^5$, $-S(O_2)R^5$;

R^1 is H, halo, alkyl, aryl or heteroaryl, wherein each of said alkyl, aryl and heteroaryl can be unsubstituted or substituted with one or more moieties which can be the same or different each moiety being independently selected from the group consisting of halo, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C(O)NR^5R^6$ and $-OR^5$;

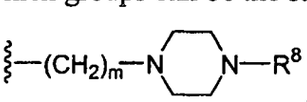
R^2 is selected from the group consisting of H, R^9, alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclylalkyl, $-CF_3$, $-C(O)R^7$,



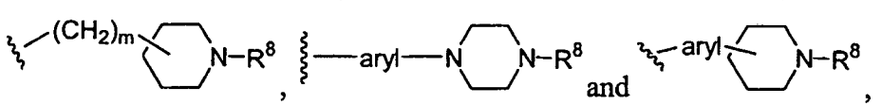
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alkyl substituted with 1-6 R^9 groups which groups can be the same or different with each R^9 being independently selected,



,



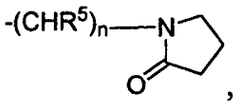
and

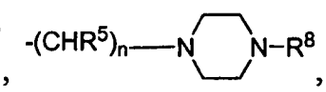
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wherein each of the above-said aryl, heteroaryl, cycloalkyl, arylalkyl and heterocyclyl can be unsubstituted or optionally independently substituted with one or more moieties

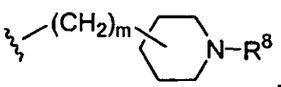
which can be the same or different, each moiety being independently selected from the group consisting of halo, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, CF_3, CN, $-OCF_3$, $-OR^6$, $-C(O)R^7$, $-NR^5R^6$, $-C(O_2)R^6$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ and $-N(R^5)C(O)NR^5R^6$;

R^3 is selected from the group consisting of H, alkyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroarylalkyl, cycloalkylalkyl, heterocyclylalkyl,



,


, $-(CHR^5)_n-OR^6$, $-S(O_2)R^6$, $-C(O)R^6$, $-S(O_2)NR^5R^6$, $-C(O)OR^6$, $-C(O)NR^5R^6$, cycloalkyl, $-CH(aryl)_2$, $-CH(heteroaryl)_2$, $-(CH_2)_m-NR^8$, and



, wherein each of said alkyl, aryl, heteroaryl and heterocyclyl can be substituted or optionally substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halo, alkyl, aryl, cycloalkyl, CF_3, CN, $-OCF_3$, $-OR^5$, $-NR^5R^6$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^6$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ and $-N(R^5)C(O)NR^5R^6$;

R^5 is H, alkyl, aryl, heteroaryl, heterocyclyl or cycloalkyl; and

R^6 is selected from the group consisting of H, alkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, wherein each of said alkyl, heteroarylalkyl, aryl, heteroaryl and arylalkyl can be unsubstituted or optionally substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl, cycloalkyl, CF_3, OCF_3, CN, $-OR^5$, $-NR^5R^6$, $-CH_2OR^5$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ and $-N(R^5)C(O)NR^5R^6$;

R^7 is selected from the group consisting of alkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, wherein each of said alkyl, heteroarylalkyl, aryl, heteroaryl and arylalkyl can be unsubstituted or optionally substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl, cycloalkyl, CF_3, OCF_3, CN, $-OR^5$, $-NR^5R^6$, $-CH_2OR^5$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ and $-N(R^5)C(O)NR^5R^6$;

R^8 is selected from the group consisting of R^6, $-C(O)NR^5R^6$, $-S(O_2)NR^5R^6$, $-C(O)R^7$, $-C(O_2)R^6$, $-S(O_2)R^7$ and $-(CH_2)$-aryl;

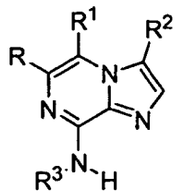
R^9 is selected from the group consisting of halogen, CN, NR^5R^6, $-C(O_2)R^6$, $-C(O)NR^5R^6$, $-OR^6$, $-C(O)R^7$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$and $-N(R^5)C(O)NR^5R^6$;

m is 0 to 4; and

p is 0-3.

Such compounds of Formula H in (h) are disclosed in WO 2008/054749, filed October 29, 2007, the entire contents of which are incorporated herein by reference thereto;

i. A compound of Formula I:



Formula I

or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, wherein:

R is H, CN, $-NR^5R^6$, cycloalkyl, cycloalkenyl, heterocyclenyl, heteroaryl, $-C(O)NR^5R^6$, $-N(R^5)C(O)R^6$, heterocyclyl, heteroaryl substituted with $(CH_2)_{1-3}$ NR^5R^6, unsubstituted alkyl, or alkyl substituted with one or more moieties which can be the same or different each moiety being independently selected from the group consisting of $-OR^5$, heterocyclyl, $-N(R^5)C(O)N(R^5R^6)$, $-N(R^5)$-$C(O)OR^6$, $-(CH_2)_{1-3}$-$N(R^5R^6)$ and $-NR^5R^6$;

R^1 is H, halo, aryl or heteroaryl, wherein each of said aryl and heteroaryl can be unsubstituted or substituted with one or more moieties which can be the same or different each moiety being independently selected from the group consisting of halo, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, $-CH_2OR^5$, $-C(O)NR^5R^6$, -C(O)OH, $-C(O)NH_2$, $-NR^5R^6$ (wherein the R^5 and R^6, together with the N of said $-NR^5R^6$, form a heterocyclyl ring), $-S(O)R^5$, $-S(O_2)R^5$, -CN, -CHO, $-SR^5$, $-C(O)OR^5$, $-C(O)R^5$ and $-OR^5$;

R^2 is H, halo, aryl, arylalkyl or heteroaryl, wherein each of said aryl, arylalkyl and heteroaryl can be unsubstituted or optionally independently be substituted with one or more

moieties which can be the same or different each moiety being independently selected from the group consisting of halo, amide, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, -C(O)OH, -C(O)NH_2, -NR^5R^6 (wherein the R^5 and R^6, together with the N of said -NR^5R^6, form a heterocyclyl ring), -CN, arylalkyl, -CH_2OR^5, -S(O)R^5, -S(O_2)R^5, -CN, -CHO, -SR^5, -C(O)OR^5, -C(O)R^5, heteroaryl and heterocyclyl;

R^3 is heterocyclyl–(CR^7R^8)$_n$-X, heterocyclenyl–(CR^7R^8)$_n$-X, heteroaryl–(CR^7R^8)$_n$-X or aryl–(CR^7R^8)$_n$-X wherein each of the heterocyclyl-, heterocyclenyl-, heteroaryl- or aryl- moieties of said R^3 can be unsubstituted or substituted with one or more moieties, independently selected from the group consisting of –CONR^{5}R^6, –OR^5 and alkyl,

n is 1-6,

X is selected from the group consisting of -NR^5R^6, -OR^5, –SO-R^5, -SR^5, SO_2R^5, heteroaryl, heterocyclyl and aryl, wherein said heteroaryl or aryl can be unsubstituted or substituted with one or more moieties, independently selected from the group consisting of –O-alkyl, alkyl, halo, or NR^5R^6;

R^7 and R^8 are each independently hydrogen, alkyl, heterocyclyl, aryl, heteroaryl or cycloalkyl;

R^5 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkoxyalkyl, -alkyl-S-alkyl, aminoalkyl, aryl, heteroaryl, heterocyclenyl, heterocycloalkyl, cycloalkyl, cyclenyl, heterocyclylalkoxyl, -S-alkylheterocyclyl, heterocyclyl, heterocyclenyl, alkylN(alkyl)$_2$, alkylNH(alkyl), alkylN(alkenyl)2, -alkylN(alkoxyl)2, -alkyl-SH, hydroxyalkyl, trihaloalkyl, dihaloalkyl, monohaloalkyl, wherein each of said alkyl, alkenyl, alkoxyalkyl, -alkyl-S-alkyl, aminoalkyl, aryl, heteroaryl, heterocyclenyl, heterocycloalkyl, cycloalkyl, cyclenyl, heterocyclylalkoxyl, -S-alkylheterocyclyl, heterocyclyl, heterocyclenyl, alkylN(alkyl)$_2$, alkylNH(alkyl), alkylN(alkenyl)2, -alkylN(alkoxyl)2, -alkyl-SH, hydroxyalkyl, trihaloalkyl, dihaloalkyl, monohaloalkyl can be unsubstituted or substituted with one or more moieties independently selected from the group consisting of alkyl, alkenyl, aryl, cyclenyl, cycloalkyl, arylalkyl, cyclenylalkyl, cycloalkylalkyl, heteroaryl, heterocyclenyl, heterocyclyl, heteroarylalkyl, heterocyclenylalkyl, heterocycloalkylalkyl, alkoxyalkyl, -alkyl-S-alkyl, -alkylSH, alkoxyl, -S-alkyl,

hydroxyalkyl, and aminoalkyl;

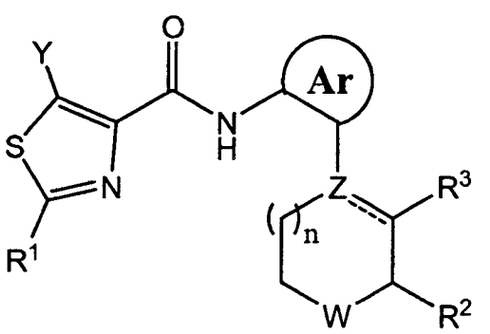
R^6 is selected from the group consisting of hydrogen, alkyl, alkenyl, aryl, cyclenyl, cycloalkyl, arylalkyl, cyclenylalkyl, cycloalkylalkyl, heteroaryl, heterocyclenyl, heterocyclyl, heteroarylalkyl, heterocyclenylalkyl, heterocycloalkylalkyl, alkoxyalkyl, -alkyl-S-alkyl, -alkylSH, alkoxyl, -S-alkyl, hydroxyalkyl, aminoalkyl, -alkyl-OC(O)alkyl, -alkylOC(O)cycloalkyl, -alkylOC(O)aryl, -alkylOC(O)aralkyl, -alkylOC(O)NR^5aryl, -alkylOC(O)NR^5alkyl, -alkylOC(O)NR^5heterocyclyl, -alkylOC(O)NR^5heteroaryl -alkylOC(O)NR^5cycloalkyl, -alkylOC(O)heterocyclyl, alkylC(O)OH, alkylC(O)Oalkyl, -alkylC(O)Ocycloalkyl, -alkylC(O)Oaryl, -alkylC(O)Oaralkyl, -alkylC(O)ONR^5aryl, -alkylC(O)ONR^5alkyl, -alkylC(O)ONR^5heterocyclyl, -alkylC(O)ONR^5heteroaryl -alkylC(O)ONR^5cycloalkyl, -alkylC(O)Oheterocyclyl, alkylC(O)OH, and alkylC(O)Oalkyl wherein each of said aryl, cyclenyl, cycloalkyl, arylalkyl, cyclenylalkyl, cycloalkylalkyl, heteroaryl, heterocyclenyl, heterocyclyl, heteroarylalkyl, heterocyclenylalkyl, heterocycloalkylalkyl, -alkyl-OC(O)alkyl, -alkylOC(O)cycloalkyl, -alkylOC(O)aryl, -alkylOC(O)aralkyl, -alkylOC(O)NR^5aryl, -alkylOC(O)NR^5alkyl, -alkylOC(O)NR^5heterocyclyl, -alkylOC(O)NR^5heteroaryl -alkylOC(O)NR^5cycloalkyl, -alkylOC(O)heterocyclyl, alkylC(O)OH, alkylC(O)Oalkyl, -alkylC(O)Ocycloalkyl, -alkylC(O)Oaryl, -alkylC(O)Oaralkyl, -alkylC(O)ONR^5aryl, -alkylC(O)ONR^5alkyl, -alkylC(O)ONR^5heterocyclyl, -alkylC(O)ONR^5heteroaryl -alkylC(O)ONR^5cycloalkyl, -alkylC(O)Oheterocyclyl, alkylC(O)OH, and alkylC(O)Oalkyl,can be unsubstituted or substituted with one or more moieties independently selected from the group consisting of alkyl, alkenyl, aryl, cyclenyl, cycloalkyl, arylalkyl, cyclenylalkyl, cycloalkylalkyl, heteroaryl, heterocyclenyl, heterocyclyl, heteroarylalkyl, heterocyclenylalkyl, heterocycloalkylalkyl, alkoxyalkyl, -alkyl-S-alkyl, -alkylSH, alkoxyl, -S-alkyl, hydroxyalkyl, aminoalkyl, amino, aminodialkyl, aminocycloalkyl, halo, trihaloalkyl, dihaloalkyl, and monohaloalkyl;

further wherein in any -NR^5R^6 in Formula I, said R^5 and R^6 can optionally be joined

together with the N of said -NR^5R^6 to form a cyclic ring or bridged cyclic ring, wherein each of said cyclic ring or bridged cyclic ring, can be unsubstituted or substituted with one or more moieties, which can be the same or different, independently selected from the group consisting of hydroxyl, -SH, alkyl, alkenyl, hydroxyalkyl, -alkyl-SH, alkoxyl, -S-alkyl, -CO_2-alkyl, -CO_2-alkenyl, arylalkyl, cyclenylalkyl, cycloalkylalkyl, heteroarylalkyl, heterocyclenylalkyl, heterocycloalkylalkyl, heteroaryl, aryl, cyclenyl, cycloalkyl, spiroheterocyclyl, spiroheterocyclenyl, spiroheteroaryl, spirocyclyl, spirocyclenyl, spiroaryl, alkoxyalkyl, -alkyl-S-alkyl, heterocyclyl, heterocyclenyl, halo, trihaloalkyl, dihaloalkyl, CN and monohaloalkyl.

Such compounds of Formula I in (i) are disclosed in PCT US 2008/007295 filed June 11, 2008;

j. A compound having the formula:



(J)

or a pharmaceutically acceptable salt, solvate, ester, prodrug or stereoisomer thereof, wherein the dashed lines indicate an optional and additional bond, and wherein:

R^1 is nitrogen-containing heteroaryl, nitrogen-containing heterocyclyl, nitrogen-containing benzofused heteroaryl or nitrogen-containing benzofused heterocyclyl, wherein R^1 is joined to the rest of the compound of formula (I) via a ring nitrogen atom, and wherein one or more ring carbon atoms of a nitrogen-containing heteroaryl, nitrogen-containing heterocyclyl, nitrogen-containing benzofused heteroaryl or nitrogen-containing benzofused heterocyclyl group can be substituted with up to 5 substituents, which may be the same or different, and are independently selected from alkyl, aryl, halo, -OH, -O-alkyl, -O-aryl, -$N(R^8)_2$, -CF_3, -NO_2, -$C(O)R^8$, -$C(O)OR^8$, -$C(O)N(R^8)_2$, -$OC(O)R^8$ or -$NHC(O)R^8$;

R^2 is –H, -alkyl, –NH_2 or –CH_2NH_2;

R^3 is –H, -alkyl, –NH_2 or –CH_2NH_2;

each occurrence of R^4 is independently –H, -alkyl, $–NH_2$, -OH, -alkylene-OH, – CH_2NH_2, $-C(O)R^5$, $-C(O)NH_2$, -C(O)NH-alkyl, $-C(O)N(alkyl)_2$, $-NHC(O)R^6$ or $–NHS(O)_2R^6$;

R^5 is –H, -alkyl, -aryl, -heteroaryl, -NHOH;

R^6 is –H, -alkyl or $–CF_3$;

R^7 is –H, -OH, $-C_1$-C_6 alkyl, -O-(C_1-C_6 alkyl), or $–CF_3$;

R^8 is –H, alkyl, aryl, heterocyclyl, heteroaryl or cycloalkyl;

Ar is -arylene- or -heteroarylene-, wherein the arylene or heteroarylene is joined via 2 of its adjacent ring carbon atoms, and wherein the -arylene- or -heteroarylene- can be substituted with up to 4 substituents, which may be the same or different, and are independently selected from –halo, alkyl, alkoxy, aryloxy, $-SR^8$, $-S(O)R^8$, $-S(O)_2R^8$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)N(R^8)_2$, $-NHC(O)R^8$, $-CF_3$, -CN or NO_2, and such that when Ar is tetrahydronaphthylene, R^1 and R^2 cannot both be hydrogen

W is –NH- or $–C(R^4)_2$-, wherein both R^4 groups and the carbon atom to which they are attached can combine to form a five to seven membered heterocyclyl or heteroaryl group;

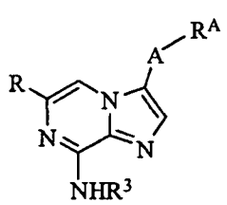
Y is –H, -halo, -alkyl or –CN;

Z is $–CR^7$- or –N-, when the optional additional bond is absent, and –C- when the optional additional bond is present;

n is an integer ranging from 0 to 2;

Such compounds of Formula J in (j) are disclosed in WO 2008/054749, filed October 29, 2007; and

(k) A compound of Formula K:



Formula K

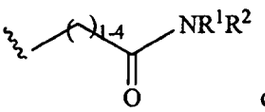
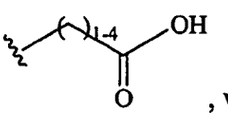
or a pharmaceutically acceptable salt, solvate, ester, prodrug or stereoisomer thereof, wherein:

R is H, halo or alkyl;

R^3 is heteroaryl-X, wherein X is heterocyclylalkyl- wherein said heterocyclyl can be unsubstituted or optionally substituted with 1-4 alkyl moieties;

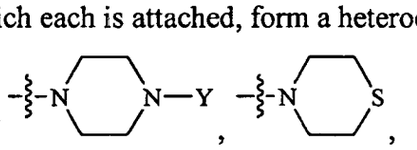
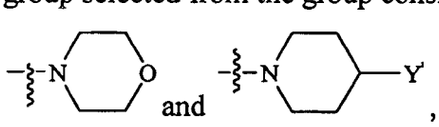
A is -aryl- , -heteroaryl-, $-N(R^1)$-aryl- or $-N(R^1)$-heteroaryl- , wherein each of said aryl and heteroaryl can be independently unsubstituted or optionally substituted with one or more

substituents, which substituents can be the same or different, each substituent being independently selected from the group consisting of alkyl, $-NO_2$, halo, hydroxy, trihaloalkyl, alkoxy, and dialkylamino;

R^A is $-(CH_2)_{1-4}$-heteroaryl,  or  , wherein said heteroaryl can optionally be fused with an aryl, wherein each of said aryl and heteroaryl can independently be optionally substituted with one or more moieties each moiety being independently selected from the group consisting of trihaloalkyl, $-NO_2$, halo, hydroxyalkyl, alkoxyalkyl and dialkylamino;

R^1 is H or alkyl;

R^2 is H, hydroxyalkyl-, arylalkyl-, heteroaryl, aryl, heteroarylalkyl-, alkyl, dialkylaminoalkyl-, alkylaminoalkyl-, cycloalkylalkyl-, cycloalkyl, heterocyclylalkyl- or heterocyclyl, wherein said aryl and aryl of arylalkyl can be unsubstituted or substituted with one or more moieties independently selected from the group consisting of trihaloalkyl, $-NO_2$, halo, hydroxyalkyl, alkoxyalkyl, dialkylamino and heterocyclylalkyl-, wherein said heterocyclylalkyl can be unsubstituted or substituted with alkyl or $-SO_2NH_2$; said heteroaryl and heteroaryl of heteroarylalkyl can be unsubstituted or substituted with one or more moieties, each moiety being independently selected from the group consisting of hydroxyalkyl, alkoxy, alkyl, halo, hydroxyl, and $-NO_2$; and said cycloalkyl is unsubstituted or substituted with hydroxyl; or

R^1 and R^2 together with the N to which each is attached, form a heterocyclic group selected from the group consisting of  ,  , wherein

Y is alkoxyalkyl, hydroxyalkyl, dialkylaminoalkyl or alkyl, further wherein Y' is hydroxyl.

Such compounds of Formula K in paragraph (k) are disclosed in U.S. provisional patent application, 61/024010, filed January 28, 2008.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a FACS (Flow Cytometric Analysis) analysis of HCT-116 colon cancer cells. Cells were treated with 1000 nM Aurora kinase inhibitor (Compound X) (WO 2008/057512, filed November 6, 2007, Example 4-3 and Claim 70 and it is represented in Formula H and Table 2, column 2, row 16 of the present application) for the indicated times, at which time, drug was washed off and replaced with new media. FACS was analyzed after a total of 72 hours. Exposure for less than 24 hours were insufficient to induce endoreduplication (>4N DNA content), while drug exposure for 24, 48, or 72 hours resulted in the accumulation of cells that underwent endoreduplication.

FIG. 2 is a FACS analysis of HCT-116 colon cancer cells treated with 1000 nM Aurora kinase inhibitor (Compound X) for the indicated times, at which time, drug was washed off and replaced with new media. FACS was analyzed after a total of 24 hours. Twenty four hour treatment was sufficient to induce endoreduplication, however less exposure time was insufficient to induce endoreduplication

FIG. 3 is a FACS analysis of HCT-116 colon cancer cells treated for 16 hours with DMSO. The cells were then exposed to DMSO or 1000 nM Aurora kinase inhibitor (Compound X) for 4, 8, or 24 hours at which time the media was changed. All cells were analyzed at the end of 24-hours.

FIG. 4 is a FACS analysis of HCT-116 colon cancer cells treated for 16 hours with 5 nM taxotere. Cells were then exposed to DMSO or 1000 nM Aurora kinase inhibitor (Compound X) for 4, 8, and 24 hours at which time the media was changed. All cells were analyzed at the end of 24-hours. Taxotere followed by Aurora kinase inhibitor (Compound X) induced endoreduplication. Endoreduplication was observed even when Aurora kinase inhibitor (Compound X) exposure was as little as 4 hours.

FIG. 5 is a FACS analysis of HCT-116 colon cancer cells pre-treated with nocodazole for 16 hours. Cells were then exposed to DMSO or 1000 nM Aurora kinase inhibitor (Compound X) for 4, 8, and 24 hours at which time the media was changed. All cells were analyzed at the end of 24-hours. Nocodazole followed by 24 hour exposure to Aurora kinase inhibitor (Compound X) induced endoreduplication, however a 4- or 8- hour exposure to Aurora inhibitor (Compound X) was insufficient to induce endoreduplication.

FIG. 6 is a FACS analysis of HCT-116 colon cancer cells treated with an Aurora kinase inhibitor (Compound X) given at the same time as taxotere, 4 hour exposure was not sufficient to induce endoreduplication and 24 hour exposure was needed to induce endoreduplication.

FIG. 7 is a FACS analysis of HCT-116 colon cancer cells treated for 16 hours with 10 nM Ispinesib (KSP inhibitor). Cells were then exposed to DMSO or 1000 nM Aurora kinase inhibitor (Compound X) for 4, 8, and 24 hours at which time the media was changed. All cells were analyzed at the end of 24-hours. Ispinesib followed by Aurora kinase inhibitor (Compound X) induced endoreduplication. Endoreduplication was observed even when Aurora kinase inhibitor (Compound X) exposure was as little as 4 hours.

FIG. 8 is a FACS (Flow Cytometric Analysis) analysis of HCT-116 colon cancer cells. Cells were treated with 25 nM Aurora kinase inhibitor (Compound Z) (PCT US2008/007295, filed June 11, 2008, Example 76-2 and Claim 25, row 7, column 4 and it is represented in Table 13, compound 76-2 of the present application) for the indicated times, at which time, drug was washed off and replaced with new media. FACS was analyzed after a total of 72 hours. Exposure for less than 24 hours were insufficient to induce endoreduplication (>4N DNA content), while drug exposure for 24, 48, or 72 hours resulted in the accumulation of cells that underwent endoreduplication.

FIG. 9 is a FACS analysis of HCT-116 colon cancer cells treated with 25 nM Aurora kinase inhibitor (Compound Z) for the indicated times, at which time, drug was washed off and replaced with new media. FACS was analyzed after a total of 24 hours. Twenty four hour treatment was sufficient to induce endoreduplication, however less exposure time was insufficient to induce endoreduplication

FIG. 10 is a FACS analysis of HCT-116 colon cancer cells treated for 16 hours with DMSO. The cells were then exposed to DMSO or 25 nM Aurora kinase inhibitor (Compound Z) for 4, 8, or 24 hours at which time the media was changed. All cells were analyzed at the end of 24-hours.

FIG. 11 is a FACS analysis of HCT-116 colon cancer cells treated for 16 hours with 5 nM taxotere. Cells were then exposed to DMSO or 25 nM Aurora kinase inhibitor (Compound Z) for 4, 8, and 24 hours at which time the media was changed. All cells were analyzed at the end of 24-hours. Taxotere followed by Aurora kinase inhibitor (Compound Z) induced endoreduplication. Endoreduplication was observed even when Aurora kinase inhibitor (Compound Z) exposure was as little as 4 hours.

FIG. 12 is a FACS analysis of HCT-116 colon cancer cells treated with an Aurora kinase inhibitor (Compound Z) given at the same time as taxotere, 4 hour exposure was not sufficient to induce endoreduplication and 24 hour exposure was needed to induce endoreduplication.

FIG. 13 is a FACS analysis of HCT-116 colon cancer cells treated for 16 hours with 10 nM Ispinesib (KSP inhibitor). Cells were then exposed to DMSO or 25 nM Aurora kinase inhibitor (Compound Z) for 4, 8, and 24 hours at which time the media was changed. All cells were analyzed at the end of 24-hours. Ispinesib followed by Aurora kinase inhibitor (Compound Z) induced endoreduplication. Endoreduplication was observed even when Aurora kinase inhibitor (Compound Z) exposure was as little as 4 hours.

FIG. 14 is a FACS analysis of HCT-116 colon cancer cells treated with an Aurora kinase inhibitor (Compound Z) given at the same time as Ispinesib (KSP inhibitor) taxotere, 4 hour exposure was not sufficient to induce endoreduplication and 24 hour exposure was needed to induce endoreduplication.

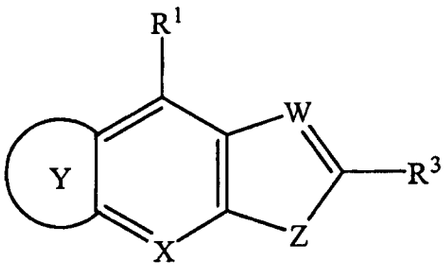
Similar to the above-described Figures (Drawings), other experimental results were obtained when, for example, the Aurora kinase inhibitor was changed from Compound X or Z to other aurora kinase inhibitors disclosed elsewhere in this present application.

DETAILED DESCRIPTION

The method of treatment using sequential administration of at least one anti-mitotic agent followed by at least one aurora kinase inhibitor described herein to a subject in need thereof is exemplified below.

In one embodiment, the present invention discloses a pharmaceutical composition for treating or ameliorating cancer comprising at least one anti-mitotic agent selected from the group consisting of Taxanes, paclitaxel, docetaxel, Cenp-E Inhibitor (such as for example GSK-923295 from Glaxo Smithkline), Abraxane, Epothilone, Monastrol, as well as KSP inhibitors such as, for example, Ispinesib SB-715992 (from Cytokinetics, South San Francisco, California) and the compounds of Formulas A-D in paragraphs a-d below:

a. A compound represented by the structural Formula A:



Formula A

or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:

ring Y is a 5- to 6-membered aryl or a 5- or 6-membered heteroaryl fused as shown in Formula A, wherein in said aryl and heteroaryl each substitutable ring carbon is independently substituted with R^2 and each substitutable ring nitrogen is independently substituted with R^6;

W is N or $C(R^{12})$;

X is N or N-oxide;

Z is S, S(=O) or $S(=O)_2$;

R^1 is H, alkyl, alkoxy, hydroxy, halo, -CN, $-S(O)_m$-alkyl, $-C(O)NR^9R^{10}$, $-(CR^9R^{10})_{1-6}OH$, or $-NR^4(CR^9R^{10})_{1-2}OR^9$;

each R^2 is independently selected from the group consisting of H, halo, alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, $-(CR^{10}R^{11})_{0-6}-OR^7$, $-C(O)R^4$, $-C(S)R^4$, $-C(O)OR^7$, $-C(S)OR^7$, $-OC(O)R^7$, $-OC(S)R^7$, $-C(O)NR^4R^5$, $-C(S)NR^4R^5$, $-C(O)NR^4OR^7$, $-C(S)NR^4OR^7$, $-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, -CN, $-OCF_3$, $-SCF_3$, $-C(=NR^7)NR^4$, $-C(O)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}OR^7$, $-C(S)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(S)NR^7(CH_2)_{1-10}OR^7$, haloalkyl and alkylsilyl, wherein each of said alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl or heteroaralkyl is independently optionally substituted with 1-5 R^9 moieties;

each R^3 is independently selected from the group consisting of H, halo, alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl,

heteroaryl, heteroaralkyl, -$(CR^{10}R^{11})_{0-6}$-OR^7, -$C(O)R^4$, -$C(S)R^4$, -$C(O)OR^7$, -$C(S)OR^7$, -$OC(O)R^7$, -$OC(S)R^7$, -$C(O)NR^4R^5$, -$C(S)NR^4R^5$, -$C(O)NR^4OR^7$, -$C(S)NR^4OR^7$, -$C(O)NR^7NR^4R^5$, -$C(S)NR^7NR^4R^5$, -$C(S)NR^4OR^7$, -$C(O)SR^7$, -NR^4R^5, -$NR^4C(O)R^5$, -$NR^4C(S)R^5$, -$NR^4C(O)OR^7$, -$NR^4C(S)OR^7$, -$OC(O)NR^4R^5$, -$OC(S)NR^4R^5$, -$NR^4C(O)NR^4R^5$, -$NR^4C(S)NR^4R^5$, -$NR^4C(O)NR^4OR^7$, -$NR^4C(S)NR^4OR^7$, -$(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, -$S(O)_{1-2}NR^4R^5$, -$N(R^7)SO_2R^7$, -$S(O)_{1-2}NR^5OR^7$, -CN, $-OCF_3$, $-SCF_3$, -$C(=NR^7)NR^4R^5$, -$C(O)NR^7(CH_2)_{1-10}NR^4R^5$, -$C(O)NR^7(CH_2)_{1-10}OR^7$, -$C(S)NR^7(CH_2)_{1-10}NR^4R^5$, -$C(S)NR^7(CH_2)_{1-10}OR^7$, haloalkyl and alkylsilyl, wherein each of said alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl or heteroaralkyl is independently optionally substituted with 1-5 R^9 moieties;

each R^4 and R^5 is independently selected from the group consisting of H, alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, -OR^7, -$C(O)R^7$, and -$C(O)OR^7$, wherein each of said alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl is optionally substituted with 1-4 R^8 moieties;

or R^4 and R^5, when attached to the same nitrogen atom, are optionally taken together with the nitrogen atom to which they are attached to form a 3-6 membered heterocyclic ring having 0-2 additional heteroatoms selected from N, O or S;

each R^6 is independently selected from the group consisting of H, alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroaralkyl, -$(CH_2)_{1-6}CF_3$, -$C(O)R^7$, –$C(O)OR^7$ and –SO_2R^7;

each R^7 is independently selected from the group consisting of H, alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, and heteroaralkyl, wherein each member of R^7 except H is optionally substituted with 1-4 R^8 moieties;

each R^8 is independently selected from the group consisting of halo, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, -NO_2, -OR^{10}, -(C_1-C_6 alkyl)-OR^{10}, –CN, –$NR^{10}R^{11}$, –$C(O)R^{10}$, -$C(O)OR^{10}$, -$C(O)NR^{10}R^{11}$, -CF_3, $-OCF_3$, $-CF_2CF_3$, –$C(=NOH)R^{10}$, –$N(R^{10})C(O)R^{11}$, -$C(=NR^{10})NR^{10}R^{11}$, and -$NR^{10}C(O)OR^{11}$, wherein each of said alkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally independently

substituted with 1-3 moieties selected from the group consisting of halo, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-NO_2$, $-OR^{10}$, $-(C_1-C_6$ alkyl$)-OR^{10}$, -CN, $-NR^{10}R^{11}$, $-C(O)OR^{10}$, $-C(O)NR^{10}R^{11}$, $-CF^3$, $-OCF_3$, $-NR^{10}C(O)OR^{11}$, and $-NR^{10}C(O)R^{40}$;

or two R^8 groups, when attached to the same carbon atom, are optionally taken together with the carbon atom to which they are attached to form a C=O or a C=S group;

each R^9 is independently selected from the group consisting of H, alkyl, alkoxy, OH, CN, halo, $-(CR^{10}R^{11})_{0-4}NR^4R^5$, haloalkyl, hydroxyalkyl, alkoxyalkyl, $-C(O)NR^4R^5$, $-C(O)OR^7$, $-OC(O)NR^4R^5$, $-NR^4C(O)R^5$, and $-NR^4C(O)NR^4R^5$;

each R^{10} is independently H or alkyl; or R^9 and R^{10}, when attached to the same nitrogen atom, are optionally taken together with the nitrogen atom to which they are attached to form a 3-6 membered heterocyclic ring having 0-2 additional heteroatoms selected from N, O or S;

each R^{11} is independently H or alkyl; or R^{10} and R^{11}, when attached to the same nitrogen atom, are optionally taken together with the nitrogen atom to which they are attached to form a 3-6 membered heterocyclic ring having 0-2 additional heteroatoms selected from N, O or S;

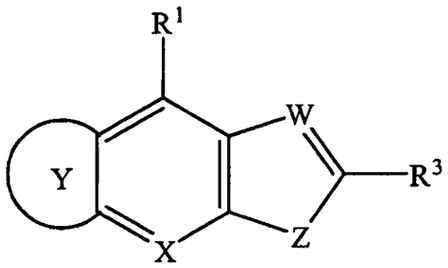
each R^{12} is independently selected from the group consisting of H, halo, alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, $-(CR^{10}R^{11})_{0-6}-OR^7$, $-C(O)R^4$, $-C(S)R^4$, $-C(O)OR^7$, $-C(S)OR^7$, $-OC(O)R^7$, $-OC(S)R^7$, $-C(O)NR^4R^5$, $-C(S)NR^4R^5$, $-C(O)NR^4OR^7$, $-C(S)NR^4OR^7$, $-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, -CN, $-OCF_3$, $-SCF_3$, $-C(=NR^7)NR^4$, $-C(O)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}OR^7$, $-C(S)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(S)NR^7(CH_2)_{1-10}OR^7$, haloalkyl and alkylsilyl, wherein each of said alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl or heteroaralkyl is independently optionally substituted with 1-5 R^9 moieties; and

R^{40} is selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl, wherein each of said cycloalkyl, heterocyclyl, aryl and heteroaryl are

optionally independently substituted with 1-3 moieties independently selected from the group consisting of -CN, -OH, halo, alkyl, haloalkyl, alkoxy, and $-NR^{10}R^{11}$;

(see WO 2006/098962, filed March 7, 2006);

b. A compound represented by the structural Formula B:



Formula B

or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:

ring Y is a 5- to 7-membered ring selected from the group consisting of cycloalkyl, cycloalkenyl, heterocyclyl or heterocyclenyl fused as shown in Formula B, wherein in each of said 5- to 7-membered ring, each substitutable ring carbon is independently substituted with 1-2 R^2 moieties and each substitutable ring heteroatom is independently substituted with R^6;

W is N or $C(R^{12})$;

X is N or N-oxide;

Z is S, S(=O) or $S(=O)_2$;

R^1 is H, alkyl, alkoxy, hydroxy, halo, -CN, $-S(O)_m$-alkyl, $-C(O)NR^9R^{10}$, $-(CR^9R^{10})_{1-6}OH$, or $-NR^4(CR^9R^{10})_{1-2}OR^9$; wherein m is 0 to 2;

each R^2 is independently selected from the group consisting of H, halo, alkyl, cycloalkyl, alkylsilyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, heteroaryl, $-(CR^{10}R^{11})_{0-6}-OR^7$, $-C(O)R^4$, $-C(S)R^4$, $-C(O)OR^7$, $-C(S)OR^7$, $-OC(O)R^7$, $-OC(S)R^7$, $-C(O)NR^4R^5$, $-C(S)NR^4R^5$, $-C(O)NR^4OR^7$, $-C(S)NR^4OR^7$, $-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, -CN, $-OCF_3$, $-SCF_3$, $-C(=NR^7)NR^4$, $-C(O)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}OR^7$, $-C(S)NR^7(CH_2)_{1-10}NR^4R^5$, and $-C(S)NR^7(CH_2)_{1-10}OR^7$, wherein each of said alkyl, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, and heteroaryl is independently optionally substituted with 1-5 R^9 moieties;

or two R^2s on the same carbon atom are optionally taken together with the carbon atom to which they are attached to form a C=O, a C=S or an ethylenedioxy group;

R^3 is independently selected from the group consisting of H, halo, alkyl, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, heteroaryl, $-(CR^{10}R^{11})_{0-6}-OR^7$, $-C(O)R^4$, $-C(S)R^4$, $-C(O)OR^7$, $-C(S)OR^7$, $-OC(O)R^7$, $-OC(S)R^7$, $-C(O)NR^4R^5$, $-C(S)NR^4R^5$, $-C(O)NR^4OR^7$, $-C(S)NR^4OR^7$, $-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, -CN, $-C(=NR^7)NR^4R^5$, $-C(O)N(R^7)-(CR^{40}R^{41})_{1-5}-C(=NR^7)NR^4R^5$, $-C(O)N(R^7)(CR^{40}R^{41})_{1-5}-NR^4R^5$, $-C(O)N(R^7)(CR^{40}R^{41})_{1-5}-C(O)-NR^4R^5$, $-C(O)N(R^7)(CR^{40}R^{41})_{1-5}-OR^7$, $-C(S)NR^7(CH_2)_{1-5}NR^4R^5$, and $-C(S)NR^7(CH_2)_{1-5}OR^7$, wherein each of said alkyl, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, and heteroaryl is independently optionally substituted with 1-5 R^9 moieties;

each of R^4 and R^5 is independently selected from the group consisting of H, alkyl, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, heteroaryl, $-OR^7$, $-C(O)R^7$, and $-C(O)OR^7$, wherein each of said alkyl, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, and heteroaryl, is optionally substituted with 1-4 R^8 moieties;

or R^4 and R^5, when attached to the same nitrogen atom, are optionally taken together with the nitrogen atom to which they are attached to form a 3-6 membered heterocyclic ring having 0-2 additional heteroatoms selected from N, O or S;

each R^6 is independently selected from the group consisting of H, alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroaralkyl, $-(CH_2)_{1-6}CF_3$, $-C(O)R^7$, $-C(O)OR^7$ and $-SO_2R^7$;

each R^7 is independently selected from the group consisting of H, alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, and heteroaralkyl, wherein each member of R^7 except H is optionally substituted with 1-4 R^8 moieties;

each R^8 is independently selected from the group consisting of halo, alkyl, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, heteroaryl, $-NO_2$, $-OR^{10}$, $-(C_1-C_6$ alkyl$)-OR^{10}$, $-CN$, $-NR^{10}R^{11}$, $-C(O)R^{10}$, $-C(O)OR^{10}$, $-C(O)NR^{10}R^{11}$, $-CF_3$, $-OCF_3$, $-CF_2CF_3$, –



$C(=NOH)R^{10}$, $-N(R^{10})C(O)R^{11}$, $-C(=NR^{10})NR^{10}R^{11}$, and $-NR^{10}C(O)OR^{11}$; wherein said each of said alkyl, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, and heteroaryl is independently optionally substituted with 1-4 R^{42} moieties; wherein when each of said cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, and heteroaryl contains two radicals on adjacent carbon atoms anywhere within said cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, and heteroaryl, such radicals may optionally and independently in each occurrence, be taken together with the carbon atoms to which they are attached, to form a five- or six-membered carbocyclic or heterocyclic ring;

or two R^8 groups, when attached to the same carbon, are optionally taken together with the carbon atom to which they are attached to form a C=O or a C=S group;

each R^9 is independently selected from the group consisting of H, alkyl, alkoxy, OH, CN, halo, $-(CR^{10}R^{11})_{0-4}NR^4R^5$, haloalkyl, hydroxyalkyl, alkoxyalkyl, $-C(O)NR^4R^5$, $-C(O)OR^7$, $-OC(O)NR^4R^5$, $-NR^4C(O)R^5$, and $-NR^4C(O)NR^4R^5$;

each R^{10} is independently H or alkyl; or R^9 and R^{10}, when attached to the same nitrogen atom, are optionally taken together with the nitrogen atom to which they are attached to form a 3-6 membered heterocyclic ring having 0-2 additional heteroatoms selected from N, O or S;

each R^{11} is independently H, alkyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heterocyclenyl, or heteroaryl; or R^{10} and R^{11}, when attached to the same nitrogen atom, are optionally taken together with the nitrogen atom to which they are attached to form a 3-6 membered heterocyclic ring having 0-2 additional heteroatoms selected from N, O or S; wherein each of said R^{11} alkyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heterocyclenyl, and heteroaryl is independently optionally substituted with 1-3 moieties selected from the group consisting of –CN, -OH, $-NH_2$, -N(H)alkyl, $-N(alkyl)_2$, halo, haloalkyl, CF_3, alkyl, hydroxyalkyl, alkoxy, aryl, aryloxy, and heteroaryl;

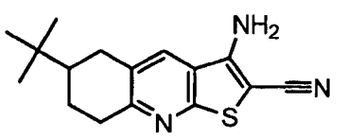
each R^{12} is independently selected from the group consisting of H, halo, alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, $-(CR^{10}R^{11})_{0-6}-OR^7$, $-C(O)R^4$, $-C(S)R^4$, $-C(O)OR^7$, $-C(S)OR^7$, $-OC(O)R^7$, $-OC(S)R^7$, $-C(O)NR^4R^5$, $-C(S)NR^4R^5$, $-C(O)NR^4OR^7$, $-C(S)NR^4OR^7$, $-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, -CN, $-OCF_3$, $-SCF_3$, $-C(=NR^7)NR^4$, $-C(O)NR^7(CH_2)_{1-}$

$_{10}NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}OR^7$, $-C(S)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(S)NR^7(CH_2)_{1-10}OR^7$, haloalkyl and alkylsilyl, wherein each of said alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl or heteroaralkyl is independently optionally substituted with 1-5 R^9 moieties;

R^{40} and R^{41} can be the same or different, each being independently selected from the group consisting of H, alkyl, aryl, heteroaryl, heterocyclyl, heterocyclenyl, cycloalkyl and cycloalkenyl;

each R^{42} is independently selected from the group consisting of halo, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-NO_2$, $-OR^{10}$, $-(C_1-C_6$ alkyl$)-OR^{10}$, $-CN$, $-NR^{10}R^{11}$, $-C(O)R^{10}$, $-C(O)OR^{10}$, $-C(O)NR^{10}R^{11}$, $-CF_3$, $-OCF_3$, $-N(R^{10})C(O)R^{11}$, and $-NR^{10}C(O)OR^{11}$;

with the proviso that when W is $C(R^{12})$, R^{12} and R^3 are optionally taken together, with the two ring carbon atoms to which they are attached to form a 6-membered ring selected from the group consisting of cycloalkenyl, aryl, heteroaryl, heterocyclyl and heterocyclenyl, wherein said 6-membered ring is optionally substituted with 1-3 moieties independently selected from oxo, thioxo, $-OR^{11}$, $-NR^{10}R^{11}$, $-C(O)R^{11}$, $-C(O)OR^{11}$, $-C(O)N(R^{10})(R^{11})$, or $-N(R^{10})C(O)R^{11}$; (see WO2006/098961, filed March 7, 2006);

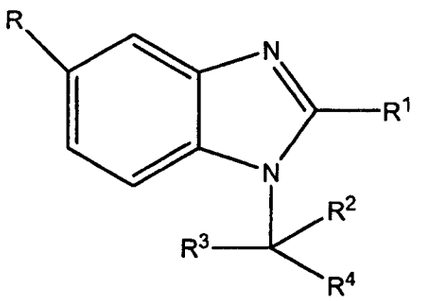
c. 

Formula C

or a pharmaceutically acceptable salt, solvate, or ester thereof;

(see U.S. Pub. No. 2006/0258699, filed March 7, 2006) and;

d. A compound of Formula D



Formula D

or a pharmaceutically acceptable salt, solvate, or ester thereof, wherein:

R is selected from the group consisting of H, alkyl, cyano, haloalkyl, halo, —SH, -S-alkyl, -S-haloalkyl, -S(=O)$_2$alkyl, -S(=O)$_2$OH, -S(=O)$_2$NH$_2$, -S(=O)$_2$NH(alkyl), S(=O)$_2$NH(cycloalkyl), -S(=O)$_2$N(alkyl)$_2$, -S(=O)$_2$heterocyclyl, -S(=O)$_2$heteroaryl, cycloalkyl, aryl, heterocyclyl, heteroaryl, -NHC(=O)alkyl, –C(=O)NH$_2$, –C(=O)NH(alkyl), -C(=O)NH(cycloalkyl), -C(=O)N(alkyl)$_2$, –C(=O)OH, –C(=O)Oalkyl, -C(=O)heterocyclyl, -C(=O)NH(aryl), wherein when each of said cycloalkyl, aryl, heterocyclyl, heteroaryl, and the "heterocyclyl" and "aryl" portions of said R groups has two substituents on adjacent carbon atoms, said substituents, may optionally be taken together with the carbon atoms to which they are attached to form a five- to six-membered cycloalkyl, aryl, heterocyclyl, heterocyclenyl, or heteroaryl ring; wherein each of the aforementioned R alkyl, aryl, cycloalkyl, heterocyclyl, and heteroaryl, and the "alkyl", "cycloalkyl", "heterocyclyl", and "aryl" portions of said R groups, optionally with said five- to six-membered aryl, heterocyclyl, heterocyclenyl, or heteroaryl ring, is optionally substituted with 1-3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, hydroxyl, cyano, halo, haloalkyl, haloalkoxy, -C(O)OH, -C(=O)Oalkyl, and -C(O)NH$_2$;

R^1 is selected from the group consisting of alkyl, heterocyclyl, -C(=O)aryl, -NH$_2$, -NH(alkyl), -NH(cycloalkyl), -N(alkyl)(cycloalkyl), -NH(heterocyclyl), -N(alkyl)(heterocyclyl), N(alkyl)$_2$, -NH(aryl), -N(alkyl)(aryl), -N(aryl)$_2$, -NH(heteroaryl), -N(alkyl)(heteroaryl), -NHC(=O)-alkyl, -N(alkyl)C(=O)-alkyl, -NHC(=O)Oalkyl, -N(alkyl)C(=O)O-alkyl, wherein each of the aforesaid alkyl, heterocyclyl, and the "alkyl", "cycloalkyl", "aryl", and "heteroaryl" portions of said R^1 groups is optionally substituted with 1-3 substituents independently selected from the group consisting of halo, heterocyclyl, aryl, heteroaryl, haloalkyl, haloalkoxy, aryloxy, cyano, –SH, -S-alkyl, -S-haloalkyl, -S(=O)$_2$alkyl, -S(=O)$_2$OH, -S(=O)$_2$NH$_2$, -S(=O)$_2$NH(alkyl), S(=O)$_2$NH(cycloalkyl), -S(=O)$_2$N(alkyl)$_2$, -S(=O)$_2$heterocyclyl, -S(=O)$_2$heteroaryl, hydroxy, alkyl, alkenyl, alkynyl, -NH$_2$, -NH(alkyl), -N(alkyl)$_2$, alkoxy, -NHC(=O)alkyl, -C(=O)H, -C(=O)alkyl, -C(=O)aryl, , -C(=O)heteroaryl, -C(=O)Oalkyl, -C(=O)NH$_2$, -C(O)NHalkyl, -C(=O)N(alkyl)$_2$; wherein when each of said heterocyclyl, aryl and heteroaryl has two substituents on adjacent carbon atoms, said substituents, may optionally be taken together with the carbon atoms to which they

are attached to form a five to six-membered aryl, heterocyclyl, heterocyclenyl, or heteroaryl ring;

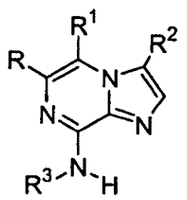
R^2 and R^3 independently are H or alkyl, or $-C(R^2)(R^3)-$ is absent;

R^4 is selected from the group consisting of alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl, wherein when each of said cycloalkyl, heterocyclyl, aryl, and heteroaryl has two substituents on adjacent carbon atoms, said substituents, may optionally be taken together with the carbon atoms to which they are attached to form a five to six-membered aryl, heterocyclyl, heterocyclenyl, or heteroaryl ring; wherein each of the aforementioned R^4 alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl, optionally with said five to six-membered aryl, heterocyclyl, heterocyclenyl, or heteroaryl ring is optionally substituted with 1-3 substituents independently selected from the group consisting of cyano, halo, haloalkyl, alkyl, alkoxy, hydroxyl, haloalkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-S(=O)_2$alkyl, $-S(=O)_2NH_2$, $-S(=O)_2NH$(alkyl), $-S(=O)_2N(alkyl)_2$, -S-alkyl, -S-haloalkyl, $-C(=O)OH$, $-NH_2$, -NH(alkyl), $-N(alkyl)_2$, and -C(=O)Oalkyl;

Compounds represented in the present application by Formula (d) are disclosed in PCT US2008/006472, filed May 21, 2008;

further comprising one or more of a second compound, wherein said second compound is an aurora kinase inhibitor selected from the group consisting of compounds represented by Formulas E-K:

e. A compound represented by the structural Formula E:



Formula E

or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, wherein:

R is H, CN, $-NR^5R^6$, cycloalkyl, cycloalkenyl, heterocyclenyl, heteroaryl, $-C(O)NR^5R^6$, $-N(R^5)C(O)R^6$, heterocyclyl, heteroaryl substituted with $(CH_2)_{1-3}$ NR^5R^6, unsubstituted alkyl, or alkyl substituted with one or more moieties which can be the same or different each moiety being independently selected from the group consisting of $-OR^5$, heterocyclyl,

$-N(R^5)C(O)N(R^5R^6)$, $-N(R^5)-C(O)OR^6$, $-(CH_2)_{1-3}-N(R^5R^6)$ and $-NR^5R^6$;

R^1 is H, halo, aryl or heteroaryl, wherein each of said aryl and heteroaryl can be unsubstituted or substituted with one or more moieties which can be the same or different each moiety being independently selected from the group consisting of halo, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, $-CH_2OR^5$, $-C(O)NR^5R^6$, -C(O)OH, $-C(O)NH_2$,
$-NR^5R^6$ (wherein the R^5 and R^6, together with the N of said $-NR^5R^6$, form a heterocyclyl ring), $-S(O)R^5$, $-S(O_2)R^5$, -CN, -CHO, $-SR^5$, $-C(O)OR^5$, $-C(O)R^5$ and $-OR^5$;

R^2 is H, halo, aryl, arylalkyl or heteroaryl, wherein each of said aryl, arylalkyl and heteroaryl can be unsubstituted or optionally independently be substituted with one or more moieties which can be the same or different each moiety being independently selected from the group consisting of halo, amide, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, -C(O)OH, $-C(O)NH_2$, $-NR^5R^6$ (wherein the R^5 and R^6, together with the N of said $-NR^5R^6$, form a heterocyclyl ring), -CN, arylalkyl,
$-CH_2OR^5$, $-S(O)R^5$, $-S(O_2)R^5$, -CN, -CHO, $-SR^5$, $-C(O)OR^5$, $-C(O)R^5$, heteroaryl and heterocyclyl;

R^3 is H, alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl, wherein:

- said alkyl shown above for R^3 can be unsubstituted or substituted with one or more moieties which can be the same or different each moiety being independently selected from the group consisting of $-OR^5$, alkoxy, heteroaryl, and $-NR^5R^6$;
- said aryl shown above for R^3 is unsubstituted, or optionally substituted, or optionally fused, with halo, heteroaryl, heterocyclyl, cycloalkyl or heteroarylalkyl, wherein each of said heteroaryl, heterocyclyl, cycloalkyl and heteroarylalkyl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different each moiety being independently selected from alkyl, $-OR^5$, $-N(R^5R^6)$ and
$-S(O_2)R^5$; and
- said heteroaryl shown above for R^3 can be unsubstituted or optionally substituted, or optionally fused, with one or more moieties which can be the same or different with each moiety being independently selected from the group consisting of halo, amino, alkoxycarbonyl, $-OR^5$, alkyl, -CHO, $-NR^5R^6$, $-S(O_2)N(R^5R^6)$,

-C(O)N(R^5R^6), -SR^5, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclenyl, and heterocyclyl;

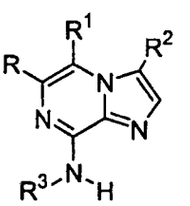
R^5 is H, alkyl, aminoalkyl, aryl, heteroaryl, heterocyclyl or cycloalkyl; and

R^6 is H, alkyl, aryl, arylalkyl, heteroaryl, heterocyclyl or cycloalkyl;

further wherein in any -NR^5R^6 in Formula I, said R^5 and R^6 can optionally be joined together with the N of said -NR^5R^6 to form a cyclic ring;

(see WO07/058942 filed November 8, 2006);

f. A compound represented by the structural formula:

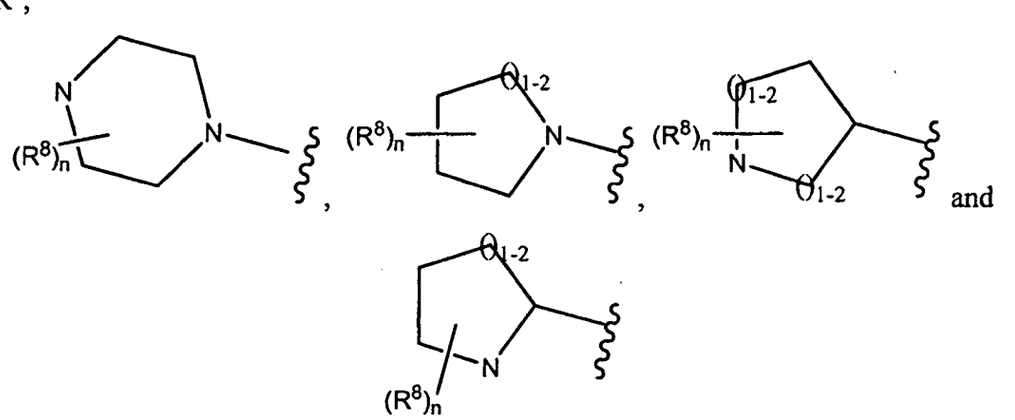


Formula F

or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, wherein:

R is selected from the group consisting of H, halogen, aryl, heteroaryl, cycloalkyl, arylalkyl, heterocyclyl, heterocyclylalkyl, alkenyl, alkynyl,

-$C(O)R^7$,



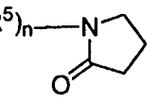
and

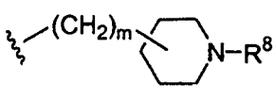
wherein each of said aryl, heteroaryl, cycloalkyl, arylalkyl, alkenyl, heterocyclyl and the heterocyclyl moieties whose structures are shown immediately above for R can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, cycloalkyl, CF_3, CN, -OCF_3,

-OR^6, -$C(O)R^7$, -NR^5R^6, -$C(O_2)R^6$, -$C(O)NR^5R^6$, -$(CHR^5)_nOR^6$, -SR^6, -$S(O_2)R^7$, -$S(O_2)NR^5R^6$, -$N(R^5)S(O_2)R^7$, -$N(R^5)C(O)R^7$ and -$N(R^5)C(O)NR^5R^6$;

R^1 is H, halogen or alkyl;

R^2 is alkyl;

R^3 is selected from the group consisting of H, aryl, heteroaryl, heterocyclyl, -$(CHR^5)_n$-aryl, - $(CHR^5)_n$-heteroaryl, -$(CHR^5)_n$-OR^6, -$S(O_2)R^6$, -$C(O)R^6$, -$S(O_2)NR^5R^6$, -$C(O)OR^6$, -$C(O)NR^5R^6$, cycloalkyl, -$CH(aryl)_2$, –$(CH_2)_m$-NR^8, -$(CHR^5)_n$-$CH(aryl)_2$, 

and 

, wherein each of said aryl, heteroaryl and heterocyclyl can be substituted or optionally substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl, cycloalkyl, CF_3, CN, -OCF_3, -OR^5, -NR^5R^6, -$C(O_2)R^5$, -$C(O)NR^5R^6$, -SR^6, -$S(O_2)R^6$, -$S(O_2)NR^5R^6$, -$N(R^5)S(O_2)R^7$, -$N(R^5)C(O)R^7$ and -$N(R^5)C(O)NR^5R^6$;

R^5 is H or alkyl;

R^6 is selected from the group consisting of H, alkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, wherein each of said alkyl, heteroarylalkyl, aryl, heteroaryl and arylalkyl can be unsubstituted or optionally substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl, cycloalkyl, CF_3, OCF_3, CN, -OR^5, -NR^5R^6, -CH_2OR^5, -$C(O_2)R^5$, -$C(O)NR^5R^6$, -SR^6, -$S(O_2)R^7$, -$S(O_2)NR^5R^6$, -$N(R^5)S(O_2)R^7$, -$N(R^5)C(O)R^7$ and -$N(R^5)C(O)NR^5R^6$;

R^7 is selected from the group consisting of alkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, wherein each of said alkyl, heteroarylalkyl, aryl, heteroaryl and arylalkyl can be unsubstituted or optionally substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl, cycloalkyl, CF_3, OCF_3, CN, -OR^5, -NR^5R^6, -CH_2OR^5, -$C(O_2)R^5$, -$C(O)NR^5R^6$, -SR^6, -$S(O_2)R^7$, -$S(O_2)NR^5R^6$, -$N(R^5)S(O_2)R^7$, -$N(R^5)C(O)R^7$ and -$N(R^5)C(O)NR^5R^6$;

R^8 is selected from the group consisting of R^6, -$C(O)NR^5R^6$, -$S(O_2)NR^5R^6$, -$C(O)R^7$, -$C(O_2)R^6$, –$S(O_2)R^7$ and –(CH_2)-aryl;

R^9 is selected from the group consisting of halogen, CN, NR^5R^6, -$C(O_2)R^6$, -$C(O)NR^5R^6$, -OR^6, -$C(O)R^7$, -SR^6, -$S(O_2)R^7$, -$S(O_2)NR^5R^6$, -$N(R^5)S(O_2)R^7$, -$N(R^5)C(O)R^7$and –$N(R^5)C(O)NR^5R^6$;

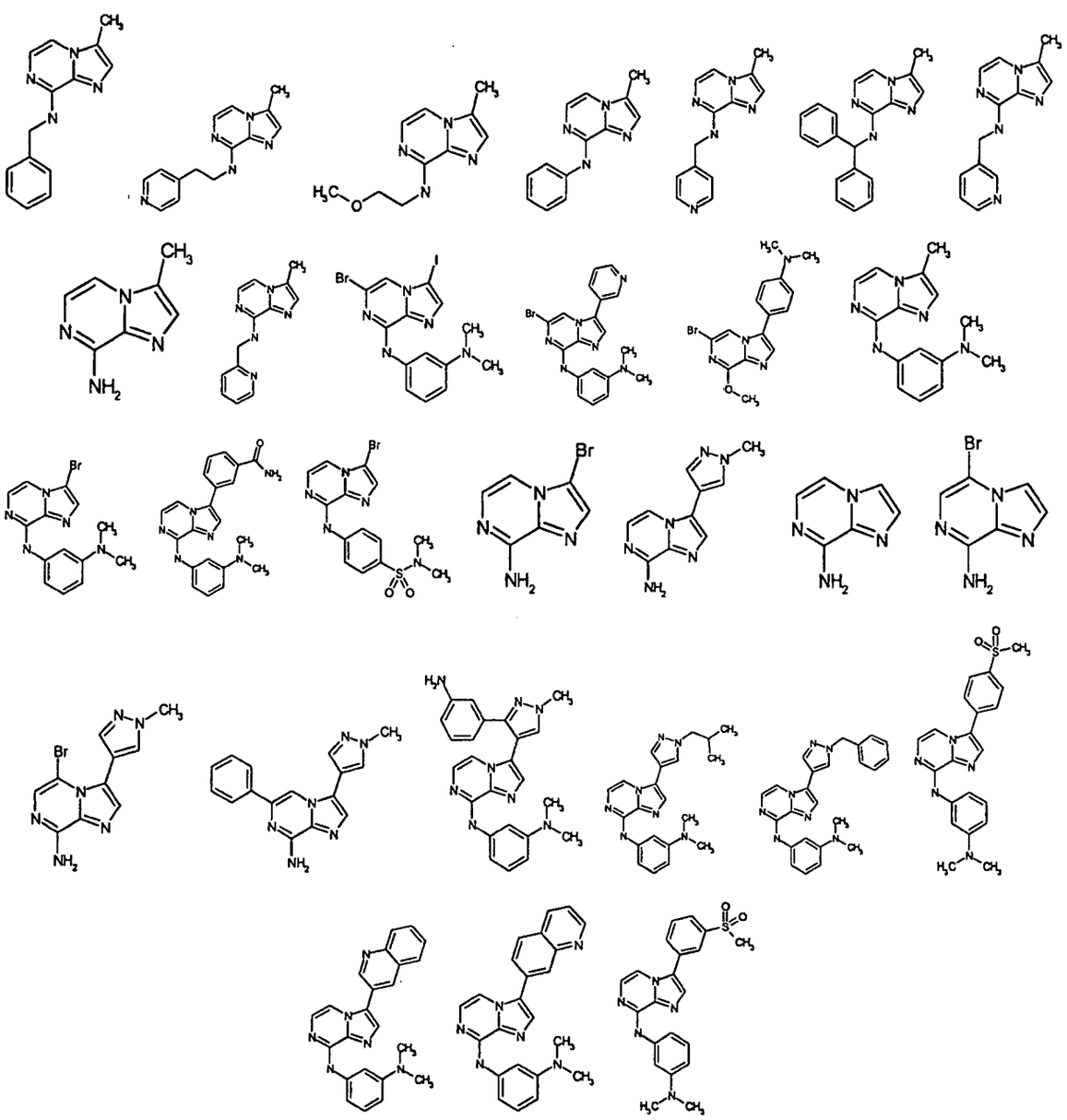
m is 0 to 4;

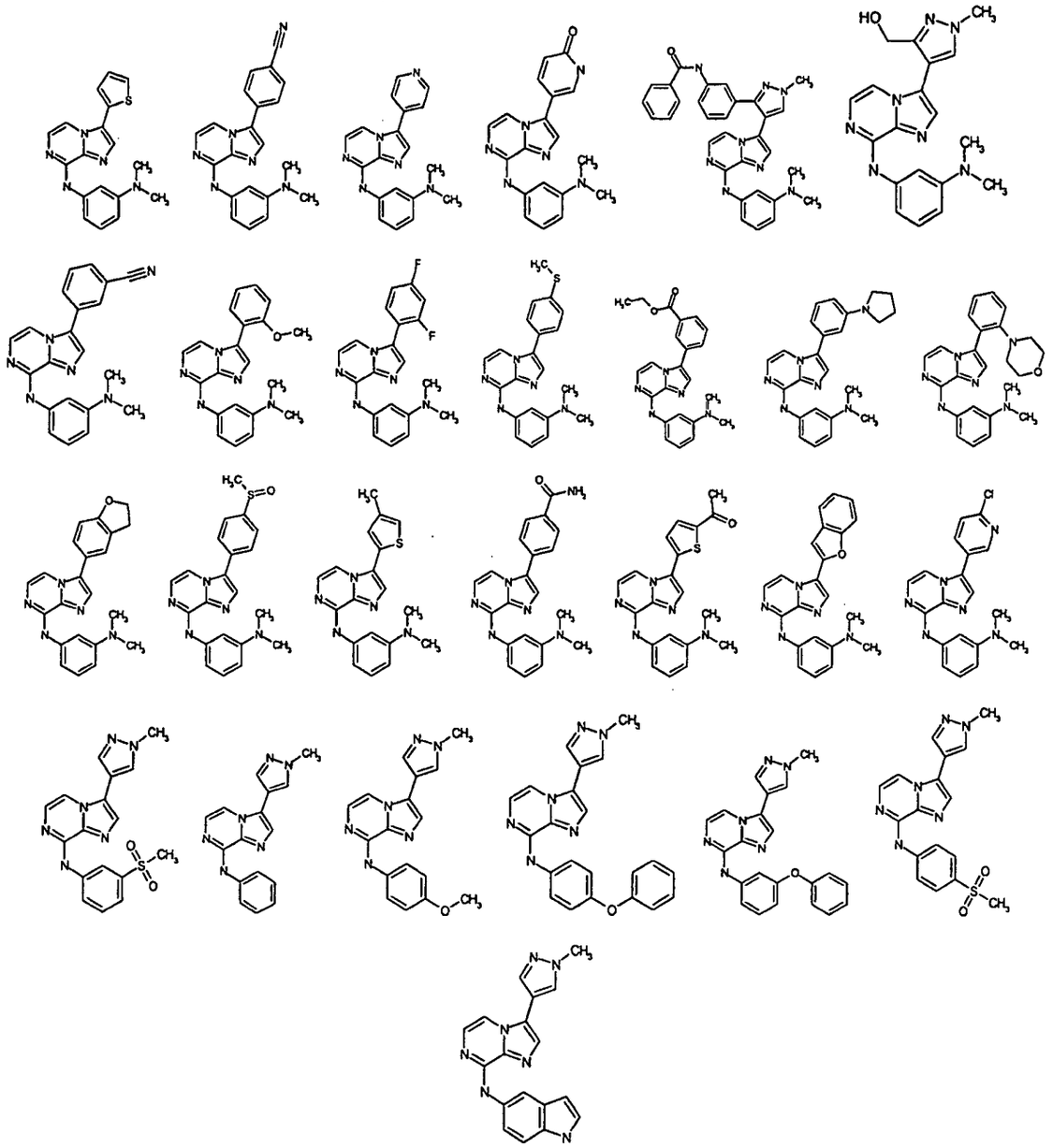
n is 1-4; and

p is 0-3;

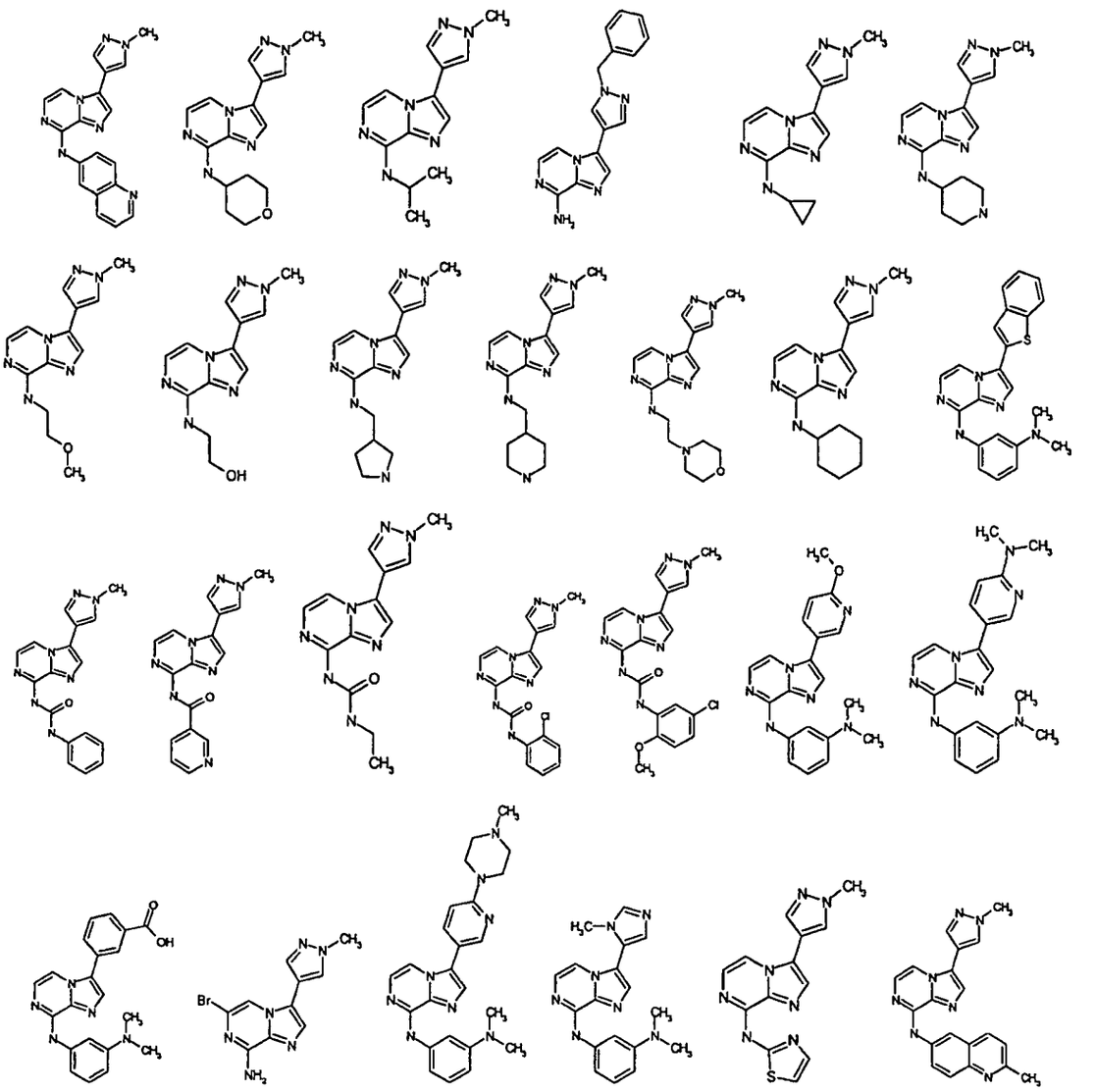
(see WO2004/026877, filed September 19, 2003);

g. A compound selected from the compounds of the formulas:

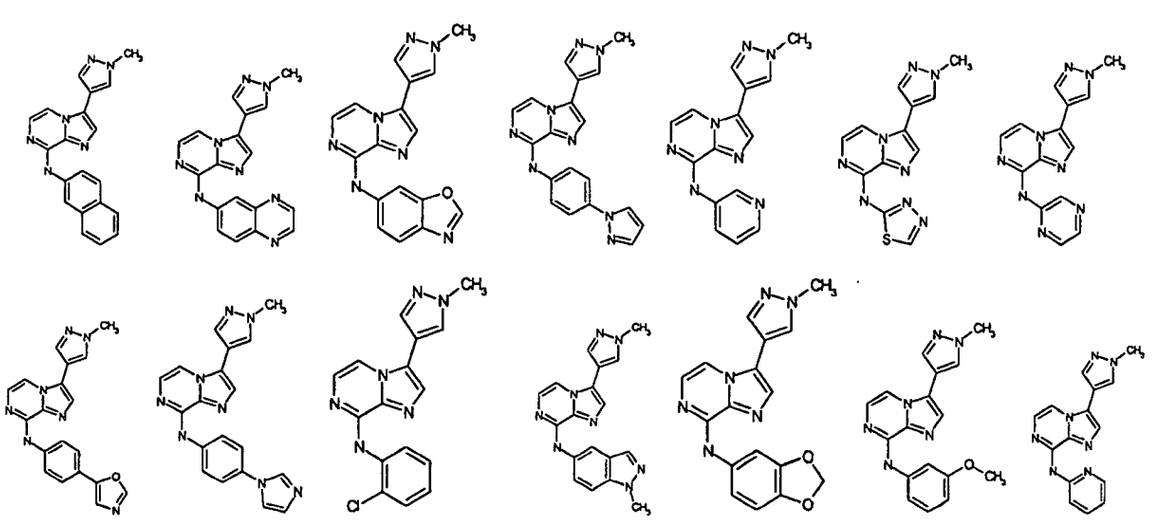


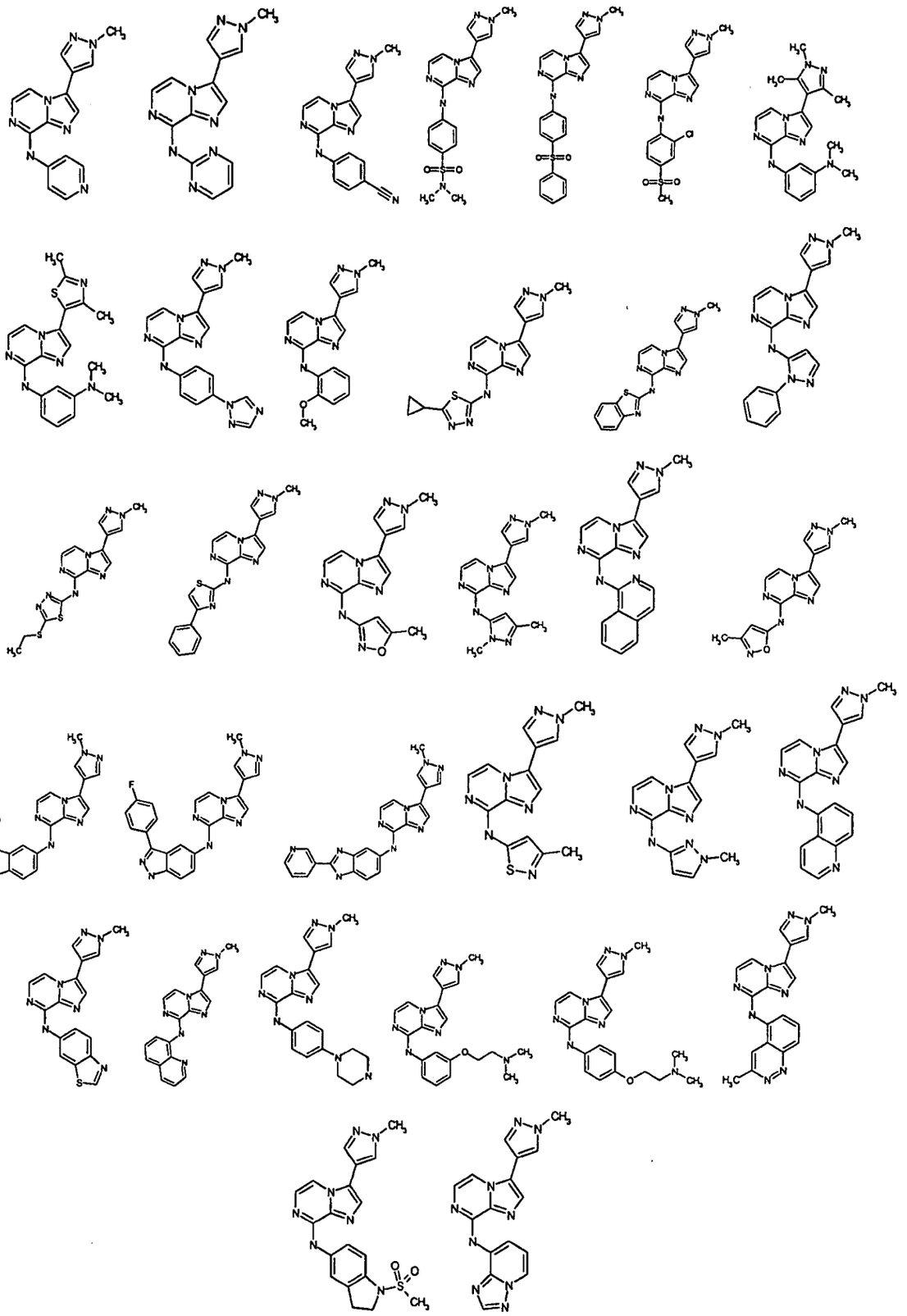


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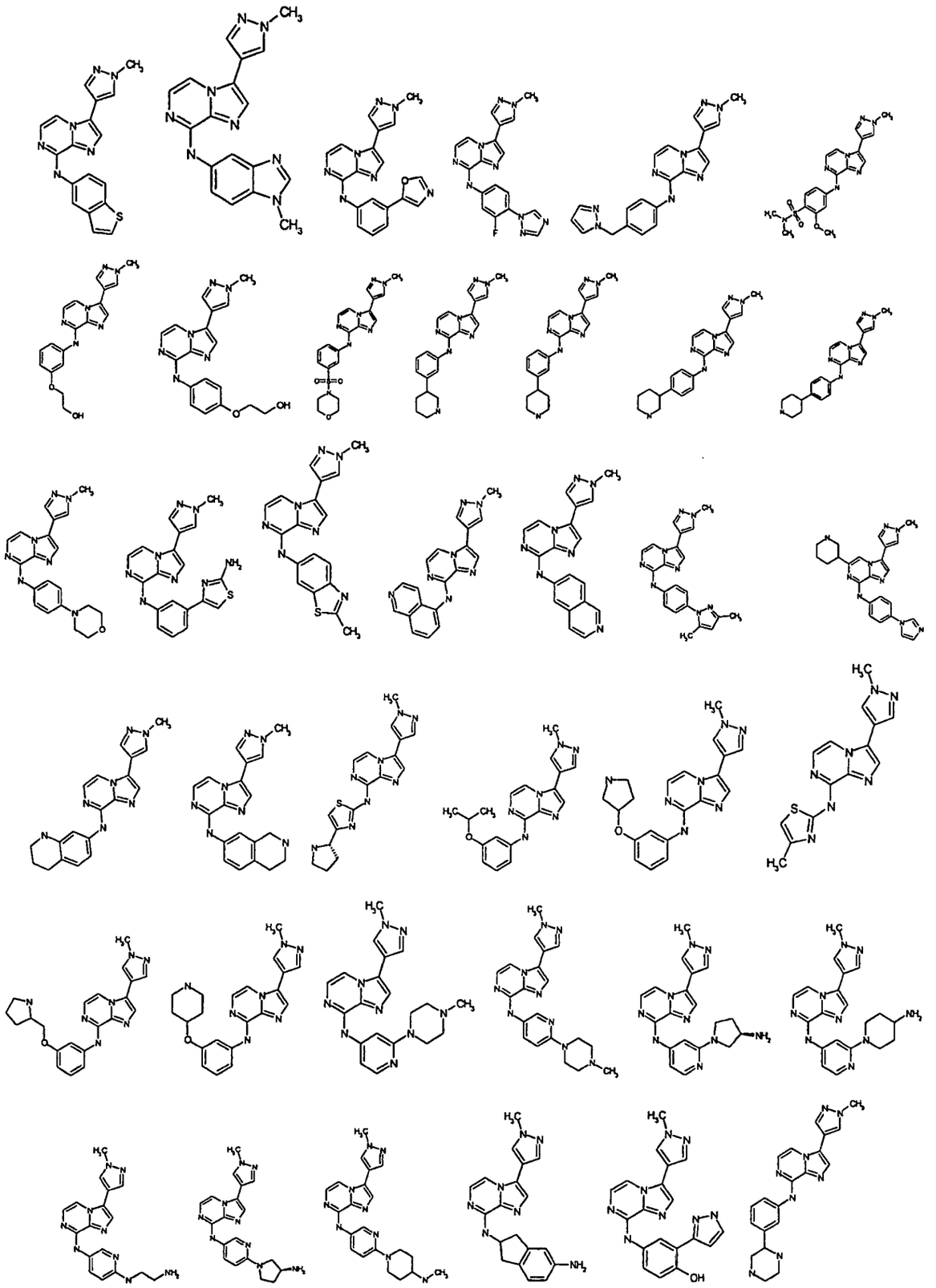


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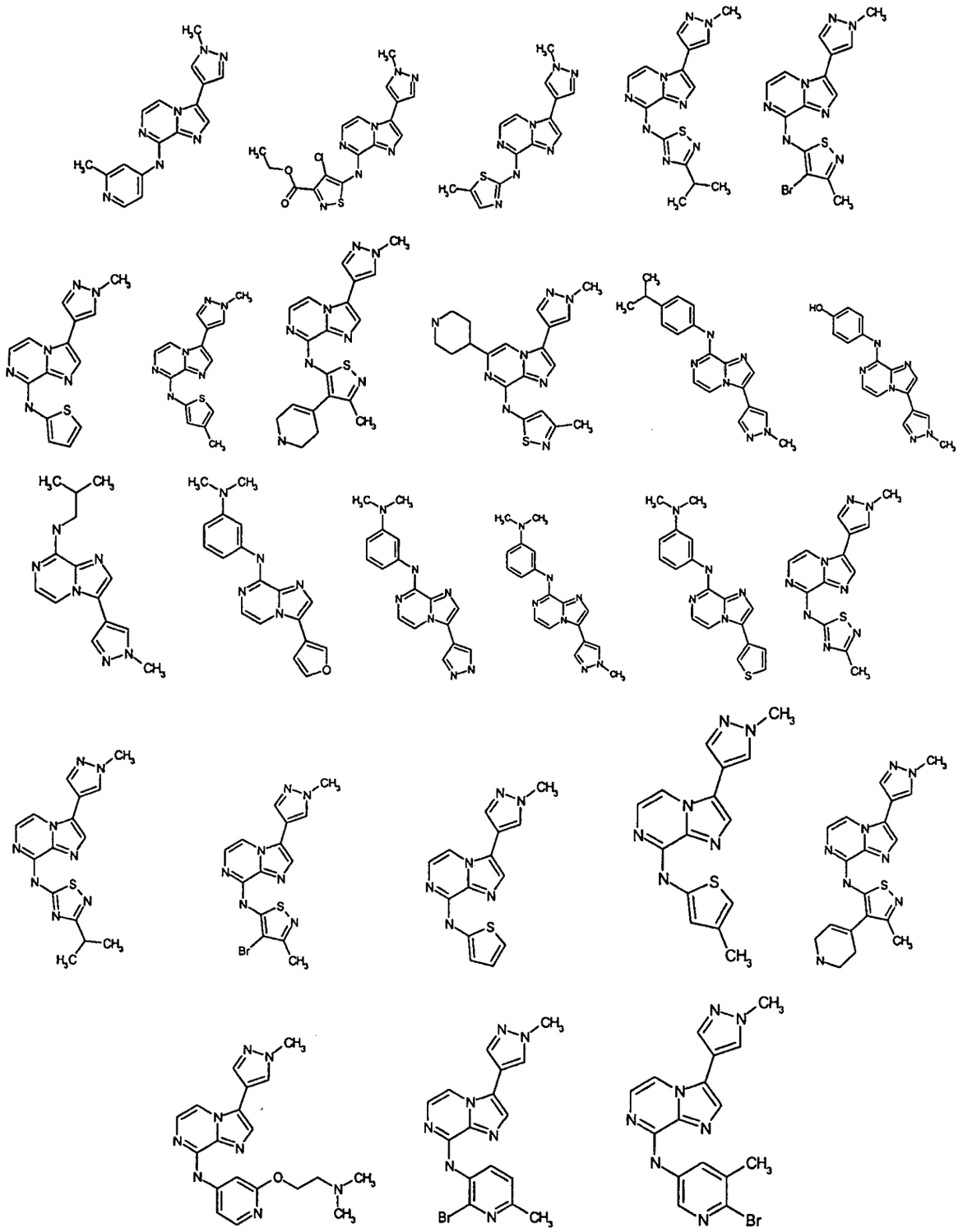




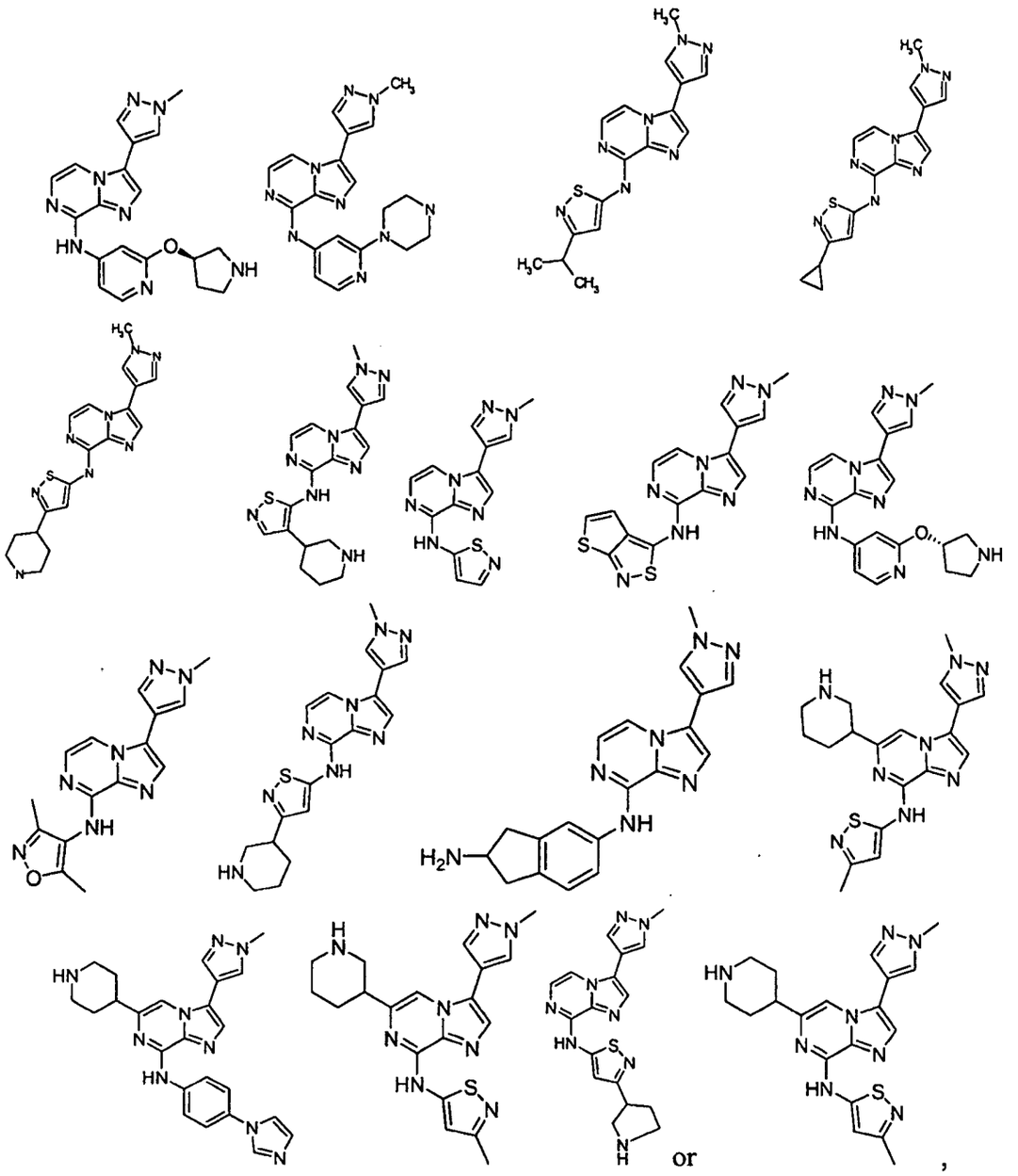
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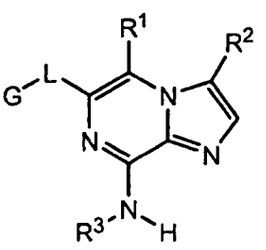


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or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, (see, WO2007/058873, filed November 8, 2006);

h. A compound of the formula:



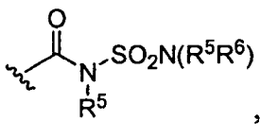
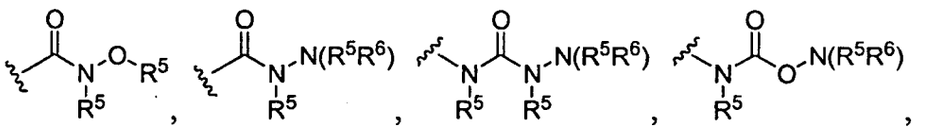
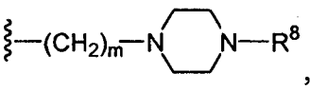
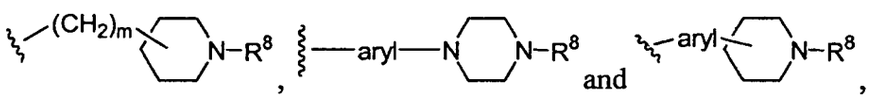
Formula H

or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, wherein:

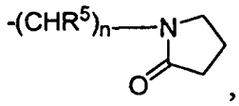
L is selected from the group consisting of S, S(O) and $S(O_2)$;

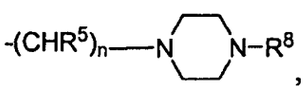
G is alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclenyl or heterocyclyl, wherein each of said alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclenyl or heterocyclyl can be unsubstituted or optionally independently substituted with one or more moieties which are independently selected from the group consisting of $-OR^5$, halo, -CN, $-C(O)NR^5R^6$, $-N(H)-C(O)R^5$,$-N(H)-C(O)-NR^5R^6$, $-S(O_2)NR^5R^6$, $-NR^5R^6$, $-C(O)R^5$, $-C(O_2)R^5$, $-SR^5$, $-S(O)R^5$, $-S(O_2)R^5$;

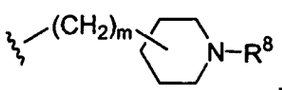
R^1 is H, halo, alkyl, aryl or heteroaryl, wherein each of said alkyl, aryl and heteroaryl can be unsubstituted or substituted with one or more moieties which can be the same or different each moiety being independently selected from the group consisting of halo, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C(O)NR^5R^6$ and $-OR^5$;

R^2 is selected from the group consisting of H, R^9, alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclylalkyl, $-CF_3$, $-C(O)R^7$,  ,  , alkyl substituted with 1-6 R^9 groups which groups can be the same or different with each R^9 being independently selected,  ,  , wherein each of the above-said aryl, heteroaryl, cycloalkyl, arylalkyl and heterocyclyl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halo, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, CF_3, CN, $-OCF_3$, $-OR^6$, $-C(O)R^7$, $-NR^5R^6$, $-C(O_2)R^6$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ and $-N(R^5)C(O)NR^5R^6$;

R^3 is selected from the group consisting of H, alkyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroarylalkyl, cycloalkylalkyl, heterocyclylalkyl,



,


, $-(CHR^5)_n-OR^6$, $-S(O_2)R^6$, $-C(O)R^6$, $-S(O_2)NR^5R^6$, $-C(O)OR^6$, $-C(O)NR^5R^6$, cycloalkyl, $-CH(aryl)_2$, $-CH(heteroaryl)_2$, $-(CH_2)_m-NR^8$, and


, wherein each of said alkyl, aryl, heteroaryl and heterocyclyl can be substituted or optionally substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halo, alkyl, aryl, cycloalkyl, CF_3, CN, $-OCF_3$, $-OR^5$, $-NR^5R^6$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^6$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ and $-N(R^5)C(O)NR^5R^6$;

R^5 is H, alkyl, aryl, heteroaryl, heterocyclyl or cycloalkyl; and

R^6 is selected from the group consisting of H, alkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, wherein each of said alkyl, heteroarylalkyl, aryl, heteroaryl and arylalkyl can be unsubstituted or optionally substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl, cycloalkyl, CF_3, OCF_3, CN, $-OR^5$, $-NR^5R^6$, $-CH_2OR^5$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ and $-N(R^5)C(O)NR^5R^6$;

R^7 is selected from the group consisting of alkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, wherein each of said alkyl, heteroarylalkyl, aryl, heteroaryl and arylalkyl can be unsubstituted or optionally substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl, cycloalkyl, CF_3, OCF_3, CN, $-OR^5$, $-NR^5R^6$, $-CH_2OR^5$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ and $-N(R^5)C(O)NR^5R^6$;

R^8 is selected from the group consisting of R^6, $-C(O)NR^5R^6$, $-S(O_2)NR^5R^6$, $-C(O)R^7$, $-C(O_2)R^6$, $-S(O_2)R^7$ and $-(CH_2)$-aryl;

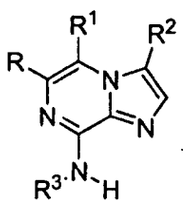
R^9 is selected from the group consisting of halogen, CN, NR^5R^6, $-C(O_2)R^6$, $-C(O)NR^5R^6$, $-OR^6$, $-C(O)R^7$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$and $-N(R^5)C(O)NR^5R^6$;

m is 0 to 4; and

p is 0-3;

(see, WO 2008/054749, filed October 29, 2007);

i. A compound of Formula I:



Formula I

or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, wherein:

R is H, CN, $-NR^5R^6$, cycloalkyl, cycloalkenyl, heterocyclenyl, heteroaryl, $-C(O)NR^5R^6$, $-N(R^5)C(O)R^6$, heterocyclyl, heteroaryl substituted with $(CH_2)_{1-3}$ NR^5R^6, unsubstituted alkyl, or alkyl substituted with one or more moieties which can be the same or different each moiety being independently selected from the group consisting of $-OR^5$, heterocyclyl, $-N(R^5)C(O)N(R^5R^6)$, $-N(R^5)-C(O)OR^6$, $-(CH_2)_{1-3}-N(R^5R^6)$ and $-NR^5R^6$;

R^1 is H, halo, aryl or heteroaryl, wherein each of said aryl and heteroaryl can be unsubstituted or substituted with one or more moieties which can be the same or different each moiety being independently selected from the group consisting of halo, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, $-CH_2OR^5$, $-C(O)NR^5R^6$, -C(O)OH, $-C(O)NH_2$, $-NR^5R^6$ (wherein the R^5 and R^6, together with the N of said $-NR^5R^6$, form a heterocyclyl ring), $-S(O)R^5$, $-S(O_2)R^5$, -CN, -CHO, $-SR^5$, $-C(O)OR^5$, $-C(O)R^5$ and $-OR^5$;

R^2 is H, halo, aryl, arylalkyl or heteroaryl, wherein each of said aryl, arylalkyl and heteroaryl can be unsubstituted or optionally independently be substituted with one or more moieties which can be the same or different each moiety being independently selected from the group consisting of halo, amide, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, -C(O)OH, $-C(O)NH_2$, $-NR^5R^6$ (wherein the R^5 and R^6, together with the N of said $-NR^5R^6$, form a heterocyclyl ring), -CN, arylalkyl, $-CH_2OR^5$, $-S(O)R^5$, $-S(O_2)R^5$, -CN, -CHO, $-SR^5$, $-C(O)OR^5$, $-C(O)R^5$, heteroaryl and heterocyclyl;

R^3 is heterocyclyl–$(CR^7R^8)_n$-X, heterocyclenyl–$(CR^7R^8)_n$-X, heteroaryl–$(CR^7R^8)_n$-X or aryl–

$(CR^7R^8)_n$-X wherein each of the heterocyclyl-, heterocyclenyl-, heteroaryl- or aryl-moieties of said R^3 can be unsubstituted or substituted with one or more moieties, independently selected from the group consisting of $-CONR^5R^6$, $-OR^5$ and alkyl,

n is 1-6,

X is selected from the group consisting of, $-NR^5R^6$, $-OR^5$, $-SO-R^5$ and $-SR^5$,

R^7 and R^8 are each independently hydrogen or alkyl;

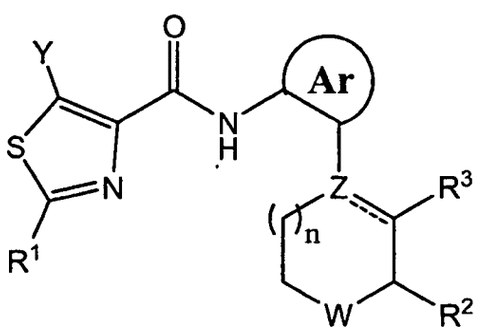
R^5 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkoxyalkyl, -alkyl-S-alkyl, aminoalkyl, aryl, heteroaryl, heterocyclenyl, heterocycloalkyl, cycloalkyl, cycloalkenyl, heterocyclylalkoxyl, -S-alkylheterocyclyl, heterocyclyl, heterocyclenyl, alkylN(alkyl)$_2$, alkylNH(alkyl), alkylN(alkenyl)2, -alkylN(alkoxyl)2, -alkyl-SH and hydroxyalkyl, wherein each of said aryl, heteroaryl, heterocyclenyl, heterocycloalkyl, cycloalkyl, cycloalkenyl, heterocyclylalkoxyl, -S-alkylheterocyclyl, heterocyclyl, heterocyclenyl can be unsubstituted or substituted with one or more moieties independently selected from the group consisting of alkyl, alkyl, alkenyl, aryl, cycloalkenyl, cycloalkyl, arylalkyl, cycloalkenylalkyl, cycloalkylalkyl, heteroaryl, heterocyclenyl, heterocyclyl, heteroarylalkyl, heterocyclenylalkyl, heterocycloalkylalkyl, alkoxyalkyl, -alkyl-S-alkyl, -alkylSH, alkoxyl, -S-alkyl, hydroxyalkyl, and aminoalky;

R^6 is selected from the group consisting of hydrogen, alkyl, alkenyl, aryl, cycloalkenyl, cycloalkyl, arylalkyl, cycloalkenylalkyl, cycloalkylalkyl, heteroaryl, heterocyclenyl, heterocyclyl, heteroarylalkyl, heterocyclenylalkyl, heterocycloalkylalkyl, alkoxyalkyl, -alkyl-S-alkyl, -alkylSH, alkoxyl, -S-alkyl, hydroxyalkyl, and aminoalkyl, wherein each of said aryl, cycloalkenyl, cycloalkyl, arylalkyl, cycloalkenylalkyl, cycloalkylalkyl, heteroaryl, heterocyclenyl, heterocyclyl, heteroarylalkyl, heterocyclenylalkyl, heterocycloalkylalkyl can be unsubstituted or substituted with one or more moieties independently selected from the group consisting of alkyl, alkyl, alkenyl, aryl, cycloalkenyl, cycloalkyl, arylalkyl, cycloalkenylalkyl, cycloalkylalkyl, heteroaryl, heterocyclenyl, heterocyclyl, heteroarylalkyl, heterocyclenylalkyl, heterocycloalkylalkyl, alkoxyalkyl, -alkyl-S-alkyl, -alkylSH, alkoxyl, -S-alkyl, hydroxyalkyl, and aminoalkyl;

further wherein in any $-NR^5R^6$ in Formula I, said R^5 and R^6 can optionally be joined together with the N of said $-NR^5R^6$ to form a cyclic ring or bridged cyclic ring, wherein each of said cyclic ring or bridged cyclic ring, can be unsubstituted or substituted with one or more moieties, which can be the same or different, independently selected from the group consisting of hydroxyl, -SH, alkyl, alkenyl, hydroxyalkyl, -alkyl-SH, alkoxyl, -S-alkyl, $-CO_2$-alkyl, $-CO_2$-alkenyl, arylalkyl, cycloalkenylalkyl, cycloalkylalkyl, heteroarylalkyl, heterocyclenylalkyl, heterocycloalkylalkyl, heteroaryl, aryl, cycloalkenyl, cycloalkyl, spiroheterocyclyl, spiroheterocyclenyl, spiroheteroaryl, spirocyclyl, spirocyclenyl, spiroaryl, alkoxyalkyl, -alkyl-S-alkyl, heterocyclyl, and heterocyclenyl;

(see, WO 2008/057512, filed November 6, 2007 and Serial No. PCT US2008/007295, filed June 11, 2008);

j. A compound having the formula:



(J)

or a pharmaceutically acceptable salt, solvate, ester, prodrug or stereoisomer thereof, wherein the dashed lines indicate an optional and additional bond, and wherein:

R^1 is nitrogen-containing heteroaryl, nitrogen-containing heterocyclyl, nitrogen-containing benzofused heteroaryl or nitrogen-containing benzofused heterocyclyl, wherein R^1 is joined to the rest of the compound of formula (I) via a ring nitrogen atom, and wherein one or more ring carbon atoms of a nitrogen-containing heteroaryl, nitrogen-containing heterocyclyl, nitrogen-containing benzofused heteroaryl or nitrogen-containing benzofused heterocyclyl group can be substituted with up to 5 substituents, which may be the same or

different, and are independently selected from alkyl, aryl, halo, -OH, -O-alkyl, -O-aryl, -$N(R^8)_2$, -CF_3, -NO_2, -$C(O)R^8$, -$C(O)OR^8$, -$C(O)N(R^8)_2$, -$OC(O)R^8$ or -$NHC(O)R^8$;

R^2 is –H, -alkyl, –NH_2 or –CH_2NH_2;

R^3 is –H, -alkyl, –NH_2 or –CH_2NH_2;

each occurrence of R^4 is independently –H, -alkyl, –NH_2, -OH, -alkylene-OH, –CH_2NH_2, -$C(O)R^5$, -$C(O)NH_2$, -C(O)NH-alkyl, -$C(O)N(alkyl)_2$, -$NHC(O)R^6$ or –$NHS(O)_2R^6$;

R^5 is –H, -alkyl, -aryl, -heteroaryl, -NHOH;

R^6 is –H, -alkyl or –CF_3;

R^7 is –H, -OH, -C_1-C_6 alkyl, -O-(C_1-C_6 alkyl), or –CF_3;

R^8 is –H, alkyl, aryl, heterocyclyl, heteroaryl or cycloalkyl;

Ar is -arylene- or -heteroarylene-, wherein the arylene or heteroarylene is joined via 2 of its adjacent ring carbon atoms, and wherein the -arylene- or -heteroarylene- can be substituted with up to 4 substituents, which may be the same or different, and are independently selected from –halo, alkyl, alkoxy, aryloxy, -SR^8, -$S(O)R^8$, -$S(O)_2R^8$, -$C(O)R^8$, -$C(O)OR^8$, -$C(O)N(R^8)_2$, -$NHC(O)R^8$, -CF_3, -CN or NO_2, and such that when Ar is tetrahydronaphthylene, R^1 and R^2 cannot both be hydrogen

W is –NH- or –$C(R^4)_2$-, wherein both R^4 groups and the carbon atom to which they are attached can combine to form a five to seven membered heterocyclyl or heteroaryl group;

Y is –H, -halo, -alkyl or –CN;

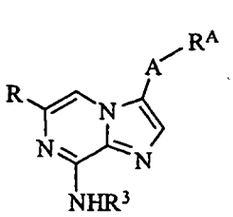
Z is –CR^7- or –N-, when the optional additional bond is absent, and –C- when the optional additional bond is present;

n is an integer ranging from 0 to 2.

Compounds represented in the present application by paragraph (j) are disclosed in WO 2008/054749, filed October 29, 2007.

(see, WO 2008/054749, filed October 29, 2007); and

(k) A compound of Formula K:



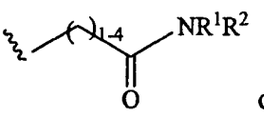
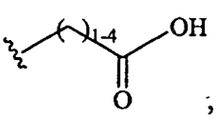
Formula K

or a pharmaceutically acceptable salt, solvate, ester, prodrug or stereoisomer thereof, wherein:

R is H, halo or alkyl;

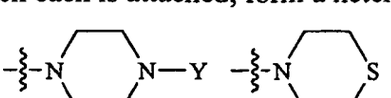
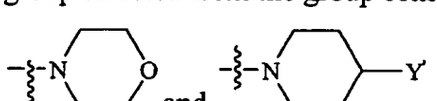
R^3 is heteroaryl-X, wherein X is heterocyclylalkyl- wherein said heterocyclyl can be unsubstituted or optionally substituted with 1-4 alkyl moieties;

A is -aryl- , -heteroaryl-, $-N(R^1)$-aryl- or $-N(R^1)$-heteroaryl- , wherein each of said aryl and heteroaryl can be independently unsubstituted or optionally substituted with one or more substituents, which substituents can be the same or different, each substituent being independently selected from the group consisting of alkyl, $-NO_2$, halo, hydroxy, trihaloalkyl, alkoxy, and dialkylamino;

R^A is $-(CH_2)_{1-4}$-heteroaryl,  or  ; wherein said heteroaryl can optionally be fused with an aryl, wherein each of said aryl and heteroaryl can independently be optionally substituted with one or more moieties each moiety being independently selected from the group consisting of trihaloalkyl, $-NO_2$, halo, hydroxyalkyl, alkoxyalkyl and dialkylamino;

R^1 is H or alkyl;

R^2 is H, hydroxyalkyl-, arylalkyl-, heteroaryl, aryl, heteroarylalkyl-, alkyl, dialkylaminoalkyl-, alkylaminoalkyl-, cycloalkylalkyl-, cycloalkyl, heterocyclylalkyl- or heterocyclyl, wherein said aryl and aryl of arylalkyl can be unsubstituted or substituted with one or more moieties independently selected from the group consisting of trihaloalkyl, $-NO_2$, halo, hydroxyalkyl, alkoxyalkyl, dialkylamino and heterocyclylalkyl-, wherein said heterocyclylalkyl can be unsubstituted or substituted with alkyl or $-SO_2NH_2$; said heteroaryl and heteroaryl of heteroarylalkyl can be unsubstituted or substituted with one or more moieties, each moiety being independently selected from the group consisting of hydroxyalkyl, alkoxy, alkyl, halo, hydroxyl, and $-NO_2$; and said cycloalkyl is unsubstituted or substituted with hydroxyl; or

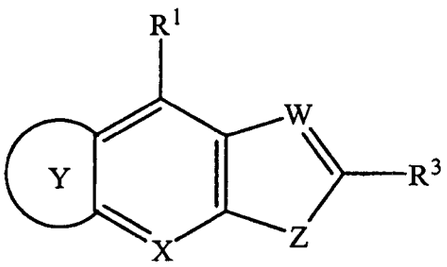
R^1 and R^2 together with the N to which each is attached, form a heterocyclic group selected from the group consisting of  ,  and , wherein

Y is alkoxyalkyl, hydroxyalkyl, dialkylaminoalkyl or alkyl, further wherein Y' is hydroxyl.

Compounds represented in the present application by Formula k are disclosed in U.S. Appln. No. 61/024010, filed January 28, 2008.

In another embodiment, the KSP inhibitor useful in the practice of this invention is represented by Formula AI:

AI. A compound represented by the structural Formula AI:



Formula AI

or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:

ring Y is a 5- to 6-membered aryl or a 5- or 6-membered heteroaryl fused as shown in Formula A, wherein in said aryl and heteroaryl each substitutable ring carbon is independently substituted with R^2 and each substitutable ring nitrogen is independently substituted with R^6;

W is N or $C(R^{12})$;

X is N or N-oxide;

Z is S, S(=O) or $S(=O)_2$;

R^1 is H, alkyl, alkoxy, hydroxy, halo, -CN, $-S(O)_m$-alkyl, $-C(O)NR^9R^{10}$, $-(CR^9R^{10})_{1-6}OH$, or $-NR^4(CR^9R^{10})_{1-2}OR^9$;

each R^2 is independently selected from the group consisting of H, halo, alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, $-(CR^{10}R^{11})_{0-6}$-OR^7, $-C(O)R^4$, $-C(S)R^4$, $-C(O)OR^7$, $-C(S)OR^7$, $-OC(O)R^7$, $-OC(S)R^7$, $-C(O)NR^4R^5$, $-C(S)NR^4R^5$, $-C(O)NR^4OR^7$, $-C(S)NR^4OR^7$, $-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, -CN, $-OCF_3$, $-SCF_3$, $-C(=NR^7)NR^4$, $-C(O)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}OR^7$, $-C(S)NR^7(CH_2)_{1-10}NR^4R^5$,



$-C(S)NR^7(CH_2)_{1-10}OR^7$, haloalkyl and alkylsilyl, wherein each of said alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl or heteroaralkyl is independently optionally substituted with 1-5 R^9 moieties;

each R^3 is independently selected from the group consisting of H, halo, alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, $-(CR^{10}R^{11})_{0-6}-OR^7$, $-C(O)R^4$, $-C(S)R^4$, $-C(O)OR^7$, $-C(S)OR^7$, $-OC(O)R^7$, $-OC(S)R^7$, $-C(O)NR^4R^5$, $-C(S)NR^4R^5$, $-C(O)NR^4OR^7$, $-C(S)NR^4OR^7$, $-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, $-CN$, $-OCF_3$, $-SCF_3$, $-C(=NR^7)NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}OR^7$, $-C(S)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(S)NR^7(CH_2)_{1-10}OR^7$, haloalkyl and alkylsilyl, wherein each of said alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl or heteroaralkyl is independently optionally substituted with 1-5 R^9 moieties;

each R^4 and R^5 is independently selected from the group consisting of H, alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, $-OR^7$, $-C(O)R^7$, and $-C(O)OR^7$, wherein each of said alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl is optionally substituted with 1-4 R^8 moieties;

or R^4 and R^5, when attached to the same nitrogen atom, are optionally taken together with the nitrogen atom to which they are attached to form a 3-6 membered heterocyclic ring having 0-2 additional heteroatoms selected from N, O or S;

each R^6 is independently selected from the group consisting of H, alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroaralkyl, $-(CH_2)_{1-6}CF_3$, $-C(O)R^7$, $-C(O)OR^7$ and $-SO_2R^7$;

each R^7 is independently selected from the group consisting of H, alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, and heteroaralkyl, wherein each member of R^7 except H is optionally substituted with 1-4 R^8 moieties;

each R^8 is independently selected from the group consisting of halo, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-NO_2$, $-OR^{10}$, $-(C_1-C_6$ alkyl$)-OR^{10}$, $-CN$, $-$

$NR^{10}R^{11}$, $-C(O)R^{10}$, $-C(O)OR^{10}$, $-C(O)NR^{10}R^{11}$, $-CF_3$, $-OCF_3$, $-CF_2CF_3$, $-C(=NOH)R^{10}$, $-N(R^{10})C(O)R^{11}$, $-C(=NR^{10})NR^{10}R^{11}$, and $-NR^{10}C(O)OR^{11}$, wherein each of said alkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally independently substituted with 1-3 moieties selected from the group consisting of halo, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-NO_2$, $-OR^{10}$, $-(C_1-C_6$ alkyl$)-OR^{10}$, -CN, $-NR^{10}R^{11}$, $-C(O)OR^{10}$, $-C(O)NR^{10}R^{11}$, $-CF^3$, $-OCF_3$, $-NR^{10}C(O)OR^{11}$, and $-NR^{10}C(O)R^{40}$;

or two R^8 groups, when attached to the same carbon atom, are optionally taken together with the carbon atom to which they are attached to form a C=O or a C=S group;

each R^9 is independently selected from the group consisting of H, alkyl, alkoxy, OH, CN, halo, $-(CR^{10}R^{11})_{0-4}NR^4R^5$, haloalkyl, hydroxyalkyl, alkoxyalkyl, $-C(O)NR^4R^5$, $-C(O)OR^7$, $-OC(O)NR^4R^5$, $-NR^4C(O)R^5$, and $-NR^4C(O)NR^4R^5$;

each R^{10} is independently H or alkyl; or R^9 and R^{10}, when attached to the same nitrogen atom, are optionally taken together with the nitrogen atom to which they are attached to form a 3-6 membered heterocyclic ring having 0-2 additional heteroatoms selected from N, O or S;

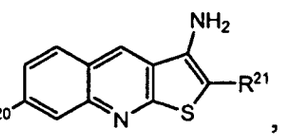
each R^{11} is independently H or alkyl; or R^{10} and R^{11}, when attached to the same nitrogen atom, are optionally taken together with the nitrogen atom to which they are attached to form a 3-6 membered heterocyclic ring having 0-2 additional heteroatoms selected from N, O or S;

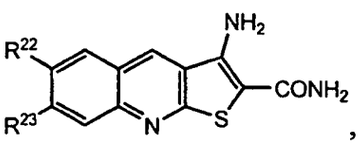
each R^{12} is independently selected from the group consisting of H, halo, alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, $-(CR^{10}R^{11})_{0-6}-OR^7$, $-C(O)R^4$, $-C(S)R^4$, $-C(O)OR^7$, $-C(S)OR^7$, $-OC(O)R^7$, $-OC(S)R^7$, $-C(O)NR^4R^5$, $-C(S)NR^4R^5$, $-C(O)NR^4OR^7$, $-C(S)NR^4OR^7$, $-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, -CN, $-OCF_3$, $-SCF_3$, $-C(=NR^7)NR^4$, $-C(O)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}OR^7$, $-C(S)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(S)NR^7(CH_2)_{1-10}OR^7$, haloalkyl and alkylsilyl, wherein each of said alkyl, cycloalkyl,

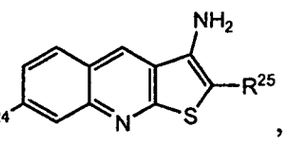
cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl or heteroaralkyl is independently optionally substituted with 1-5 R^9 moieties; and

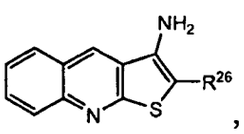
R^{40} is selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl, wherein each of said cycloalkyl, heterocyclyl, aryl and heteroaryl are optionally independently substituted with 1-3 moieties independently selected from the group consisting of -CN, -OH, halo, alkyl, haloalkyl, alkoxy, and $-NR^{10}R^{11}$;

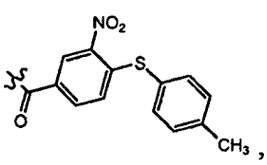
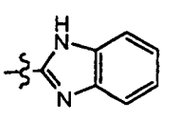
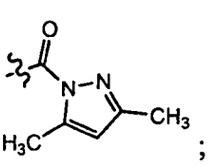
with the proviso that the compound of Formula AI excludes any one of the following:

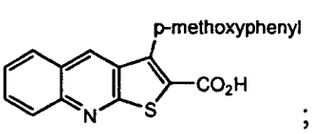
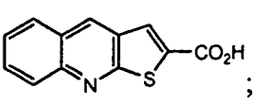
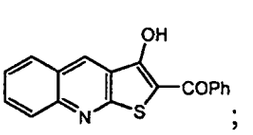
(1)  , wherein R^{20} is H, $-CH_3$ or $-OCH_3$ and R^{21} is $-C(O)CH_3$, -C(O)CH=CH-phenyl or -C(O)CH=CH-(4-methoxyphenyl);

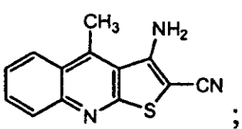
(2)  , wherein R^{22} and R^{23} are independently H or methoxy;

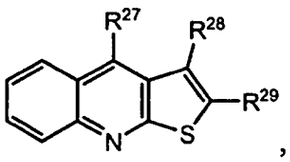
(3)  , wherein R^{24} is methyl, methoxy or –Cl and R^{25} is $-CONH_2$ or $-CO_2Et$;

(4)  , wherein R^{26} is $-CO_2Me$, $-CO_2Et$, $-CO_2H$, -C(O)-phenyl, -C(O)-p-methylphenyl, -C(O)-p-bromophenyl, $-C(O)CH_3$, -CN, -C(O)NH-phenyl, -C(O)NH-p-methoxyphenyl, $-C(O)NHNH_2$, -C(O)NH-p-chlorophenyl,

 ,  or  ;

(5)  ; (6)  ; (7)  ;

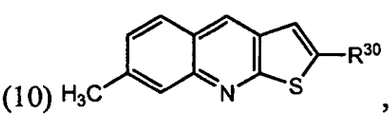
(8)  ;

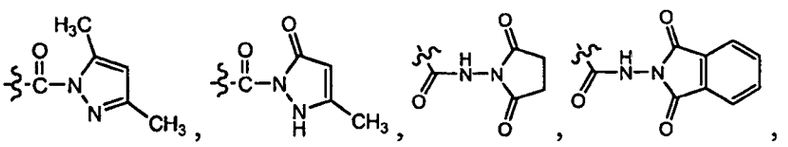
(9)  , wherein:

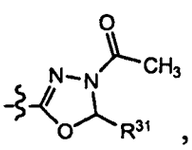
R^{27} is H, -OH, $-OCH_3$ or $-OCH(CH_3)_2$,

R^{28} is –OH, $-OCH_2CN$ or $–OC(O)NH(CH_2)_5CN$, and

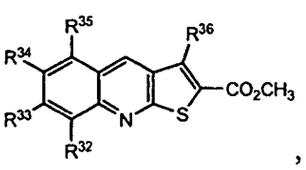
R^{29} is $–C(O)OCH(CH_3)_2$ or –C(O)O-cyclohexyl;

(10)  , wherein:

R^{30} is 

 ,

$-CO_2CH_3$, $–CO_2C_2H_5$, $-C(O)NH_2$, $-C(O)NHNH_2$, or $-C(O)NHCH_3$ and R^{31} is C_6H_5, p-OHC_6H_4 or p-$CH_3C_6H_4$;

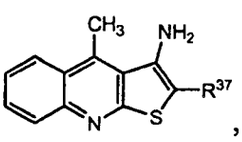
(11)  , wherein:

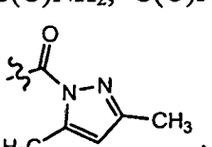
R^{32} is H or NO_2,

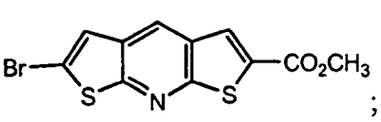
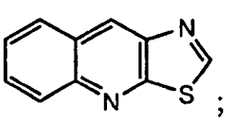
R^{33} and R^{34} are independently H, $-OCH_3$ or $-OC_2H_5$,

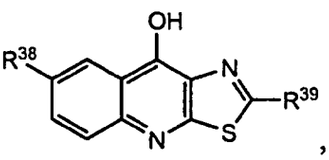
R^{35} is H or $-OCH_3$, and

R^{36} is H, CH_3 or C_6H_5;

(12)  , wherein:

R^{37} is $-CO_2Me$, $-CO_2Et$, $-CO_2H$, $-C(O)NH_2$, $-C(O)NHNH_2$, -CN, -C(O)NH-p-methoxyphenyl, -C(O)NH-(2-pyridyl) or  ;

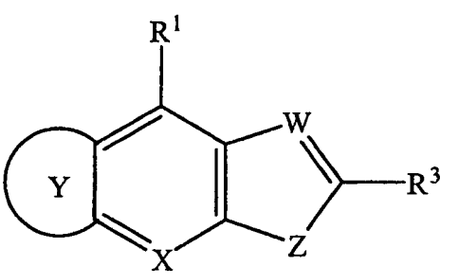
(13)  ; (14)  ; and

(15)  , wherein R^{38} is H, methyl or CF_3 and R^{39} is SMe, SOMe, SO_2Me, Cl, $NH(CH_2)NEt_2$, or N-(N'-methyl)piperazinyl.

Compounds represented in the present application by Formula AI are disclosed in WO 2006/098962, filed March 7, 2006.

In another embodiment, the KSP inhibitor useful in the practice of this invention is represented by Formula BI:

BI. A compound represented by the structural Formula BI:



Formula BI

or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:

ring Y is a 5- to 7-membered ring selected from the group consisting of cycloalkyl, cycloalkenyl, heterocyclyl or heterocyclenyl fused as shown in Formula B, wherein in each of said 5- to 7-membered ring, each substitutable ring carbon is independently substituted with 1-2 R^2 moieties and each substitutable ring heteroatom is independently substituted with R^6;

W is N or $C(R^{12})$;

X is N or N-oxide;

Z is S, S(=O) or $S(=O)_2$;

R^1 is H, alkyl, alkoxy, hydroxy, halo, -CN, $-S(O)_m$-alkyl, $-C(O)NR^9R^{10}$, $-(CR^9R^{10})_{1-6}OH$, or $-NR^4(CR^9R^{10})_{1-2}OR^9$; wherein m is 0 to 2;

each R^2 is independently selected from the group consisting of H, halo, alkyl, cycloalkyl, alkylsilyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, heteroaryl, $-(CR^{10}R^{11})_{0-6}-OR^7$, $-C(O)R^4$, $-C(S)R^4$, $-C(O)OR^7$, $-C(S)OR^7$, $-OC(O)R^7$, $-OC(S)R^7$, $-C(O)NR^4R^5$, $-C(S)NR^4R^5$, $-C(O)NR^4OR^7$, $-C(S)NR^4OR^7$, $-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, -

CN, $-OCF_3$, $-SCF_3$, $-C(=NR^7)NR^4$, $-C(O)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}OR^7$, $-C(S)NR^7(CH_2)_{1-10}NR^4R^5$, and $-C(S)NR^7(CH_2)_{1-10}OR^7$, wherein each of said alkyl, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, and heteroaryl is independently optionally substituted with 1-5 R^9 moieties;

or two R^2 moieties on the same carbon atom are optionally taken together with the carbon atom to which they are attached to form a C=O, a C=S or an ethylenedioxy group;

R^3 is independently selected from the group consisting of H, halo, alkyl, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, heteroaryl, $-(CR^{10}R^{11})_{0-6}-OR^7$, $-C(O)R^4$, $-C(S)R^4$, $-C(O)OR^7$, $-C(S)OR^7$, $-OC(O)R^7$, $-OC(S)R^7$, $-C(O)NR^4R^5$, $-C(S)NR^4R^5$, $-C(O)NR^4OR^7$, $-C(S)NR^4OR^7$, $-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, -CN, $-C(=NR^7)NR^4R^5$, $-C(O)N(R^7)-(CR^{40}R^{41})_{1-5}-C(=NR^7)NR^4R^5$, $-C(O)N(R^7)(CR^{40}R^{41})_{1-5}-NR^4R^5$, $-C(O)N(R^7)(CR^{40}R^{41})_{1-5}-C(O)-NR^4R^5$, $-C(O)N(R^7)(CR^{40}R^{41})_{1-5}-OR^7$, $-C(S)NR^7(CH_2)_{1-5}NR^4R^5$, and $-C(S)NR^7(CH_2)_{1-5}OR^7$, wherein each of said alkyl, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, and heteroaryl is independently optionally substituted with 1-5 R^9 moieties;

each of R^4 and R^5 is independently selected from the group consisting of H, alkyl, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, heteroaryl, $-OR^7$, $-C(O)R^7$, and $-C(O)OR^7$, wherein each of said alkyl, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, and heteroaryl, is optionally substituted with 1-4 R^8 moieties;

or R^4 and R^5, when attached to the same nitrogen atom, are optionally taken together with the nitrogen atom to which they are attached to form a 3-6 membered heterocyclic ring having 0-2 additional heteroatoms selected from N, O or S;

each R^6 is independently selected from the group consisting of H, alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroaralkyl, $-(CH_2)_{1-6}CF_3$, $-C(O)R^7$, $-C(O)OR^7$ and $-SO_2R^7$;

each R^7 is independently selected from the group consisting of H, alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, and heteroaralkyl, wherein each member of R^7 except H is optionally substituted with 1-4 R^8 moieties;

each R^8 is independently selected from the group consisting of halo, alkyl, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, heteroaryl, $-NO_2$, $-OR^{10}$, $-(C_1-C_6$ alkyl$)-OR^{10}$, $-CN$, $-NR^{10}R^{11}$, $-C(O)R^{10}$, $-C(O)OR^{10}$, $-C(O)NR^{10}R^{11}$, $-CF_3$, $-OCF_3$, $-CF_2CF_3$, $-C(=NOH)R^{10}$, $-N(R^{10})C(O)R^{11}$, $-C(=NR^{10})NR^{10}R^{11}$, and $-NR^{10}C(O)OR^{11}$; wherein said each of said alkyl, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, and heteroaryl is independently optionally substituted with 1-4 R^{42} moieties; wherein when each of said cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, and heteroaryl contains two radicals on adjacent carbon atoms anywhere within said cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, and heteroaryl, such radicals may optionally and independently in each occurrence, be taken together with the carbon atoms to which they are attached, to form a five- or six-membered carbocyclic or heterocyclic ring;

or two R^8 groups, when attached to the same carbon, are optionally taken together with the carbon atom to which they are attached to form a C=O or a C=S group;

each R^9 is independently selected from the group consisting of H, alkyl, alkoxy, OH, CN, halo, $-(CR^{10}R^{11})_{0-4}NR^4R^5$, haloalkyl, hydroxyalkyl, alkoxyalkyl, $-C(O)NR^4R^5$, $-C(O)OR^7$, $-OC(O)NR^4R^5$, $-NR^4C(O)R^5$, and $-NR^4C(O)NR^4R^5$;

each R^{10} is independently H or alkyl; or R^9 and R^{10}, when attached to the same nitrogen atom, are optionally taken together with the nitrogen atom to which they are attached to form a 3-6 membered heterocyclic ring having 0-2 additional heteroatoms selected from N, O or S;

each R^{11} is independently H, alkyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heterocyclenyl, or heteroaryl; or R^{10} and R^{11}, when attached to the same nitrogen atom, are optionally taken together with the nitrogen atom to which they are attached to form a 3-6 membered heterocyclic ring having 0-2 additional heteroatoms selected from N, O or S; wherein each of said R^{11} alkyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heterocyclenyl, and heteroaryl is independently optionally substituted with 1-3 moieties selected from the group consisting of $-CN$, $-OH$, $-NH_2$, $-N(H)$alkyl, $-N(alkyl)_2$, halo, haloalkyl, CF_3, alkyl, hydroxyalkyl, alkoxy, aryl, aryloxy, and heteroaryl;

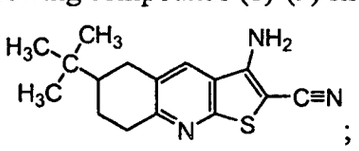
each R^{12} is independently selected from the group consisting of H, halo, alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, $-(CR^{10}R^{11})_{0-6}-OR^7$, $-C(O)R^4$, $-C(S)R^4$, $-C(O)OR^7$, $-C(S)OR^7$, $-OC(O)R^7$, $-OC(S)R^7$, $-C(O)NR^4R^5$, $-C(S)NR^4R^5$, $-C(O)NR^4OR^7$, $-C(S)NR^4OR^7$, $-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, $-CN$, $-OCF_3$, $-SCF_3$, $-C(=NR^7)NR^4$, $-C(O)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}OR^7$, $-C(S)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(S)NR^7(CH_2)_{1-10}OR^7$, haloalkyl and alkylsilyl, wherein each of said alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl or heteroaralkyl is independently optionally substituted with 1-5 R^9 moieties;

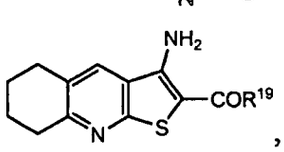
R^{40} and R^{41} can be the same or different, each being independently selected from the group consisting of H, alkyl, aryl, heteroaryl, heterocyclyl, heterocyclenyl, cycloalkyl and cycloalkenyl;

each R^{42} is independently selected from the group consisting of halo, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-NO_2$, $-OR^{10}$, $-(C_1-C_6$ alkyl$)-OR^{10}$, $-CN$, $-NR^{10}R^{11}$, $-C(O)R^{10}$, $-C(O)OR^{10}$, $-C(O)NR^{10}R^{11}$, $-CF_3$, $-OCF_3$, $-N(R^{10})C(O)R^{11}$, and $-NR^{10}C(O)OR^{11}$;

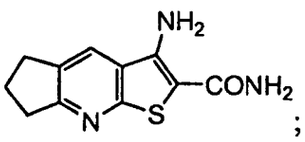
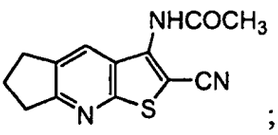
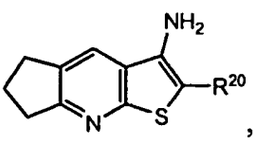
with the proviso that when W is $C(R^{12})$, R^{12} and R^3 are optionally taken together, with the two ring carbon atoms to which they are attached to form a 6-membered ring selected from the group consisting of cycloalkenyl, aryl, heteroaryl, heterocyclyl and heterocyclenyl, wherein said 6-membered ring is optionally substituted with 1-3 moieties independently selected from oxo, thioxo, $-OR^{11}$, $-NR^{10}R^{11}$, $-C(O)R^{11}$, $-C(O)OR^{11}$, $-C(O)N(R^{10})(R^{11})$, or $-N(R^{10})C(O)R^{11}$;

with the further proviso that the compound of Formula (BI) is other than any of the following compounds (1)-(9) shown immediately below:

(1)  ;

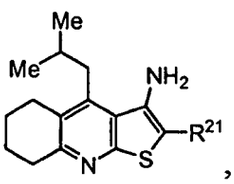
(2)  , wherein:

R^{19} is -NHOH, -OMe, -OEt, -O-n-propyl, or -O-i-propyl;

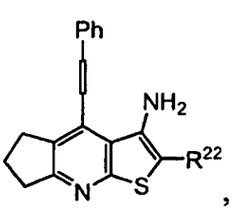
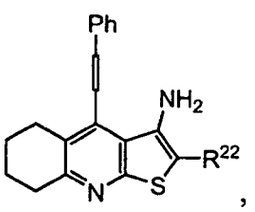
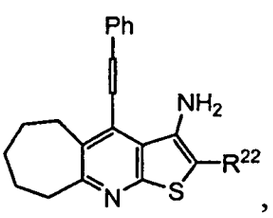
(3)  ; (4)  ; (5)  ,

wherein:

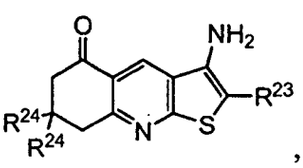
R^{20} is –CN, -C(O)C_6H_5, -$CO_2C_2H_5$, -CO_2H, or –C(O)NH_2;

(6)  , wherein:

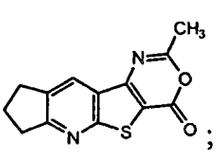
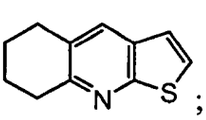
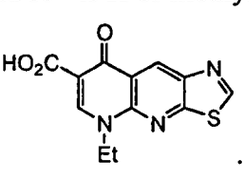
R^{21} is 4-$ClC_6H_4C(O)$- or 4-$PhC_6H_4C(O)$-;

(7)  ,  ,  , wherein:

R^{22} is –CN, -C(O)CH_3 or -$CO_2C_2H_5$;

(8)  , wherein:

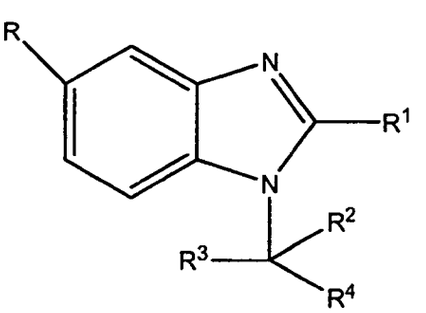
R^{23} is –C(O)NH_2, -C(O)NHPh, or benzoyl and R^{24} is H or methyl;

(9)  ; (10)  ; and (11)  .

Compounds represented in the present application by Formula BI are disclosed in WO2006/098961, filed March 7, 2006.

In another embodiment, the KSP inhibitor useful in the practice of this invention is represented by Formula DI:

D1: A compound of Formula DI





Formula DI

or a pharmaceutically acceptable salt, solvate, or ester thereof, wherein:

R is selected from the group consisting of H, alkyl, cyano, haloalkyl, halo, —SH, -S-alkyl, -S-haloalkyl, $-S(=O)_2$alkyl, $-S(=O)_2OH$, $-S(=O)_2NH_2$, $-S(=O)_2NH$(alkyl), $S(=O)_2NH$(cycloalkyl), $-S(=O)_2N(alkyl)_2$, $-S(=O)_2$heterocyclyl, $-S(=O)_2$heteroaryl, cycloalkyl, aryl, heterocyclyl, heteroaryl, -NHC(=O)alkyl, –$C(=O)NH_2$, –C(=O)NH(alkyl), -C(=O)NH(cycloalkyl), $-C(=O)N(alkyl)_2$, –C(=O)OH, –C(=O)Oalkyl, -C(=O)heterocyclyl, -C(=O)NH(aryl), wherein when each of said cycloalkyl, aryl, heterocyclyl, heteroaryl, and the "heterocyclyl" and "aryl" portions of said R groups has two substituents on adjacent carbon atoms, said substituents, may optionally be taken together with the carbon atoms to which they are attached to form a five- to six-membered cycloalkyl, aryl, heterocyclyl, heterocyclenyl, or heteroaryl ring; wherein each of the aforementioned R alkyl, aryl, cycloalkyl, heterocyclyl, and heteroaryl, and the "alkyl", "cycloalkyl", "heterocyclyl", and "aryl" portions of said R groups, optionally with said five- to six-membered aryl, heterocyclyl, heterocyclenyl, or heteroaryl ring, is optionally substituted with 1-3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, hydroxyl, cyano, halo, haloalkyl, haloalkoxy, -C(O)OH, -C(=O)Oalkyl, and $-C(O)NH_2$;

R^1 is selected from the group consisting of alkyl, heterocyclyl, -C(=O)aryl, -NH_2, -NH(alkyl), -NH(cycloalkyl), -N(alkyl)(cycloalkyl), -NH(heterocyclyl), -N(alkyl)(heterocyclyl), $N(alkyl)_2$, -NH(aryl), -N(alkyl)(aryl), $-N(aryl)_2$, -NH(heteroaryl), -N(alkyl)(heteroaryl), -NHC(=O)-alkyl, -N(alkyl)C(=O)-alkyl, -NHC(=O)Oalkyl, -N(alkyl)C(=O)O-alkyl, wherein each of the aforesaid alkyl, heterocyclyl, and the "alkyl", "cycloalkyl", "aryl", and "heteroaryl" portions of said R^1 groups is optionally substituted with 1-3 substituents independently selected from the group consisting of halo, heterocyclyl, aryl, heteroaryl, haloalkyl, haloalkoxy, aryloxy, cyano, –SH, -S-alkyl, -S-haloalkyl, $-S(=O)_2$alkyl, $-S(=O)_2OH$, $-S(=O)_2NH_2$, $-S(=O)_2NH$(alkyl), $S(=O)_2NH$(cycloalkyl), $-S(=O)_2N(alkyl)_2$, $-S(=O)_2$heterocyclyl, $-S(=O)_2$heteroaryl, hydroxy, alkyl, alkenyl, alkynyl, $-NH_2$, -NH(alkyl), $-N(alkyl)_2$, alkoxy, -NHC(=O)alkyl, -C(=O)H, -C(=O)alkyl, -C(=O)aryl, , -C(=O)heteroaryl, -C(=O)Oalkyl, $-C(=O)NH_2$, -C(O)NHalkyl, $-C(=O)N(alkyl)_2$; wherein when each of said heterocyclyl, aryl and heteroaryl has two substituents on adjacent carbon atoms,

said substituents, may optionally be taken together with the carbon atoms to which they are attached to form a five to six-membered aryl, heterocyclyl, heterocyclenyl, or heteroaryl ring;

R^2 and R^3 independently are H or alkyl, or -C(R^2)(R^3)- is absent;

R^4 is selected from the group consisting of alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl, wherein when each of said cycloalkyl, heterocyclyl, aryl, and heteroaryl has two substituents on adjacent carbon atoms, said substituents, may optionally be taken together with the carbon atoms to which they are attached to form a five to six-membered aryl, heterocyclyl, heterocyclenyl, or heteroaryl ring; wherein each of the aforementioned R^4 alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl, optionally with said five to six-membered aryl, heterocyclyl, heterocyclenyl, or heteroaryl ring is optionally substituted with 1-3 substituents independently selected from the group consisting of cyano, halo, haloalkyl, alkyl, alkoxy, hydroxyl, haloalkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, -S(=O)$_2$alkyl, -S(=O)$_2$NH$_2$, -S(=O)$_2$NH(alkyl), -S(=O)$_2$N(alkyl)$_2$, -S-alkyl, -S-haloalkyl, -C(=O)OH, -NH$_2$, -NH(alkyl), -N(alkyl)$_2$, and -C(=O)Oalkyl;

with the proviso that:

(1) when R is –C(=O)Oalkyl, R^1 is NH(aryl) wherein said aryl is optionally substituted, R^2 and R^3 are both H, and R^4 is phenyl, then said R^4 phenyl is substituted with at least one haloalkyl group;

(2) when R is –C(=O)Oalkyl, R^1 is NH(aryl) or NH(alkyl), wherein the "alkyl" and "aryl" portions of said R^1 are independently optionally substituted, R^2 and R^3 are both H, and R^4 is optionally substituted heteroaryl, then said R^4 heteroaryl is other than thiophenyl and furanyl;

(3) when R is –C(=O)Oalkyl wherein said alkyl is optionally substituted, and R^1 is NH(aryl) wherein said aryl is unsubstituted or substituted with at least one substituent selected from the group consisting of halo, nitro, and alkyl, then R^4 is other than unsubstituted cycloalkyl;

(4) when R is –C(=O)Oalkyl wherein said alkyl is optionally substituted, R^1 is –NH$_2$, and -CR^2R^3 is absent, then R^4 is other than optionally substituted cycloalkyl;

(5) when R is –C(=O)NH$_2$, then R^1 is –NH(alkyl) or –N(alkyl)(aryl), wherein each of said alkyl and aryl are independently optionally substituted;

(6) when R is –COOH or –C(=O)Oalkyl, wherein said alkyl is optionally substituted, R^1 is –NH(alkyl), or –$N(alkyl)_2$ wherein the "alkyl" portion of each of said R^1 is optionally substituted, and -CR^2R^3 is absent, then R^4 is other than unsubstituted cycloalkyl;

(7) when R is –C(=O)Oalkyl wherein said alkyl is optionally substituted, R^1 is –NH_2, NH(alkyl), or NH(aryl), wherein the "alkyl" and "aryl" portion each of said R^1 is optionally independently substituted, then R^4 is other than unsubstituted alkyl or alkyl substituted with at least one moiety selected from the group consisting of alkoxy, -$N(alkyl)_2$, heterocyclyl, and heteroaryl;

(8) when R is –C(=O)Oalkyl wherein said alkyl is optionally substituted , R^1 is –NH_2, and -$C(R^2)(R^3)$- is absent, then R^4 is other than optionally substituted cycloalkyl, cycloalkenyl, heterocyclenyl, or heteroaryl;

(9) when R is –C(=O)Oalkyl, wherein said alkyl is optionally substituted, R^1 is –NH(heterocyclyl) wherein said heterocyclyl is optionally substituted, R^2 and R^3 are both H, then R^4 is other than optionally substituted heteroaryl;

(10) when R is –C(=O)Oalkyl, wherein said alkyl is optionally substituted, R^2 and R^3 are both H, and R^4 is optionally substituted aryl or heteroaryl, then R^1 is other than –NH_2 or –NH(alkyl) wherein said alkyl is optionally substituted;

(11) when R is –C(=O)OH, -$C(R^2)(R^3)$- is absent, and R^4 is optionally substituted cycloalkyl, then R^1 is other than –NHC(=O)alkyl, -NH(aryl), or –N(alkyl)(aryl) wherein the "alkyl" and "aryl" portions of said R^1 are optionally independently substituted;

(12) when R is –C(=O)OH, R^1 is –NH_2, and R^2 and R^3 are both H, then R^4 is other than optionally substituted aryl;

(13) when R is –C(=O)Oalkyl wherein said alkyl is optionally substituted, R^1 is optionally substituted heterocyclyl or heteroaryl, R^2 and R^3 are both H, and R^4 is aryl, then said R^4 aryl is substituted with at least one haloalkyl group;

(14) when R is –C(=O)OH, R^1 is optionally substituted heterocyclyl, R^2 and R^3 are both H, and R^4 is aryl, then said R^4 aryl is substituted with at least one haloalkyl group; or

(15) when R is H or halo, and R^4 is aryl, then said R^4 aryl is substituted with at least one haloalkyl group,

(16) when R is H, R^2 and R^3 are both H, R^1 is –NH(aryl), and R^4 is aryl substituted with at least one haloalkyl group, then said "aryl" of R^1 is substituted with group(s) other than halo or haloalkyl;

(17) when R is –C(=O)NH(aryl) or –C(=O)N(alkyl)(aryl), then R^1 is other than optionally substituted heterocyclyl; or

(18) when R is H, R^1 is other than $–NH_2$ or –NH(heterocyclyl.

Compounds represented in the present application by Formula DI are disclosed in PCT U.S. 2008/007295, filed June 11, 2008.

In another embodiment, the present invention discloses a method of treating or ameliorating cancer comprising administering sequentially to a mammal in need of such treatment an amount of at least one first compound, wherein said first compound is an anti-mitotic agent selected from the group consisting of Taxanes, paclitaxel, docetaxel, Cenp-E Inhibitor (such as for example GSK-923295), Abraxane, Epothilone, Monastrol, and KSP inhibitors such as Ispinesib SB-715992 (Cytokinetics), and compounds of Formulas A-D as described above; followed by administering at least one second compound, wherein said second compound is an aurora kinase inhibitor selected from the group consisting of compounds represented by Formulas E-K as described above.

In another embodiment, the present invention discloses a method of inducing endoreduplication in cancer cells comprising pretreatment of cancer cells with at least one anti-mitotic agent, wherein said anti-mitotic agent is selected from the group consisting of Taxanes, paclitaxel, docetaxel, Cenp-E Inhibitor (such as for example GSK-923295), Abraxane, Epothilone, Monastrol, and KSP inhibitors such as Ispinesib SB-715992 (Cytokinetics) and compounds represented by Formulas A-D as described above; with subsequent exposure to aurora kinase inhibitor for about 1-12 hours, for example about 4 hours, wherein said aurora kinase inhibitor is selected from the group of compounds represented by Formulas E-K as described above.

In another embodiment, the present invention results in endoreduplication of the cancer cells, which results in death of the cancer cells, which include (but is not limited to) the following:

tumor of the bladder, breast (including BRCA-mutated breast cancer), colorectal, colon, kidney, liver, lung (including small cell lung cancer and non-small cell lung cancer), head and

neck, esophagus, bladder, gall bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, and skin, including squamous cell carcinoma;

leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T- cell lymphoma, Hodgkins lymphoma, non-Hodgkins lymphoma, hairy cell lymphoma, mantle cell lymphoma, myeloma and Burkett's lymphoma;

chronic lymphocytic leukemia ("CLL"),

acute and chronic myelogenous leukemia, myelodysplastic syndrome and promyelocytic leukemia;

fibrosarcoma, rhabdomyosarcoma;

mantle cell lymphoma, myeloma;

astrocytoma, neuroblastoma, glioblastoma, malignant glial tumors, hepatocellular carcinoma, gastrointestinal stromal tumors ("GIST") and schwannomas;

melanoma, multiple myeloma, seminoma, teratocarcinoma, osteosarcoma, xenoderoma pigmentosum, keratoctanthoma, thyroid follicular cancer and Kaposi's sarcoma.

Furthermore, the present invention results in endoreduplication of the cancer cells, which include more preferably, colon cancer cells, breast cancer cells, lung cancer cells, prostrate cancer cells and ovarian cancer cells.

In another embodiment, administration of the combination treatment of at least one anti-mitotic agent followed by at least one of the aurora kinase inhibitors of the present invention can be useful in the chemoprevention of cancer. Chemoprevention is defined as inhibiting the development of invasive cancer by either blocking the initiating mutagenic event or by blocking the progression of pre-malignant cells that have already suffered an insult or inhibiting tumor relapse.

The combination treatment of the present invention may also be useful in inhibiting tumor angiogenesis and metastasis.

In another embodiment, cancer cells are pretreated with at least one anti-mitotic agent preferably for about 1 to 72 hours.

In another embodiment, cancer cells are pretreated with at least one anti-mitotic agent preferably for about 12 to 72 hours.

In another embodiment, cancer cells are pretreated with at least one anti-mitotic agent more preferably, for about 12 to 24 hours.

In another embodiment, cancer cells are pretreated with at least one anti-mitotic agent most preferably for about 16 hours.

In another embodiment, cancer cells are pretreated with at least one anti-mitotic agent most preferably for about 4 hours.

In another embodiment, cancer cells are pretreated with at least one anti-mitotic agent most preferably for about 2 hours.

In another embodiment, cancer cells are pretreated with at least one anti-mitotic agent most preferably for about 1 hour.

In another embodiment, cancer cells are exposed to said aurora kinase inhibitor for about 1 -72 hours after the antimotic agent has been administered.

In another embodiment, cancer cells are exposed to said aurora kinase inhibitor for about 2 -24 hours after the antimotic agent has been administered.

In another embodiment, cancer cells are exposed to said aurora kinase inhibitor preferably for about 1 -12 hours after the antimotic agent has been administered.

In another embodiment, cancer cells are exposed to said aurora kinase inhibitor more preferably, for about 1 -6 hours after the antimotic agent has been administered.

In another embodiment, cancer cells are exposed to said aurora kinase inhibitor more preferably, for about 1 -4 hours after the antimotic agent has been administered.

In another embodiment, cancer cells are exposed to said aurora kinase inhibitor more preferably, for about 2-4 hours after the antimotic agent has been administered.

In another embodiment, cancer cells are exposed to said aurora kinase inhibitor most preferably for about 2 hours after the antimotic agent has been administered.

In another embodiment, cancer cells are exposed to said aurora kinase inhibitor most preferably for about 4 hours after the antimotic agent has been administered.

In another embodiment, cancer cells are exposed to said aurora kinase inhibitor for about 1-4 hours after the antimotic agent has been administered to said cancer cells for about 1-16 hours.

In another embodiment, cancer cells are exposed to said aurora kinase inhibitor for about 1-4 hours after the antimotic agent has been administered to said cancer cells for about 2-16 hours.

In another embodiment, cancer cells are exposed to said aurora kinase inhibitor for about 1-4 hours after the antimotic agent has been administered to said cancer cells for about 2 hours.

In another embodiment, cancer cells are exposed to said aurora kinase inhibitor for about 1-4 hours after the antimotic agent has been administered to said cancer cells for about 4 hours.

In another embodiment, cancer cells are exposed to said aurora kinase inhibitor for about 1 hour after the antimotic agent has been administered to said cancer cells for about 1 hours.

In another embodiment, cancer cells are exposed to said aurora kinase inhibitor for about 2 hours after the antimotic agent has been administered to said cancer cells for about 2 hours.

In another embodiment, cancer cells are exposed to said aurora kinase inhibitor for about 4 hours after the antimotic agent has been administered to said cancer cells for about 4 hours.

In another embodiment, the anti-mitotic agents used in the present invention include Taxanes, paclitaxel, docetaxel, Cenp-E Inhibitor (such as for example GSK-923295), Abraxane, Epothilone, Monastrol, and KSP inhibitors such as Ispinesib SB-715992 (Cytokinetics), and compounds of Formulas A-D as described above.

In yet another embodiment, a method of retarding the growth of a tumor in vivo comprising the steps of (a) first administering to tumor in vivo at least one anti-mitotic agent selected from the group consisting of Taxanes, paclitaxel, docetaxel, Cenp-E Inhibitor (such as for example GSK-923295), Abraxane, Epothilone, Monastrol, and KSP inhibitors such as Ispinesib SB-715992 (Cytokinetics), and compounds represented by Formulas A-D as described above

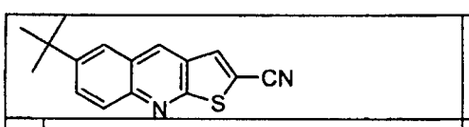
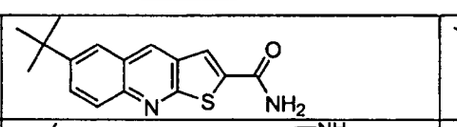
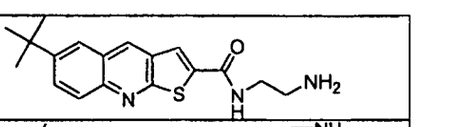
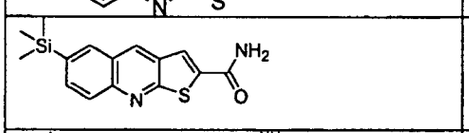
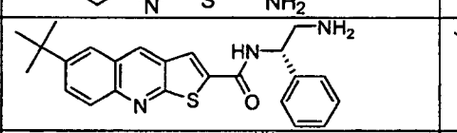
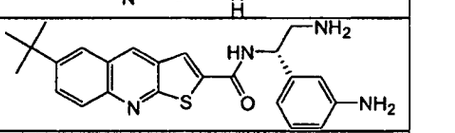
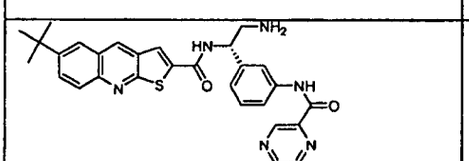
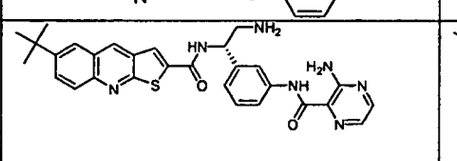
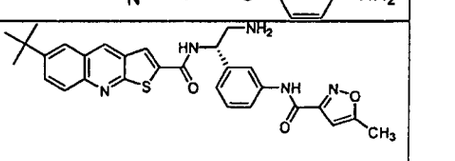
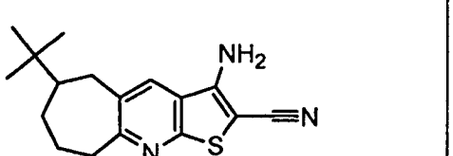
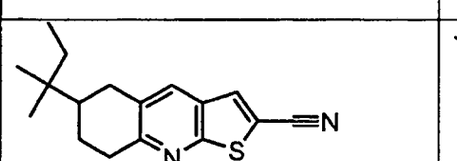
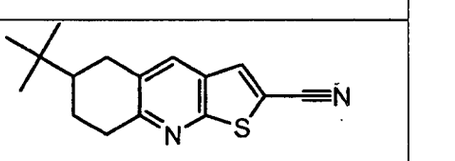
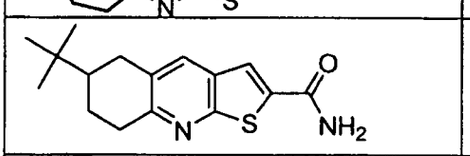
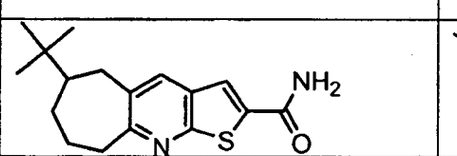
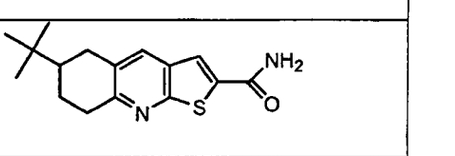
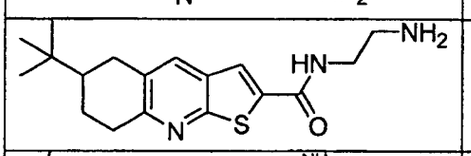
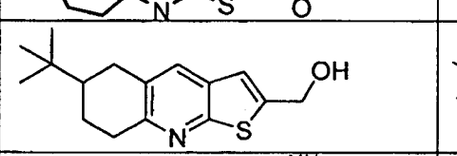
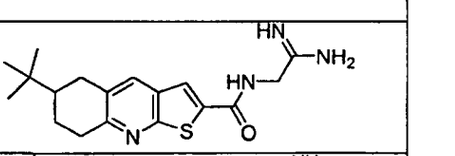
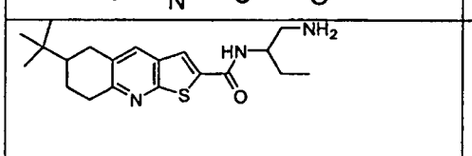
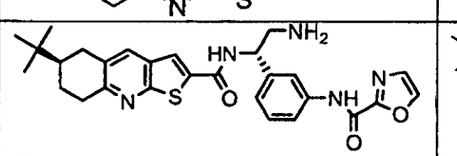
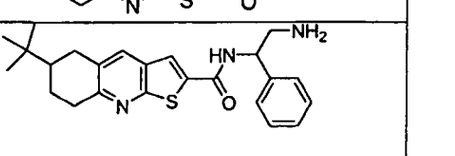
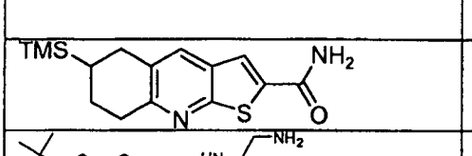
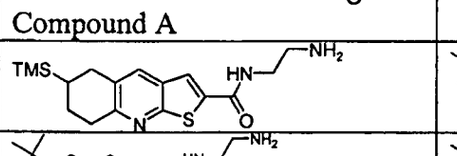
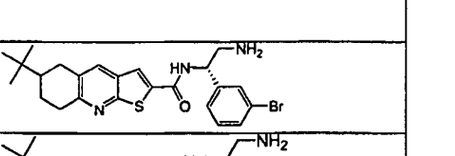
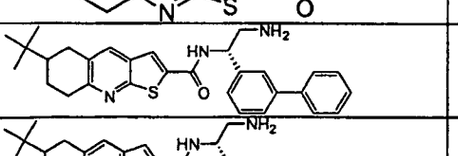
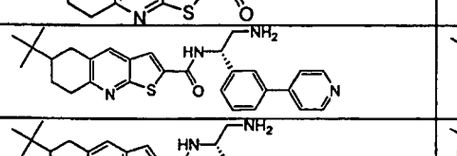
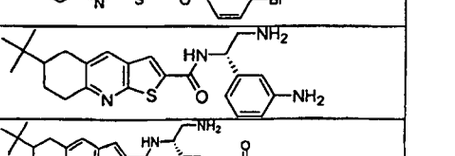
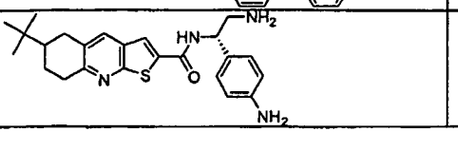
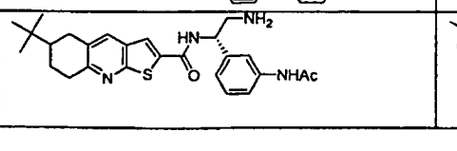
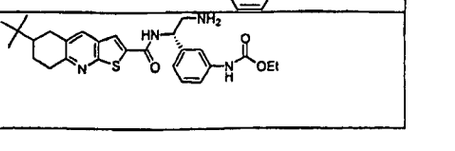
and (b) subsequently administering to said tumor at least one aurora kinase inhibitor, wherein said aurora kinase inhibitor is selected from the group consisting of a compound represented by Formulas E-K as described above.

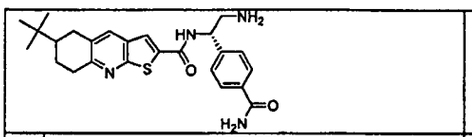
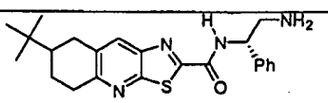
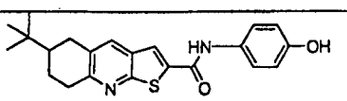
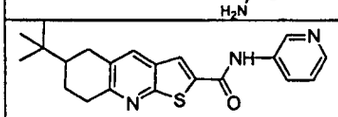
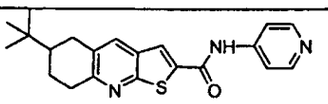
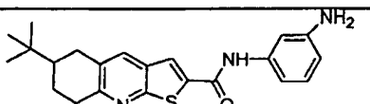
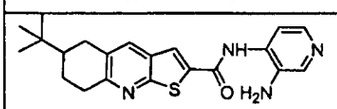
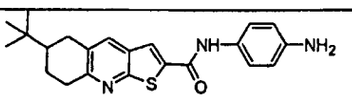
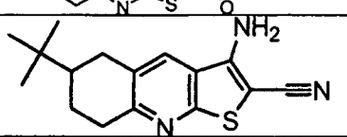
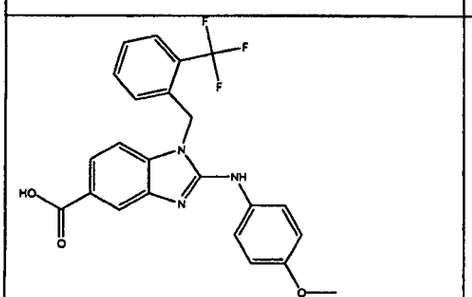
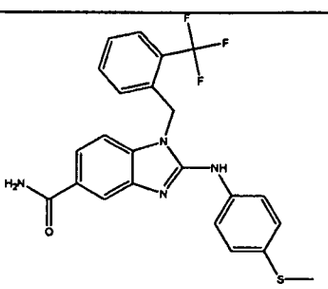
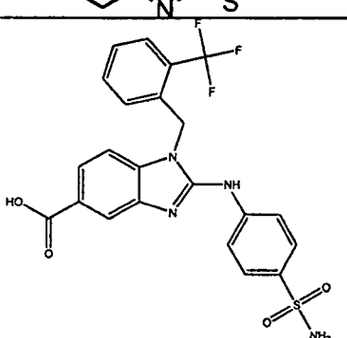
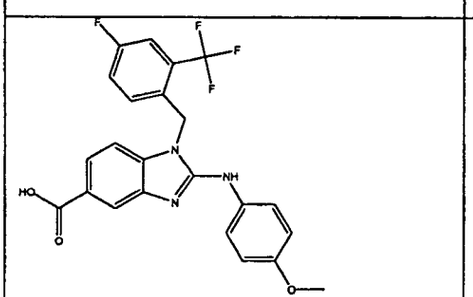
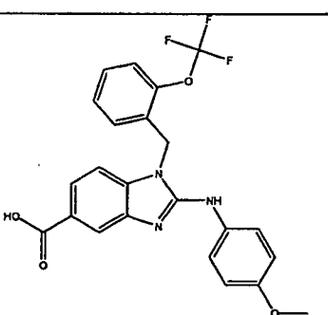
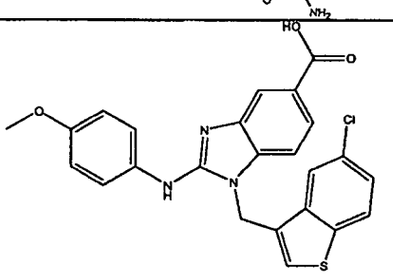
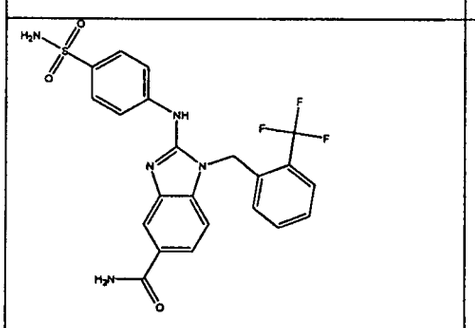
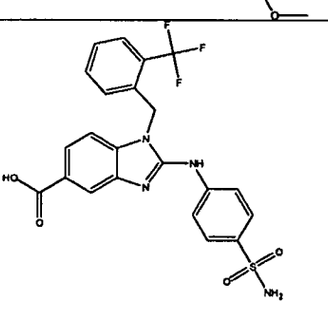
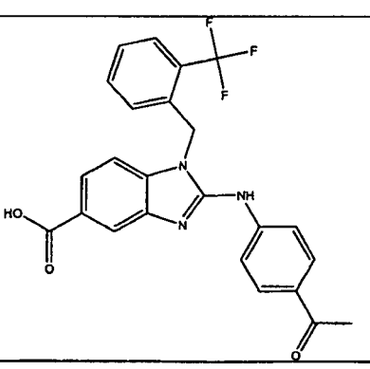
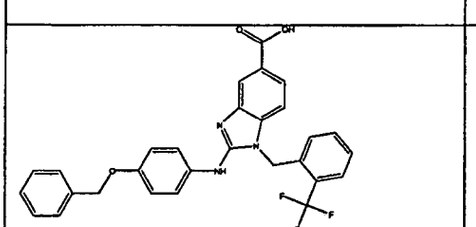
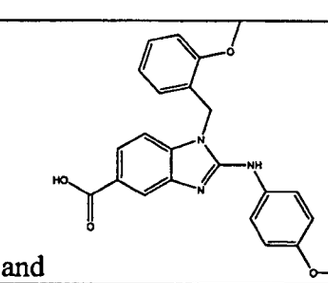
In another embodiment, the present invention provides a method of inducing polyploidy in cancer cells comprising the steps of (a) first administering to cancer cells vivo at least one anti-mitotic agent selected from the group consisting of Taxanes, paclitaxel, docetaxel, Cenp-E Inhibitor (such as for example GSK-923295), Abraxane, Epothilone,

Monastrol, and KSP inhibitors such as Ispinesib SB-715992 (Cytokinetics), and compounds represented by Formulas A-D as described above and (b) subsequently administering to said cancer cells at least one aurora kinase inhibitor, wherein said aurora kinase inhibitor is selected from the group consisting of a compound represented by Formulas E-K as described above.

Another embodiment of the present invention provides a pharmaceutical composition and method of treatment wherein the compounds covered by Formulas A-D are selected from the group consisting of compounds listed in Table 1 shown immediately below:

Table 1

		
		
		
		
		
		
	 Compound A	
		
		
		

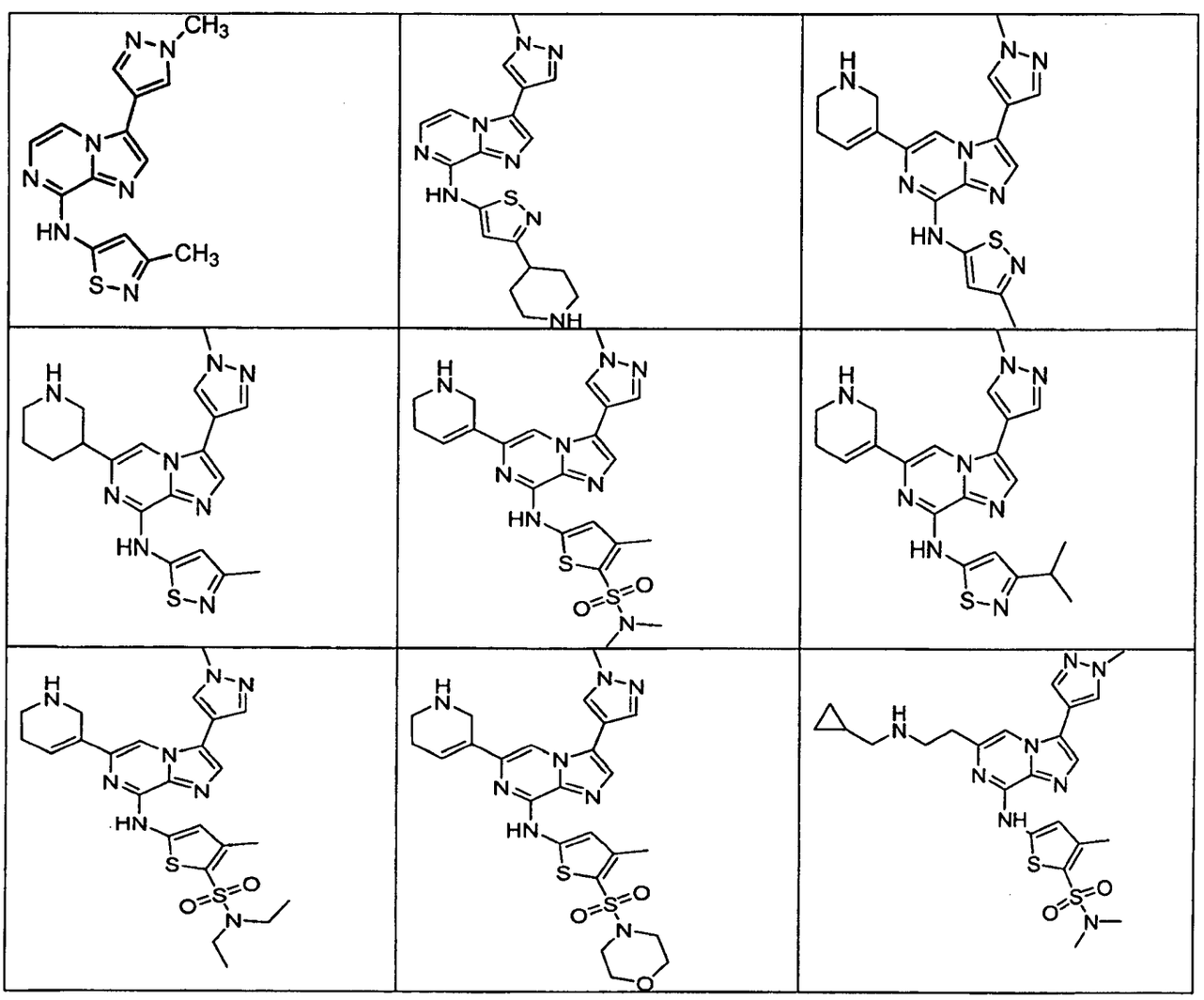
		
		
		
		
		
		
	 and	

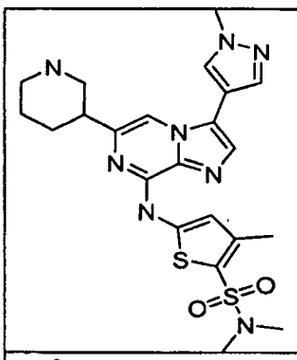
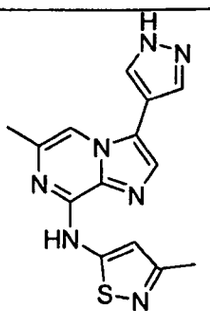
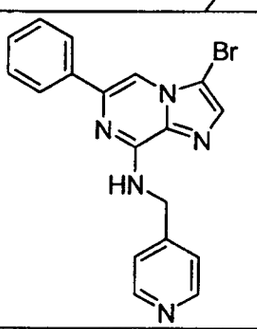
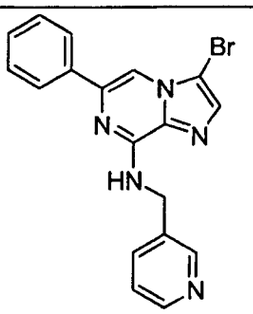
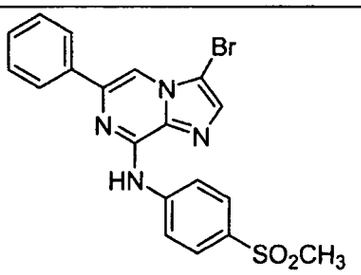
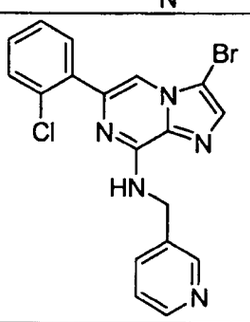
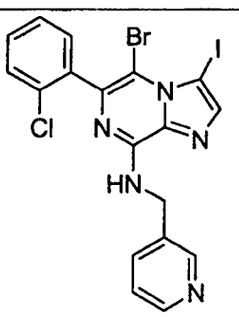
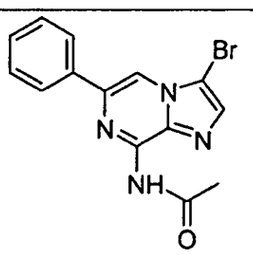
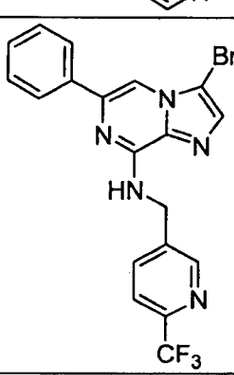
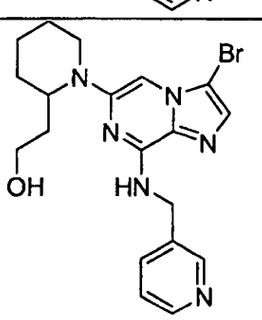
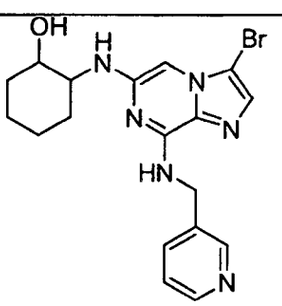
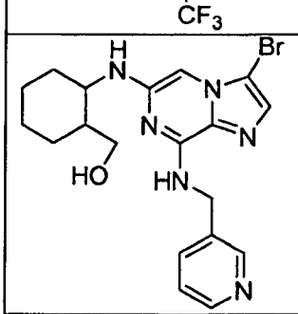
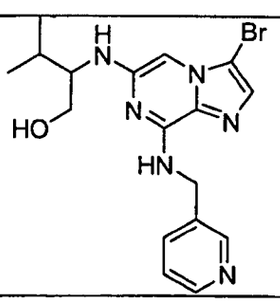


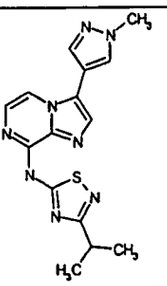
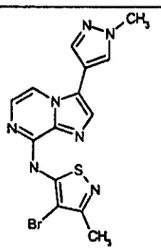
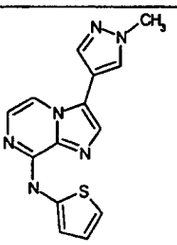
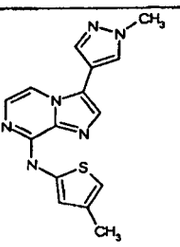
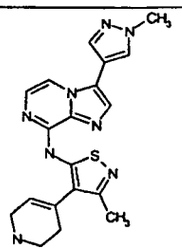
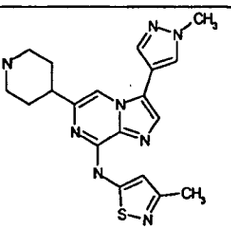
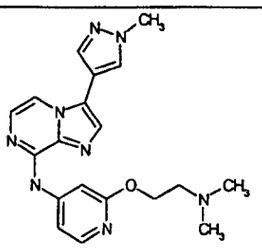
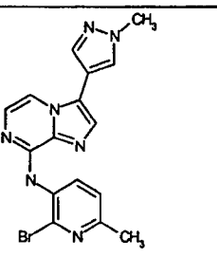
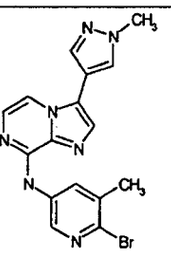
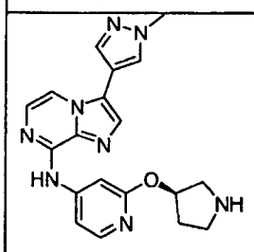
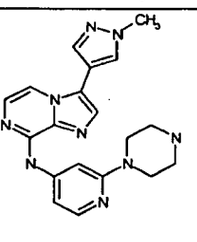
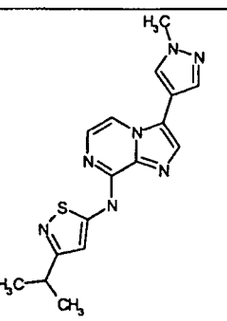
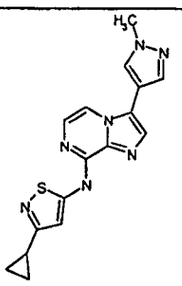
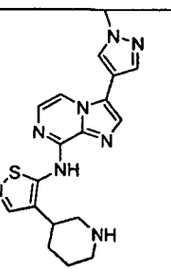
or a pharmaceutically acceptable salt or solvate thereof. The compounds of Table 1 above are disclosed in the following references: WO 2006/098962, filed March 7, 2006, WO2006/098961, filed March 7, 2006, U.S. Pub. No. 2006/0258699, filed March 7, 2006, and U.S. Appln. No. 60/939963, filed May 24, 2007.

In yet another embodiment, the present invention provides a pharmaceutical composition and method of treatment as described earlier wherein the compounds covered by Formulas E-K are selected by the group of compounds listed in **Table 2** shown immediately below:

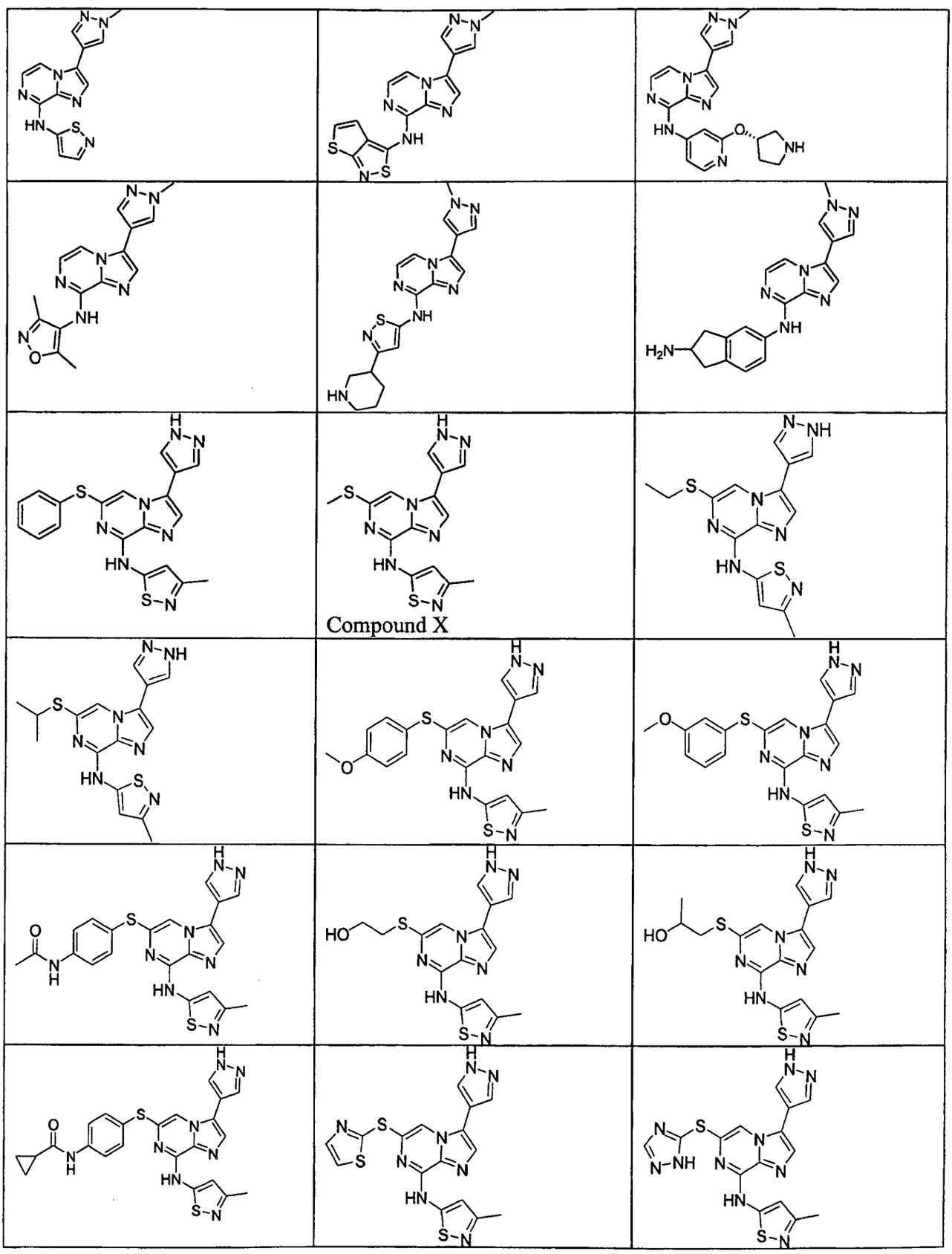
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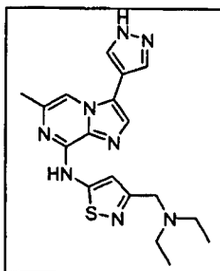
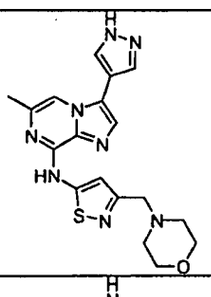
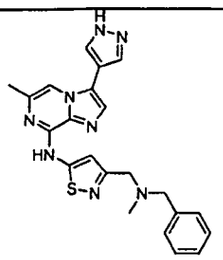
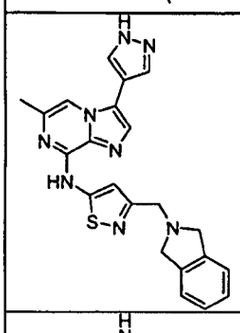
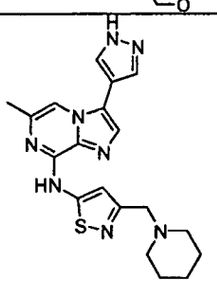
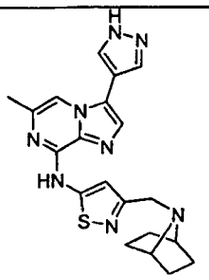
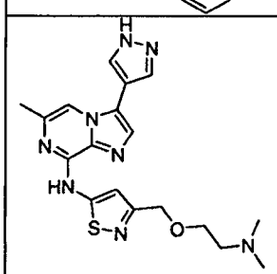
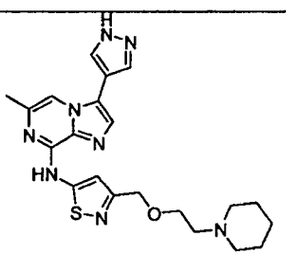
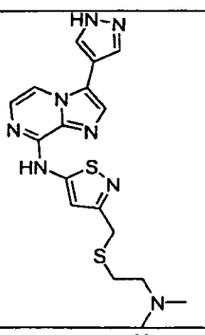
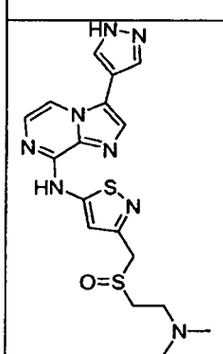
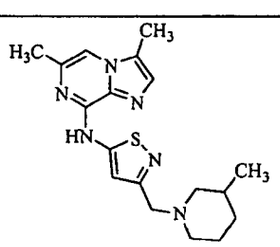
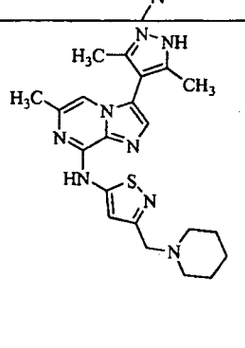
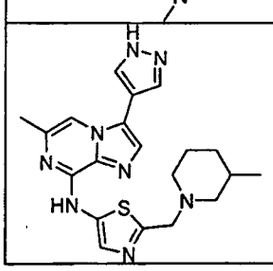
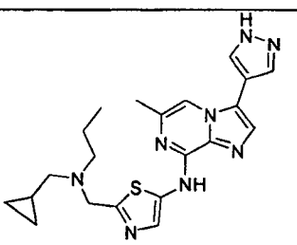
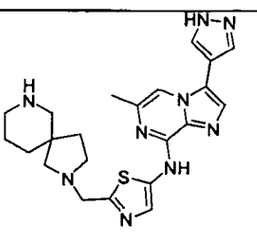


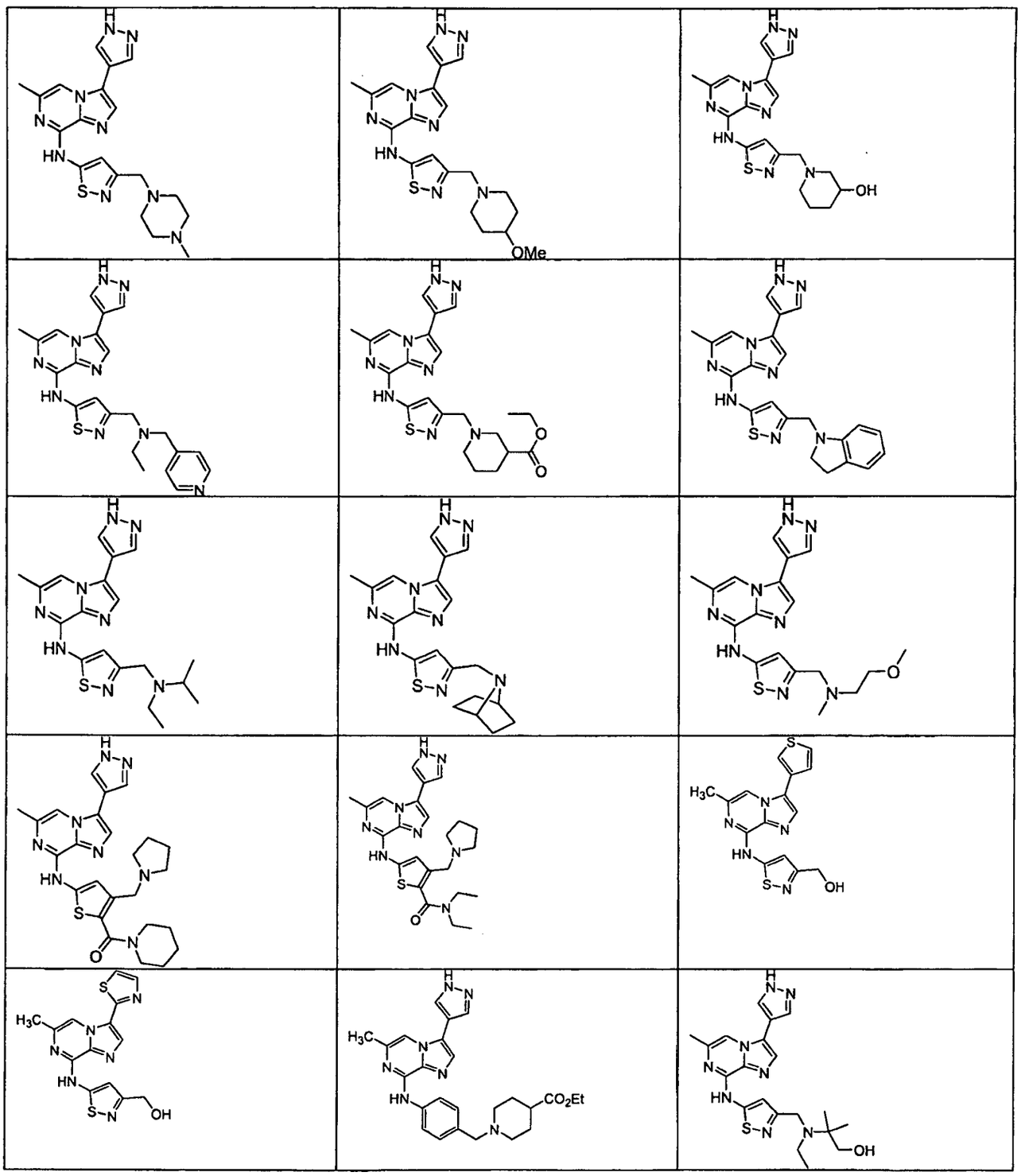
		
		
		
		
		

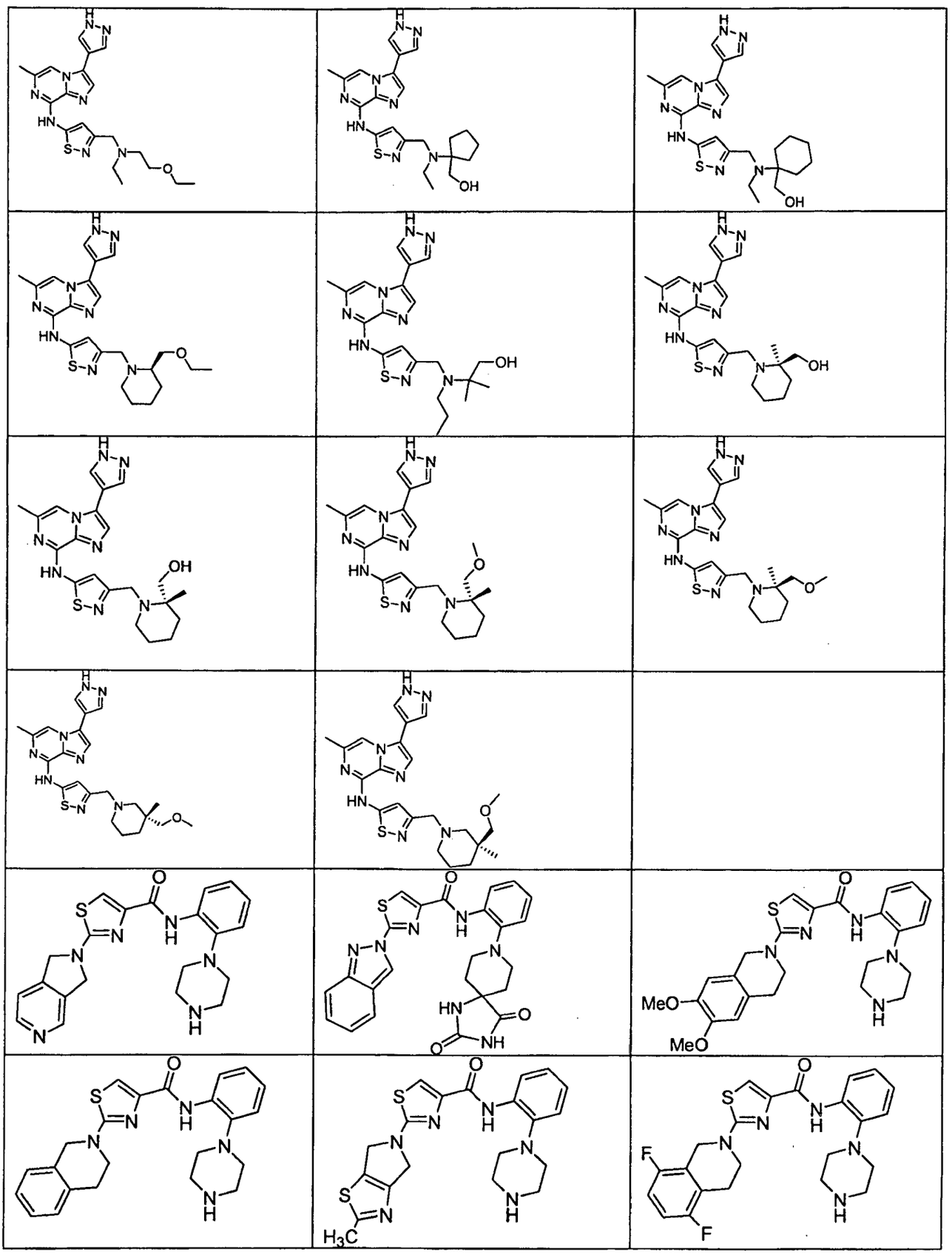
		
		
		
		
		
		

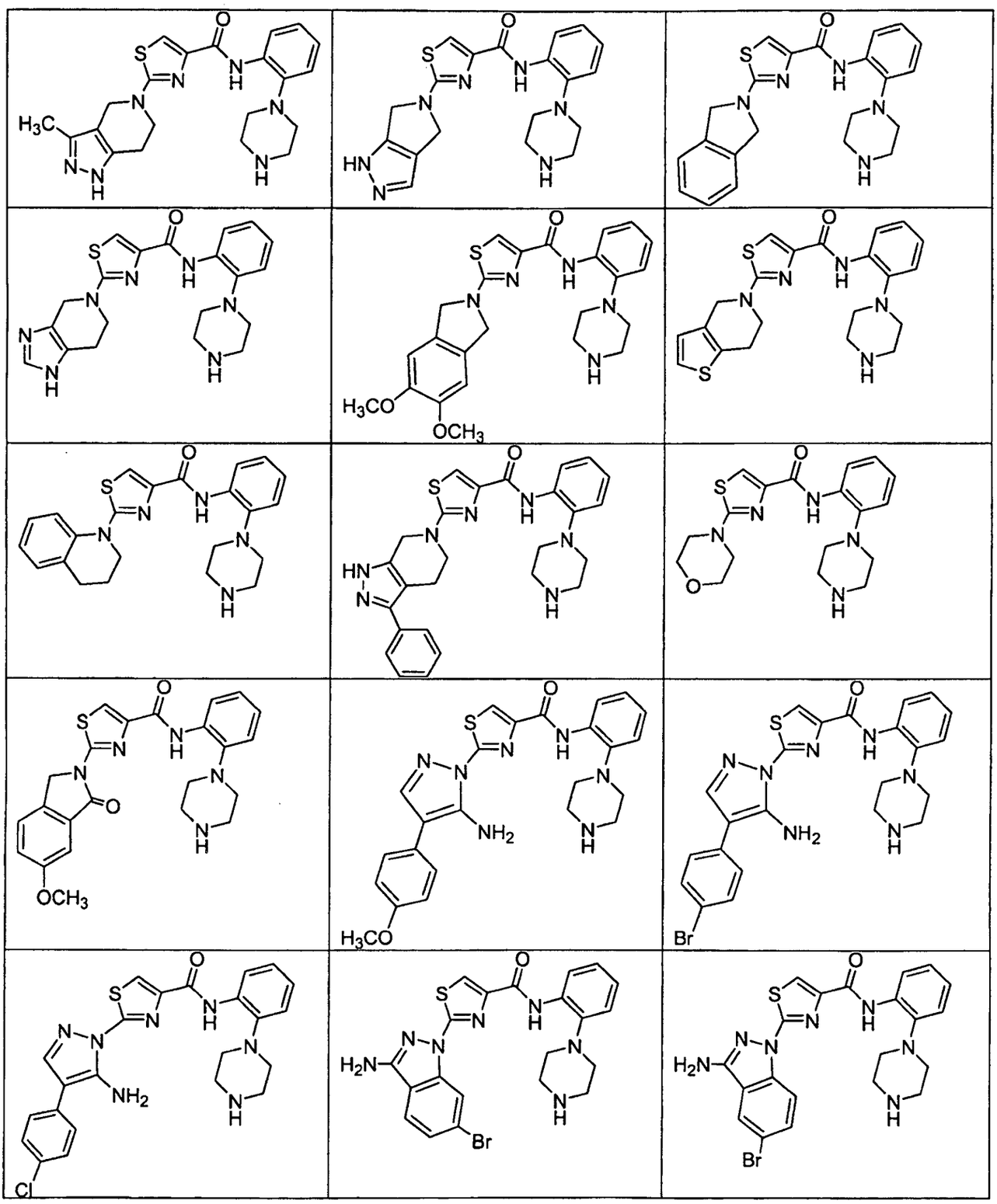


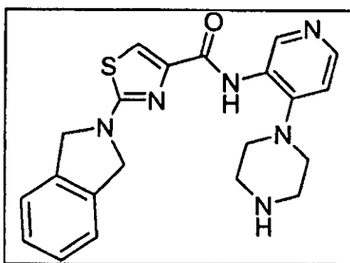
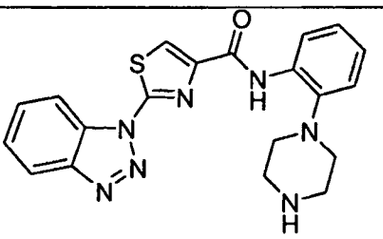
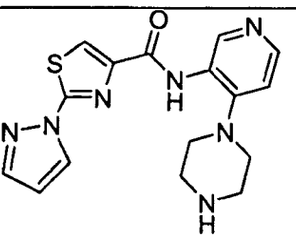
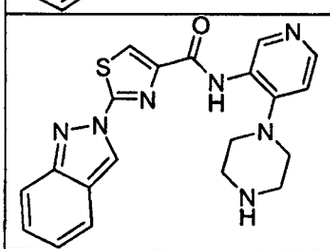
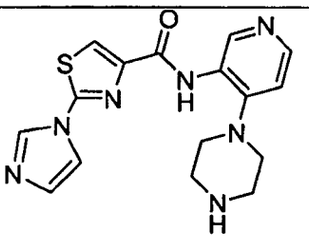
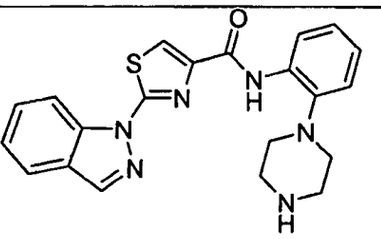
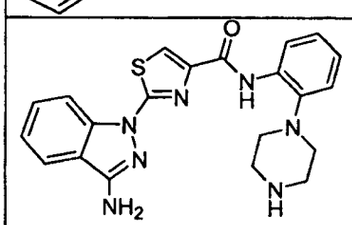
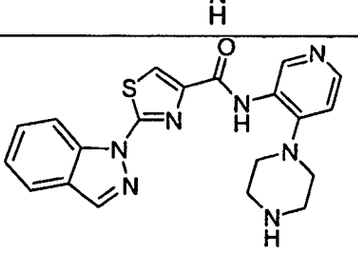
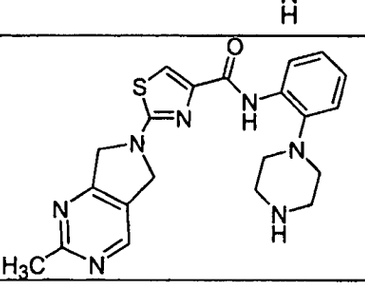
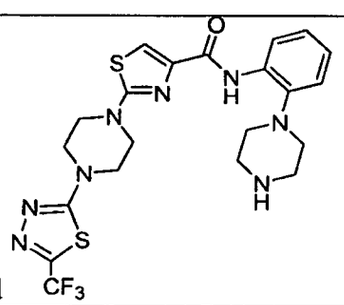

Compound X

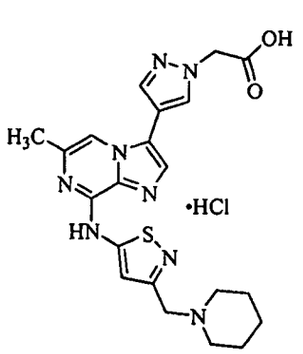
		
		
		
		
		

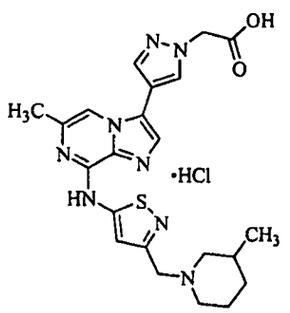


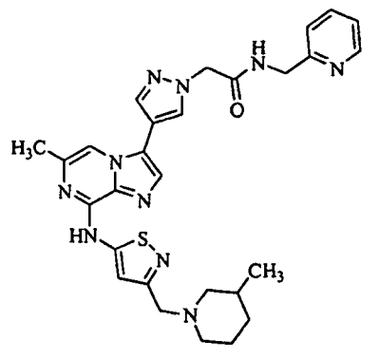


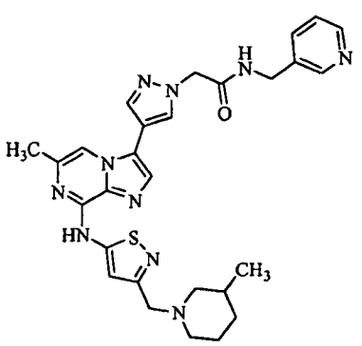


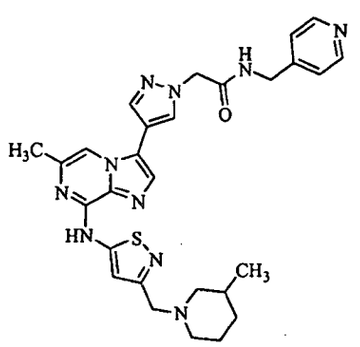
		
		
		
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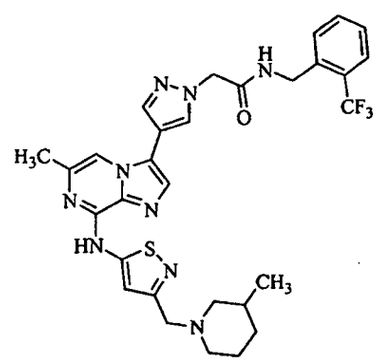


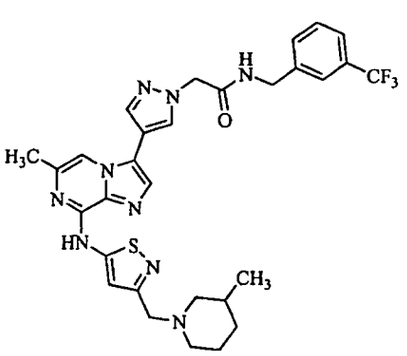


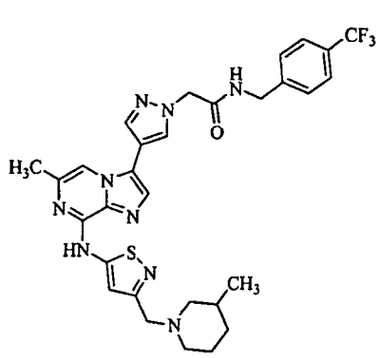


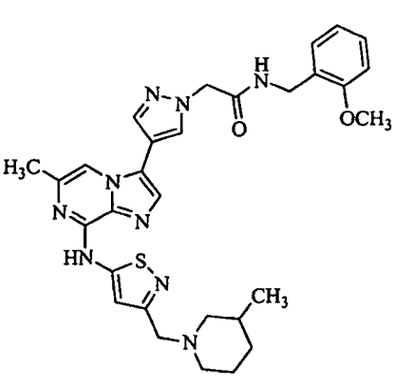


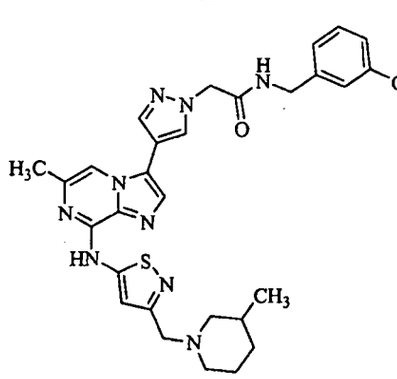


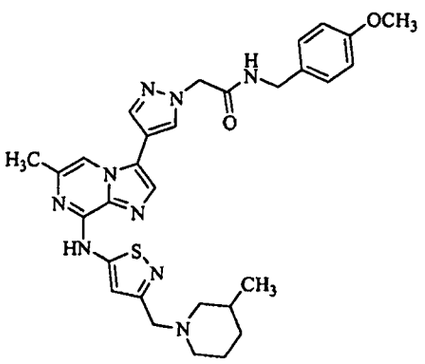


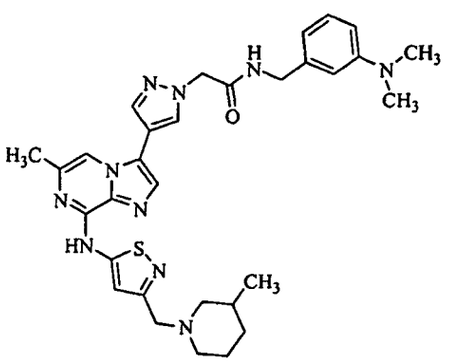


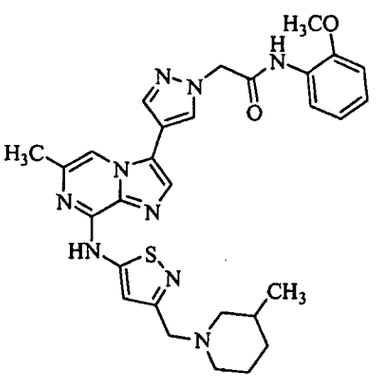


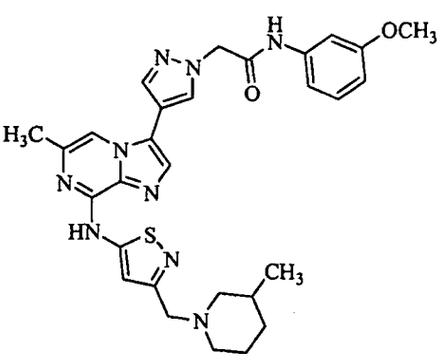


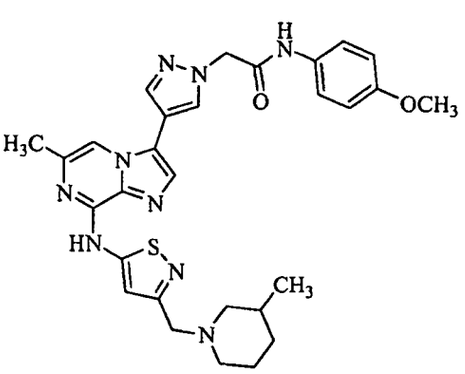


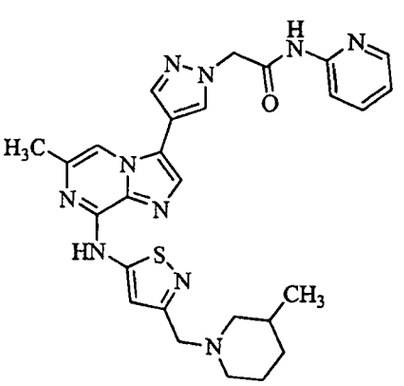


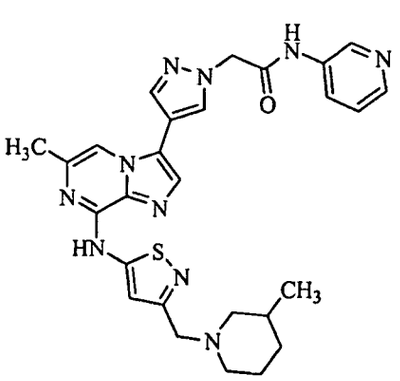


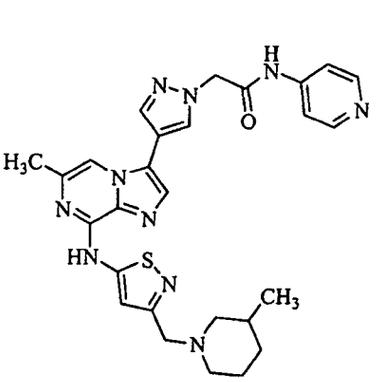


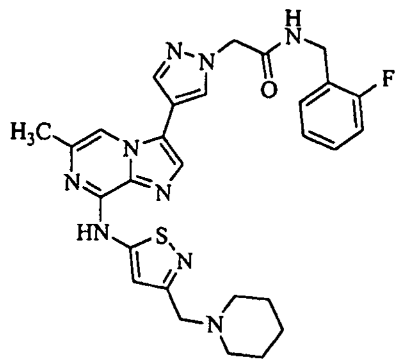


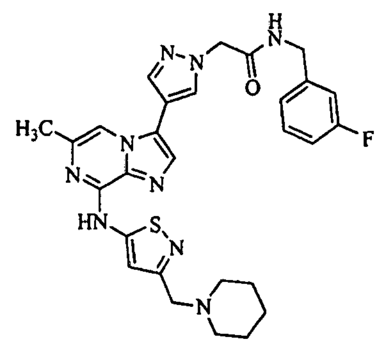


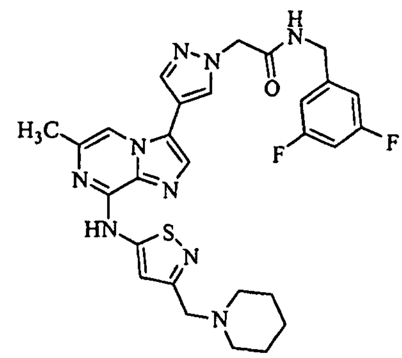


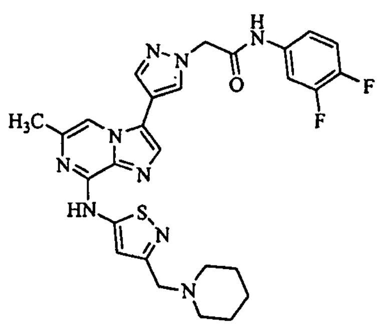


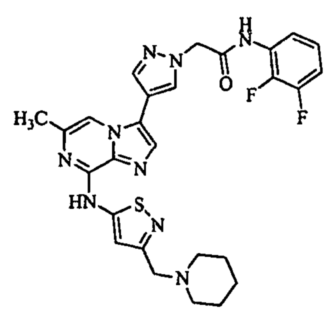


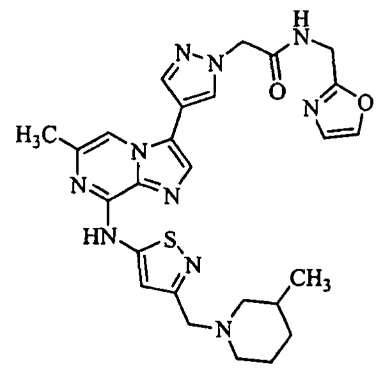


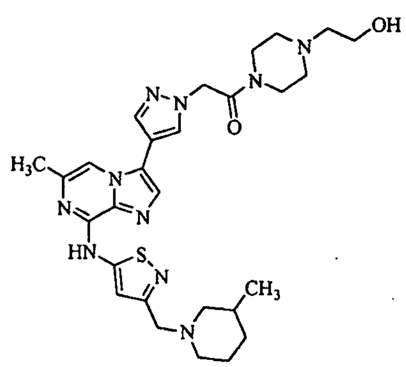


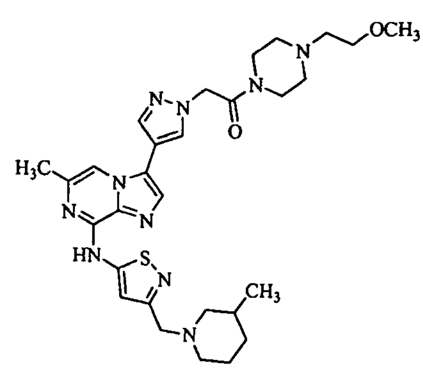


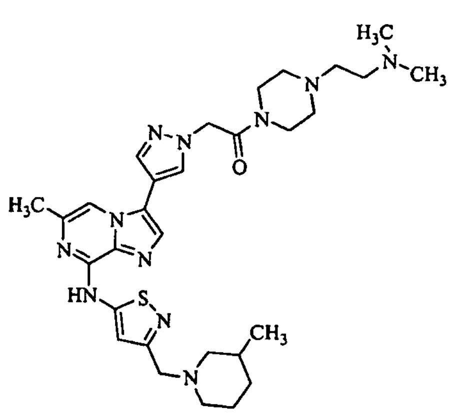


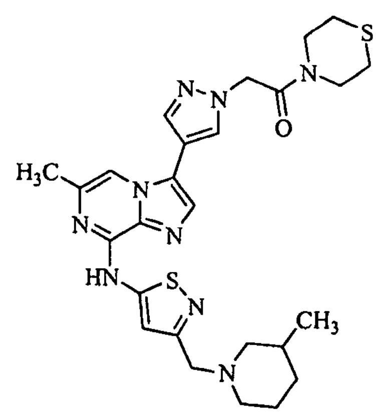


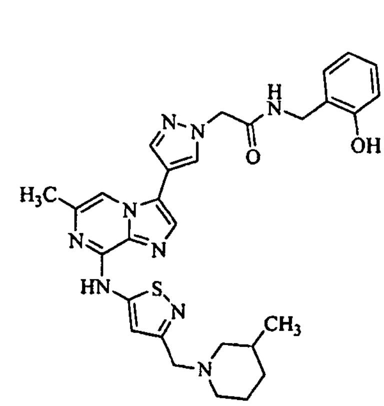


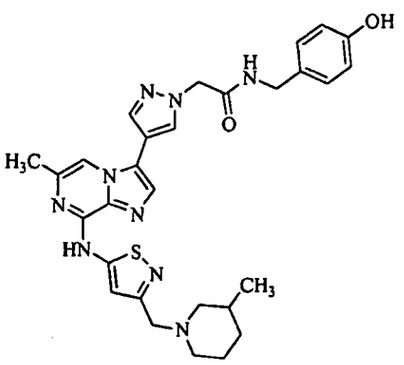


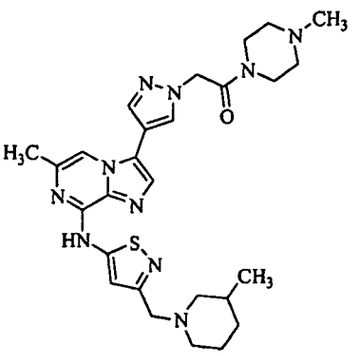


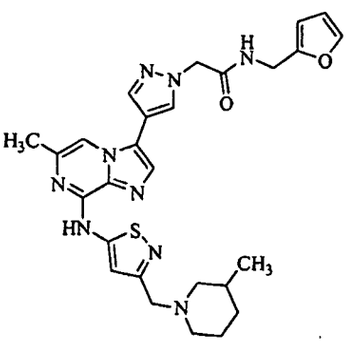


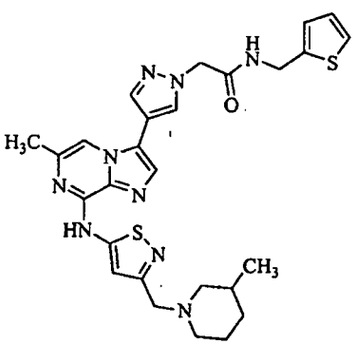


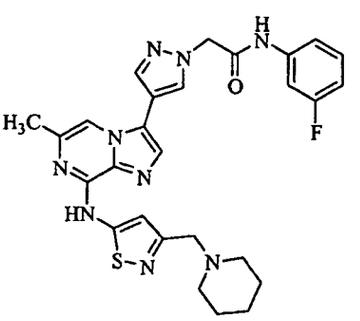


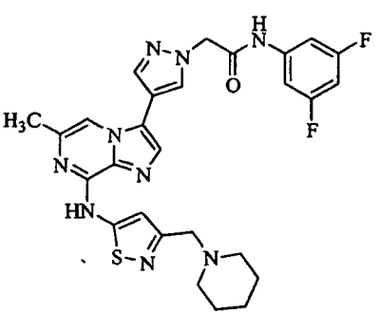


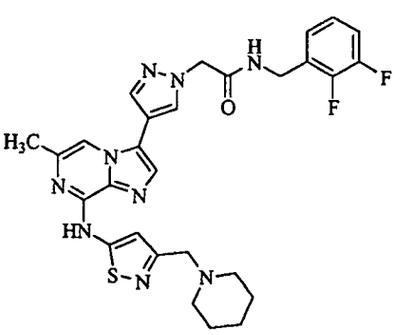


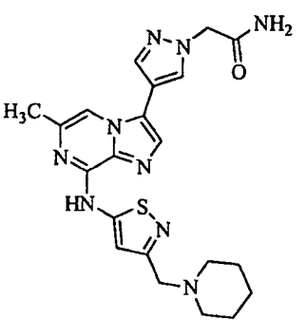


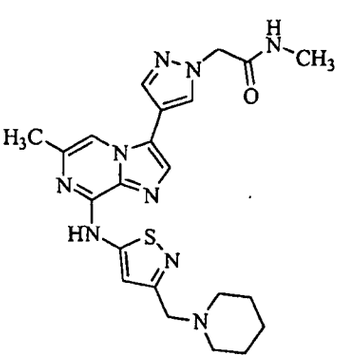


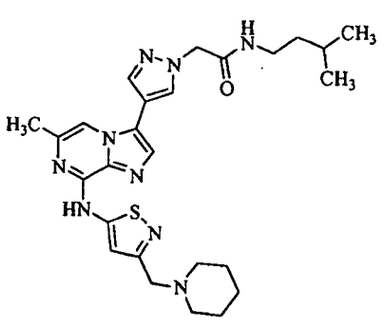


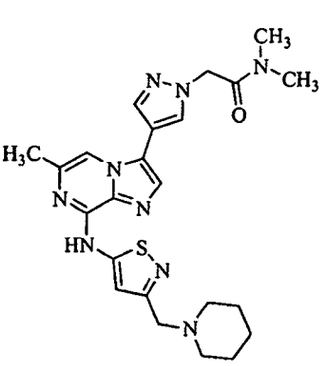


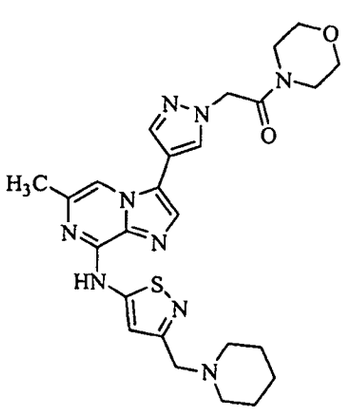


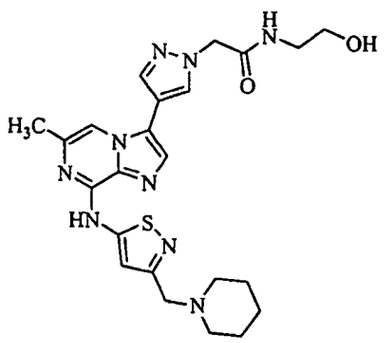


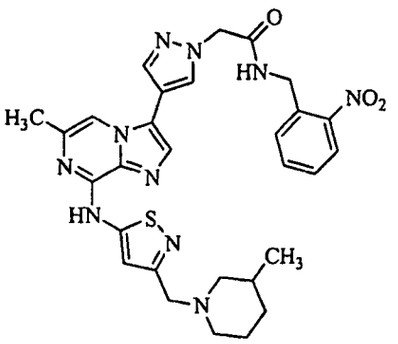


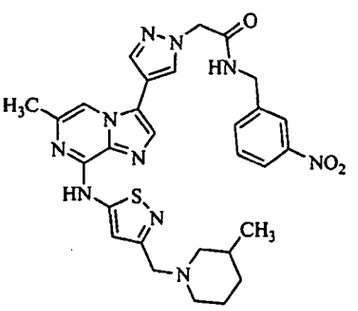


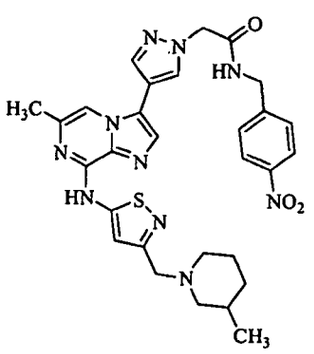


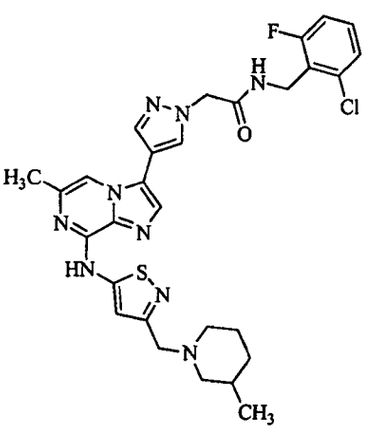


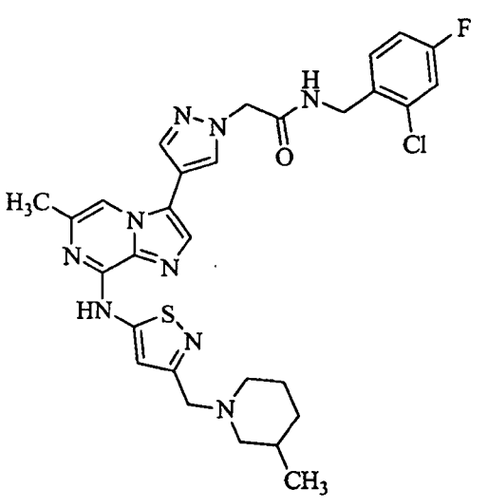


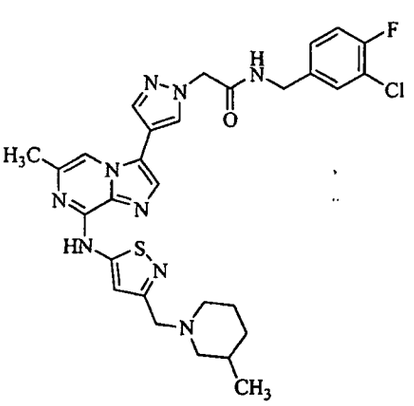


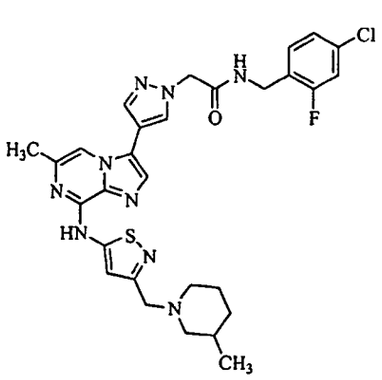


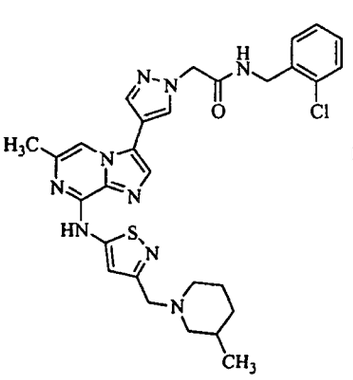


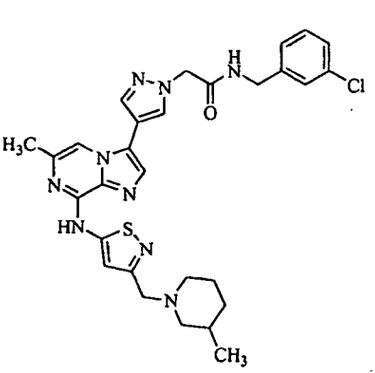


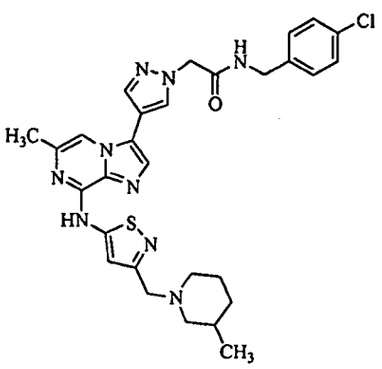


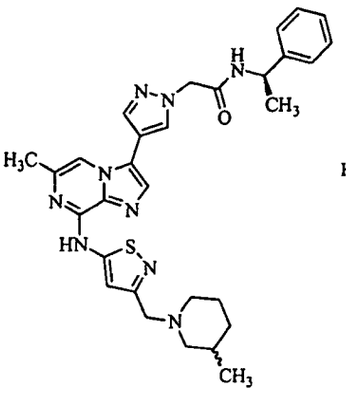


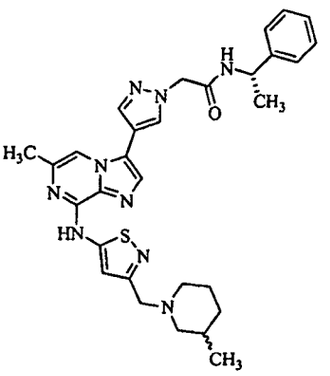


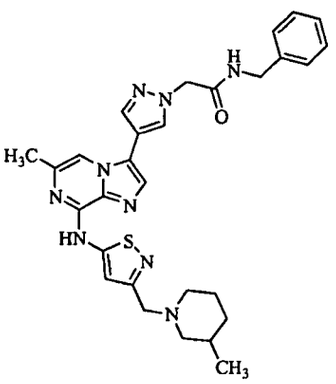


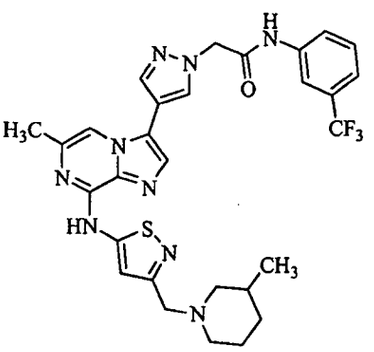


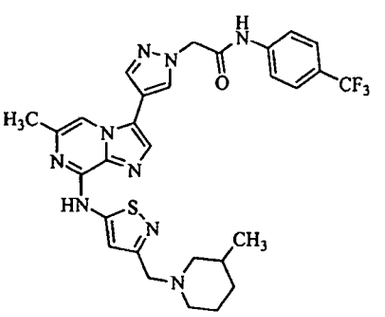


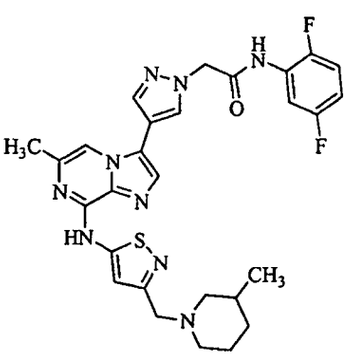


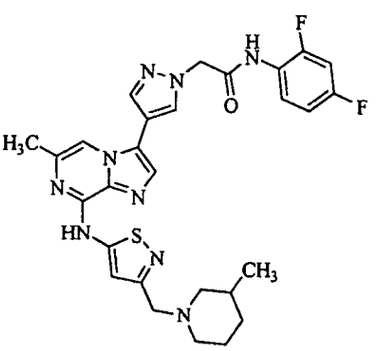


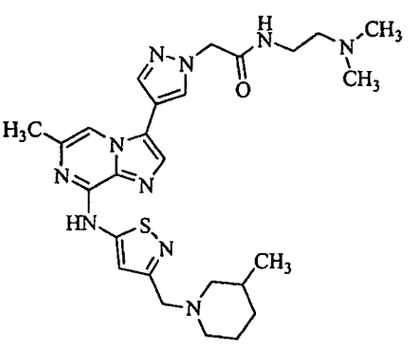


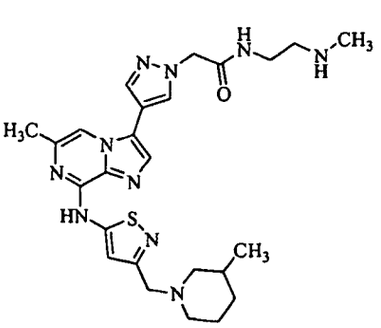


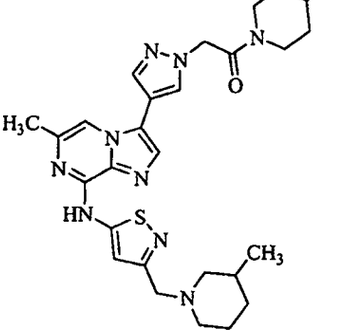


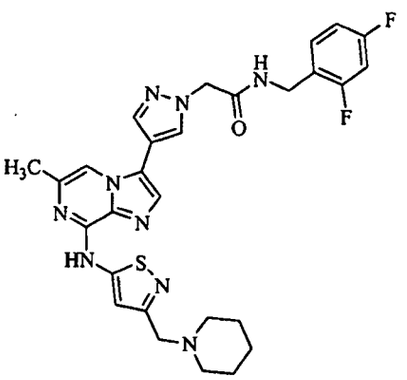


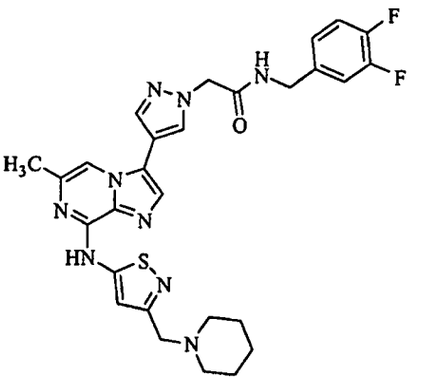


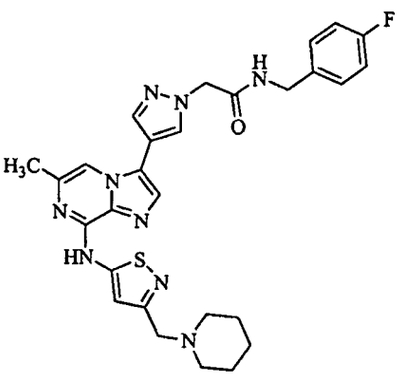


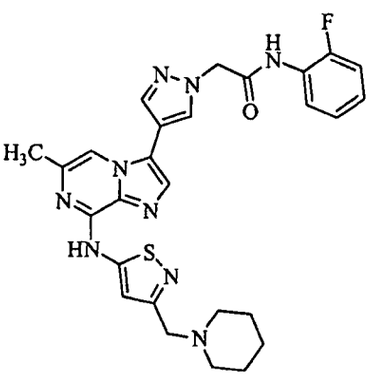


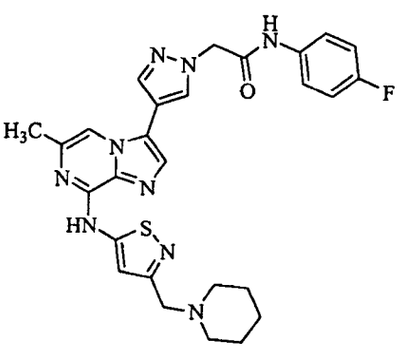


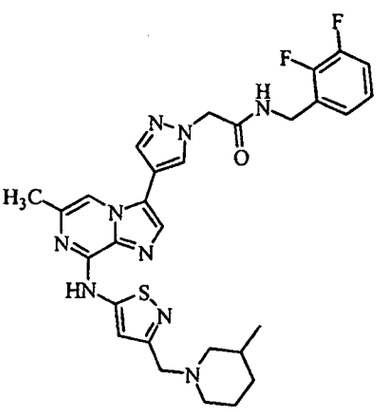


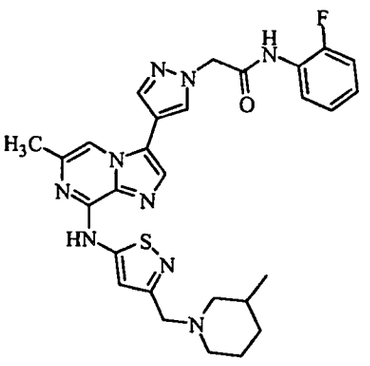


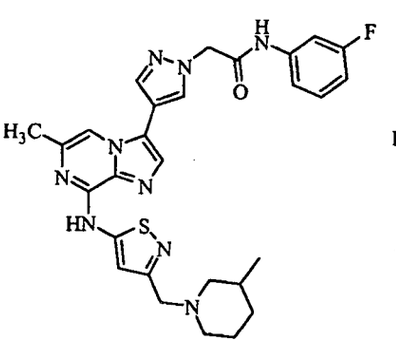


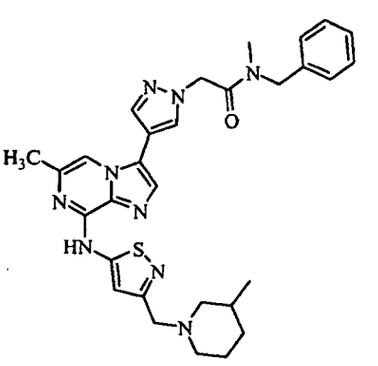


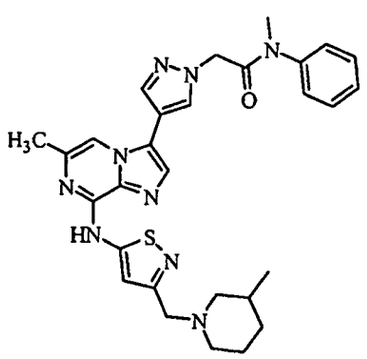


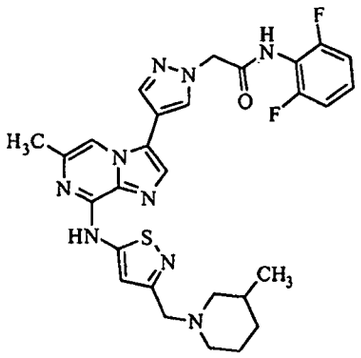


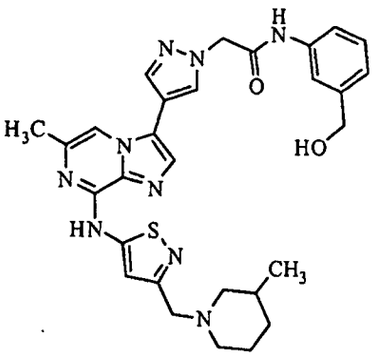


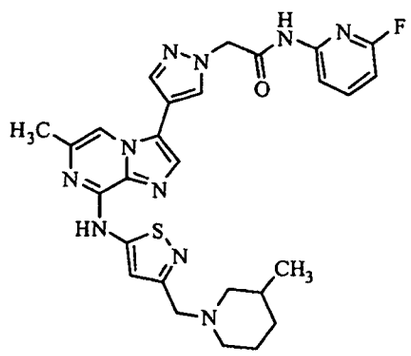


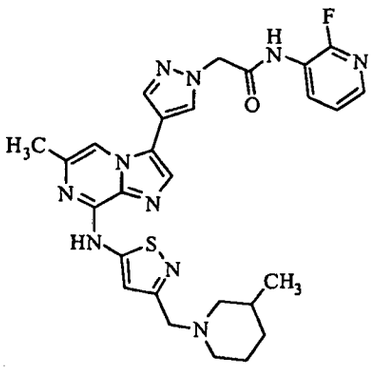


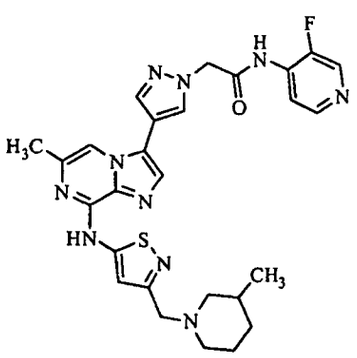


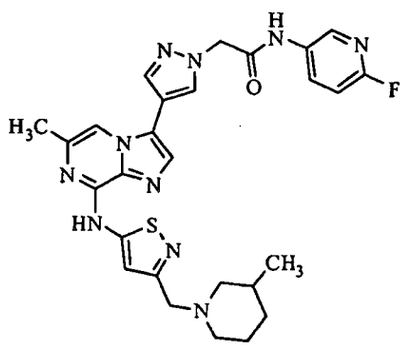


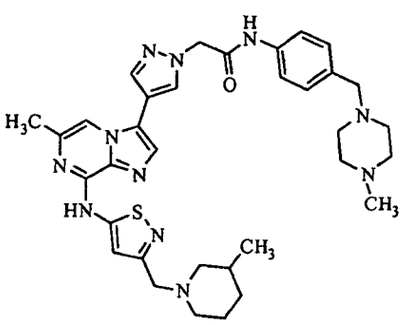


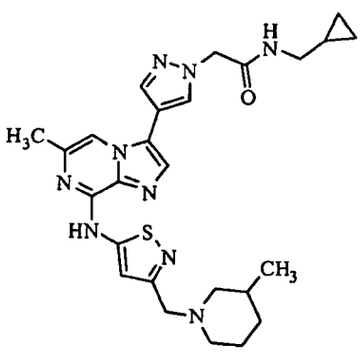


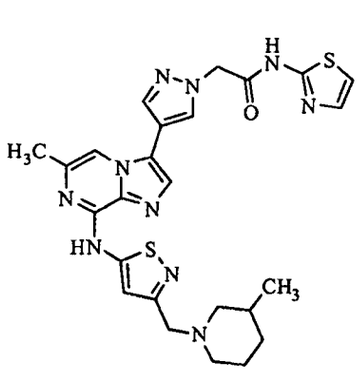


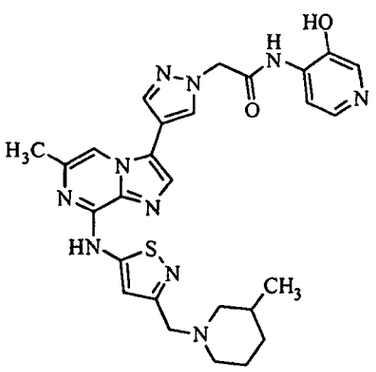


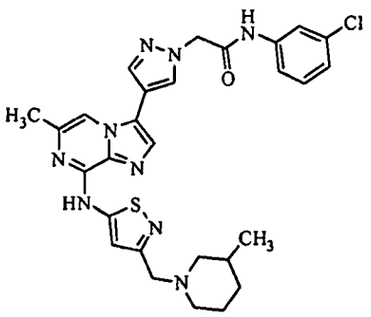


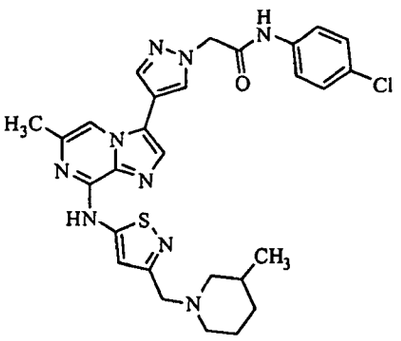


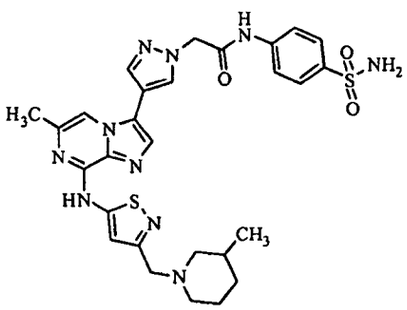


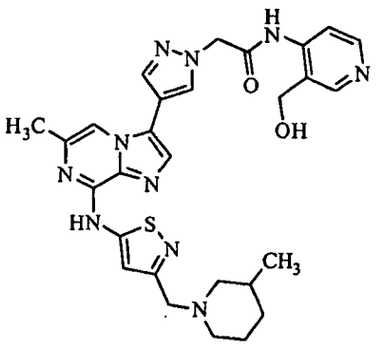


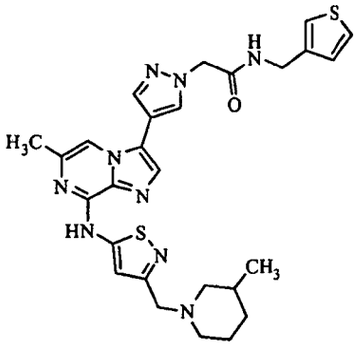


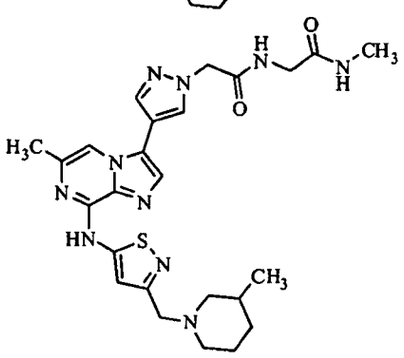


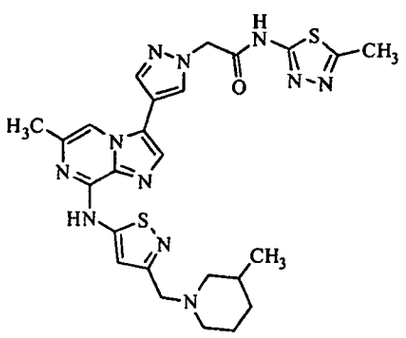


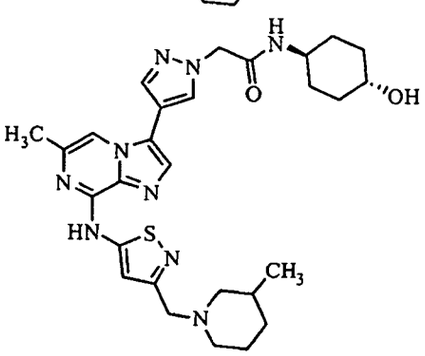


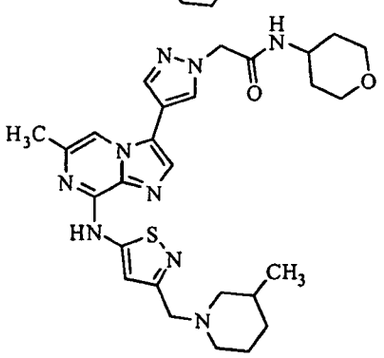


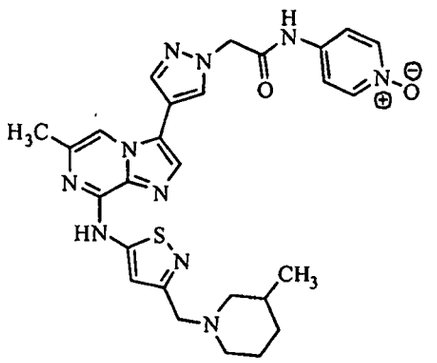


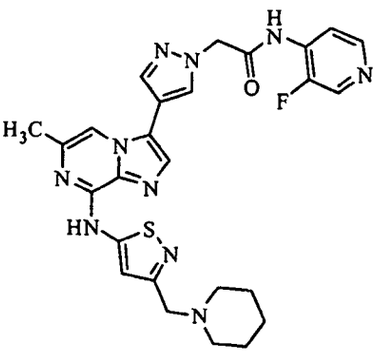


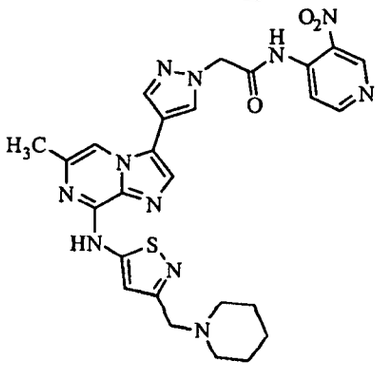


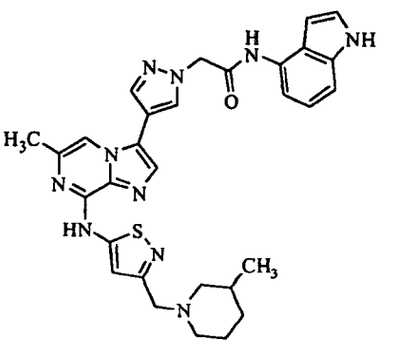


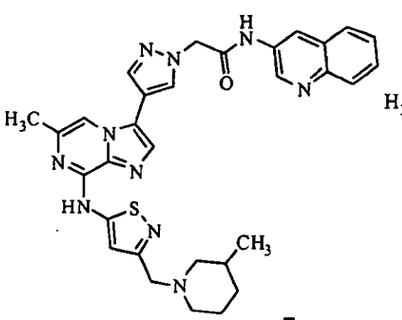


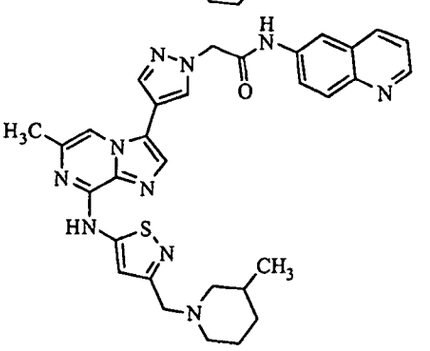


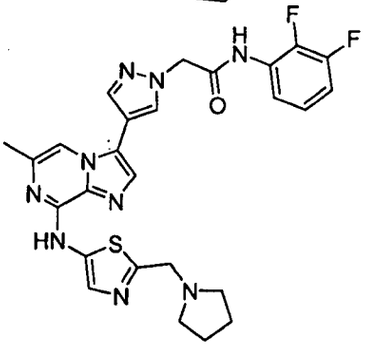


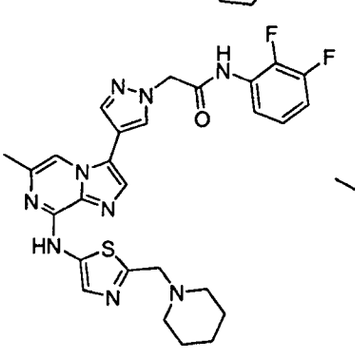


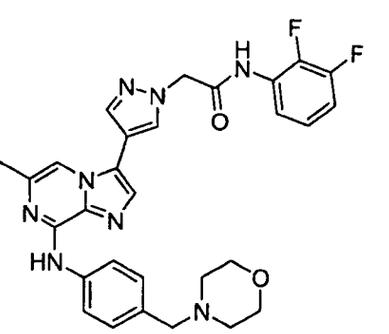


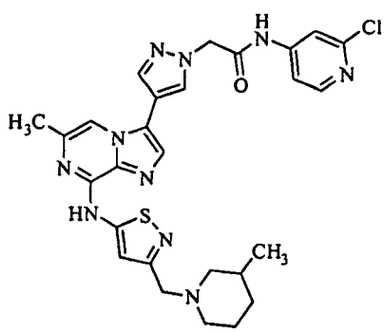


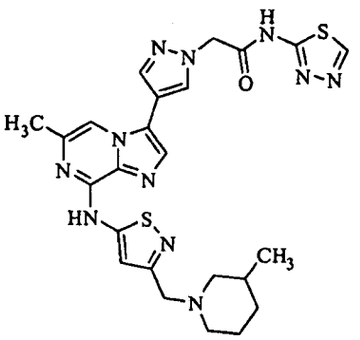


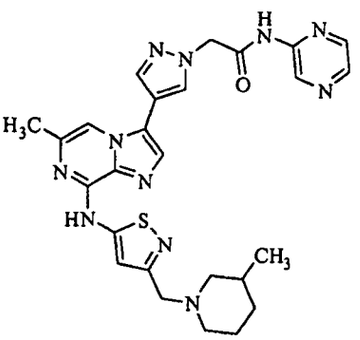


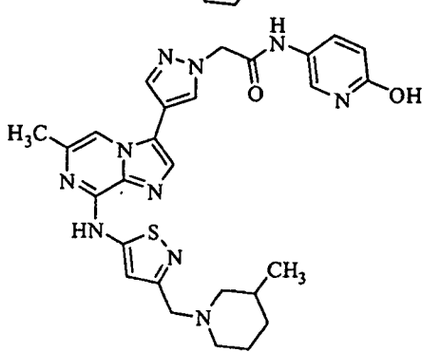


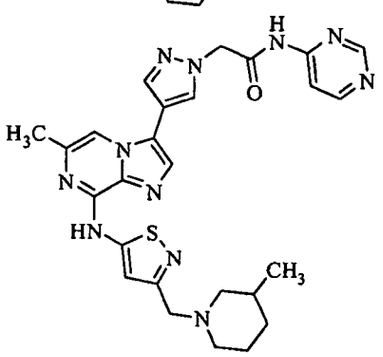


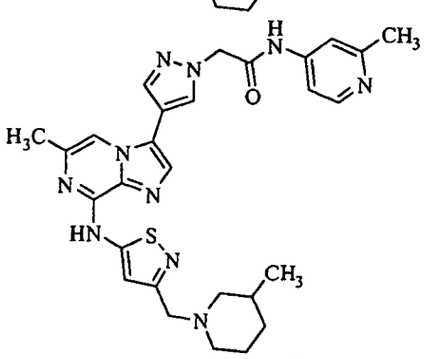


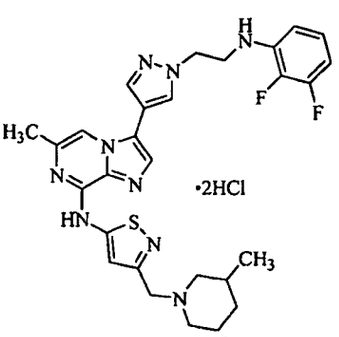


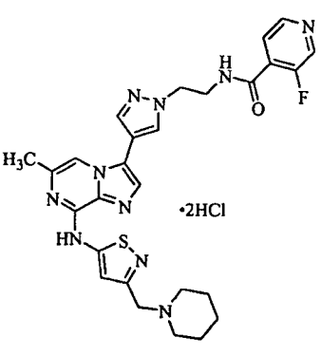


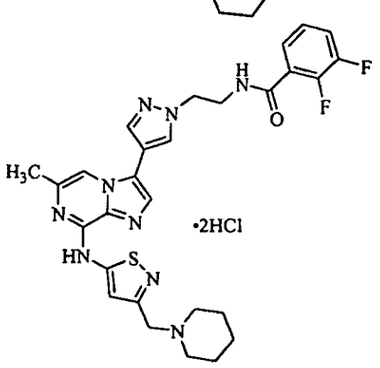


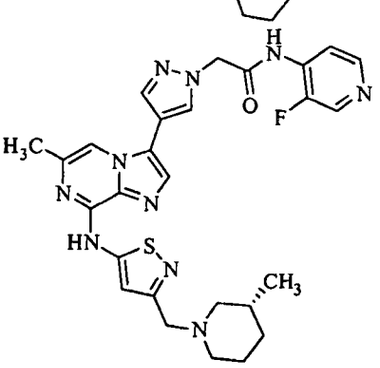


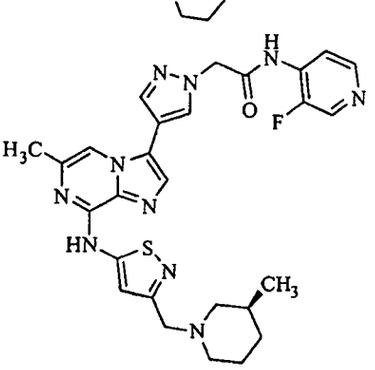


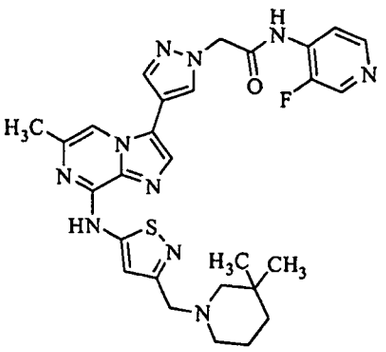

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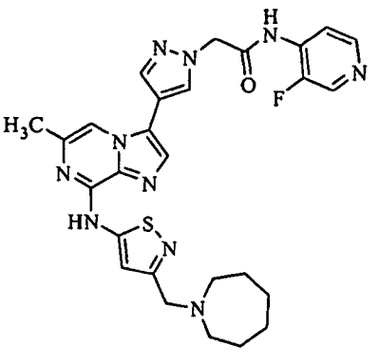

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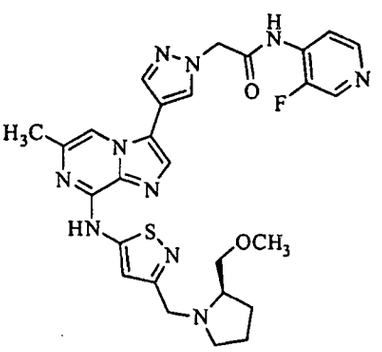

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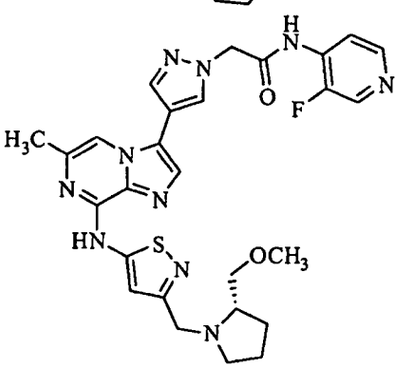


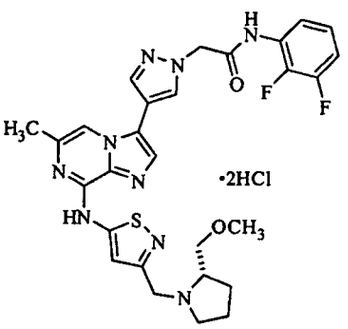


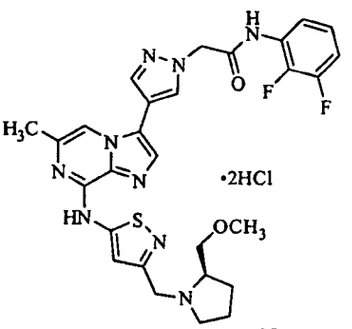


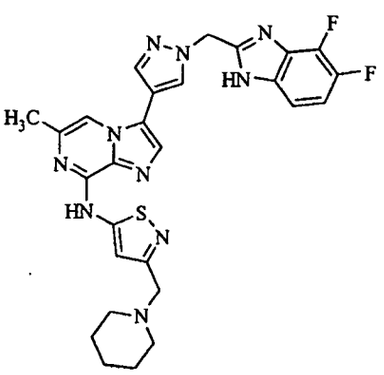


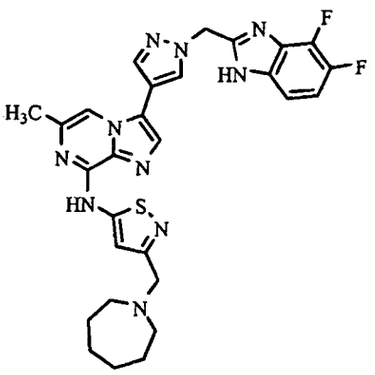


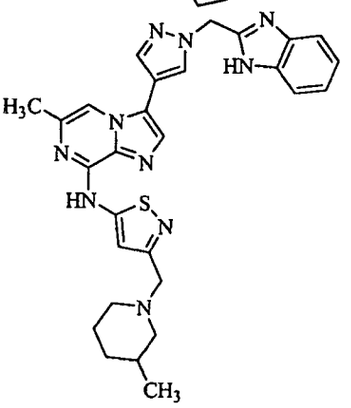


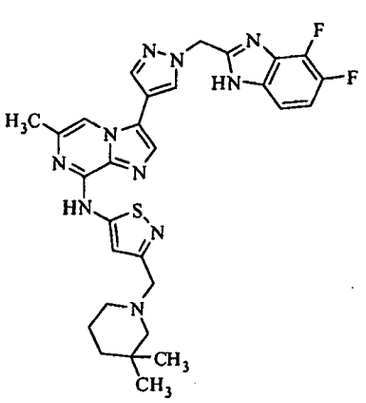

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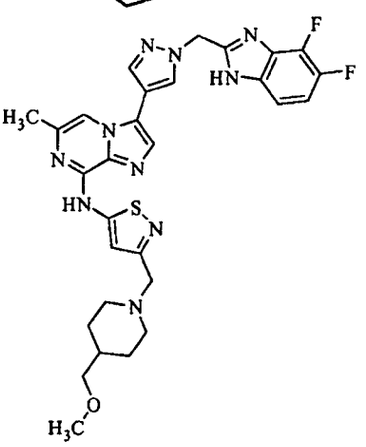

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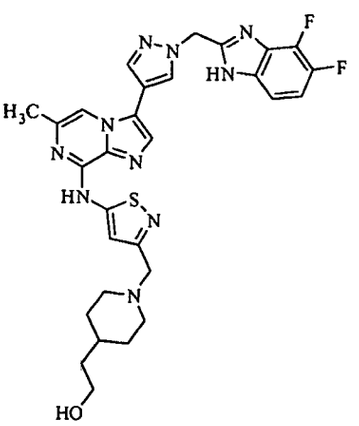


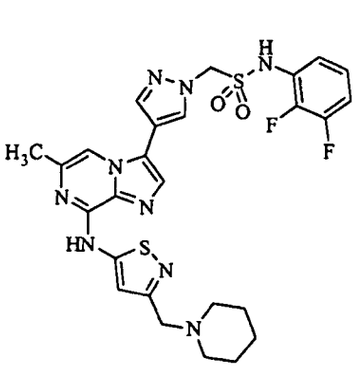


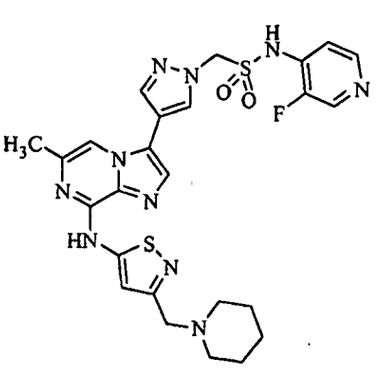


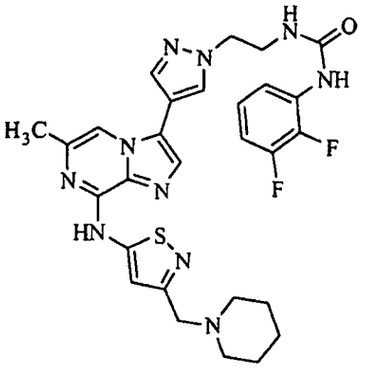


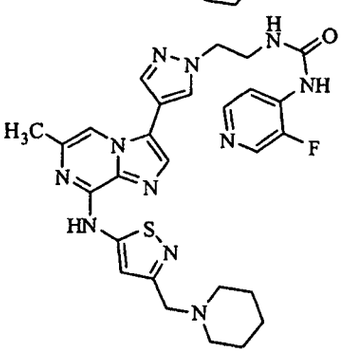


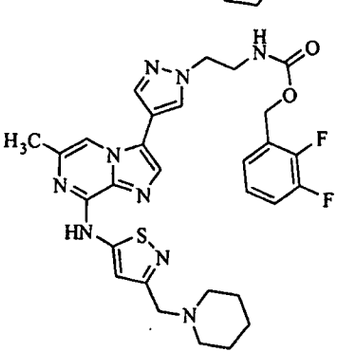


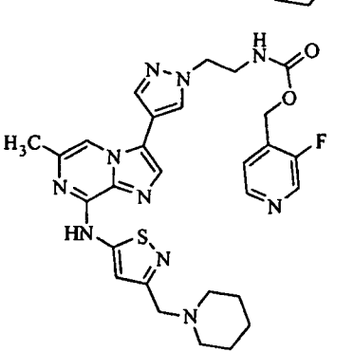


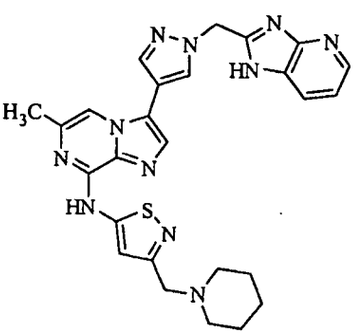


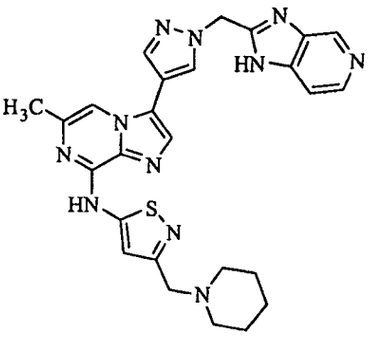


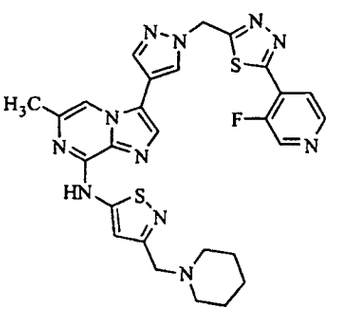


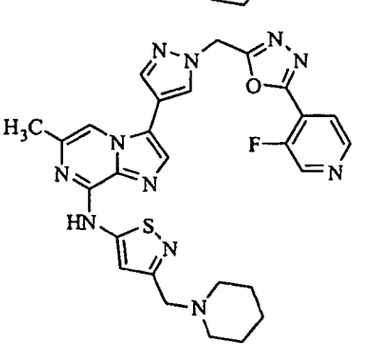


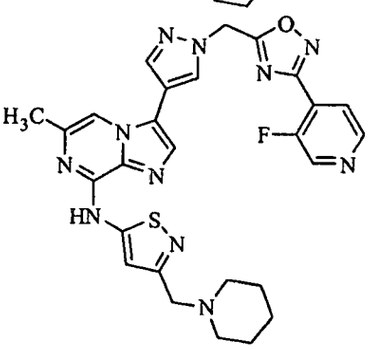


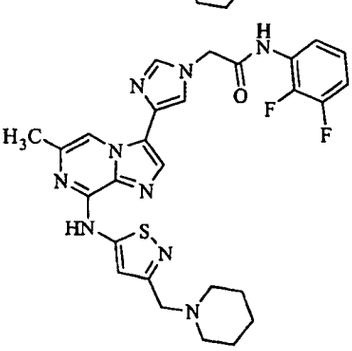


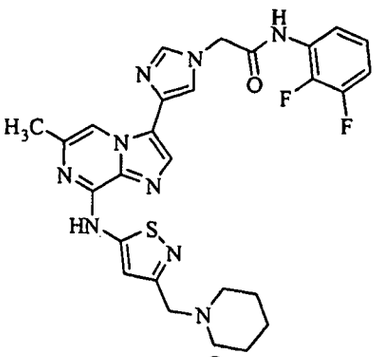


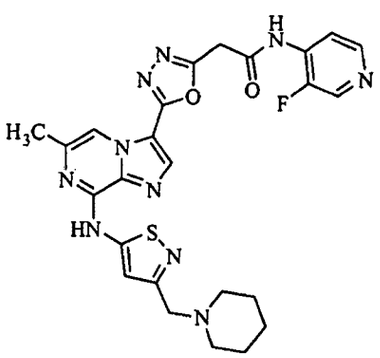


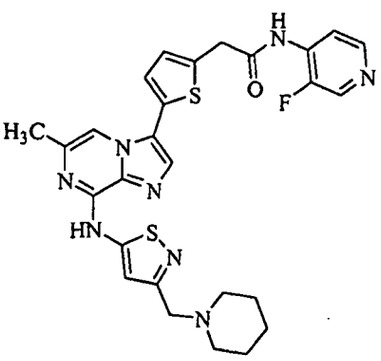


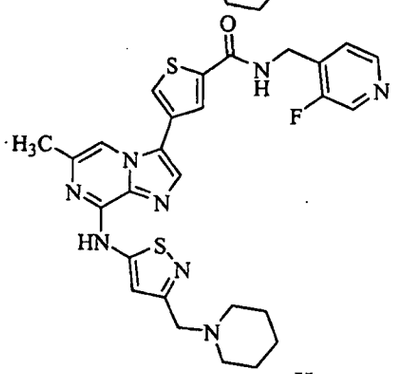


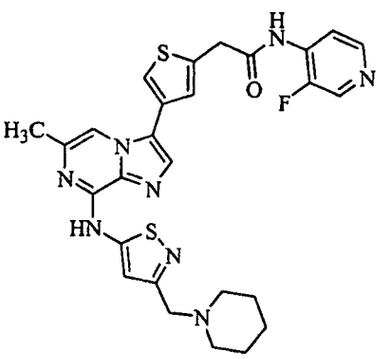


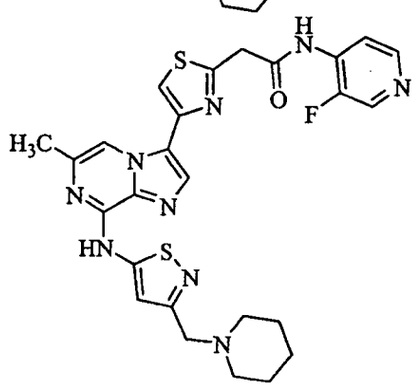


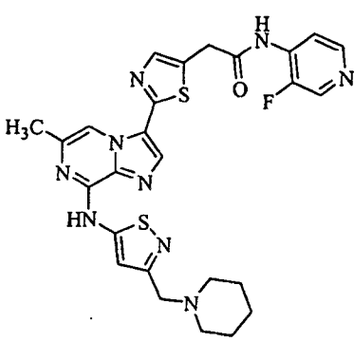


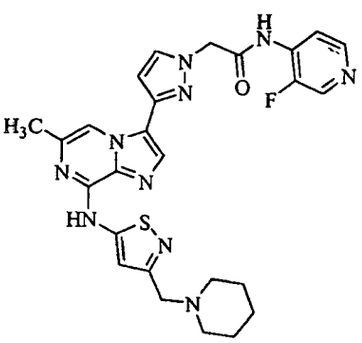


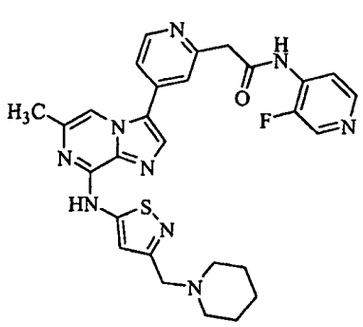


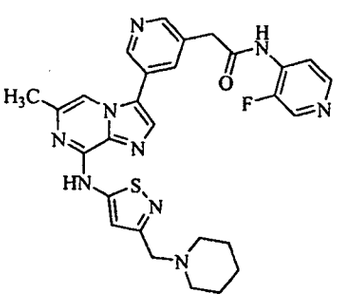


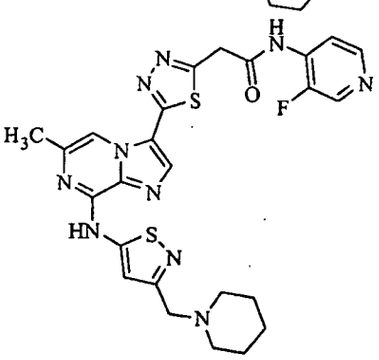


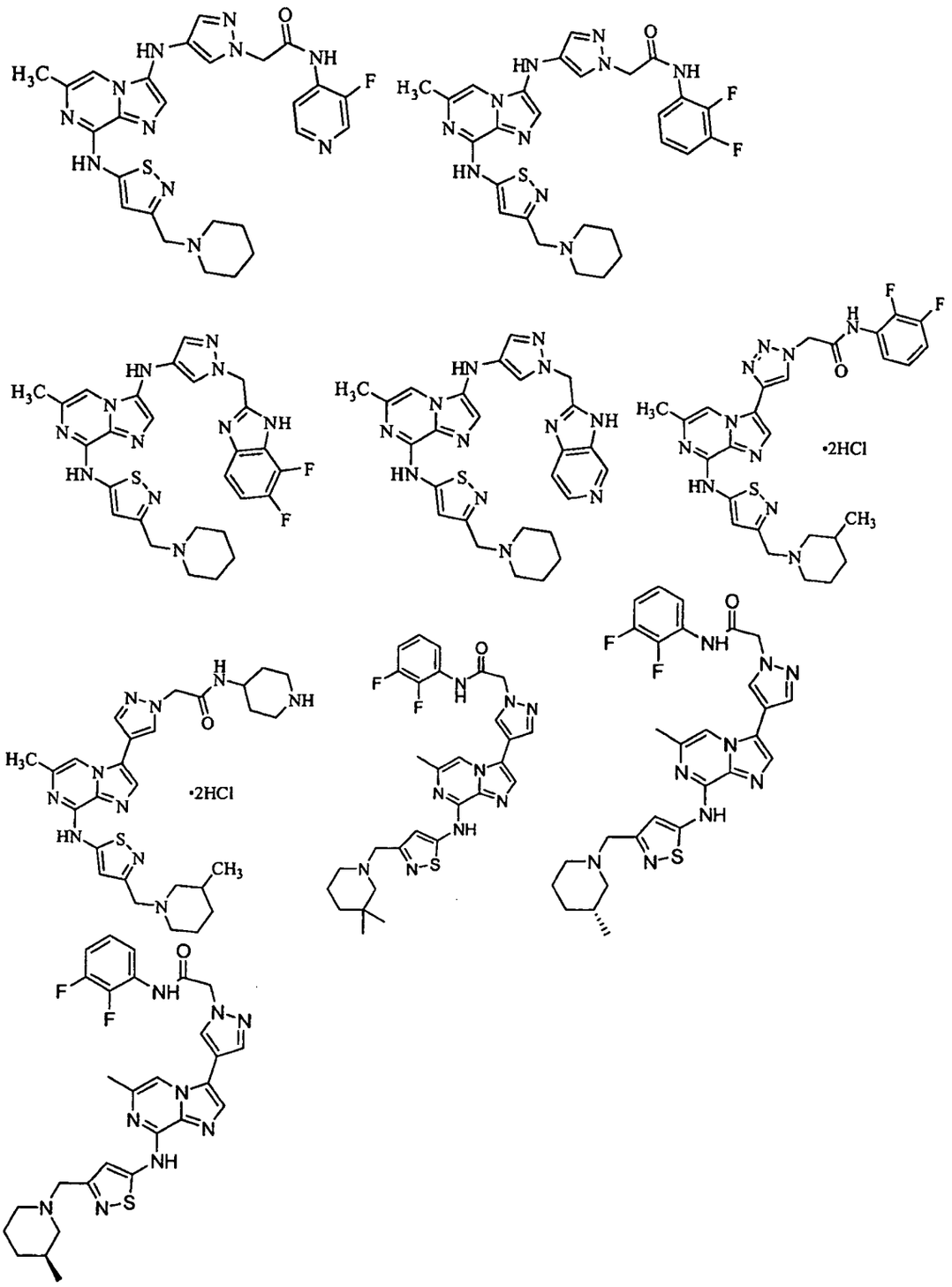












or pharmaceutically acceptable salts, solvates, esters or prodrugs thereof. The compounds listed in **Table 2** above are disclosed in the following references WO2007/058942 filed November 8, 2006, WO2004/026877, filed September 19, 2003, WO2007/058873, filed November 8, 2006, U.S. Appln. No. 60/943999, filed June 14, 2007, U.S. Application Serial

No. 60/987932, filed November 14, 2007and U.S. Appln. No. 60/855421, filed October 31, 2006, as well as from U.S. provisional patent application, Serial No. ------ (with Attorney Docket No. OC06760L01), filed of even date herewith.

As used above, and throughout this disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings, including any possible substitutions of the stated groups or moieties:

"Antimitotic agent" is a compound that inhibits cell growth by stopping cell division. These compounds specifically inhibit a cell in mitosis. These include compounds that target the cell's microtubules, centrosome, or spindles.

"Endoreduplication" is the process in a cell where there is an accumulation of polyploidy or aneuploidy DNA as a result of cell cycle rounds in the absence of cytokinesis (physical cell division).

"Polyploidy" is a cell possessing more DNA than two complete sets of chromosomes.

"Aneuploidy" is a cell containing abnormal chromosome content.

"Patient" includes both human and animals.

"Mammal" means humans and other mammalian animals.

"Alkyl" means an aliphatic hydrocarbon group which may be straight or branched and comprising about 1 to about 20 carbon atoms in the chain. Preferred alkyl groups contain about 1 to about 12 carbon atoms in the chain. More preferred alkyl groups contain 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 having about 1 to about 6 carbon atoms in the chain which may be straight or branched. "Alkyl" may be unsubstituted or optionally substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of halo, alkyl, aryl, cycloalkyl, cyano, hydroxy, alkoxy, alkylthio, amino, oxime (e.g., =N-OH), -NH(alkyl), -NH(cycloalkyl), -N(alkyl)$_2$, -O-C(O)-alkyl, -O-C(O)-aryl, -O-C(O)-cycloalkyl, carboxy and –C(O)O-alkyl. Non-limiting examples of suitable alkyl groups include methyl, ethyl, n-propyl, isopropyl and t-butyl.

"Alkenyl" means an aliphatic hydrocarbon group containing at least one carbon-carbon double bond and which may be straight or branched and comprising about 2 to about 15 carbon atoms in the chain. Preferred alkenyl groups have 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, are attached to a linear alkenyl chain. "Lower alkenyl" means about 2 to about 6 carbon atoms in the chain which may be straight or branched. "Alkenyl" may be unsubstituted or optionally substituted by one or more substituents which may be the same or different, each substituent being 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.

"Alkylene" means a difunctional group obtained by removal of a hydrogen atom from an alkyl group that is defined above. Non-limiting examples of alkylene include methylene, ethylene and propylene.

"Alkynyl" means an aliphatic hydrocarbon group containing at least one carbon-carbon triple bond and which may be straight or branched and comprising about 2 to about 15 carbon atoms in the chain. Preferred alkynyl groups have 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 about 2 to about 6 carbon atoms in the chain which may be straight or branched. Non-limiting examples of suitable alkynyl groups include ethynyl, propynyl, 2-butynyl and 3-methylbutynyl. "Alkynyl" may be unsubstituted or optionally substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of alkyl, aryl and cycloalkyl.

"Aryl" 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 "ring system substituents" which may be the same or different, and are as defined herein. Non-limiting examples of suitable aryl groups include phenyl and naphthyl.

"Bridged cyclic ring" is a hydrocarbon ring such as cycloalkyl, cycloalkenyl, or aryl or heteroatom containing ring such as, heterocyclyl, heterocyclenyl, or heteroaryl as described herein, that contains a bridge, which is a valence bond or an atom or an unbranched chain of atoms connecting two different parts of the ring. The two tertiary carbon atoms connected through the bridge are termed "bridgeheads".

"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 contain about 5 to about 6 ring atoms. The "heteroaryl" can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein. 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. "Heteroaryl" may also include a heteroaryl as defined above fused to an aryl as defined above. Non-limiting examples of suitable heteroaryls include pyridyl, pyrazinyl, furanyl, thienyl, pyrimidinyl, pyridone (including N-substituted pyridones), isoxazolyl, isothiazolyl, oxazolyl, thiazolyl, pyrazolyl, furazanyl, pyrrolyl, pyrazolyl, triazolyl, 1,2,4-thiadiazolyl, pyrazinyl, pyridazinyl, quinoxalinyl, phthalazinyl, oxindolyl, 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 and the like. The term "heteroaryl" also refers to partially saturated heteroaryl moieties such as, for example, tetrahydroisoquinolyl, tetrahydroquinolyl and the like.

"Aralkyl" or "arylalkyl" means an aryl-alkyl- group in which the aryl and alkyl are as previously described. Preferred aralkyls comprise a lower alkyl group. Non-limiting examples of suitable aralkyl groups include benzyl, 2-phenethyl and naphthalenylmethyl. The bond to the parent moiety is through the alkyl.

"Alkylaryl" means an alkyl-aryl- group in which the alkyl and aryl are as previously described. Preferred alkylaryls comprise a lower alkyl group. Non-limiting example of a suitable alkylaryl group is tolyl. The bond to the parent moiety is through the aryl.

"Cycloalkyl" 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. Preferred cycloalkyl rings contain about 5 to about 7 ring atoms. The cycloalkyl can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined above. Non-limiting examples of suitable monocyclic cycloalkyls include cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl and the like. Non-limiting examples of suitable multicyclic cycloalkyls include 1-decalinyl, norbornyl, adamantyl and the like.

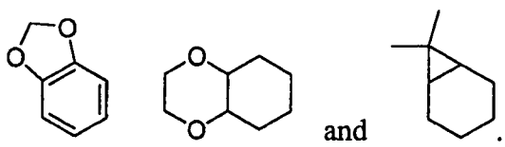
"Cycloalkylalkyl" means a cycloalkyl moiety as defined above linked via an alkyl moiety (defined above) to a parent core. Non-limiting examples of suitable cycloalkylalkyls include cyclohexylmethyl, adamantylmethyl and the like.

"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 which contain 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 "ring system substituents" which may be the same or different, and are as defined above. Non-limiting examples of suitable monocyclic cycloalkenyls include cyclopentenyl, cyclohexenyl, cyclohepta-1,3-dienyl, and the like. Non-limiting example of a suitable multicyclic cycloalkenyl is norbornylenyl.

"Cycloalkenylalkyl" means a cycloalkenyl moiety as defined above linked via an alkyl moiety (defined above) to a parent core. Non-limiting examples of suitable cycloalkenylalkyls include cyclopentenylmethyl, cyclohexenylmethyl and the like.

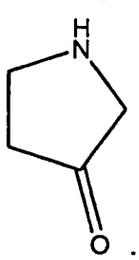
"Halogen" means fluorine, chlorine, bromine, or iodine. Preferred are fluorine, chlorine and bromine.

"Ring system substituent" means a substituent attached to an aromatic or non-aromatic ring system which, for example, replaces an available hydrogen on the ring system. Ring system substituents may be the same or different, each being independently selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, alkylaryl, heteroaralkyl, heteroarylalkenyl, heteroarylalkynyl, alkylheteroaryl, hydroxy, hydroxyalkyl, alkoxy, aryloxy, aralkoxy, acyl, aroyl, halo, nitro, cyano, carboxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylthio, arylthio, heteroarylthio, aralkylthio, heteroaralkylthio, cycloalkyl, heterocyclyl, amide, -CHO, -O-C(O)-alkyl, -O-C(O)-aryl, -O-C(O)-cycloalkyl, -C(=N-CN)-NH_2, -C(=NH)-NH_2, -C(=NH)-NH(alkyl), oxime (e.g., =N-OH), Y_1Y_2N-, Y_1Y_2N-alkyl-, $Y_1Y_2NC(O)$-, $Y_1Y_2NSO_2$- and -$SO_2NY_1Y_2$, wherein Y_1 and Y_2 can be the same or different and are independently selected from the group consisting of hydrogen, alkyl, aryl, cycloalkyl, and aralkyl. "Ring system substituent" may also mean a single moiety which simultaneously replaces two available hydrogen on two adjacent carbon atoms (one H on each carbon) on a ring system. Examples of such moiety are methylene dioxy, ethylenedioxy, -$C(CH_3)_2$- and the like which form moieties such as, for example:



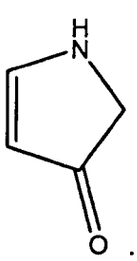
"Heteroarylalkyl" means a heteroaryl moiety as defined above linked via an alkyl moiety (defined above) to a parent core. Non-limiting examples of suitable heteroaryls include 2-pyridinylmethyl, quinolinylmethyl and the like.

"Heterocyclyl" 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. Any –NH in a heterocyclyl ring may exist protected such as, for example, as an -N(Boc), -N(CBz), -N(Tos) group and the like; such protections are also considered part of this invention. The heterocyclyl can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein. 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, 1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothiophenyl, lactam, lactone, and the like. "Heterocyclyl" may also mean a single moiety (e.g., carbonyl) which simultaneously replaces two available hydrogen on the same carbon atom on a ring system. Example of such moiety is pyrrolidone:



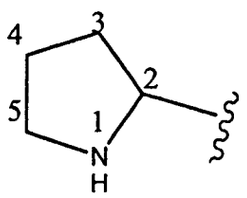
"Heterocyclylalkyl" means a heterocyclyl moiety as defined above linked via an alkyl moiety (defined above) to a parent core. Non-limiting examples of suitable heterocyclylalkyls include piperidinylmethyl, piperazinylmethyl and the like.

"Heterocyclenyl" 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 nitrogen, oxygen or sulfur atom, alone or in combination, 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 ring system substituents, wherein "ring system substituent" is as defined above. 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 heterocyclenyl groups include 1,2,3,4- tetrahydropyridinyl, 1,2-dihydropyridinyl, 1,4-dihydropyridinyl, 1,2,3,6-tetrahydropyridinyl, 1,4,5,6-tetrahydropyrimidinyl, 2-pyrrolinyl, 3-pyrrolinyl, 2-imidazolinyl, 2-pyrazolinyl, dihydroimidazolyl, dihydrooxazolyl, dihydrooxadiazolyl, dihydrothiazolyl, 3,4-dihydro-2H-pyranyl, dihydrofuranyl, fluorodihydrofuranyl, 7-oxabicyclo[2.2.1]heptenyl, dihydrothiophenyl, dihydrothiopyranyl, and the like. "Heterocyclenyl" may also mean a single moiety (e.g., carbonyl) which simultaneously replaces two available hydrogen on the same carbon atom on a ring system. Example of such moiety is pyrrolidinone:



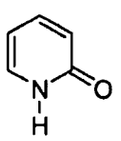
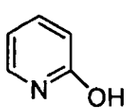
"Heterocyclenylalkyl" means a heterocyclenyl moiety as defined above linked via an alkyl moiety (defined above) to a parent core.

It should be noted that in hetero-atom containing ring systems of this invention, there are no hydroxyl groups on carbon atoms adjacent to a N, O or S, as well as 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.

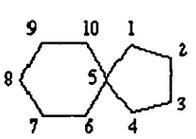
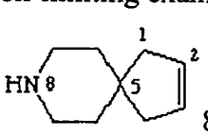
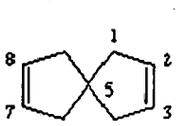
It should also be noted that tautomeric forms such as, for example, the moieties:

 and 

are considered equivalent in certain embodiments of this invention.

"Alkynylalkyl" means an alkynyl-alkyl- group in which the alkynyl and alkyl are as previously described. Preferred alkynylalkyls contain a lower alkynyl and a lower alkyl group. The bond to the parent moiety is through the alkyl. Non-limiting examples of suitable alkynylalkyl groups include propargylmethyl.

"Heteroaralkyl" means a heteroaryl-alkyl- group in which the heteroaryl and alkyl are as previously described. Preferred heteroaralkyls contain a lower alkyl group. Non-limiting examples of suitable aralkyl groups include pyridylmethyl, and quinolin-3-ylmethyl. The bond to the parent moiety is through the alkyl.

"Spiro ring systems" have two or more rings linked by one common atom. Preferred spiro ring systems include spiroheteroaryl, spiroheterocyclenyl, spiroheterocyclyl, spirocycloalkyl, spirocyclenyl, and spiroaryl. The spiro ring systems can be optionally substituted by one or more ring system substituents, wherein "ring system substituent" is as defined above. Non-limiting examples of suitable spiro ring systems include  spiro[4.5]decane,  8-azaspiro[4.5]dec-2-ene, and  spiro[4.4]nona-2,7-diene.

"Hydroxyalkyl" means a HO-alkyl- group in which alkyl is as previously defined. Preferred hydroxyalkyls contain lower alkyl. Non-limiting examples of suitable hydroxyalkyl groups include hydroxymethyl and 2-hydroxyethyl.

"Acyl" means an H-C(O)-, alkyl-C(O)- or cycloalkyl-C(O)-, group in which the various groups are as previously described. 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 and propanoyl.

"Aroyl" means an aryl-C(O)- group in which the aryl group is as previously described. The bond to the parent moiety is through the carbonyl. Non-limiting examples of suitable groups include benzoyl and 1- naphthoyl.

"Alkoxy" means an alkyl-O- group in which the alkyl group is as previously described. Non-limiting examples of suitable alkoxy groups include methoxy, ethoxy, n-propoxy, isopropoxy and n-butoxy. The bond to the parent moiety is through the ether oxygen.

"Aryloxy" means an aryl-O- group in which the aryl group is as previously described. Non-limiting examples of suitable aryloxy groups include phenoxy and naphthoxy. The bond to the parent moiety is through the ether oxygen.

"Aralkyloxy" means an aralkyl-O- group in which the aralkyl group is as previously described. Non-limiting examples of suitable aralkyloxy groups include benzyloxy and 1- or 2-naphthalenemethoxy. The bond to the parent moiety is through the ether oxygen.

"Alkylthio" means an alkyl-S- group in which the alkyl group is as previously described. Non-limiting examples of suitable alkylthio groups include methylthio and ethylthio. The bond to the parent moiety is through the sulfur.

"Arylthio" means an aryl-S- group in which the aryl group is as previously described. Non-limiting examples of suitable arylthio groups include phenylthio and naphthylthio. The bond to the parent moiety is through the sulfur.

"Aralkylthio" means an aralkyl-S- group in which the aralkyl group is as previously described. Non-limiting example of a suitable aralkylthio group is benzylthio. The bond to the parent moiety is through the sulfur.

"Alkoxycarbonyl" means an alkyl-O-CO- group. Non-limiting examples of suitable alkoxycarbonyl groups include methoxycarbonyl and ethoxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Aryloxycarbonyl" means an aryl-O-C(O)- group. Non-limiting examples of suitable aryloxycarbonyl groups include phenoxycarbonyl and naphthoxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Aralkoxycarbonyl" means an aralkyl-O-C(O)- group. Non-limiting example of a suitable aralkoxycarbonyl group is benzyloxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Alkylsulfonyl" means an alkyl-$S(O_2)$- group. Preferred groups are those in which the alkyl group is lower alkyl. The bond to the parent moiety is through the sulfonyl.

"Arylsulfonyl" means an aryl-$S(O_2)$- group. The bond to the parent moiety is through the sulfonyl.

The term "substituted" means that one or more hydrogen 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 (e.g. from a reaction mixture), 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 (e.g., chromatography, recrystallization and the like) , in sufficient purity to be characterizable by standard analytical techniques described herein or well known to the skilled artisan.

It should also be noted that any carbon as well as heteroatom with unsatisfied valences in the text, schemes, examples and Tables herein is assumed to have the sufficient number of hydrogen atom(s) to satisfy the valences.

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^2, etc.) occurs more than one time in any constituent or in any of Formulas A-J, 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.

Prodrugs and solvates of the compounds of the invention are also contemplated herein. 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. The term "prodrug" means a compound (e.g., a drug precursor) that is transformed *in vivo* to yield a compound of any of Formulas A-J or a pharmaceutically acceptable salt, hydrate or solvate of the compound. The transformation may occur by various mechanisms (e.g., by metabolic or chemical processes), such as, for example, through hydrolysis in blood. A discussion of the use of prodrugs is provided by T. Higuchi and W. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

For example, if a compound of any of Formulas A-J 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})alkanoyloxymethyl, 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-(alkoxycarbonyl)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 any of Formulas A-J 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)alkanoyloxy)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 any of Formulas A-J 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-carbonyl, RO-carbonyl, NRR'-carbonyl where R and R' are each independently (C_1-C_{10})alkyl, (C_3-C_7) cycloalkyl, benzyl, or R-carbonyl is a natural α-aminoacyl or natural α-aminoacyl, —C(OH)C(O)OY^1 wherein Y^1 is H, (C_1-C_6)alkyl or benzyl, —C(OY^2)Y^3 wherein Y^2 is (C_1-C_4) alkyl and Y^3 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^4)Y^5 wherein Y^4 is H or methyl and Y^5 is mono-N— or di-N,N-(C_1-C_6)alkylamino morpholino, piperidin-1-yl or pyrrolidin-1-yl, and the like.

One or more compounds of the invention may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and it is intended that the invention embrace both solvated and unsolvated forms. "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.

One or more compounds of the invention may optionally be 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) describes 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).

"Effective amount" or "therapeutically effective amount" is meant to describe an amount of compound or a composition of the present invention effective in inhibiting the above-noted diseases and thus producing the desired therapeutic, ameliorative, inhibitory or preventative effect.

The compounds of any of Formulas A-J can form salts which are also within the scope of this invention. Reference to a compound of any of Formulas A-J 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 any of Formulas A-J 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, although other salts are also useful. Salts of the compounds of any of Formulas A-J may be formed, for example, by reacting a compound of any of Formulas A-J 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.

Exemplary acid addition salts include acetates, ascorbates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, fumarates, hydrochlorides, hydrobromides, hydroiodides, lactates, maleates, methanesulfonates, naphthalenesulfonates, nitrates, oxalates, phosphates, propionates, salicylates, succinates, sulfates, tartarates, thiocyanates, toluenesulfonates (also known as tosylates,) and the like. Additionally, acids which are generally considered suitable for the formation of pharmaceutically useful salts from basic pharmaceutical compounds are discussed, for example, by P. Stahl *et al*, Camille G. (eds.) *Handbook of Pharmaceutical Salts.*

Properties, Selection and Use. (2002) Zurich: Wiley-VCH; 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; and in *The Orange Book* (Food & Drug Administration, Washington, D.C. on their website). These disclosures are incorporated herein by reference thereto.

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, salts with organic bases (for example, organic amines) such as dicyclohexylamines, t-butyl amines, 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, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g. dimethyl, diethyl, and dibutyl sulfates), long chain halides (e.g. decyl, lauryl, and stearyl chlorides, bromides and iodides), aralkyl halides (e.g. benzyl and phenethyl bromides), and others.

All such acid salts 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.

Pharmaceutically acceptable esters of the present compounds include the following groups: (1) carboxylic acid esters obtained by esterification of the hydroxy groups, in which the non-carbonyl moiety of the carboxylic acid portion of the ester grouping is selected from straight or branched chain alkyl (for example, acetyl, n-propyl, t-butyl, or n-butyl), alkoxyalkyl (for example, methoxymethyl), aralkyl (for example, benzyl), aryloxyalkyl (for example, phenoxymethyl), aryl (for example, phenyl optionally substituted with, for example, halogen, C_{1-4}alkyl, or C_{1-4}alkoxy or amino); (2) sulfonate esters, such as alkyl- or aralkylsulfonyl (for example, methanesulfonyl); (3) amino acid esters (for example, L-valyl or L-isoleucyl); (4) phosphonate esters and (5) mono-, di- or triphosphate esters. The phosphate esters may be further esterified by, for example, a C_{1-20} alcohol or reactive derivative thereof, or by a 2,3-di (C_{6-24})acyl glycerol.

Compounds of any of Formulas A-J, and salts, solvates, esters 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.

The compounds of any of Formulas A-J may contain asymmetric or chiral centers, and, therefore, exist in different stereoisomeric forms. It is intended that all stereoisomeric forms of

the compounds of any of Formulas A-J as well as mixtures thereof, including racemic mixtures, form part of the present invention. In addition, the present invention embraces all geometric and positional isomers. For example, if a compound of any of Formulas A-J incorporates a double bond or a fused ring, both the cis- and trans-forms, as well as mixtures, are embraced within the scope of the invention.

Diastereomeric 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 diastereomeric 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 any of Formulas A-J 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.

It is also possible that the compounds of any of Formulas A-J 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.

All stereoisomers (for example, geometric isomers, optical isomers and the like) of the present compounds (including those of the salts, solvates, esters and prodrugs of the compounds as well as the salts, solvates and esters 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, as are positional isomers (such as, for example, 4-pyridyl and 3-pyridyl). (For example, if a compound of any of Formulas A-J incorporates a double bond or a fused ring, both the cis- and trans-forms, as well as mixtures, 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.) 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", "ester", "prodrug" and the like, is intended to equally apply to the salt, solvate, ester and prodrug of enantiomers, stereoisomers, rotamers, tautomers, positional isomers, racemates or prodrugs of the inventive compounds.

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

Certain isotopically-labelled compounds of any of Formulas A-J (e.g., those labeled with ^{3}H and ^{14}C) are useful in compound and/or substrate tissue distribution assays. Tritiated (i.e., ^{3}H) and carbon-14 (i.e., ^{14}C) isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (i.e., ^{2}H) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased in vivo half-life or reduced dosage requirements) and hence may be preferred in some circumstances. Isotopically labeled compounds of any of Formulas A-J 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.

Polymorphic forms of the compounds of any of Formulas A-J, and of the salts, solvates, esters and prodrugs of the compounds of any of Formulas A-J, are intended to be included in the present invention.

More specifically, the combination treatment of the present invention comprising first administration of the anti-mitotic agent described above, followed by administration of the compounds of any of Formulas E-K can be useful in the treatment of a variety of cancers, including (but not limited to) the following:

tumor of the bladder, breast (including BRCA-mutated breast cancer), colorectal, colon, kidney, liver, lung (including small cell lung cancer and non-small cell lung cancer), head and neck, esophagus, bladder, gall bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, and skin, including squamous cell carcinoma;

leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T- cell lymphoma, Hodgkins lymphoma, non-Hodgkins lymphoma, hairy cell lymphoma, mantle cell lymphoma, myeloma and Burkett's lymphoma;

chronic lymphocytic leukemia ("CLL"),

acute and chronic myelogenous leukemia, myelodysplastic syndrome and promyelocytic leukemia;

fibrosarcoma, rhabdomyosarcoma;

mantle cell lymphoma, myeloma;

astrocytoma, neuroblastoma, glioblastoma, malignant glial tumors, hepatocellular carcinoma, gastrointestinal stromal tumors ("GIST") and schwannomas;

melanoma, multiple myeloma, seminoma, teratocarcinoma, osteosarcoma, xenoderoma pigmentosum, keratoctanthoma, thyroid follicular cancer and Kaposi's sarcoma.

The combination treatment of the present invention can be useful in the chemoprevention of cancer. Chemoprevention is defined as inhibiting the development of invasive cancer by either blocking the initiating mutagenic event or by blocking the progression of pre-malignant cells that have already suffered an insult or inhibiting tumor relapse.

The combination treatment of the present invention may also be useful in inhibiting tumor angiogenesis and metastasis.

Non-limiting examples of suitable anti-mitotic agent is selected from the group consisting of a taxotere (docetaxel) , taxol (paclitaxel), KSP inhibitors (such as, for example, those of Formulas A-D described herein or Ispinesib SB-715992 (Cytokinetics), and centrosome associated protein E ("CENP-E") inhibitor (e.g., GSK-923295), ABRAXANE® (Abraxis BioScience Inc and AstraZeneca Pharmaceuticals), and epothilone including epothilone A, B or D.

At least one aurora kinase inhibitor of any of Formulas E-K should be administered following administration of at least one anti-mitotic agent or when a combination formulation of at least one anti-mitotic agent and at least one aurora kinase inhibitor is administered, the aurora kinase inhibitor would be time released after the release of the anti-mitotic agent. Such techniques are within the skills of persons skilled in the art as well as attending physicians.

Accordingly, in an aspect, this invention includes combinations comprising an amount of one or more anti-mitotic agents listed above and an amount of at least one compound of any

of Formulas E-K, or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, wherein the combination also includes a time release agent that releases the aurora kinase inhibitor after the antimitotic agent, in amounts and at a time that results in a desired therapeutic effect.

Another aspect of the present invention is a method of inhibiting one or more Aurora kinases in a patient in need thereof, comprising administering to the patient, a therapeutically effective amount of at least one compound of any of Formulas E-K or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof following administration of one or more anti-mitotic agents described above.

Another aspect of the present invention is a method of treating, or slowing the progression of, a disease associated with one or more Aurora kinases in a patient in need thereof, comprising administering a therapeutically effective amount of at least one compound of any of Formulas E-K or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof following administration of an anti-mitotic agent described above.

Yet another aspect of the present invention is a method of treating one or more diseases associated with Aurora kinase, comprising administering to a mammal in need of such treatment an amount of a first compound, which is an anti-mitotic agent or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof; and an amount of at least one second compound, the second compound being a compound of any of Formulas E-K, wherein the amounts of the first compound and the second compound result in a therapeutic effect.

Another aspect of the present invention is a method of treating, or slowing the progression of, a disease associated with one or more Aurora kinases in a patient in need thereof, comprising administering an anti-mitotic agent followed by a therapeutically effective amount of a pharmaceutical composition comprising in combination at least one pharmaceutically acceptable carrier and at least one compound according to any of Formulas E-K, or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof.

In the above methods, the Aurora kinase to be inhibited can be Aurora B and/or Aurora A/B, A/B/C, or B/C.

The pharmacological properties of the pharmaceutical compositions which comprise separately at least one anti-mitotic agent and at least one compound of any of Formulas E-K, or a pharmaceutically acceptable salt, solvate, ester or prodrug of said compound and at least one pharmaceutically acceptable carrier may be confirmed by a number of pharmacological

assays. The exemplified pharmacological assays which are described herein below have been carried out with pharmaceutical compositions according to the invention.

This invention is also directed to pharmaceutical compositions which comprise separately at least one anti-mitotic agent and at least one compound of any of Formulas E-K, or a pharmaceutically acceptable salt, solvate, ester or prodrug of said compound and at least one pharmaceutically acceptable carrier.

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's Pharmaceutical Sciences,* 18th Edition, (1990), Mack Publishing Co., Easton, Pennsylvania.

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 that 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.

The compounds of this invention may also be delivered subcutaneously.

Preferably the compound is administered orally or intravenously.

Also contemplated are delivery methods that are combinations of the above-noted delivery methods. Such methods are typically decided by those skilled in the art.

Preferably, the pharmaceutical preparation is in a unit dosage form. In such form, the preparation is subdivided into suitably sized unit doses containing appropriate quantities of the active components, e.g., an effective amount of antimotic agent and an effective amount of aurora kinase inhibitor of Formula E – J, to achieve the desired purpose.

Another aspect of this invention is a kit comprising a separately a therapeutically effective amount of at least one anti-mitotic agent and at least one compound of any of Formulas E-K, or a pharmaceutically acceptable salt, solvate, ester or prodrug of said compound and a pharmaceutically acceptable carrier, vehicle or diluent.

SYNTHETIC EXAMPLES

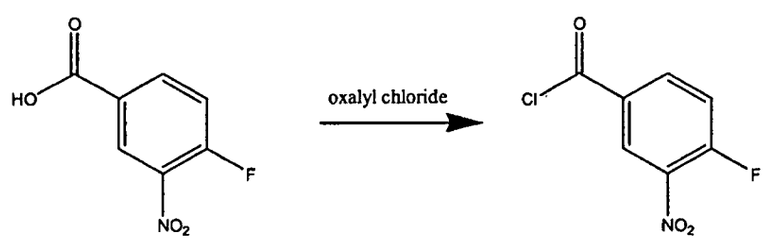
The synthesis of compounds of paragraphs (d), (h), (i), (j) and (k), which are unpublished as of the filing date of the present patent application, is shown below, as reported respectively in U.S. provisional patent application, Serial Nos. 60/939963, 60/858244, 60/987932 (and 60/943999), 60/855421 and Attorney Docket No. OC06760L01 (filed of even date herewith).

The synthesis of the compounds of paragraph (d) as described in U.S. application, Serial No. 60/939963 is shown below.

Method A

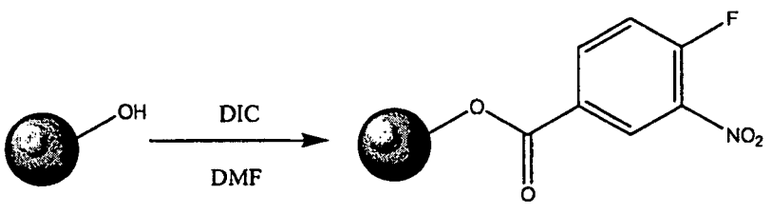
Standard operating procedure (SOP) For Solid Phase Synthesis of Benzimidazoles

4-Fluoro-3-nitrobenzoyl chloride



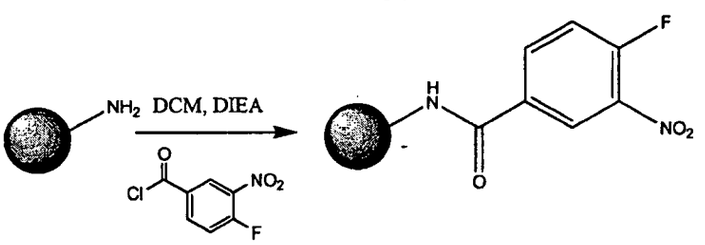
4-Fluoro-4-nitrobenzoic acid (277 mg, 1.5 mmol) was dissolved in DCM (5mL) and oxalyl chloride was added (630μL, 5 eq.) followed by 2 μL DMF. The solution was stirred for 1h at rt. then concentrated to give 1.5 mmol of acid chloride which is stored under argon and must be used in the next step fresh.

RESIN 1



To Wang resin (3.0mmol) was added DMF (30mL) and 4-fluoro-3-nitrobenzoic acid (1.66g, 9.0mmol), DIC (1.4mL, 9.0mmol) and DMAP (80mg). The mixture was stirred overnight at rt. and filtered. The resin was washed with DMF (4x), i-PrOH, DCM (3x each, Et_2O and dried in vacuo.

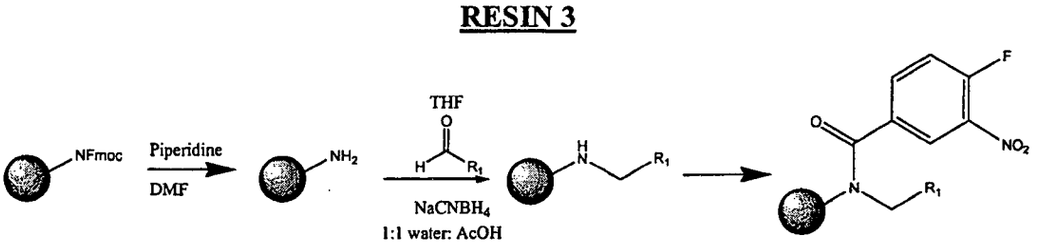
RESIN 2



To Rink AM resin (Novabiochem, 0.4 mmol) was added a mixture of piperidine and DMF (6mL, 50%) and the mixture was shaken for 45 min and filtered. The resin was thoroughly washed with DMF, i-PrOH, DCM (3x each), Et_2O and dried.

To the resin was added DCM (5mL), DIEA (315μL, 1.8mmol) and freshly prepared 4-fluoro-3-nitrobenzoyl chloride (1.5mmol) in 3mL DCM. The mixture was stirred overnight at rt. then filtered. The resin was washed with DCM, i-PrOH, DCM (3x each), Et_2O and dried.

RESIN 3



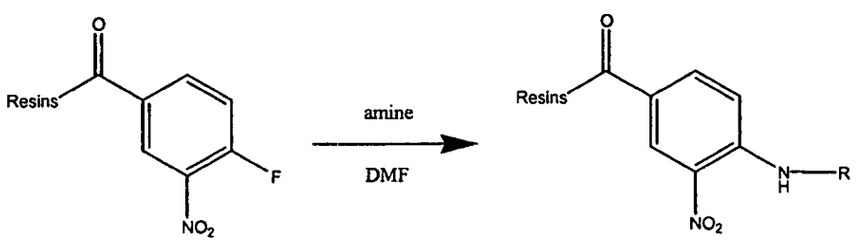
To Rink AM resin (Novabiochem, 0.4 mmol) was added a mixture of piperidine and DMF (6mL, 50%) and the mixture was shaken for 45 min and filtered. The resin was thoroughly washed with DMF, i-PrOH, DCM (3x each), Et_2O and dried.

To the resin was added THF (8mL), a mixture of aldehydes (0.4 mmol total) followed by a mixture of acetic acid and deionized water (50%, 800 μL). The mixture was shaken for 5 min and then $NaCNBH_3$ in THF was added (1M, 400 μL). The mixture was

shaken for 3 hours at rt. and filtered (handle waste separately due to cyanoborohydride). The resin was washed with THF, H_2O, MeOH, THF, DCM (3x each), Et_2O and dried.

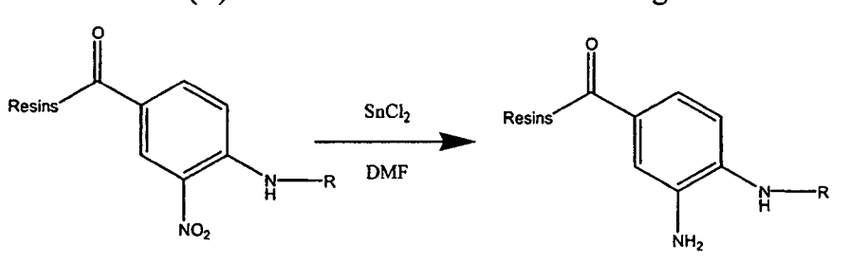
To the resin was added DCM (5mL), DIEA (315μL, 1.8mmol) and freshly prepared 4-fluoro-3-nitrobenzoyl chloride (1.5mmol) in 3mL DCM. The mixture was stirred overnight at rt. then filtered. The resin was washed with DCM, i-PrOH, DCM (3x each), Et_2O and dried.

4-(R)Amino-3-nitrobenzoic acid analogs



To resin (0.1mmol) was added 5% DIEA in DMF (1mL) and the amine (2.3 eq.) and the mixture was shaken overnight at rt. To vessels that contain hindered or slow reacting building blocks, a fast reacting building block from the same building block set was added (5 eq) and the mixture was shaken for 3h at rt (capping). The resin was filtered off, washed with DMF, i-PrOH, DCM (3x each), Et_2O and dried.

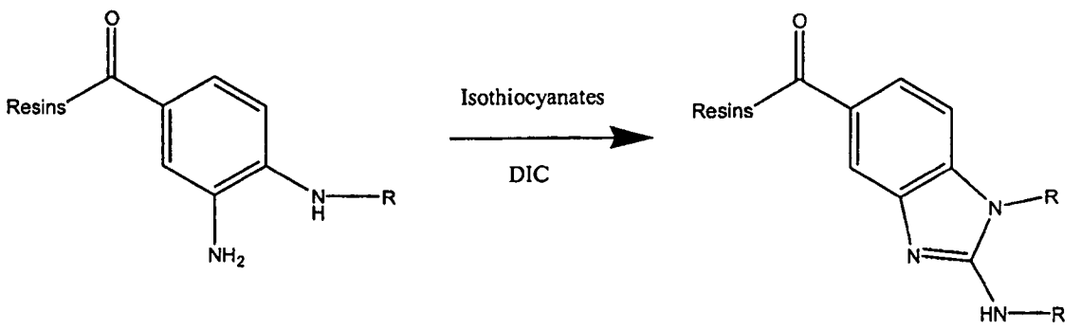
4-(R)Amino-3-aminobenzoic acid analogs



(Fresh anhydrous tin(II)-chloride and DMF are used for this step)

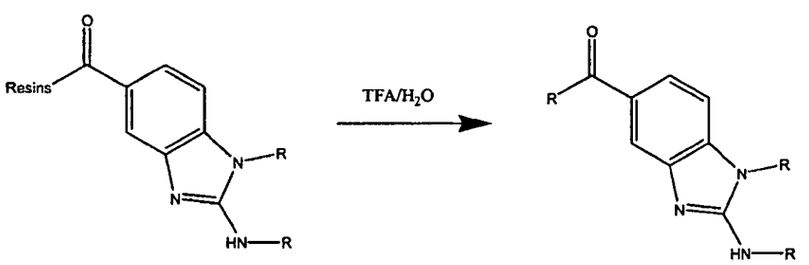
To resin (0.1mmol) was added a 2M solution of tin(II)-chloride (fresh, anhydrous) in DMF (anhydrous, 1mL) and the mixture was shaken overnight at rt. The resin was filtered off, washed with DMF, i-PrOH, DCM (3x each), Et_2O and dried.

Benzimidazole analogs



To resin (0.1mmol) was added DMF (0.8mL) and isothiocyanate (0.5mmol) and the mixture was shaken for 1 day at rt. DIC (79μL, 0.5mmol) was injected and the mixture was shaken overnight at rt. The resin was filtered off, washed with DMF, i-PrOH, DCM (3x each), Et_2O and dried.

Cleavage



To the resin (0.1-0.2 mmol) was added TFA/H_2O (95:5, 1mL) and the mixture was stirred for 1h at rt. The resin was filtered and washed with acetonitrile (2x2mL). The filtrate was concentrated in vacuo to yield the product.

Method B

Similar reaction sequence and conditions to above protocol, however reaction was carried out in solution.

Method C

Compounds were further modified after the cleavage step in Method A.

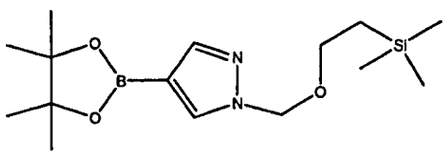
The synthesis of the compounds of paragraph (h) as described in U.S. application, Serial No. 60/858244 is shown below.

SYNTHESIS OF COMPOUNDS (h):

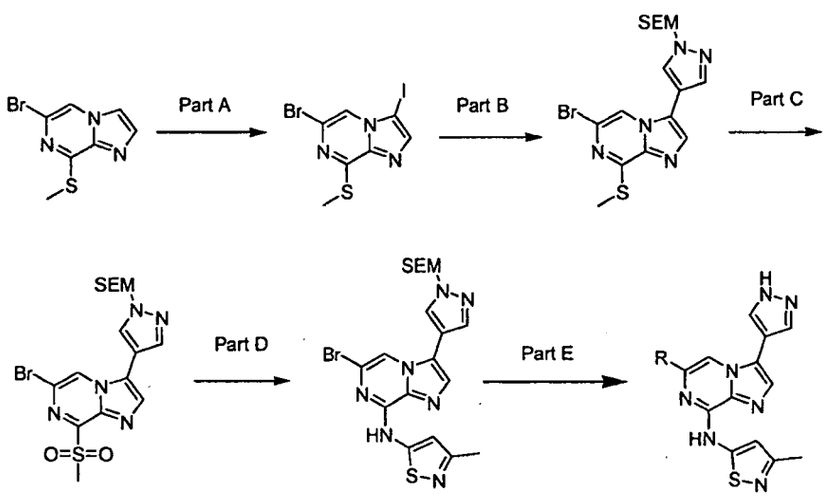
Preparative Example 1:

To a suspension of potassium carbonate (5.85 g, 1.5 equiv) and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1h-pyrazole (5.48 g, 1.0 equiv) in

NMP (50 mL) at rt was added SEMCl (5.2 mL, 1.05 equiv) dropwise (mildly exothermic). The resulting mixture was allowed to stir an additional 45 min at rt. The reaction was diluted with ethyl acetate, rinsed with water (2x), brine and dried (sodium sulfate). Filtration and concentration afforded the title compound that was used without purification. $MH^+ = 325$.



Preparative Example 2



Part A

To a solution of bromide (US2006/0106023) (2.00 g, 8.19 mmol) in DMF (50 mL) was added N-iodosuccinimide (1.84 g, 8.19 mmol). The reaction mixture was stirred at 60°C for 16 h. The mixture was cooled to rt and concentrated. Purification by column chromatography (SiO_2, 40% ethyl acetate/hexanes) afforded compound 4 as a white solid 2.30 g (76%). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.3 (s, 1H), 7.8 (s, 1H), 2.6 (s, 3H). $MH^+ = 371$.

Part B

A flask was charged with iodide from Part A (1.83 g, 1.00 equiv), boronate from Preparative Example 1 (2.08 g, 1.3 equiv), $PdCl_2$(dppf) (0.4 g, 0.1 equiv) and potassium phosphate monohydrate (3.4 g, 3.0 equiv). After purging the flask with argon, 1,4-dioxane (50 mL) and water (5 mL) were added and the resulting mixture was heated at 40°C overnight (23 h). The reaction was cooled to rt. EtOAc was added to the reaction mixture and filtered through Celite. After concentration the residue was purified by column chromatography (silica gel, 25% EtOAc/hexane) to give the title compound (46%).

Part C

To a solution of compound from Part B (1.02 g, 1.0 equiv) in DCM (10 mL) was added *m*-CPBA (1.1 g, 77%, 2.05 equiv) in one portion. The resulting mixture was stirred at rt for 30 min. The mixture was concentrated and then partitioned between EtOAc and water. The organic layer was washed with $NaHCO_3$ (sat. aq., twice), brine and dried (Na_2SO_4). After concentration, the crude product compound 6 was used in the next step directly without further purification.

Part D

To a solution of 5-amino-3-methylisothiazole hydrochloride (0.135 g, 1.4 equiv) in DMSO (9 mL) at rt was added NaH (0.11 g of 60% dispersion in oil, 3.0 equiv) in one portion. After ca. 10 min, compound from Part C (0.30 g, 1.00 equiv) was added in one portion. After 15 min at rt, the reaction was quenched with sat. aq. ammonium chloride and then extracted with ethyl acetate (x2). The combined organic layers were washed with water (x2), brine and dried (sodium sulfate). The crude residue was purified by chromatography affording the title compound (0.18 g. 56%). $MH^+ = 506$.

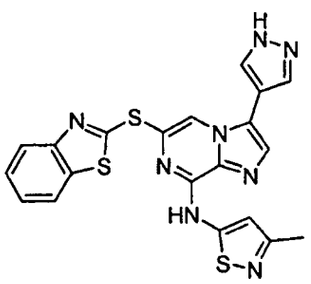
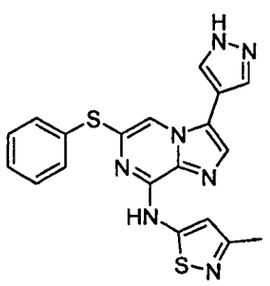
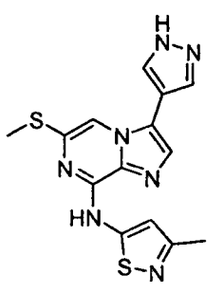
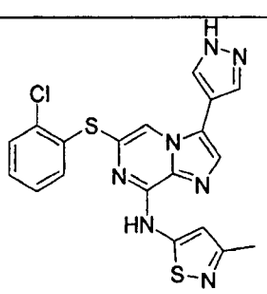
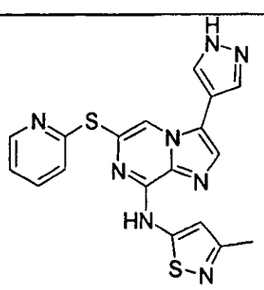
Part E

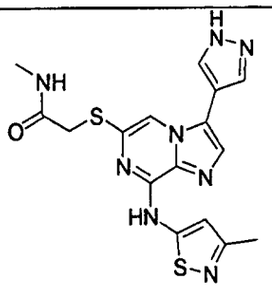
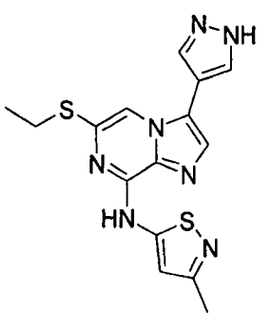
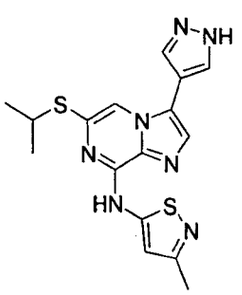
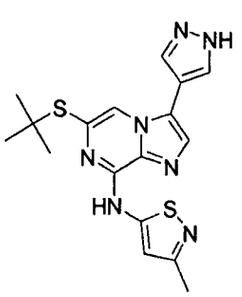
A mixture of bromide from preparative example 3, Part D (30 mg, 0.059 mmol, 1 equiv), sodium methanethiolate (1.4 equiv), $PdCl_2$(dppf) (0.07 equiv), sodium *t*-butoxide (1.1 equiv) in 1,2-dimethoxyethane (1mL) was stirred at 85°C under Ar for 16 hours. The reaction mixture was cooled to room temperature, filtered through Celite and the filtrate concentrated. The residue was taken back up in ethyl acetate and washed with water, brine, dried over anhydrous sodium sulfate and concentrated to afford the crude residue. $MH^+ = 488$. A solution of crude compound in THF (1 mL) was treated with 4N HCl in dioxane solution (1 mL) at 60°C for 10 min. The solvent was removed and the residue was purified by Prep-LC. Conversion to a hydrochloric salt afforded the title compound.

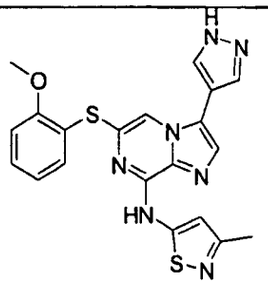
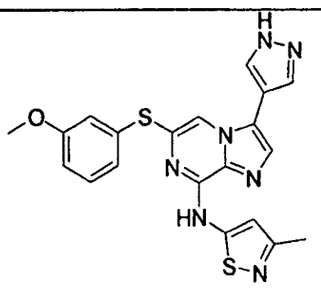
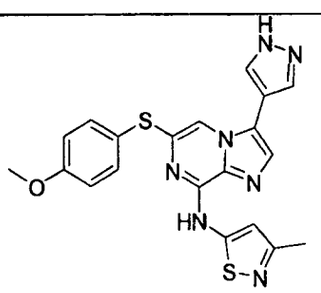
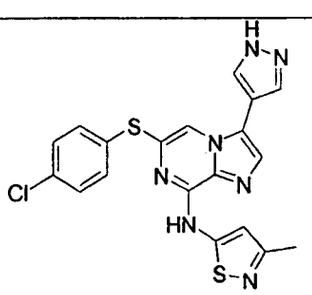
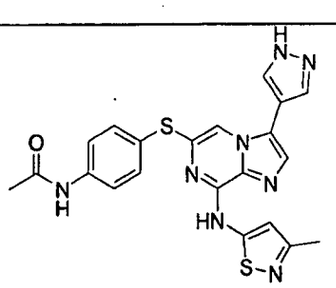
The compounds in shown immediately below in Table A were prepared by essentially the same procedure as in preparative example 4.

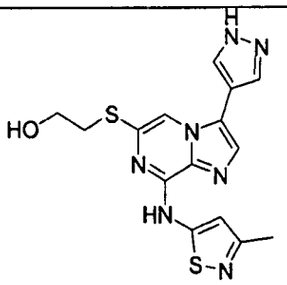
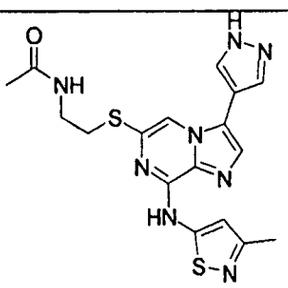
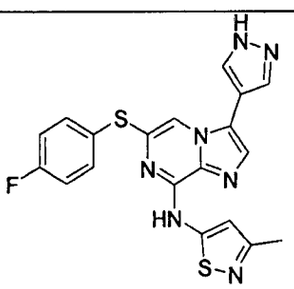
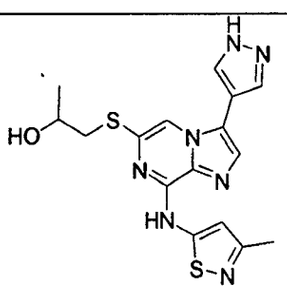
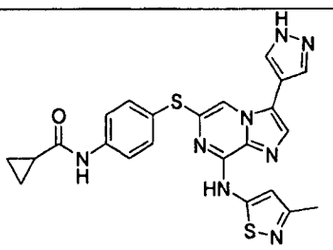
Table A

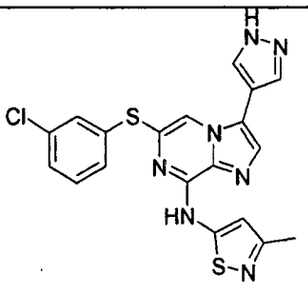
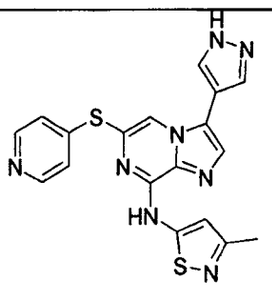
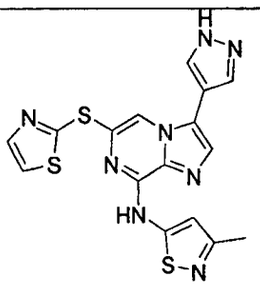
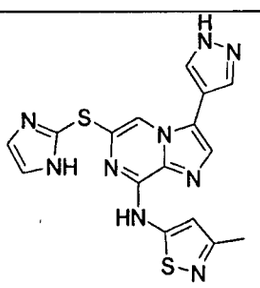
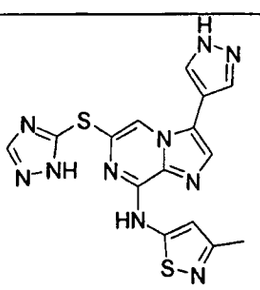
Example	*Compound*	*Exact mass*	*MS m/z (MH)+*	*HPLC MS t_R*

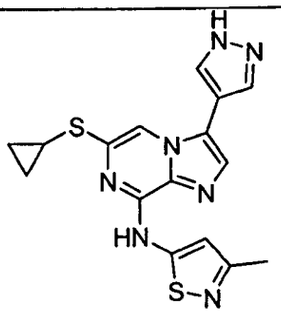
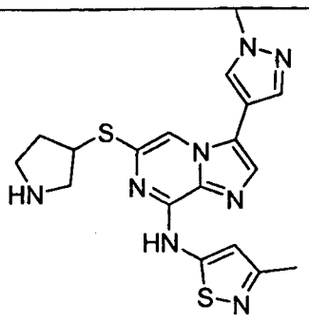
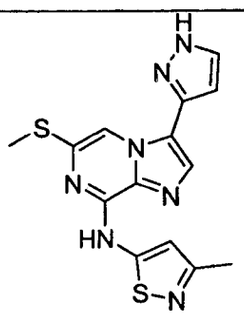
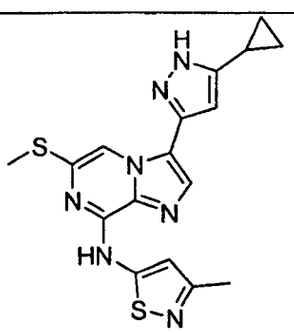
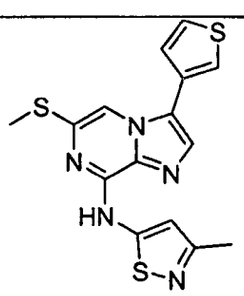
4-1		462	463	1.45
4-2		405	406	1.38
4-3		343	344	1.12
4-4		439.04	440.0	3.75
4-5		406.08	407.0	2.78

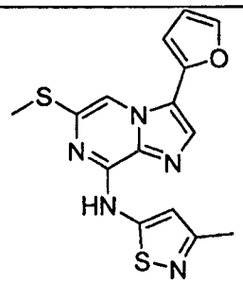
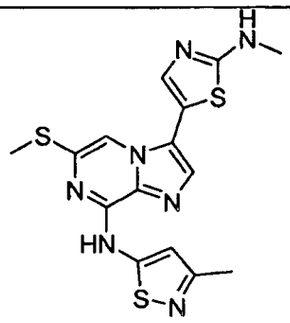
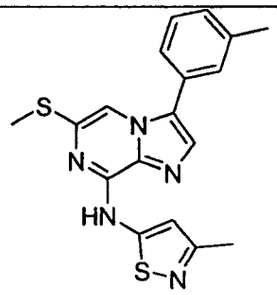
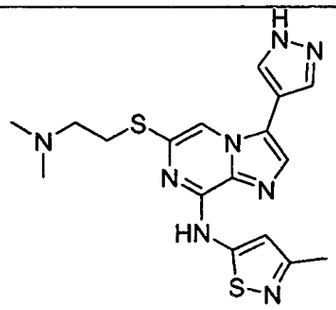
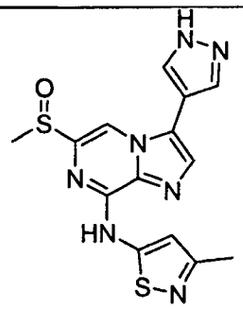
4-6		400.09	401.0	2.43
4-7		357.08	358.1	3.17
4-8		371.1	372.1	3.41
4-9		385.1	386.1	3.48

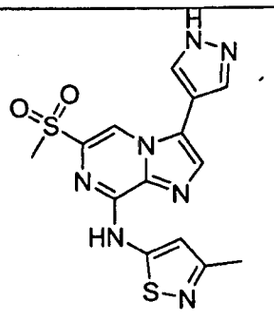
4-10		435.09	436.1	3.40
4-11		435.09	436.1	3.54
4-12		435.09	436.1	3.61
4-13		439.04	440.0	3.91
4-14		462.1	463.1	3.07

4-15		373.08	374.0	2.44
4-16		414.1	415.1	2.53
4-17		423.07	424.1	3.63
4-18		387.09	388.1	2.64
4-19		488.12	489.1	3.44

4-20		439.04	440.0	3.88
4-21		406.08	407.0	2.36
4-22		412.03	413.0	2.89
4-23		395.07	396.1	2.07
4-24		396.07	397.1	2.28

4-25		369.1	370.1	
4-26		412.1	413.1	2.5
4-27		343.1	344.1	1.38
4-28		383.1	384.1	1.48
4-29		395.0	396.0	5.63

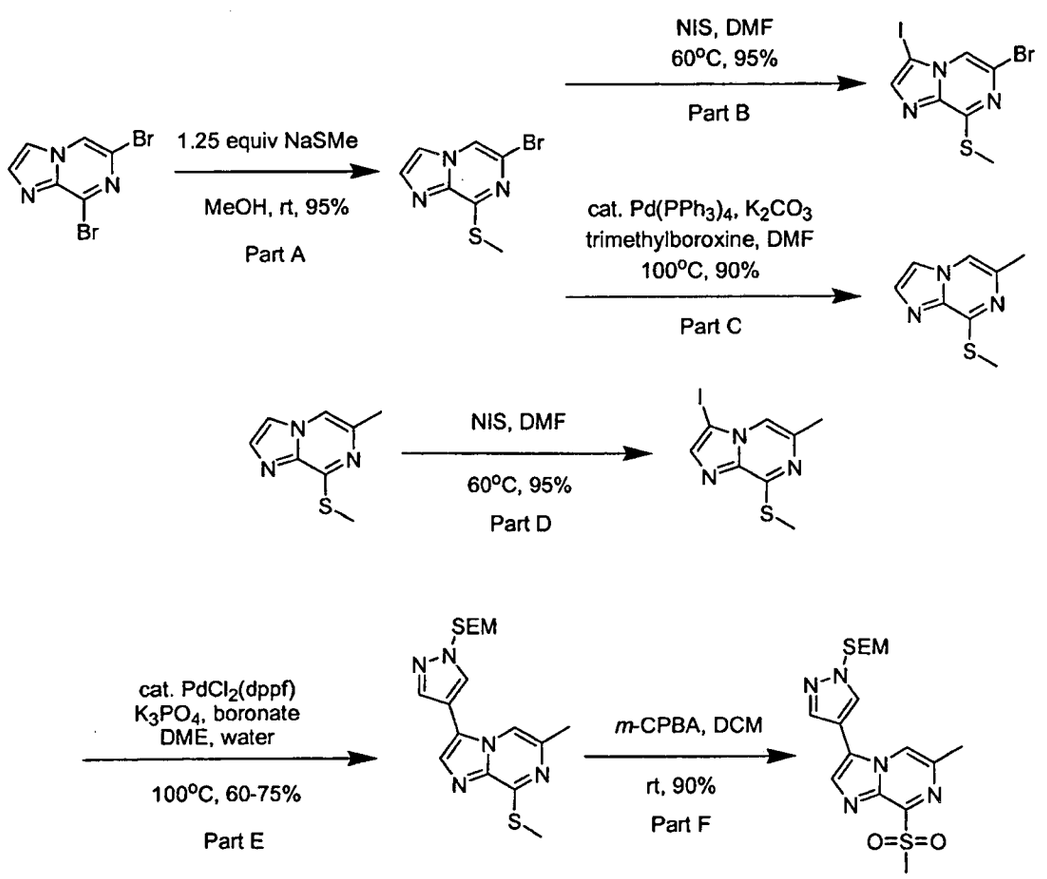
4-30		343.1	344.1	5.5
4-31		389.1	390.1	3.8
4-32		367.1	367.1	6.2
4-33		400.1	401.1	0.85
4-34		359.1	360.1	2.6

4-35		375.1	376.1	2.6

SYNTHESIS OF COMPOUNDS OF (i):

The synthesis of the compounds of paragraph (i) as described in U.S. applications, Serial No. 60/943999 filed June 14, 2007 and Serial No. 60/987932, filed November 14, 2007 is shown below.

EXAMPLE 1



Part A: Prepared according to US20060106023 (A1).

Part B: To a solution of compound from Example 1, Part A (2.00 g, 8.19 mmol) in DMF (50 mL) was added N-iodosuccinimide (1.84 g, 8.19 mmol). The reaction mixture was stirred at 60C for 16 hours. The mixture was cooled to 25C and concentrated. The residue was dissolved

in DCM with a small amount of methanol and then loaded on the column. Purification by column chromatography (SiO_2, 40% ethyl acetate/hexanes) afforded compound 4 as a white solid 2.30 g (76%). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.3 (s, 1H), 7.8 (s, 1H), 2.6 (s, 3H). HPLC-MS t_R = 1.87 Min (UV $_{254nm}$). Mass calculated for formula $C_7H_5BrIN3S$ 370.01, observed LC/MS m/z 370.9 (M+H).

Part C: A suspension of bromide from Part B (45.6 g), Pd(PPh3)4 (10.8 g), potassium carbonate (77.4 g), trimethylboroxine (46.9 g) and potassium carbonate (77.4 g) in DMF (410 mL) was heated overnight under nitrogen at 105C. After cooling, the mixture was diluted with ethyl acetate (1 L), washed with brine (2 x 500 mL), dried (magnesium sulfate), filtered, concentrated and purified by chromatography on silica gel. The title compound was obtained as a pale yellow solid (21.4 g, 64%).

Part D: To a DMF (400 mL) solution of compound from Example 1, Part C (21.8 g) was added N-iodosuccinimide (26.9 g) and the resulting mixture was heated overnight at 60C. The mixture was concentrated and water (400 mL) was added. After stirring 1 hr at rt, saturated sodium carbonate was added (250 mL) and subsequently stirred an additional 30 min at rt. The mixture was filtered, washed with water, methanol (100 mL) and the filter cake was dried overnight under vacuum. A brown solid was obtained (31.4 g, 87%).

Part E: A flask was charged with iodide from Part D (1.00 equiv), Bpin-compound 5a (1.3 equiv), PdCl2(dppf) (0.1 equiv) and potassium phosphate monohydrate (3.0 equiv). After purging the flask with argon, 1,4-dioxane (50 mL) and water (5) were added and the resulting mixture was heated at 80C overnight (23 h). The reaction was cooled to room temperature. EtOAc was added to the reaction mixture and filtered through Celite. After concentration the residue was purified by column chromatography (silica gel, 25% EtOAc/hexane) to give the title compound.

Part F: To a solution of compound from Example 1, Part E (1.0 equiv) in DCM (10 mL) was added *m*-CPBA (2.05 equiv) in one portion. The resulting mixture was stirred at room temperature for 30 min. The mixture was concentrated and then partitioned between EtOAc and water. The organic layer was washed with $NaHCO_3$ (sat. aq., twice), brine and dried (Na_2SO_4). After concentration, the title compound was obtained and used in the next step directly without further purification.

EXAMPLE 2



1 2

To a solution of 1[1] (1.04 g, 5.98 mmol) in 20 mL of DMF, was added K_2CO_3 (2.48 g, 17.9 mmol) and MeI (1.27 g, 8.96 mmol). The reaction was stirred at room temperature overnight. It was diluted with 200 mL of 50% EtOAc/hexanes and washed with water (200 mL) and brine (100 mL). The organic was concentrated. To the residue was added 20 mL of hexanes. The solid was collected by filtration to give 2. The filtrate was concentrated and purified by column eluting with 25% EtOAc/hexanes to give additional amount of 2. The combined yield of 2 is 1.05 g. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1H), 4.05 (s, 3H).

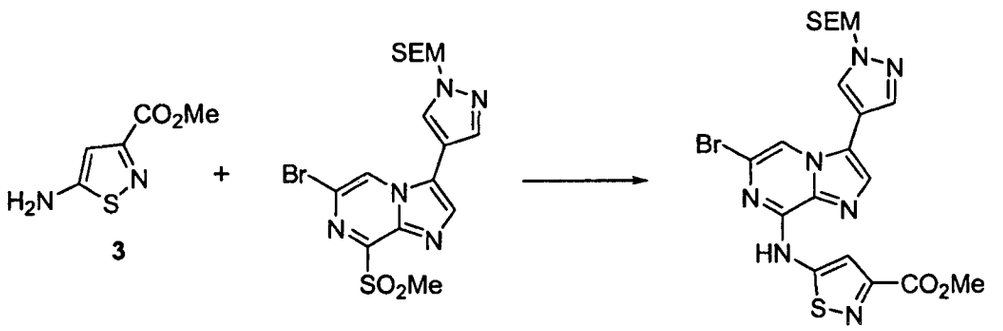
EXAMPLE 3



2 3

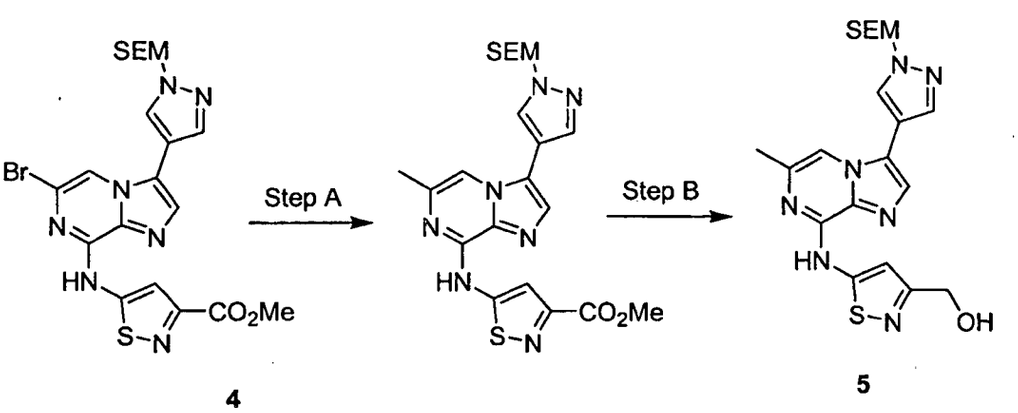
To a solution of 2 (260 mg, 1.38 mmol) in 6 mL of AcOH was added iron powder (774 mg, 13.8 mmol). The reaction mixture was heated at 70-75 °C for 12 min. The mixture was cooled to room temperature and then added 20 mL of MeOH. The resulting mixture was filtered through celite (the celite was rinsed with additional amount MeOH). The filtrate was concentrated to remove most of AcOH. To the residue was added 15 mL of 20% MeOH/CH_2Cl_2 followed by 20 mL of saturated aqueous $NaHCO_3$. The mixture was stirred until it stops bobbling. The mixture was extracted by EtOAc (60 mL x 2), dried over Na_2SO_4, and then concentrated. To the residue was added 5 mL of ether followed by 5 mL of hexanes. The solid was collected by filtration to give 160 mg of crude 3 which contains a little acylated amine but pure enough for the sulfone displacement reaction. The filtrate was purified by column with 20% of AcOEt/ CH_2Cl_2 to give additional 30 mg of 3. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85 (s, 1H), 4.61 (brs, 2H), 3.92 (s, 3H).

EXAMPLE 4



To a solution of compound 3 (89 mg, 0.56 mmol) and 6-bromo-8-methanesulfonyl-3-[1-(2-trimethylsilanyl-ethoxymethyl)-1H-pyrazol-4-yl]-imidazo[1,2-a]pyrazine (258 mg, 0.55 mmol) in 2 mL of DMF, was added NaH (60% dispersion in oil, 44 mg, 1.1 mmol). The reaction was stirred at room temperature for 15 min. It was quenched with 5 mL of saturated aqueous NH_4Cl and diluted with 30 mL of water. The solid was collected by filtration, washed with water and MeOH. It was dried under vacuum to give 255 mg of compound 4. ^1H NMR (400 MHz, DMSO-d_6) δ 8.85 (s, 1H), 8.22 (s, 1H), 8.15 (s, 1H), 7.96 (s, 1H), 7.62 (s, 1H), 5.50 (s, 2H), 3.85 (s, 3H), 3.60 (t, 2H), 1.83 (t, 2H), 0.00 (s, 9H).

EXAMPLE 5

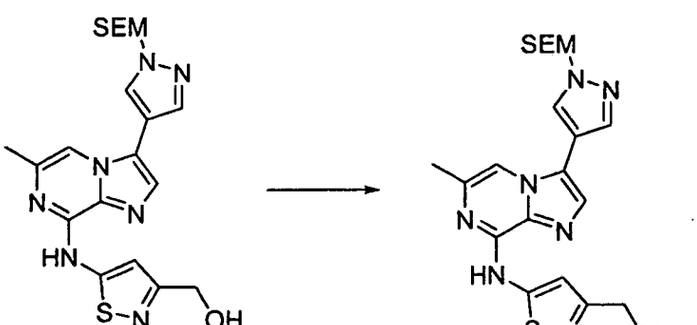


Step A: To a solution of 4 (76 mg, 0.14 mmol) in 6 mL of THF was added $Pd(PPh_3)_4$ (16 mg, 0.014 mmol) and 0.35 mL of MeZnCl (2 M solution in THF, 0.69 mmol). The reaction was stirred at 80 °C for 20 min. It was cooled to room temperature and quenched by adding 0.5 mL of MeOH. It was diluted with 30 mL of CH_2Cl_2 and washed with 20 mL of 0.5 N aqueous HCl solution. The solvent was removed under vacuum. The residue was purified by flash chromatography eluting with 5% MeOH/CH_2Cl_2 to give 50 mg of 5-{6-methyl-3-[1-(2-trimethylsilanyl-ethoxymethyl)-1H-pyrazol-4-yl]-imidazo[1,2-a]pyrazin-8-ylamino}-

isothiazole-3-carboxylic acid methyl ester contaminated by a small amount of triphenylphosphine oxide.

Step B: The above crude material was dissolved in 5 mL of THF. To the solution was added 0.5 mL of $LiBHEt_3$ (1 M solution in THF). The reaction was stirred at room temperature for 30 min. It was quenched by adding 5 mL of saturated aqueous NH_4Cl solution. The mixture was extracted by 30 mL of CH_2Cl_2. The organic was concentrated and purified by flash chromatography eluting with 5% MeOH/CH_2Cl_2 to give 25 mg of compound 5. NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.82 (s, 1H), 7.60 (s, 1H), 7.48 (s, 1H), 6.90 (s, 1H), 5.55 (s, 2H), 4.75 (brs, 2H), 3.65 (t, 2H), 2.50 (s, 3H), 1.00 (t, 2H), 0.00 (s, 9H).

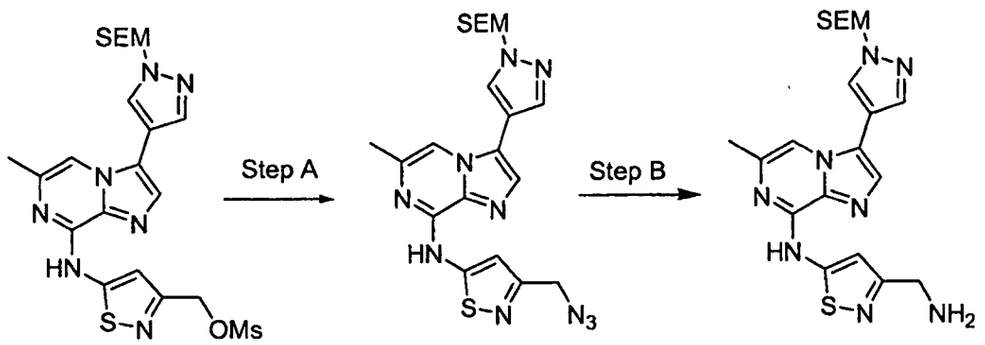
EXAMPLE 6



5 6

To a solution of compound 5 (200 mg, 0.438 mmol) in 20 mL of THF, was added triethylamine (0.21 mL, 1.5 mmol) and methanesulfonylchloride (0.10 mL, 1.3 mmol). The reaction was stirred at room temperature for 30 min. It was quenched by adding 1 mL of MeOH. The solution was diluted by 30 mL of CH_2Cl_2, washed consecutively with 15 mL of 2 N aqueous HCl, water, and brine. The solvent was removed under vacuum to give 230 mg of crude compound 6 which was used in further transformations without further purification.

EXAMPLE 7

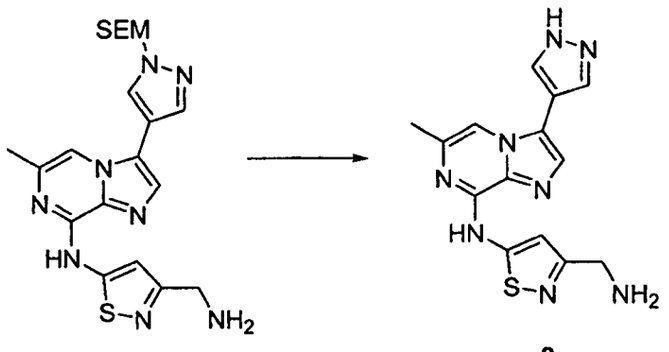


6 7

Step A: Mixture of compound 6 (17 mg, 0.032 mmol) and sodium azide (15 mg, 0.23 mmol) in 1 mL of DMF was heated at 70 °C for 3 h. It was cooled to room temperature and added 10 mL of water. The resulting solid was collected by filtration and purified by flash chromatography eluting with 5% MeOH/CH_2Cl_2 to give 12 mg of (3-azidomethyl-isothiazol-5-yl)-{6-methyl-3-[1-(2-trimethylsilanyl-ethoxymethyl)-1H-pyrazol-4-yl]-imidazo[1,2-a]pyrazin-8-yl}-amine.

Step B: The above material was dissolved in 3 mL of MeOH. To the solution was added 15 mg of 10% wt. Pd/C. The mixture was stirred under H_2 (1 atm) for 1 h. It was filtered through celite. The filtrate was concentrated under vacuum to give 12 mg of compound 7. NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.80 (s, 1H), 7.60 (s, 1H), 7.47 (s, 1H), 6.86 (s, 1H), 5.55 (s, 2H), 4.00 (brs, 2H), 3.65 (t, 2H), 2.50 (s, 3H), 1.00 (t, 2H), 0.00 (s, 9H).

EXAMPLE 8

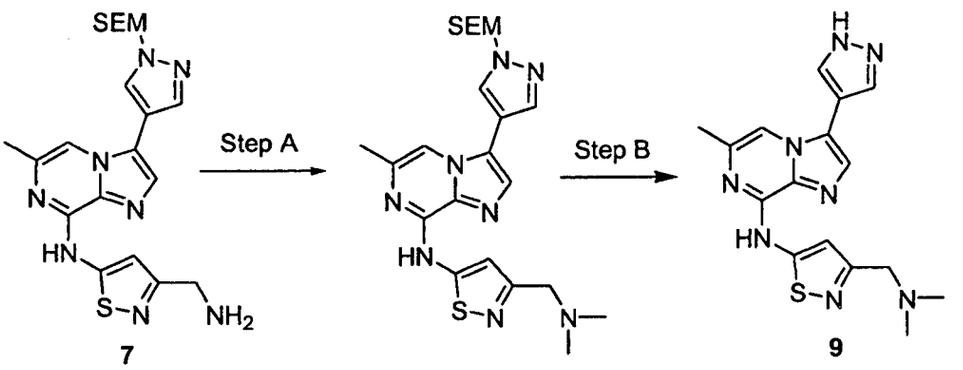


7 8

To a solution of compound 7 (12 mg, 0.026 mmol) in 2 mL of THF heated at 70 °C, was added 0.5 mL of 4 N HCl in dioxane. To the resulting mixture was added MeOH until it became homogeneous. The reaction was stirred at 70 °C for 1 h and then cooled to room temperature. The solid was collected by filtration and washed with ether to give 9 mg of compound 8 as its HCl salt form. NMR (400 MHz, CD_3OD) δ 8.23 (s, 1H), 8.20 (s, 2H), 8.03 (s, 1H), 7.20 (s,

1H), 4.22 (s, 2H), 2.59 (s, 3H). HPLC-MS t_R = 1.82 min (UV $_{254nm}$). Mass calculated for formula $C_{14}H_{14}N_8S$ 326.1; observed MH^+ (LCMS) 327.2 (m/z).

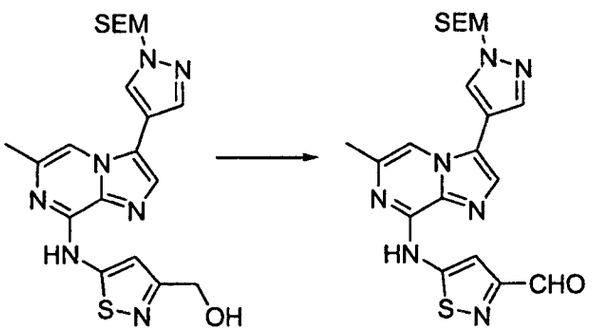
EXAMPLE 9



Step A: To a solution of compound 7 (9 mg, 0.02 mmol) in 1 mL of MeOH/CH_2Cl_2 (1:1), was added formaldehyde (40% wt. in water, 6 mg, 0.2 mmol). It was stirred at room temperature for 15 min when $NaBH_4$ (16 mg, 0.4 mmol) was added in two portions. The mixture was purified by flash chromatography eluting with NH4Cl (aq.)/MeOH/CH_2Cl_2 (1:5:190) to give 5 mg of (3-dimethylaminomethyl-isothiazol-5-yl)-{6-methyl-3-[1-(2-trimethylsilanyl-ethoxymethyl)-1H-pyrazol-4-yl]-imidazo[1,2-a]pyrazin-8-yl}-amine.

Step B: The above material was then dissolved in 2 mL of THF. The resulting solution was heated at 70 °C when 0.5 mL of 4 N HCl in dioxane was added. To the resulting mixture was added 1 mL of MeOH. The reaction was stirred at 70 °C for 1 h and then cooled to room temperature. Most of the solvent was removed under vacuum. To the residue was added 5 mL of ether. The solid was collected by filtration and washed with ether to give 5 mg of compound 9 as its HCl salt form. NMR (400 MHz, CD_3OD) δ 8.21 (s, 1H), 8.18 (s, 2H), 8.08 (s, 1H), 7.30 (s, 1H), 4.42 (s, 2H), 2.95 (s, 6H), 2.59 (s, 3H). HPLC-MS t_R = 2.04 min (UV $_{254nm}$). Mass calculated for formula $C_{16}H_{18}N_8S$ 354.1; observed MH^+ (LCMS) 355.2 (m/z).

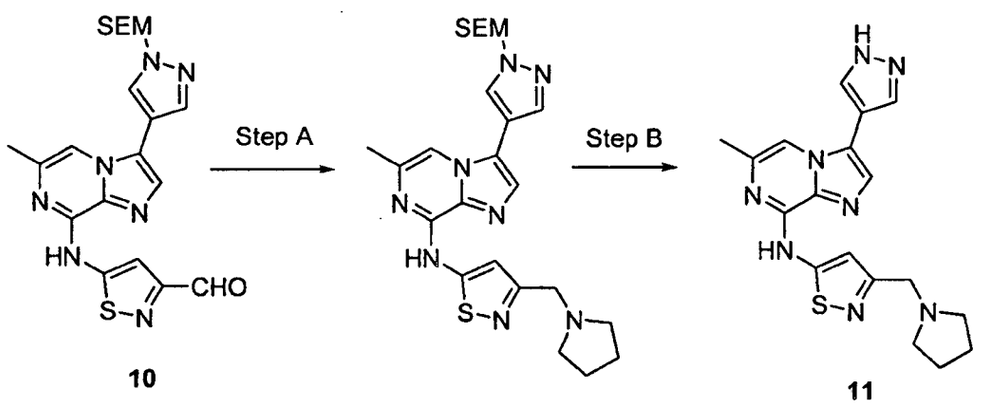
EXAMPLE 10



5 10

To a solution of compound 5 (2.50 g, 5.47 mmol) in 100 mL of THF, was added 0.3 mL of water followed by Dess-Martin periodinane (6.96 g, 16.4 mmol). The reaction was stirred at room temperature for 30 min. The solid was filtered off. The filtrate was diluted with 200 mL of CH_2Cl_2, and washed with 100 mL of saturated aqueous NH_4Cl solution. The organic was dried over anhydrous Na_2SO_4 and then concentrated. To the residue was added 30 mL of acetonitrile. The solid was collected by filtration to give 2.05 g of compound 10. NMR (400 MHz, DMSO-d_6) δ 12.38 (s, 1H), 9.84 (s, 1H), 8.60 (s, 1H), 8.11 (s, 1H), 7.96 (s, 1H), 7.91 (s, 1H), 7.55 (s, 1H), 5.50 (s, 2H), 3.60 (t, 2H), 2.45 (s, 3H), 1.83 (t, 2H), 0.00 (s, 9H).

EXAMPLE 11



10 11

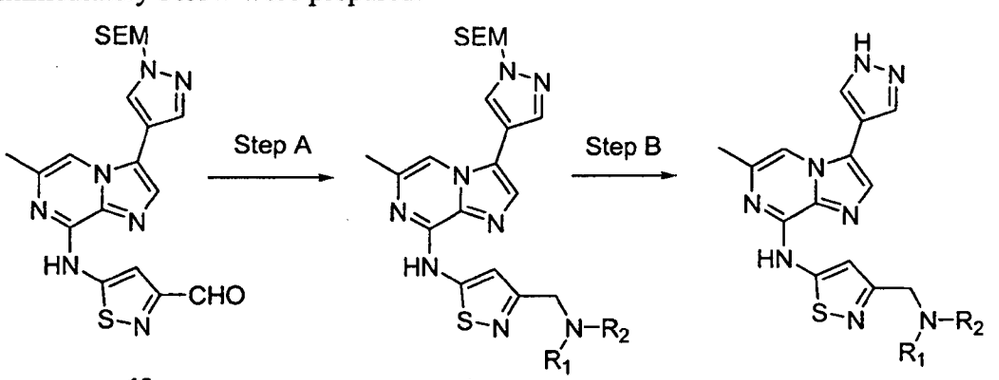
Step A: A solution of compound 10 (100 mg, 0.220 mmol) and pyrrolidine (156 mg, 2.20 mmol) in 14 mL of CH_2Cl_2 was stirred at room temperature for 20 min. To the solution was added two drops of acetic acid, followed by $NaBH_4$ (67 mg, 1.8 mmol). The resulting mixture was stirred at room temperature for 5 min when 3 mL of MeOH was added. The stirring was continued for additional 20 min. The reaction was quenched by adding 15 mL of saturated aqueous $NaHCO_3$ solution. After diluted with 20 mL of CH_2Cl_2, the organic was isolated. The solvent was removed under vacuum. The residue was purified by flash chromatography

eluting with NH_4Cl (aq.)/MeOH/CH_2Cl_2 (1:10:190) to give 98 mg of {6-methyl-3-[1-(2-trimethylsilanyl-ethoxymethyl)-1H-pyrazol-4-yl]-imidazo[1,2-a]pyrazin-8-yl}-(3-pyrrolidin-1-ylmethyl-isothiazol-5-yl)-amine. NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.81 (s, 1H), 7.60 (s, 1H), 7.48 (s, 1H), 6.96 (s, 1H), 5.55 (s, 2H), 3.80 (s, 2H), 3.65 (t, 2H), 2.70 (brs, 4H), 2.50 (s, 3H), 1.85 (brs, 4H), 0.96 (t, 2H), 0.00 (s, 9H).

Step B: To a solution of {6-methyl-3-[1-(2-trimethylsilanyl-ethoxymethyl)-1H-pyrazol-4-yl]-imidazo[1,2-a]pyrazin-8-yl}-(3-pyrrolidin-1-ylmethyl-isothiazol-5-yl)-amine (98 mg, 0.19 mmol) in 8 mL of THF heated at 70 °C, was added 2 mL of 4 N HCl in dioxane. To the resulting mixture was added MeOH until it became homogeneous. The reaction was stirred at 70 °C for 1 h and then cooled to room temperature. To the mixture was added 3 mL of ether. The solid was collected by filtration and washed with ether to give 79 mg of compound 11 as its HCl salt form. NMR (400 MHz, CD_3OD) δ 8.18 (s, 2H), 8.13 (s, 1H), 8.00 (s, 1H), 7.22 (s, 1H), 4.50 (s, 2H), 3.62-3.68 (m, 2H), 3.06-3.15 (m, 2H), 2.58 (s, 3H), 1.95-2.22 (m, 4H). HPLC-MS t_R = 2.03 min (UV $_{254nm}$). Mass calculated for formula $C_{18}H_{20}N_8S$ 380.2; observed MH^+ (LCMS) 381.2 (m/z).

EXAMPLE 12

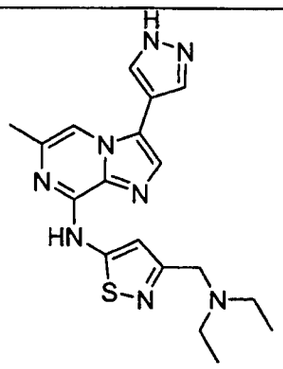
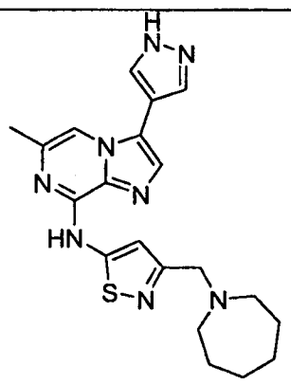
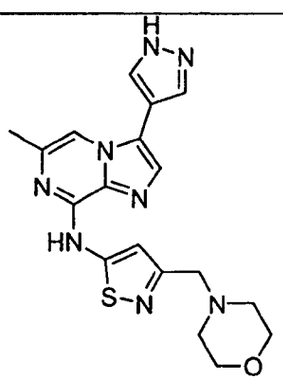
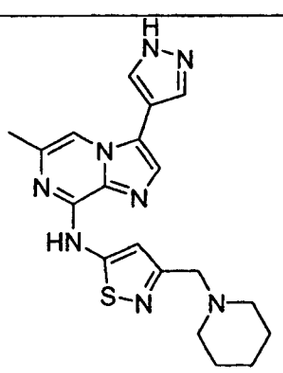
By essentially the same procedure set forth in Example 11, only replacing pyrrolidine with other respective aliphatic amines in step A, compounds shown in column 2 of Table 1 shown immediately below were prepared.

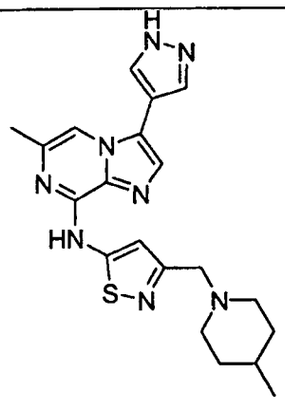
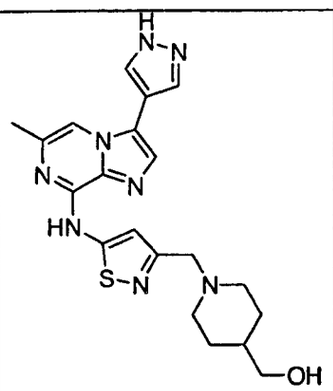
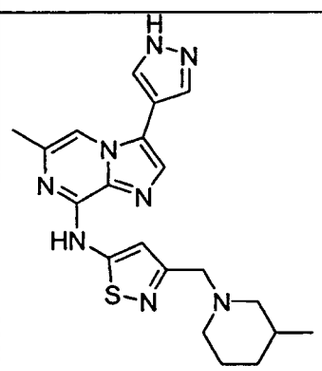
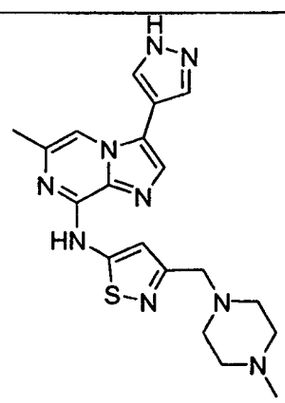


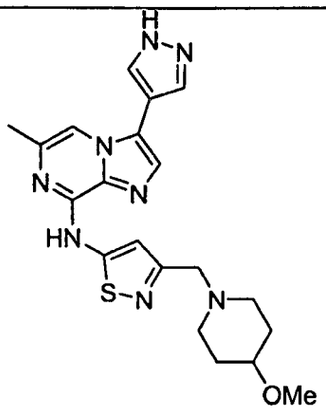
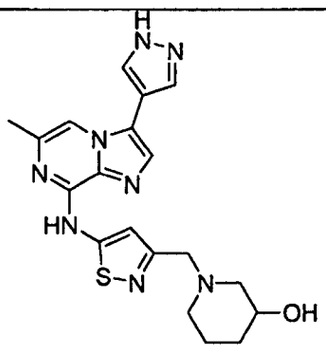
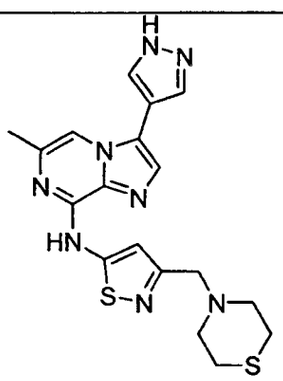
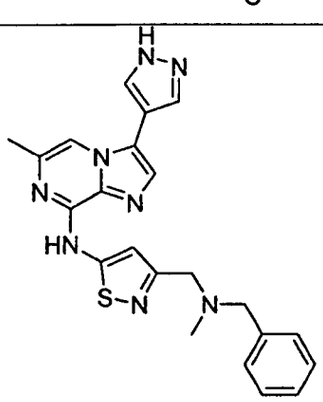
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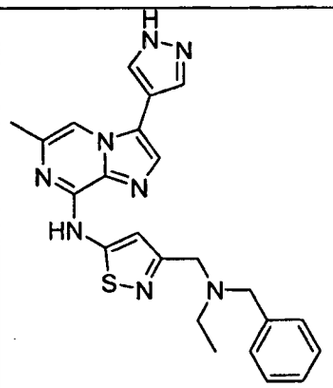
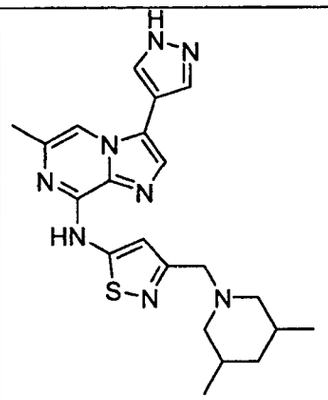
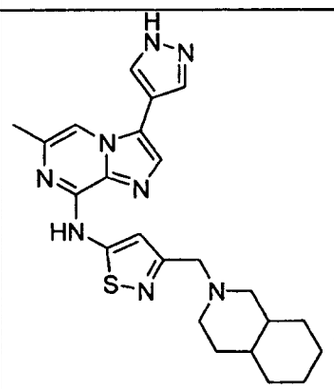
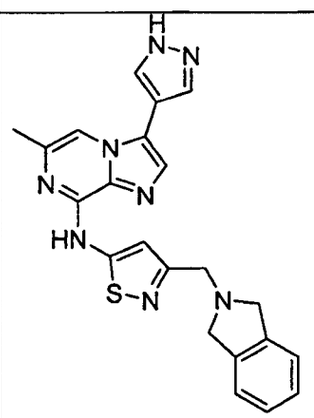
TABLE 1

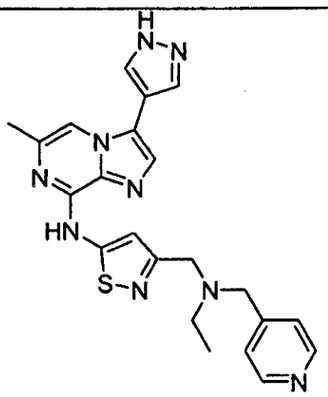
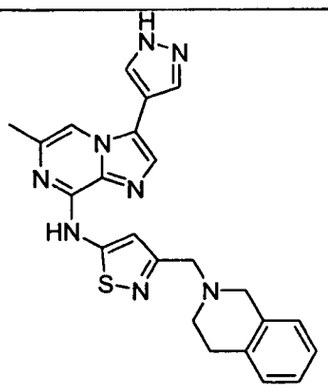
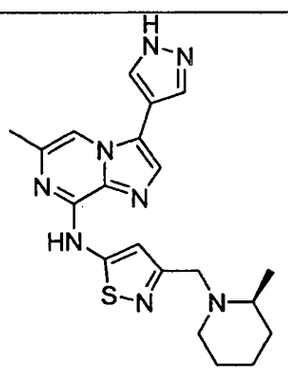
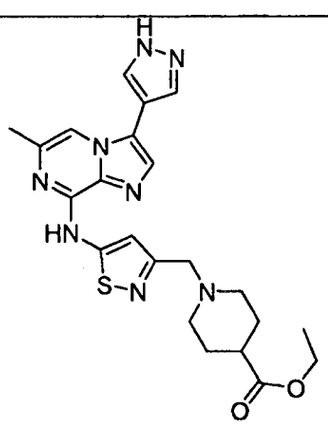
Example	Column 2	MW	LCMS MH^+ m/z	HPLC MS t_R

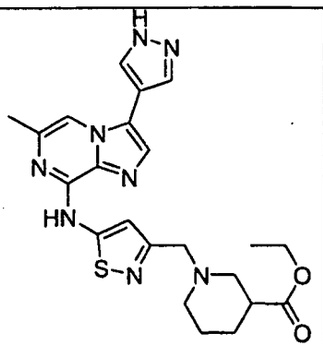
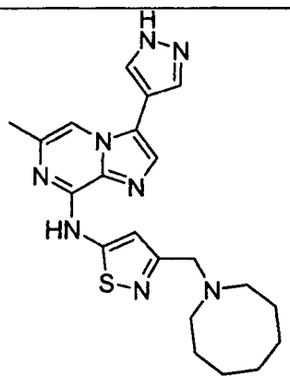
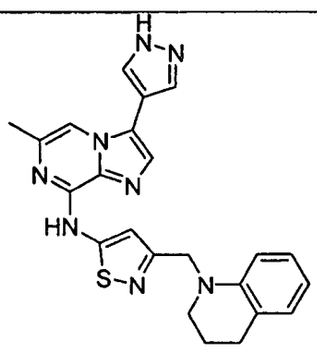
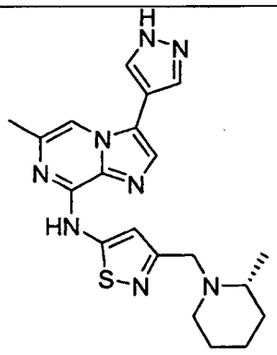
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12-2		408.5	409.2	2.31
12-3		396.5	229.2	1.49
12-4		394.5	395.2	2.18

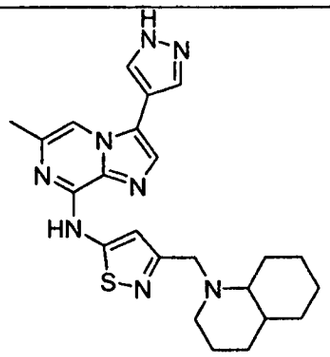
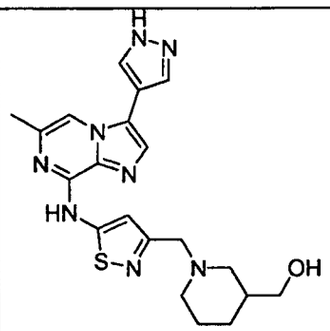
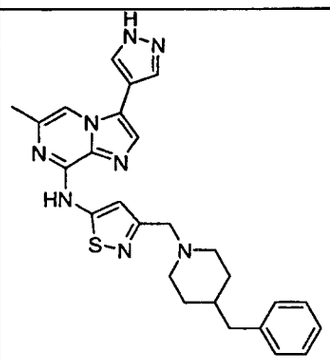
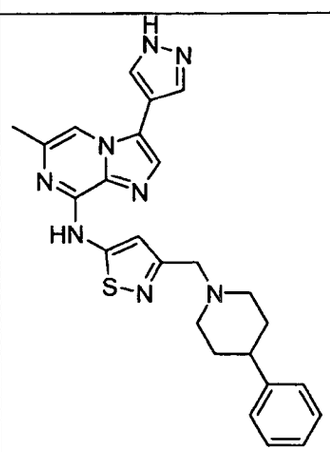
12-5		408.5	409.2	2.26
12-6		424.5	425.2	1.95
12-7		408.5	409.2	2.35
12-8		409.5	410.2	1.76

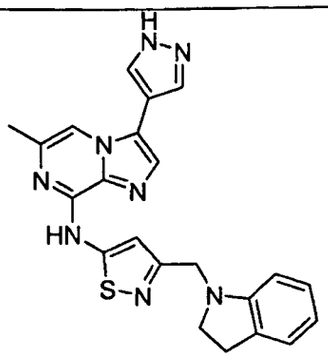
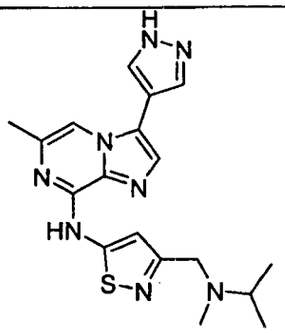
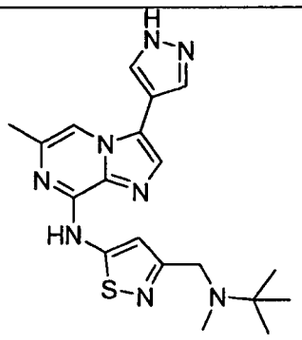
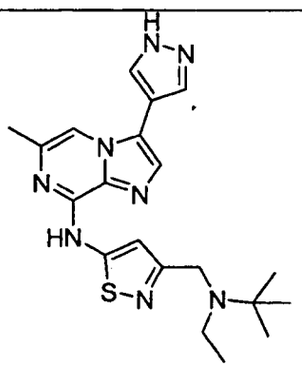
12-9		424.5	425.2	2.18
12-10		410.5	411.2	2.04
12-11		412.5	413.2	2.23
12-12		430.5	431.2	2.35

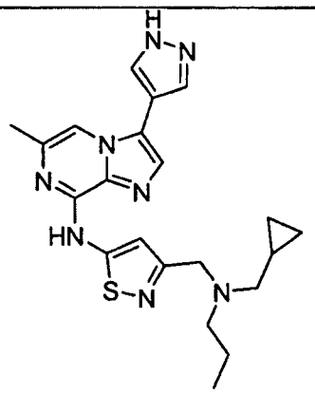
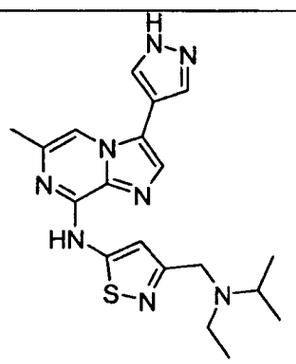
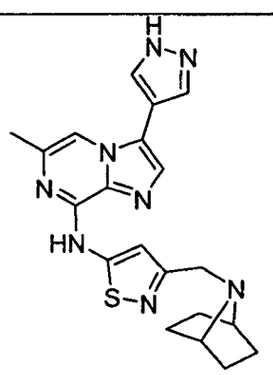
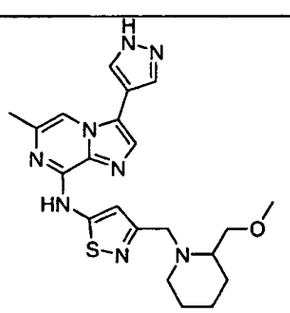
12-13		444.6	445.2	2.40
12-14		422.5	423.2	2.50
12-15		448.6	449.2	2.69
12-16		428.5	429.2	2.34

12-17		445.5	446.2	1.76
12-18		442.5	443.2	2.39
12-19		408.5	409.2	2.15
12-20		466.6	467.3	2.23

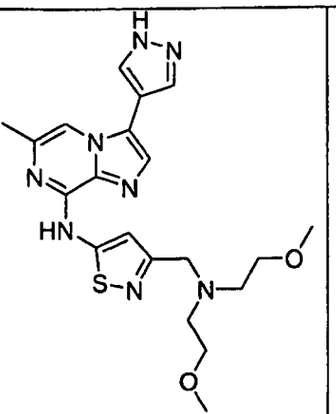
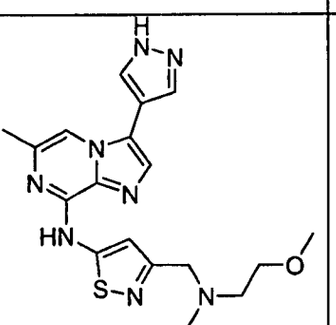
12-21		466.6	467.3	2.24
12-22		422.5	423.2	2.41
12-23		442.5	443.2	3.51
12-24		408.5	409.2	2.32

12-25		448.5	449.2	2.65
12-26		424.5	425.2	2.07
12-27		484.6	485.3	2.79
12-28		470.6	471.3	2.60

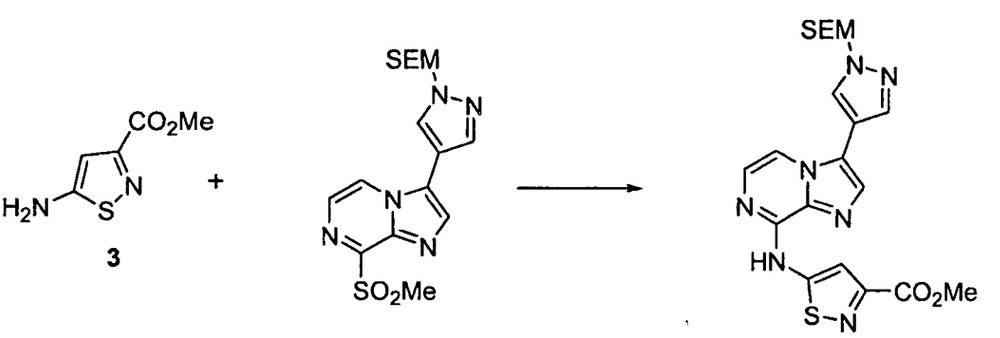
12-29		428.5	429.2	3.27
12-30		382.17	393.17	1.97
12-31		396.18	397.18	2.01
12-32		410.20	411.20	2.04

12-33		422.20	423.20	2.52
12-34		396.18	397.18	2.25
12-35		406.17	407.17	2.24
12-36		438.20	439.20	2.36

160

12-37		442.19	443.19	2.30
12-38		398.16	399.16	2.12

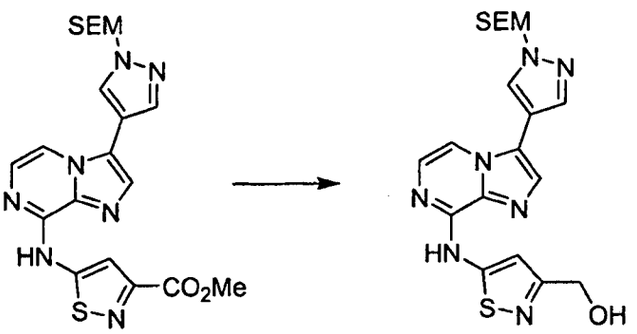
EXAMPLE 13



3 13

By essentially the same procedure set forth in Example 4, only replacing 6-bromo-8-methanesulfonyl-3-[1-(2-trimethylsilanyl-ethoxymethyl)-1H-pyrazol-4-yl]-imidazo[1,2-a]pyrazine with 8-methanesulfonyl-3-[1-(2-trimethylsilanyl-ethoxymethyl)-1H-pyrazol-4-yl]-imidazo[1,2-a]pyrazine, compound 13 was prepared. NMR (400 MHz, DMSO-d_6) δ 8.66 (s, 1H), 8.22 (d, 1H), 8.21 (s, 1H), 8.03 (s, 1H), 7.82 (d, 1H), 5.58 (s, 2H), 3.96 (s, 3H), 3.69 (t, 2H), 3.40 (s, 1H), 0.95 (t, 2H), 0.02 (s, 9H).

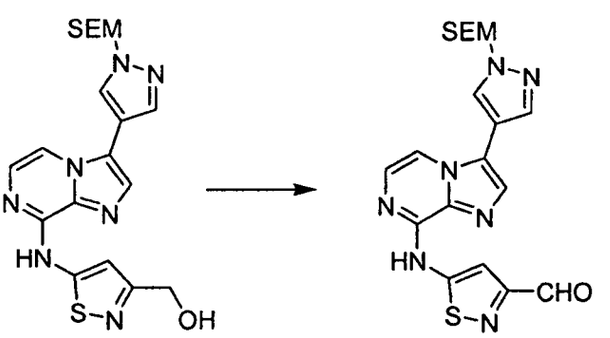
EXAMPLE 14



13 14

To a solution of compound 13 (830 mg, 1.76 mmol) in 50 mL of CH_2Cl_2 stirred at 0 °C, was added 7.05 mL of $LiBHEt_3$ (1 M solution in THF). The reaction was stirred at room temperature for 10 min. It was quenched by adding saturated aqueous NH_4Cl solution. The organic was separated and washed with saturated aqueous $NaHCO_3$ solution. The solvent was removed under vacuum. To the residue was added 10 mL of MeOH. The solid was collected by filtration to give 530 mg of compound 14. NMR (400 MHz, CD_3OD) δ 8.38 (s, 1H), 7.98 (s, 1H), 7.97 (d, 2H), 7.78 (s, 1H), 7.69 (d, 2H), 7.15 (s, 1H), 5.55 (s, 2H), 4.62 (s, 2H), 3.66 (t, 2H), 0.92 (t, 2H), 0.00 (s, 9H).

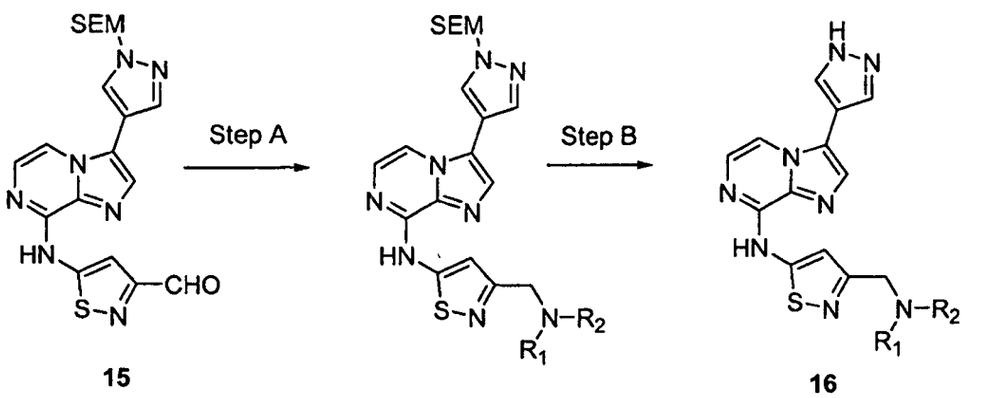
EXAMPLE 15



14 15

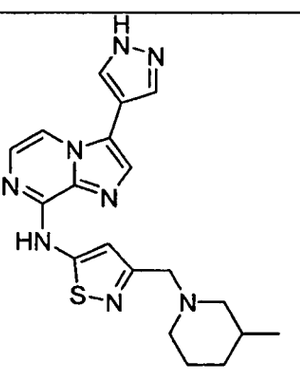
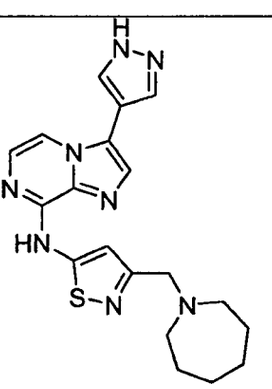
To a solution of compound 14 (258 mg, 0.582 mmol) in 20 mL of THF, was added 0.05 mL of water followed by Dess-Martin periodinane (740 mg, 1.75 mmol). The reaction was stirred at room temperature for 1.5 h. The solid was filtered off. The filtrate was diluted with 100 mL of CH_2Cl_2, and washed with water and brine. The solvent was removed under vacuum, the residue was purified by flash chromatography eluting with 5% of MeOH/CH_2Cl_2 to give 230 mg of compound 15.

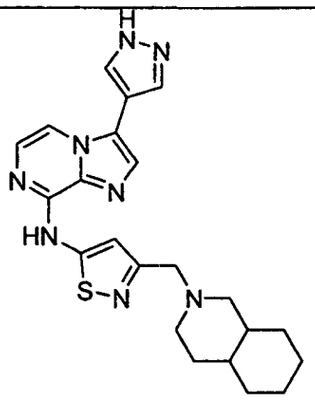
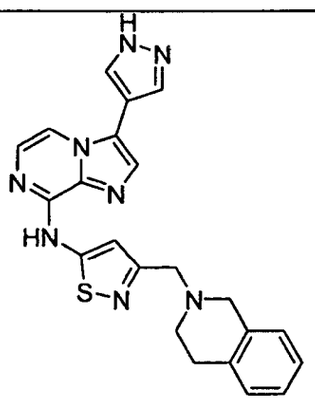
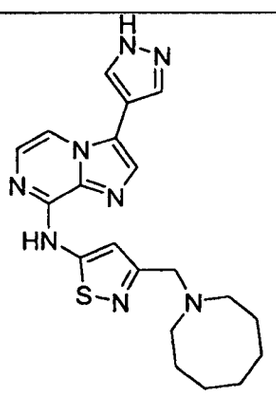
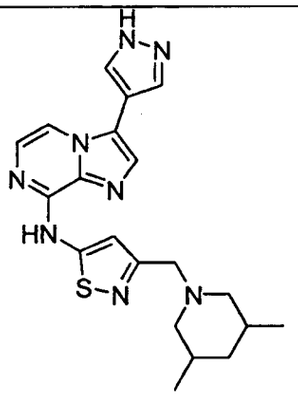
EXAMPLE 16

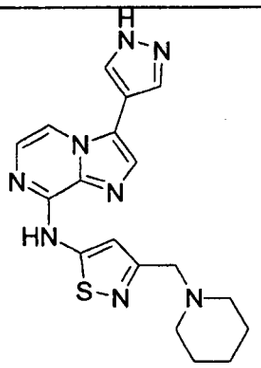
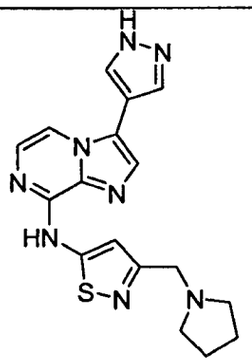


By essentially the same procedure set forth in Example 11, compounds shown in column 2 of Table 2 (shown immediately below) were prepared by replacing compound 10 with compound 15, and replacing pyrrolidine with other respective aliphatic amines in step A.

TABLE 2

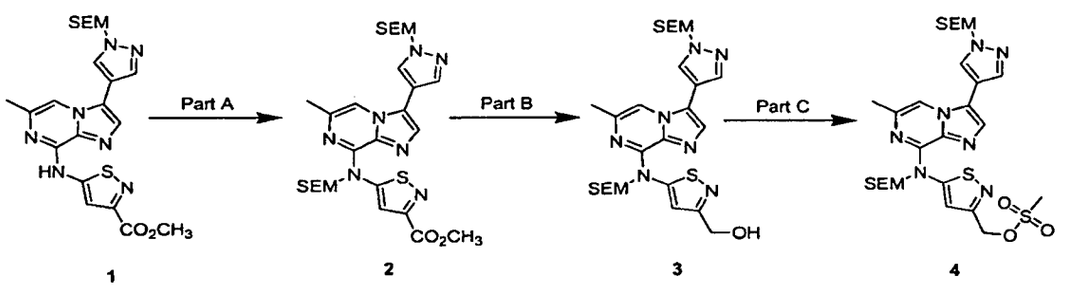
Example	Column 2	MW	LCMS MH^+ m/z	HPLC MS t_R
16-1		394.5	395.2	2.02
16-2		394.5	395.2	2.13

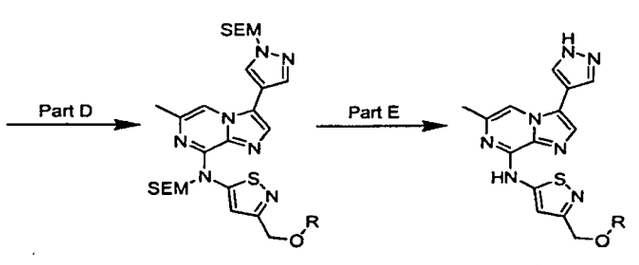
16-3		434.6	435.2	2.50
16-4		428.5	429.2	2.22
16-5		408.5	409.2	2.18
16-6		408.5	409.2	2.21

16-7		381.2	382.2	2.55
16-8		366.14	367.14	2.43

1) Walsh R.J.A.; Wooldridge, K. R. H. *J. Chem. Soc. Perkin Trans.* 1972, 1247.

EXAMPLE 17





Part A: A solution of ester (2.38 g, 4.91 mmol, 1 equivalent) in DMF (40 mL) was treated with NaH (60% dispersion in oil, 1.5 equivalents) for 20 min at rt, at which time, the reaction mixture was cooled to -10C and 2-(trimethylsilyl)ethoxymethyl chloride (0.87 mL, 1 equivalent) added to the reaction mixture. The resulting solution was allowed to slowly warm

to rt and continued to stir at rt for a further 1h. LC-MS analysis indicated the reaction was complete. The reaction was quenched with methanol (15 mL), diluted with ethyl acetate (300 mL) and washed with sat. sodium bicarbonate, water, brine, dried (sodium sulfate) and concentrated. Purification by column chromatography (SiO_2 40% ethyl acetate / hexanes) afforded the desired product as a yellow solid 1.2 g (40%). HPLC-MS t_R = 2.79 Min (UV $_{254nm}$). Mass calculated for formula $C_{27}H_{41}N_7O_4SSi_2$ 615.25, observed LC/MS m/z 616.2 (M+H).

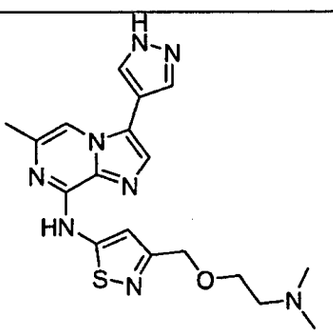
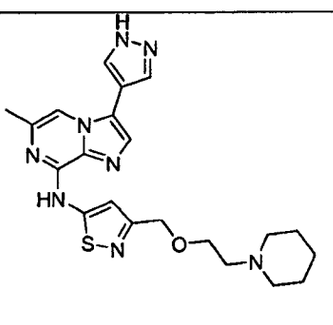
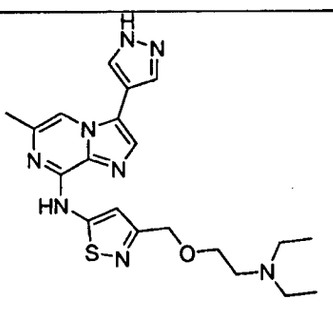
Part B: To a solution of compound from Part A (1.2 g, 1.90 mmol, 1 equivalent) in THF (100 mL) was added superhydride solution (4 equivalents) at rt. The resulting solution was stirred at rt for 30 minutes at which time LC-MS analysis indicated the reaction was complete. The reaction was quenched with sat. aq. ammonium chloride and then extracted with dichloromethane (x2). The combined organic layers were dried (sodium sulfate) and concentrated. Purification by column chromatography (SiO_2 60 % ethyl acetate / hexanes) afforded alcohol as a clear oil (47%). HPLC-MS t_R = 2.49 Min (UV $_{254nm}$). Mass calculated for formula $C_{26}H_{41}N_7O_3SSi_2$ 587.25, observed LC/MS m/z 588.3 (M+H).

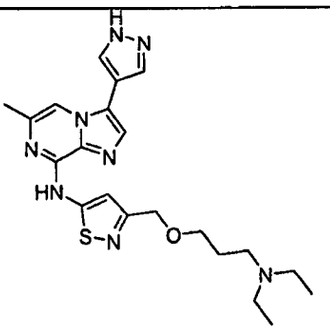
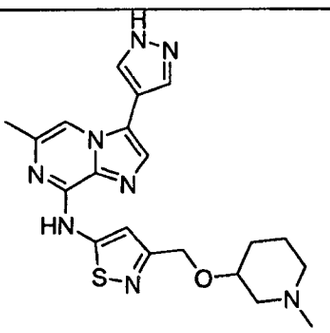
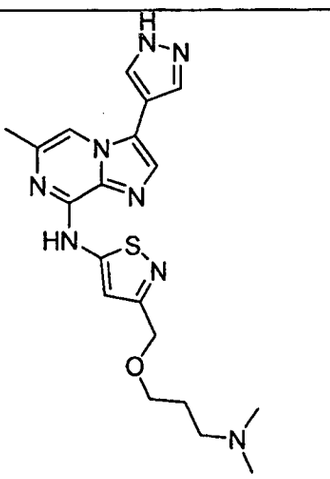
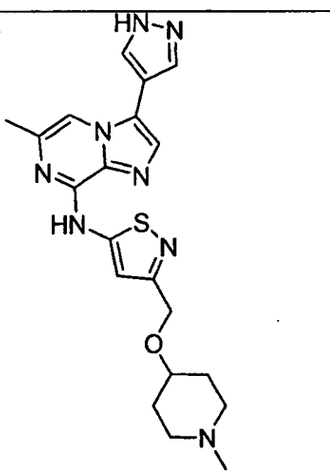
Part C: A solution of alcohol from Part B (0.52 g, 0.88 mmol, 1 equivalent) in DCM (15 mL) was treated with triethylamine (1.5 equivalents) for 15 min at 0C (ice-bath), at which time, methanesulfonyl chloride (1.2 equivalents) was added to the reaction at 0C. The resulting solution was allowed to slowly warm to rt and continued to stir at rt for a further 3h. LC-MS analysis indicated the reaction was complete. The reaction mixture was diluted with ethyl acetate (100mL) and washed with water, brine, dried (anh. sodium sulfate) and concentrated to afford mesylate as a red/brown oil 0.59 g (100%) which was used without further purification. HPLC-MS t_R = 2.66 Min (UV $_{254nm}$). Mass calculated for formula C27H43N7O5S2Si2 665.23, observed LC/MS m/z 666.1 (M+H).

Part D: A solution of the respective alcohol (3 equivalents) in THF (1.5 mL) was treated with NaH (60% dispersion in oil, 2 equivalents) for 15 min at rt, at which time, mesylate from Part C (40 mg, 0.06 mmol, 1 equivalent) was added to the reaction mixture. After stirring at rt for 1h, LC-MS analysis indicated the reaction was complete. The reaction was quenched with sat. aq. ammonium chloride and then extracted with ethyl acetate (twice). The combined organic layer was dried (sodium sulfate) and concentrated to afford crude ether, which was used without further purification.

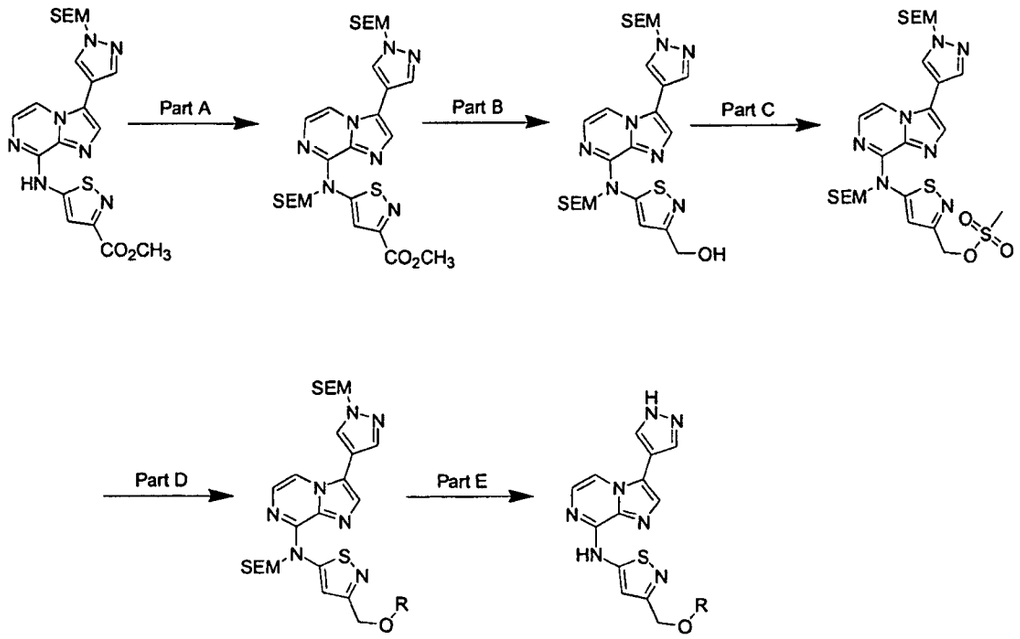
Part E: A solution of compound from Part D in 1,4-dioxane (1 mL) was treated with 4N HCl in 1,4-dioxane solution (1 mL) at 60C for 10 min at which time HPLC-MS indicated that the reaction was complete. The solvent was removed and the residue was purified by Prep-LC. Conversion to a hydrochloric salt afforded compounds listed in Table 3(shown immediately below):

TABLE 3

Example	Column 2	MW	LCMS MH^+ m/z	HPLC MS t_R
17-1		398.16	399.2	2.55
17-2		438.2	439.3	2.79
17-3		426.2	427.3	2.68

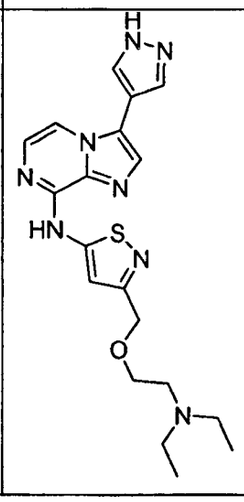
17-4		440.21	441.2	2.75
17-5		424.18	425.2	2.59
17-6		412.18	413.2	2.54
17-7		424.18	425.2	2.61

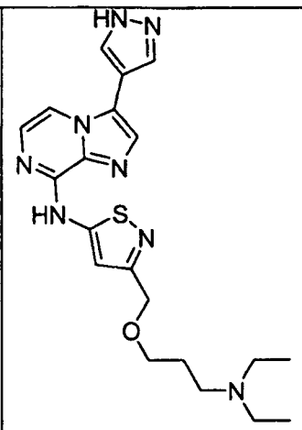
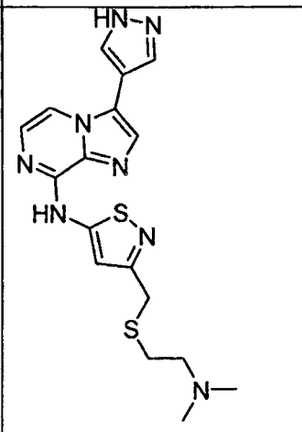
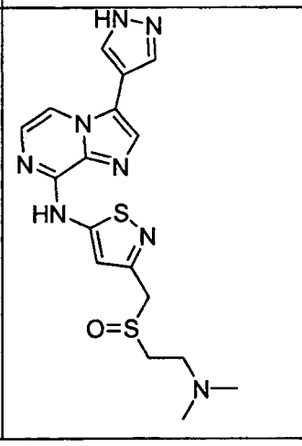
EXAMPLE 18



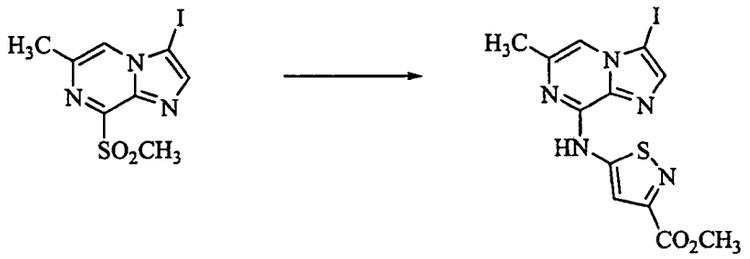
By essentially the same procedures given in Preparative Example 17, compounds given in Table 4 (shown immediately below) can be prepared.

TABLE 4

Example	Column 2	Exact mass	MS m/z (M+H)	HPLC MS t_R
18-1		412.18	413.2	2.36

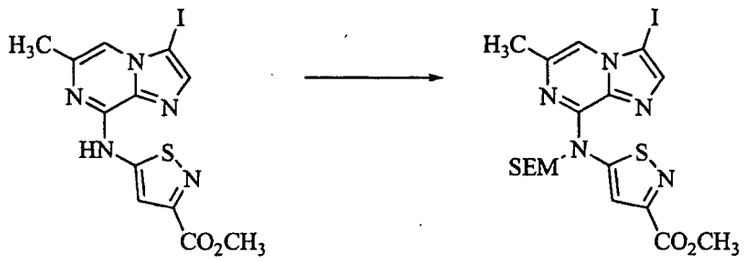
18-2		426.2	427.1	2.71
18-3		400.13	401.1	2.47
18-4		416.12	417.1	2.23

EXAMPLE 19



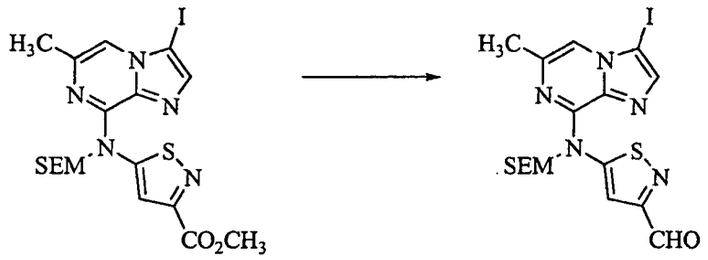
Example 19 was prepared in similar manner to Example 4. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.4 (bs, 1H), 7.81 (s, 1H), 7.75 (s, 1H), 7.59 (s, 1H), 3.85 (s, 3H), 2.49 (s, 3H).

EXAMPLE 20



Example 20 was prepared in similar manner to Example 17, Part A. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.73 (s, 1H), 7.63 (s, 1H), 6.61 (s, 2H), 3.98 (s, 3H), 3.74 (t, J = 8 Hz, 2H), 2.62 (s, 3H), 0.94 (t, J = 8 Hz, 2H), -0.83 (s, 9H).

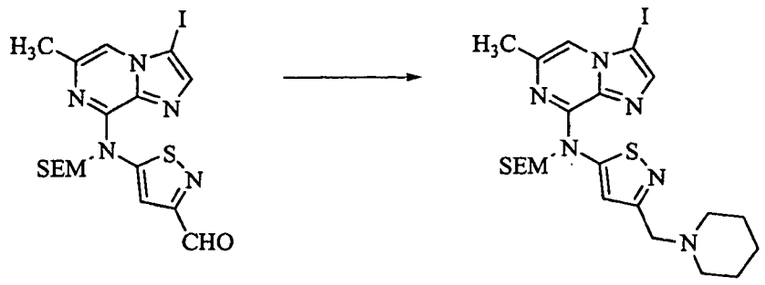
EXAMPLE 21



To a stirring solution of ester (2.40 g, 4.40 mmol) in tetrahydrofuran (96 mL) at –78 °C was added DIBAL-H (1M in dichloromethane, 11.0 mL, 11.0 mmol) dropwise. The mixture was stirred at –78 °C for 3 hours at which time thin layer chromatography (30% ethyl acetate/hexanes) indicated the reaction was complete. The mixture was quickly poured into stirring saturated aqueous sodium potassium tartrate and stirred at room temperature for 14 hours. The mixture was extracted with ethyl acetate (2×250 mL), the organic layers were combined, washed with brine (100 mL), dried over magnesium sulfate, filtered, and

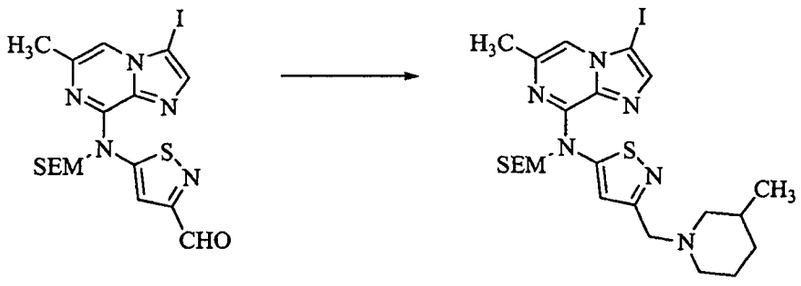
concentrated under reduced pressure affording compound 21 as a yellow solid 2.20 g (97%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.99 (s, 1H), 7.74 (s, 1H), 7.73 (s, 1H), 7.65 (s, 1H), 6.60 (s, 2H), 3.74 (t, J = 8 Hz, 2H), 2.64 (s, 3H), 0.94 (t, J = 8 Hz, 2H), -0.07 (s, 9H).

EXAMPLE 22



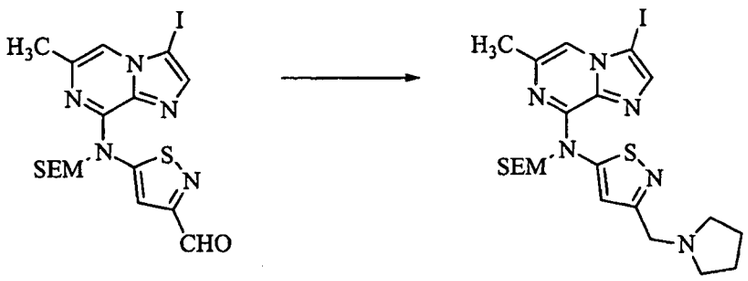
To a stirring solution of aldehyde (1.30 g, 2.52 mmol), piperidine (257 mg, 3.02 mmol), and acetic acid (150 μL, 2.52 mmol) in 1,2-dichloroethane (17 mL) at room temperature was added sodium triacetoxyborohydride (801 mg, 3.78 mmol) in one portion. The mixture was stirred at room temperature for 2 hours at which time thin layer chromatography (40% ethyl acetate/hexanes) indicated the reaction was complete. The reaction was quenched with 1N sodium hydroxide (25 mL) and stirred for 20 minutes. The mixture was extracted with chloroform (3×20 mL), the organic layers were combined, dried over sodium sulfate, filtered, and concentrated under reduced pressure. Afforded compound 22 as a yellow solid 1.35 g (92%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.59 (s, 1H), 7.23 (s, 1H), 6.58 (s, 2 H), 3.72 (t, J = 8 Hz, 2H), 3.62 (s, 2H), 2.58 (s, 3H), 2.47 (m, 4H), 1.58 (m, 6H), 0.93 (t, J = 8 Hz, 2H), -0.086 (s, 9H).

EXAMPLE 23



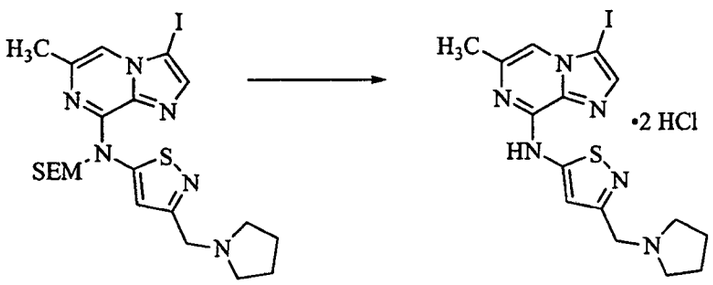
Example 23 was prepared in a similar manner to example 22 with the substitution of 3-methylpiperidine for piperidine. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.59 (s, 1H), 7.23 (s, 1H), 6.58 (s, 2H), 3.72 (t, J = 8 Hz, 2H), 3.62 (s, 2H), 2.85 (m, 2H), 2.59 (s, 3H), 1.98 (m, 1H), 1.65 (m, 6H), 0.93 (t, J = 8 Hz, 2H), 0.84 (d, J = 6 Hz, 3H), -0.076 (s, 9H).

EXAMPLE 24



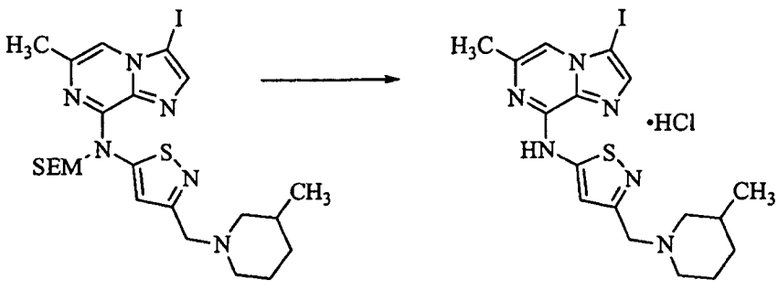
Example 24 was prepared in a similar manner to example 23 with the substitution of pyrrolidine for piperidine. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.59 (s, 1H), 7.23 (s, 1H), 6.58 (s, 2H), 3.77 (s, 2H), 3.72 (t, J = 8 Hz, 2H), 2.61 (m, 4H), 2.59 (s, 3H), 1.81 (m, 4H), 0.92 (t, J = 8 Hz, 2H), -0.90 (s, 9H).

EXAMPLE 25



A solution of iodide from Example 24 (20 mg, 0.035 mmol) in 1,4-dioxane (1 mL) was treated with 4N HCl in 1,4-dioxane (1 mL). The mixture was sonicated at room temperature for 2.5 hours, at which time HPLC indicated the reaction was complete. The mixture was concentrated under reduced pressure and the resulting residue was purified by prep-HPLC and conversion to the hydrochloride salt afforded compound 25 as a white solid 15 mg (83%). ^{1}H NMR (300 MHz, CD_3OD) δ 7.88 (s, 1H), 7.79 (s, 1H), 7.17 (s, 1H), 4.51 (s, 2H), 3.71 (m, 2H), 3,22 (m, 2H), 2.57 (s, 3H), 2.07 (m, 4H). HPLC t_R = 4.83 min (UV $_{254\ nm}$). Mass calculated for formula $C_{15}H_{17}IN_6S$ 440.03; observed MH^+ (MS) 441.5 (m/z).

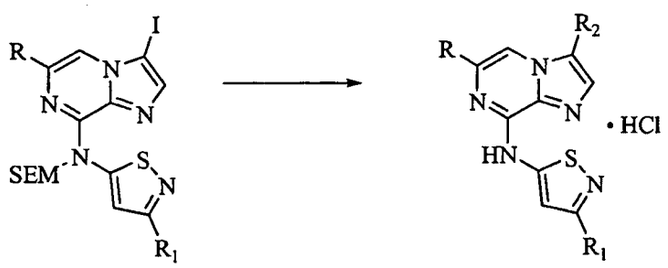
EXAMPLE 26



Example 26 was prepared in a similar manner to example 25. ^{1}H NMR (300 MHz, CD_3OD) δ 7.87 (s, 1H), 7.79 (s, 1H), 7.22 (s, 1H), 4.39 (s, 2H), 3.52 (m, 2H), 2.96 (m, 1H), 2.70 (m, 1H), 2.57 (s, 3H), 1.90 (m, 4H), 1.21 (m, 1H), 0.99 (d, J = 6 Hz, 3H). HPLC t_R = 5.06 min (UV $_{254nm}$). Mass calculated for $C_{17}H_{21}IN_6S$ 468.3; observed MH^+ (MS) 469.7 (m/z).

EXAMPLE 27

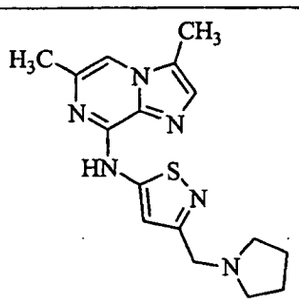
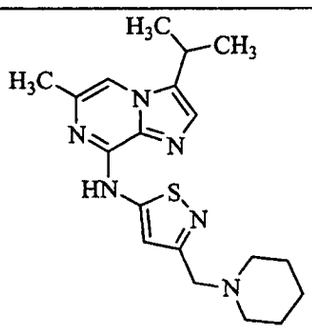
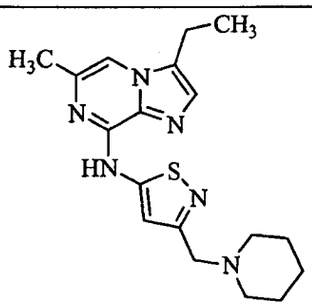
The compounds shown in column 2 of Table 5 (shown immediately below) were prepared as follows:

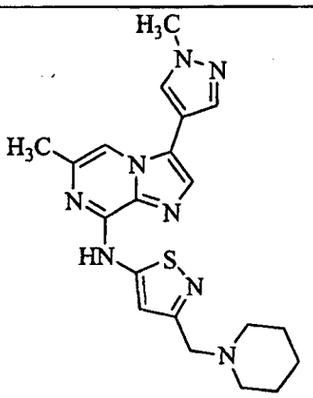
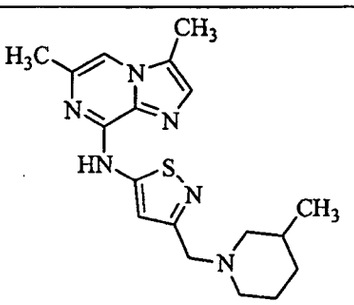
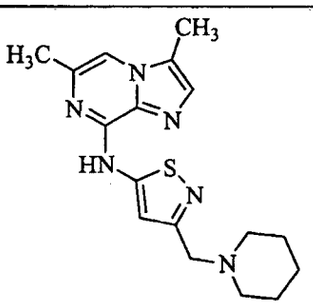
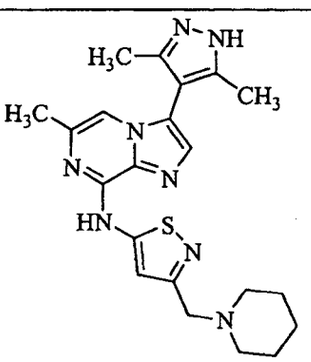


A flask containing the prepared aryl iodide scaffolds (compound from Example 22, 23, or 24, 1 equivalent), commercially available or readily prepared in 1 to 3 steps aryl/heteroaryl/alkyl boronic acid/ester/boroxine or aryl/heteroaryl/alkyl magnesium bromide or aryl/heteroaryl/alkyl zinc chloride (1.5 – 3 equivalents), potassium phosphate or potassium carbonate (2- 3 equivalents) and $Pd(PPh_3)_4$ or $PdCl_2$dppf (0.05 – 0.10 equivalents) was evacuated, backfilled with nitrogen and repeated. 1,4-Dioxane or N,N-dimethylformamide or 1,2-dimethoxyethane (1 – 3 mL) was added and the mixture was stirred at 50 – 130 °C until reaction was complete as judged by thin layer chromatography (ethyl acetate/hexanes) or HPLC. The mixture was diluted with water (3 – 10 mL) and extracted with ethyl acetate (2-3 × 10-30 mL). The organic layers were combined, washed with brine (15 – 30 mL), dried over magnesium sulfate, filtered, concentrated, and purified by column chromatography (SiO_2, ethyl acetate/hexanes). The product obtained was dissolved in 1,4-dioxane (1 mL) and treated with 4 N HCl in 1,4-dioxane (1 mL) and sonicated at room temperature for 1-5 hours, at which time

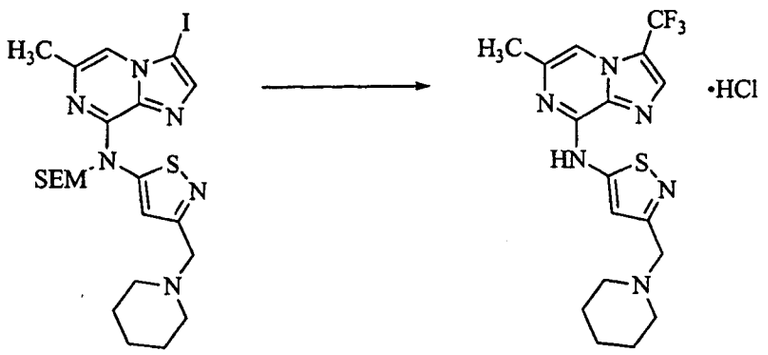
HPLC indicated the reaction was complete. The mixture was concentrated under reduced pressure and the resulting residue was purified by prep-HPLC and conversion to the hydrochloride salt afforded compounds 27-1 to 27-7.

TABLE 5

Example	Column 2	MW	MS MH^+ m/z	HPLC t_R
27-1		328.4	329.1	3.52
27-2		370.5	371.1	4.34
27-3		356.4	357.4	3.98

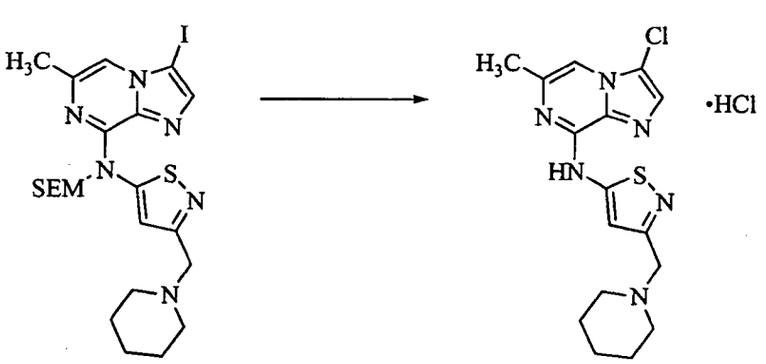
27-4		408.5	409.6	4.21
27-5		356.4	357.4	3.91
27-6		342.4	343.2	3.71
27-7		422.5	423.2	3.87

EXAMPLE 28



A mixture of iodide (60 mg, 0.103 mmol), trimethyl(trifluoromethyl)silane (44 mg, 0.308 mmol), copper iodide (73 mg, 0.385 mmol), potassium fluoride (15 mg, 0.257 mmol), and anhydrous DMF (1.0 mL) was degassed with nitrogen then heated at 80 °C in a sealed tube overnight. The mixture was cooled to room temperature, diluted with water (30 mL), and extracted with ethyl acetate (100 mL). The organic layer was dried over sodium sulfate, filtered, concentrated under reduced pressure, and purified by column chromatography (SiO_2, 90:10:0.25 methylene chloride/methanol/concentrated ammonium hydroxide). The resulting residue was dissolved in anhydrous 1,4-dioxane (1mL) and 4 M HCl in dioxane (1 mL) was added. The resulting solution was sonicated at room temperature for 2 hours and concentrated under reduced pressure to dryness. Purification by preparative HPLC and conversion to the hydrochloride salt afforded the title compound as an off-white solid 3.1 mg (6%). ^{1}H NMR (300 MHz, CD_3OD) δ 8.07 (s, 1H), 7.85 (s, 1H), 7.24 (s, 1H), 4.40 (s, 2H), 3.61 (d, J = 12.3 Hz, 2H), 3.07 (t, J= 12.3 Hz, 2H), 2.55 (s, 3H), 1.75–2.03 (m, 5H), 1.56 (m, 1H). HPLC t_R = 7.19 min. Mass calculated for formula $C_{17}H_{19}F_3N_6S$ 396.13; observed MH^+ 397.2 (m/z).

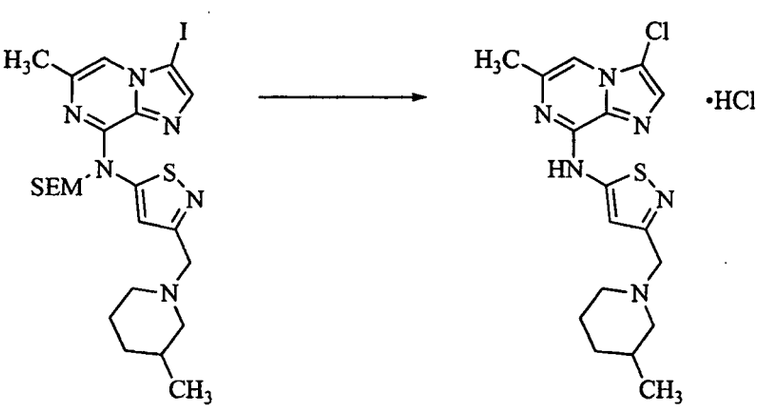
EXAMPLE 29



A mixture of iodide (100 mg, 0.171 mmol) in anhydrous THF (2.0 mL) was cooled to -78 °C and *n*-butyl lithium (2.5 M solution in hexanes, 89 μL, 0.222 mmol) was added dropwise. After stirring for 15 minutes a solution of hexachloroethane (45 mg, 0.188 mmol) in

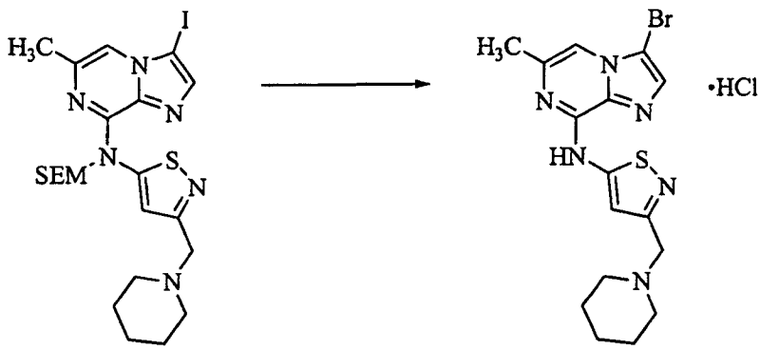
THF (1.0 mL) was added dropwise. After stirring the reaction at –78 °C for 30 minutes the solution was quenched with a saturated aqueous solution of ammonium chloride (3.0 mL) and warmed to room temperature. The reaction was concentrated under reduced pressure, extracted with ethyl acetate (50 mL) and the organic layer dried over sodium sulfate, filtered, concentrated under reduced pressure, and purified by column chromatography (SiO_2, 90:10:0.25 methylene chloride/methanol/concentrated ammonium hydroxide). The resulting residue was dissolved in anhydrous 1,4-dioxane (1mL) and 4 M HCl in dioxane (1 mL) was added. The resulting solution was sonicated at room temperature for 2 hours and concentrated under reduced pressure to dryness. Purification by preparative HPLC and conversion to the hydrochloride salt afforded the title compound as an off-white solid 30 mg (40%). ^{1}H NMR (300 MHz, CD_3OD) δ 7.80 (s, 1H), 7.73 (s, 1H), 7.22 (s, 1H), 4.39 (s, 2H), 3.59 (d, J = 12.3 Hz, 2H), 3.08 (t, J= 12.3 Hz, 2H), 2.55 (s, 3H), 1.75–2.03 (m, 5H), 1.56 (m, 1H). HPLC t_R = 4.79 min. Mass calculated for formula $C_{16}H_{19}ClN_6S$ 362.11; observed MH^+ 363.7 (m/z).

EXAMPLE 30



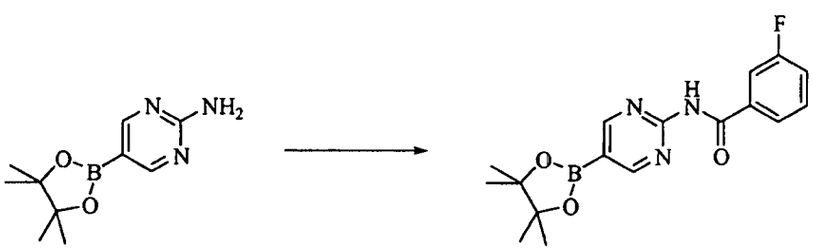
Example 30 was prepared in a similar manner as Example 29. ^{1}H NMR (300 MHz, CD_3OD) δ 7.77 (s, 1H), 7.68 (s, 1H), 7.20 (s, 1H), 4.39 (s, 2H), 3.47–3.67 (m, 2H), 2.97 (m, 1H), 2.71 (m, 1H), 2.55 (s, 3H), 1.77–2.01 (m, 4H), 1.20 (m, 1H), 1.00 (d, J = 6.4 Hz, 3H). HPLC t_R = 4.98 min. Mass calculated for formula $C_{17}H_{21}ClN_6S$ 376.12; observed MH^+ 377.6 (m/z).

EXAMPLE 31



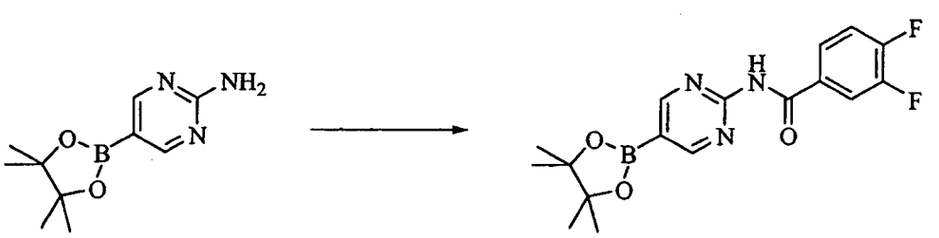
Example 31 was prepared in a similar manner to compound 29 with the substitution of tetrachlorodibromoethane for hexachloroethane. ^{1}H NMR (300 MHz, CD_3OD) δ 7.84 (s, 1H), 7.83 (s, 1H), 7.25 (s, 1H), 4.41 (s, 2H), 3.61 (d, J = 12.3 Hz, 2H), 3.08 (t, J= 12.3 Hz, 2H), 2.57 (s 3H), 1.77–2.03 (m, 5H), 1.55 (m, 1H). HPLC t_R = 5.19 min. Mass calculated for formula $C_{16}H_{19}BrN_6S$ 406.06; observed MH^+ 407.4 (m/z).

EXAMPLE 32



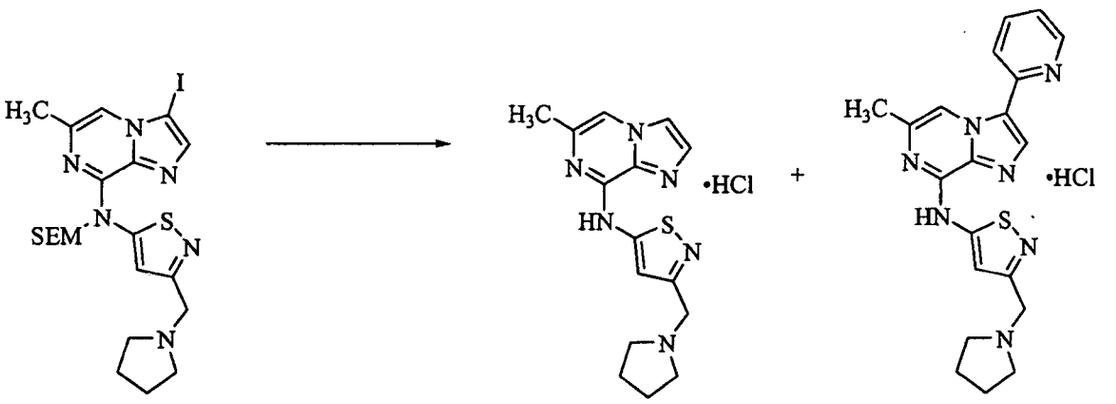
To a solution of aminopyrimidine (100 mg, 0.452 mmol) in anhydrous pyridine (2.0 mL) was added 3-fluorobenzoyl chloride (72 mg, 0.452 mmol). After stirring at room temperature overnight, the reaction was concentrated under reduced pressure, diluted with water (30 mL), and extracted with methylene chloride (100 mL). The organic layer was dried over sodium sulfate, filtered and concentrated to afford the title compound as an off-white solid 124 mg (80%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.95 (s, 2H), 8.72 (s, 1H), 7.66–7.72 (m, 2H), 7.49 (m, 2H), 1.36 (s, 12H).

EXAMPLE 33



Prepared in a similar manner as compound 31 affording the title compound as an off-white solid 131 mg (80%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.93 (s, 2H), 8.65 (s, 1H), 7.83 (m, 1H), 7.69 (m, 1H), 7.30 (m, 1H), 1.34 (s, 12H).

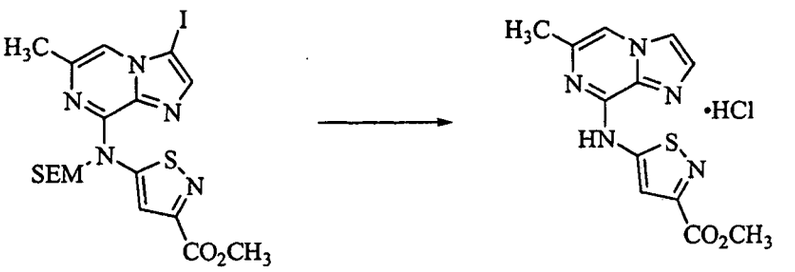
EXAMPLE 34



A mixture of iodide (60 mg, 0.103 mmol), tri-*n*-butyl(pyridyl)tin (57 mg, 0.154 mmol), dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloromethane adduct (8 mg, 0.0103 mmol), and potassium fluoride (18 mg, 0.309 mmol) in anhydrous 1,4-dioxane (1.0 mL) was degassed with nitrogen then heated at 85 °C in a sealed tube overnight. The mixture was cooled to room temperature, diluted with water (30 mL), and extracted with ethyl acetate (2 × 100 mL). The organic layer was then separated, dried over sodium sulfate, filtered, concentrated under reduced pressure to residue, and purified by column chromatography (SiO_2, 90:10:0.25 methylene chloride/methanol/ concentrated ammonium hydroxide). The resulting residue was then dissolved in anhydrous 1,4-dioxane (1mL) and 4 M HCl in dioxane (1 mL) was added. The resulting solution was sonicated at room temperature for 2 hours and then concentrated under reduced pressure to dryness. Purification by preparative HPLC and conversion to the hydrochloride salt afforded de-halogenated product 3.2 mg (10%) as an off-white solid: ^{1}H NMR (300 MHz, CD_3OD) δ 8.23 (s, 1H), 8.13 (s, 2H), 7.29 (s, 1H), 4.55 (s, 2H), 3.72 (br s, 2H), 3.29 (m, 2H), 2.61 (s, 3H), 2.05–2.18 (m, 4H). HPLC t_R =3.49 min. Mass calculated for formula $C_{15}H_{16}N_6S$ 314.13; observed MH^+ 315.2 (m/z).

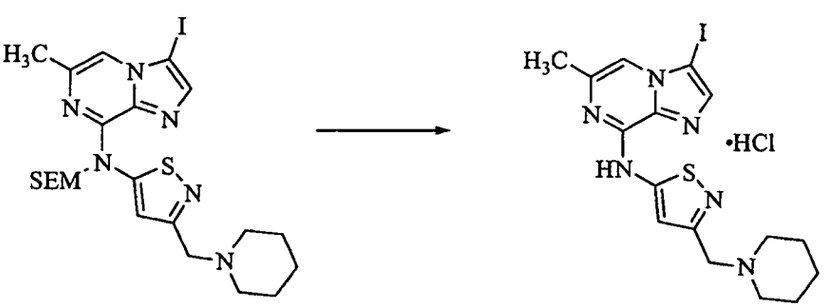
Also afforded coupling product 5.0 mg (10%) as an off-white solid: ^{1}H NMR (300 MHz, CD_3OD) δ 8.95 (s, 1H), 8.86 (d, J = 5.1 Hz, 1H), 8.50 (s, 1H), 8.28 (t, J = 7.5 Hz, 1H), 8.18 (d, J = 7.8 Hz, 1H), 7.70 (t, J = 6.3 Hz, 1H), 7.26 (s, 1H), 4.54 (s, 2H), 3.74 (m, 2H), 3.29 (m, 2H), 1.99–2.30 (m, 4H). HPLC t_R =4.80 min. Mass calculated for formula $C_{20}H_{21}N_7S$ 391.16; observed MH^+ 392.5 (m/z).

EXAMPLE 35



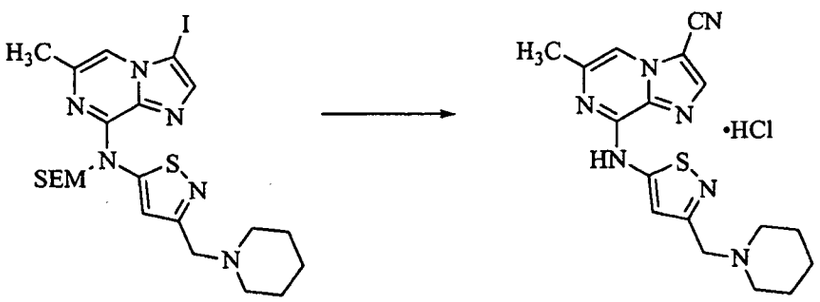
Sodium borohydride (3 mg, 0.073 mmol) was added to a room temperature suspension of iodide (15 mg, 0.037) in methanol (1 mL). The reaction was allowed to stir for 30 minutes then quenched with water (20 mL). The mixture was diluted with diethyl ether (20 mL) and the phases were allowed to separate. The organic layer was dried (sodium sulfate), filtered and concentrated to afford a protected de-halogenated intermediate. The reduced product (7 mg, 0.017 mmol) was subjected to the acidic conditions outlined previously to afford the title compound as a yellow solid 2 mg (17%). ^{1}H NMR (300 MHz, CD_3OD) δ 7.94 (s, 1H), 7.90 (s, 1H), 7.74 (s, 1H), 7.55 (s, 1H), 3.94 (s, 3H), 2.50 (s, 3H). HPLC t_R = 4.67 min (UV $_{254nm}$). Mass calculated for formula $C_{12}H_{11}N_5O_2S$ 289.06; observed MH^- (ESI MS) 288.0 (m/z).

EXAMPLE 36



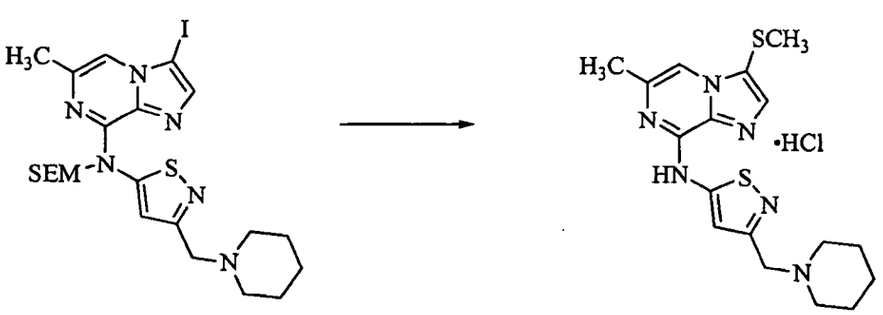
Example 36 was prepared in a similar manner to Example 31. ^{1}H NMR (300 MHz, CD_3OD) δ 7.72 (s, 1H), 7.69 (s, 1H), 7.15 (s, 1H), 4.38 (s, 2H), 3.69-3.52 (m, 2H), 3.17-2.96 (m, 2H), 2.54 (s, 3H), 2.06-1.70 (m, 5H), 1.65-1.44 (m, 1H). HPLC t_R = 5.00 min (UV $_{254nm}$). Mass calculated for formula $C_{16}H_{19}IN_6S$ 454.04; observed MH^+ (ESI MS) 455.0 (m/z).

EXAMPLE 37



$Pd_2(dba)_3$ (5 mg, 0.005 mmol) was added to a room temperature solution of DPPF (6 mg, 0.103 mmol) in *N,N'*-dimethylformamide (1 mL) and stirred for 10 minutes. The mixture was then added to a solution of iodide (60 mg, 0.103 mmol), $Zn(CN)_2$ (12 mg, 0.103 mmol) in *N,N'*dimethylformamide (4 mL). The reaction was heated to 150 °C in the microwave for 30 minutes, cooled to room temperature then concentrated to dryness. Purification of the resultant residue by flash chromatography (SiO_2; 12 g; 10% methanol in methylene chloride) afforded impure nitrile as a yellow solid. The impure nitrile (22 mg, 0.045 mmol) was dissolved in 2 N HCl (4 mL) without further purification. The resultant solution was sonicated at 45 °C for 2 hours. Upon completion, the reaction was concentrated to dryness. Purification of the resultant residue by prep-HPLC afforded the title compound as a white solid 8 mg (18%). ^1H NMR (300 MHz, CD_3OD) δ 8.22 (s, 1H), 7.93 (s, 1H), 7.22 (s, 1H), 4.40 (s, 2H), 3.73-3.52 (m, 2H), 3.20-2.97 (m, 2H), 2.55 (s, 3H), 2.06-1.71 (m, 5H), 1.66-1.42 (m, 1H). HPLC $t_R = 4.50$ min (UV $_{254nm}$). Mass calculated for formula $C_{17}H_{19}N_7S$ 353.14; observed MH^+ (ESI MS) 354.3 (m/z).

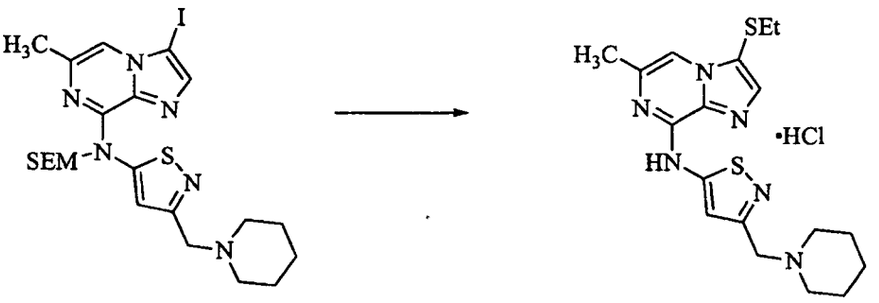
EXAMPLE 38



A mixture of iodide (70 mg, 0.12 mmol), $Pd(dppf)Cl_2$ (9 mg, 0.012 mmol), sodium *tert*-butoxide (35 mg, 0.36 mmol) and sodium thiomethoxide (17 mg, 0.24 mmol) was flushed with nitrogen then dissolved into 1,4-dioxane (5 mL). The solution was heated to 95 °C in the microwave for 90 minutes. The reaction was cooled to room temperature, diluted with ethyl

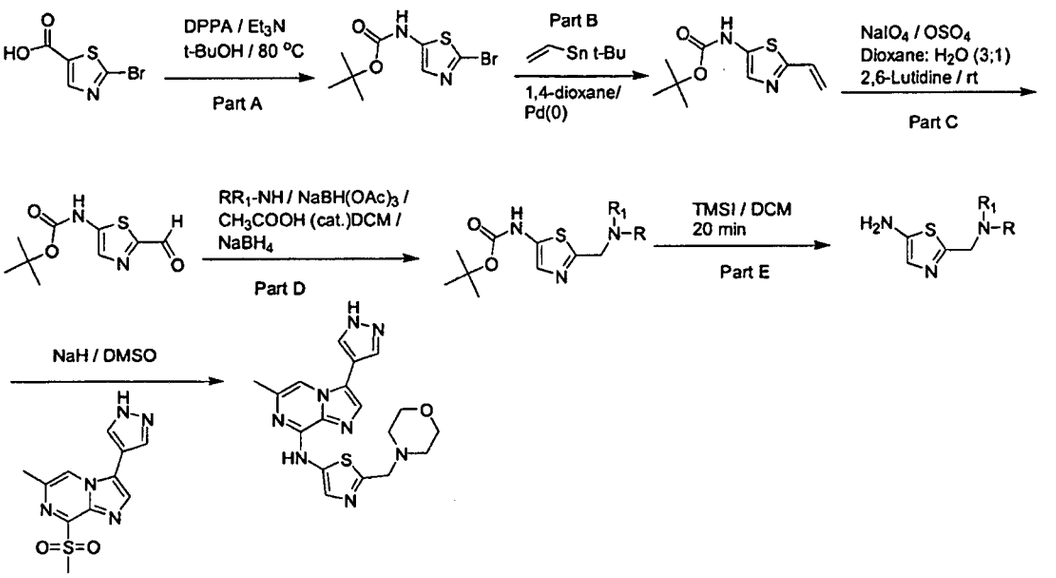
acetate (100 mL), and filtered through celite. The organic layer was washed with water (50 mL) and brine (50 mL) then dried (sodium sulfate), filtered and concentrated to dryness. Purification of the resultant residue by prep-HPLC afforded the protected thiomethylether. The thiomethylether (35 mg, 0.07 mmol) was subjected to the reaction conditions outlined in example 110 to afford the title compound as a white solid 6 mg (11%). ^{1}H NMR (300 MHz, CD_3OD) δ 8.28 (s, 1H), 8.25 (s, 1H), 7.34 (s, 1H), 4.43 (s, 2H), 3.68-3.52 (m, 2H), 3.18-2.98 (m, 2H), 2.67 (s, 3H), 2.49 (s, 3H), 2.05-1.71 (m, 5H), 1.65-1.44 (m, 1H). HPLC t_R = 4.74 min (UV $_{254nm}$). Mass calculated for formula $C_{17}H_{22}N_6S_2$ 374.13; observed MH^+ (ESI MS) 375.3 (m/z).

EXAMPLE 39



A combined mixture of iodide (70 mg, 0.12 mmol), sodium thioethoxide (20 mg, 0.24 mmol), $Pd(dppf)Cl_2$ (9 mg, 0.012 mmol) and sodium *tert*-butoxide (35 mg, 0.36 mmol) was flushed with nitrogen gas then dissolved into 1,4-dioxane (5 mL). The reaction was heated to 95 °C and stirred for 72 hours. The reaction was then cooled to room temperature, diluted with ethyl acetate (100 ml), and filtered through celite. The filtrate was washed with water (50 mL) and brine (50 mL) then dried (sodium sulfate), filtered and concentrated to dryness. Purification of the resultant residue by flash chromatography (SiO_2; 12 g; 0% to 10% methanol in methylene chloride) afforded a thioethylether intermediate as a yellow solid. The thioethylether (10 mg, 0.019 mmol) was subjected to the reaction conditions outlined in example 110 to afford the title compound as a white solid 2 mg (4%). ^{1}H NMR (300 MHz, CD_3OD) δ 8.32 (s, 1H), 8.28 (s, 1H), 7.35 (s, 1H), 4.43 (s, 2H), 3.68-3.55 (m, 2H), 3.17-3.01 (m, 2H), 2.90 (q, J = 7.3 Hz, 2H), 2.67 (s, 3H), 2.07-1.71 (m, 5H), 1.65-1.42 (m, 1H), 1.28 (t, J = 7.3 Hz, 3H). HPLC t_R = 5.27 min (UV $_{254nm}$). Mass calculated for formula $C_{18}H_{24}N_6S_2$ 388.15; observed MH^+ (ESI MS) 389.7 (m/z).

EXAMPLE 40



Part A: To a stirred solution of 2-Bromo-thiazole-5-carboxylic acid (2.0 g, 9.615 mmol) in *t*-Butanol (30 mL) and triethyl amine (1.5 mL, 10.57 mmol) was added diphenylphosphoryl azide (2.9 g, 10.57 mmol) and reaction mixture was heated to 80 °C and stirred for 12 hrs, LCMS showed the complete disappearance of the starting material. Reaction mixture was cooled to room temp., solvent removed under vacuum, water (100 mL) added and extracted with ethyl acetate (3 x 100 mL). Organic layer was washed with water, brine, dried over sodium sulfate and concentrated, crude material was passed through small pad of silica gel and resultant (2-Bromo-thiazol-5-yl)-carbamic acid tert-butyl ester (solid) was used as such in the next step, yield 2.5 g (90%). ^{1}H NMR (400 MHz, DMSO-d_6 δ 7.10 (s, 1H), 7.05 (s, 1H), 1.51 (s, 9H).Mass calculated for formula $C_8H_{11}BrN_2O_2S$ 277.97; observed MH^+ (LCMS) 279.0 (m/z).

Part B: To a stirred solution of (2-Bromo-thiazol-5-yl)-carbamic acid tert-butyl ester (2.5 g, 8.9928 mmol) in 1,4-dioxane (20.0 mL) were added tributy(vinyl)tin (2.9 mL, 9.892 mmol), 2,6-di-tert-butyl-4-methylphenol (cat. amt) and tetrakis(triphenyl phosphine) palladium(0) (506.0 mg, 0.4496 mmol). The reaction mixture was heated to 100 °C and stirred for 12 hrs, LCMS showed the complete disappearance of the starting material. Reaction mixture was cooled to room temp, filtered and solid washed with ethyl acetate, combined filtrate (organic solvent) was removed under vacuum, crude material was purified using biotage HPLC using hexane / ethyl acetate gradient 0.0 to 100 % to yield (2-Vinyl-thiazol-5-yl)-carbamic acid tert-butyl ester (solid) 1.1 g (54%). ^{1}H NMR (400 MHz, $CDCl_3$ δ 7.27 (d, J = 12.7 Hz,2H), 7.19

(brs, 1H), 6.84-6.77 (m, 1H), 6.87 (d, J = 17.0 Hz, 1H), 5.43 (d, J = 10.5 Hz,1H), 1.52 (s, 9H). Mass calculated for formula $C_{10}H_{14}N_2O_2S$ 226.08; observed MH^+ (LCMS) 227.1 (m/z).

Part C: To a stirred solution of (2-Vinyl-thiazol-5-yl)-carbamic acid tert-butyl ester (0.76 g, 2.857 mmol) in 1,4-dioxane : water (30 : 9 mL), were added sodium periodate (2.5 g, 11.43 mmol) osmium tetroxide (2.5% solution in 2-propanol) (0.5 mL) and 2,6-lutidine (0.663 mL, 5.714 mmol) and reaction mixture was stirred for 4 hrs, LCMS showed the almost disappearance of the starting material. Reaction mixture was diluted with water (100 mL) and extracted with ethyl acetate, organic layer was washed with water, brine, dried over sodium sulfate and concentrated under high vacuum to yield aldehyde 710 mg (92%). Crude product was used as such in the next reaction. ^1H NMR (400 MHz, DMSO-d_6 δ 11.45 (s, 1H), 9.76 (s, 1H), 7.58 (s, 1H), 1.40 (s, 9H). Mass calculated for formula $C_9H_{12}N_2O_3S$ 228.06; observed MH^+ (LCMS) 229.1 (m/z).

Part D: To a stirred solution of (2-Formyl-thiazol-5-yl)-carbamic acid tert-butyl ester (0.76 g, 2.857 mmol) in 1,2-dichloroethane(10 mL) were added Morpholine (250 mg, 1.1135 mmol) triacetoxysodium borohydride (472 mg, 2.227 mmol) and Cat amount acetic acid (three drops) and stirred for two hrs at room temp. To the reaction mixture was added sodium borohydride (126 mg, 3.3405 mmol) and stirred for one hrs. LCMS showed the disappearance of the starting material. Reaction mixture was diluted with water (100 mL) and extracted with dichloromethane, organic layer was washed with water, brine, dried over sodium sulfate and concentrated under high vacuum to yield (2-Morpholin-4-ylmethyl-thiazol-5-yl)-carbamic acid tert-butyl ester 298 mg (91%). Crude product was used as such in the next reaction. Mass calculated for formula C14H25N3O3S 315.43; observed MH^+ (LCMS) 300.3 (m/z).

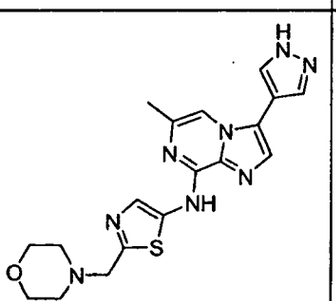
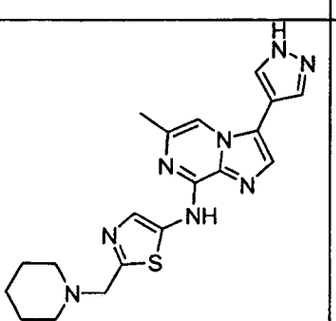
Part E: To a stirred solution of (2-Morpholin-4-ylmethyl-thiazol-5-yl)-carbamic acid tert-butyl ester (80.0 mg, 0.268 mmol) in dichloromethane(5 mL) was added iodotirmethylsilane (44 μL, 0.321 mmol) and stirred for 10 min. LCMS showed the disappearance of the starting material. Reaction mixture was diluted with water (10 mL), 1N aqueous NaOH solution (5 mL) and extracted with 10% 2-propanol in DCM (3 x 25 mL) and organic layer dried over sodium sulfate and concentrated under high vacuum to yield 2-Morpholin-4-ylmethyl-thiazol-5-ylamine 30.0 mg (56%). Crude product was used as such in the next reaction. Mass calculated for formula C8H13N3OS 199.27; observed MH^+ (LCMS) 200.1 (m/z).

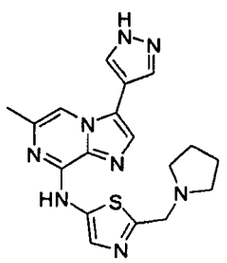
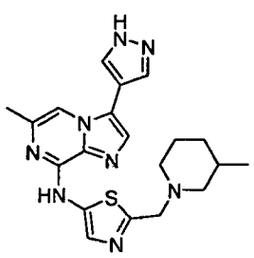
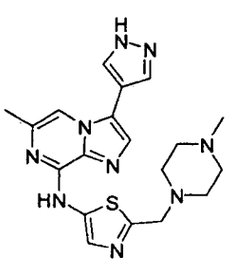
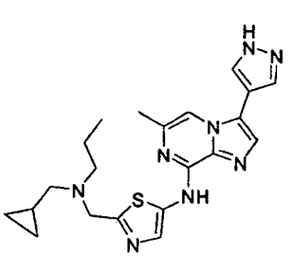
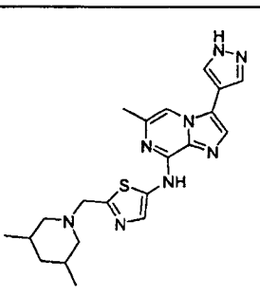
Part F: To a stirred solution of 2-Morpholin-4-ylmethyl-thiazol-5-ylamine (30.0 mg, 0.151 mmol) in DMSO (2.5 mL) was added 8-Methanesulfonyl-6-methyl-3-(1H-pyrazol-4-yl)-

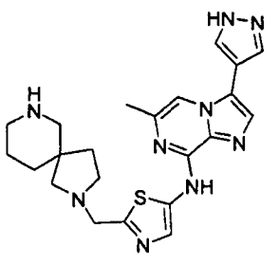
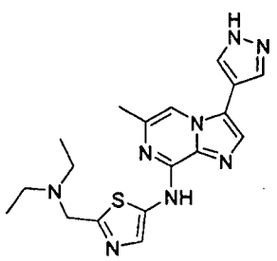
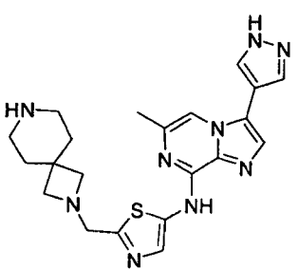
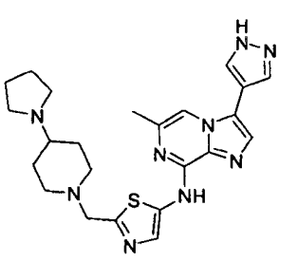
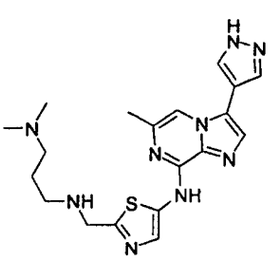
imidazo[1,2-a]pyrazine (25.0 mg, 0.09045 mmol) followed by NaH 60% in mineral oil (48 mg, 1.206 mmol) and stirred for 30 min. LCMS showed the disappearance of the starting material. Reaction mixture was quenched 1:1 mixture of acetonitrile and saturated ammonium chloride (10 mL), and extracted with 10% 2-propanol in DCM (3 x 25 mL) and organic layer was concentrated under high vacuum to yield crude [6-Methyl-3-(1H-pyrazol-4-yl)-imidazo[1,2-a]pyrazin-8-yl]-(2-morpholin-4-ylmethyl-thiazol-5-yl)-amine which was subsequently purified by Agilent reverse phase HPLC using formic acid method to yield 10 mg (28%). HPLC-MS (10 min method) t_R = 2.06 min (UV $_{254nm}$). Mass calculated for formula $C_{18}H_{20}N_8OS$ 396.47; observed MH^+ (LCMS) 397.5 (m/z).

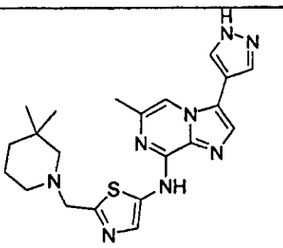
The compounds shown in Table 6 (shown immediately below) were prepared using procedures described in Example 40.

TABLE 6

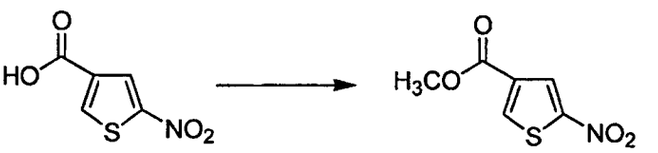
Example	Column 2	MW	LCMS MH^+ m/z	HPLC MS t_R
40-1		396.47	397.5	2.06
40-2		394.50	395.5	2.38

40-3		380.47	381.5	2.25
40-4		408.52	409.2	2.56
40-5		409.51	410.3	2.14
40-6		422.55	423.5	2.74
40-7		422.55	423.3	2.75

40-8		449.58	450.3	1.85
40-9		382.49	383.2	2.28
40-10		435.55	436.44	1.78
40-11		463.60	464.27	1.90
40-12		411.53	412.25	1.76

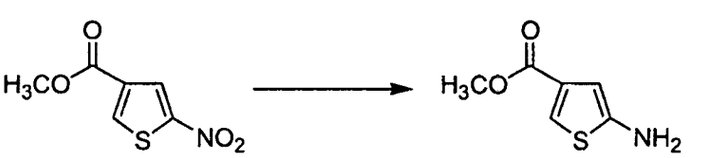
40-13		422.55	423.28	2.74

EXAMPLE 41



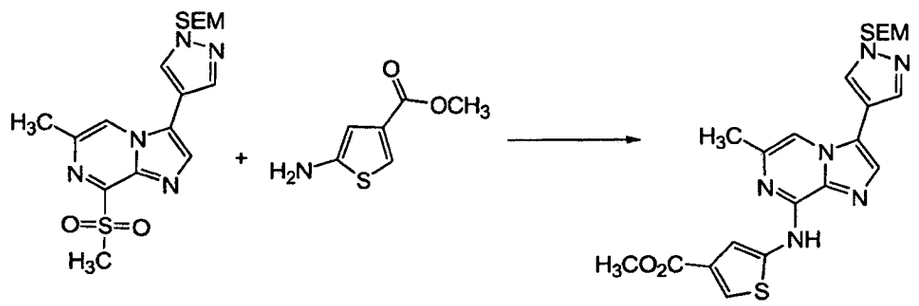
To a solution of 5-nitrothiophene-3-carboxylic acid (5.00 g, 28.88 mmol) in dimethylformamide (40 mL) was added potassium carbonate (11.98 g, 86.71 mmol) and iodomethane (2.70 mL, 43.37 mmol). The reaction mixture was stirred at RT for 16 hr. After the starting material had been consumed, the reaction was diluted with 50% ethyl acetate/hexanes (350 mL) and extracted with H_2O (350 mL). The organic layer was washed with brine (150 mL) and concentrated. Hexanes (50 mL) was added to the solid and concentrated again to yield 5.456 g (99%) of product. ^1H NMR (400 MHz) $CDCl_3$ δ 8.30 (s, 1H), 8.25 (s, 1H), 3.93 (s, 3H). Mass calculated for formula $C_6H_5NO_4S$ 187.17; observed $M4H^+$ (MS) 191.15 (m/z).

EXAMPLE 42



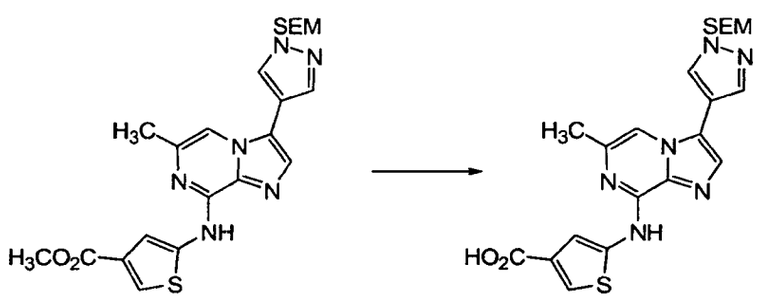
To a solution of the nitro-ester (1.006 g, 5.375 mmol) in TFA (15 mL), Fe powder (1.5135 g, 27.10 mmol) was slowly added to the round bottom flask. The reaction was heated to 60°C for 45 min at which time TLC (1:1, ethyl acetate to hexanes) showed consumption of starting material. The reaction was diluted with ethyl acetate and the Fe was filtered off. The filtrate was neutralized with aqueous Na_2CO_3 and allowed to stir for 1 hr. The aqueous layer was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated to give 0.701 g (83%) of a yellow solid. ^1H NMR (400 MHz) CD_3OD δ 7.29 (s, 1H), 6.44 (s, 1H), 3.79 (s, 3H). Mass calculated for formula $C_6H_7NO_2S$ 157.19; observed MH^+ (LCMS) 158.1 (m/z).

EXAMPLE 43



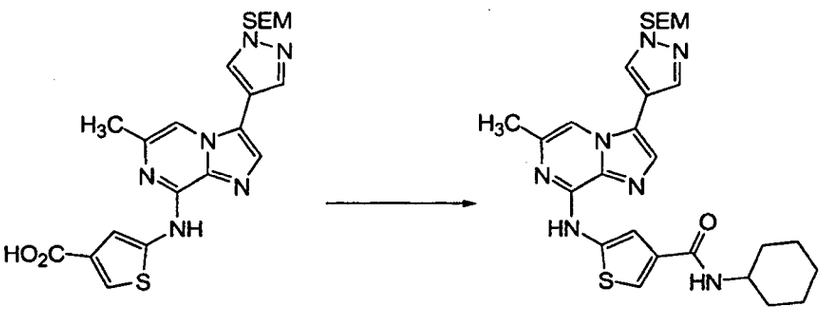
A solution of the sulfone (1.27 g, 3.11 mmol) and 2-aminothiophene-4-carboxylate methyl ester (0.701 g, 4.46 mmol) in DMF (35 mL) were treated with NaH (60% dispersion in oil, 0.402 g, 10.05 mmol) at room temperature until mass spectrometry and thin layer chromatography (50% ethyl acetate/hexanes) indicated that the reaction was complete. Saturated ammonium chloride (15 mL) and water (50 mL) were added to the reaction. The reaction was stirred for 10 minutes. The precipitated solid was collected via filtration to yield the desired product. ^{1}H NMR (400 MHz) $CDCl_3$ δ 8.78 (s, 1H), 7.88 (s, 1H), 7.82 (s, 3H), 7.68 (s, 1H), 7.58 (s, 1H), 7.44 (s, 1H), 7.16 (s, 3H), 5.54 (s, 2H), 3.87 (s, 3H), 3.67 (t, 2H), 2.46 (s, 3H), 0.97 (t, 2H), 0.01 (s, 9H). Mass calculated for formula $C_{22}H_{28}N_6O_3SSi$ 484.65; observed MH^+ (MS) 485.1 (m/z).

EXAMPLE 44



A solution of the ester prepared in Example 43 (0.565 g, 1.17 mmol) in THF (10 mL) and MeOH (3 mL) was treated with solid NaOH (9 pellets) followed by H_2O (5 mL). The reaction was stirred vigorously at room temperature for 16 hr. The THF and MeOH were removed in vacuo and the residue was extracted with EtOAc (3 x 20 mL). The aqueous phase was brought to a pH of 3-4 with aqueous HCl. The acidified aqueous phase was extracted with EtOAc (5 x 20 mL) and concentrated in vacuo to give 0.393 g (71%) of the desired carboxylic acid.

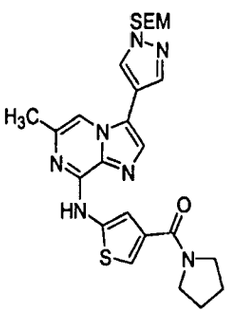
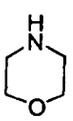
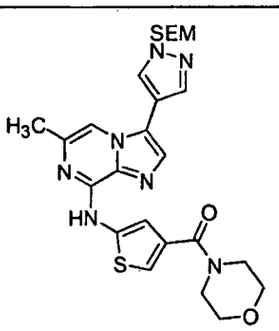
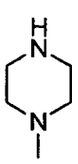
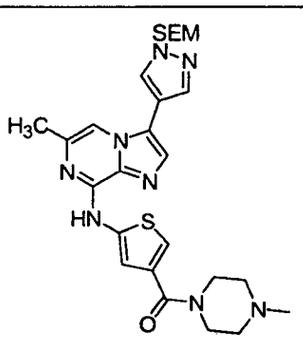
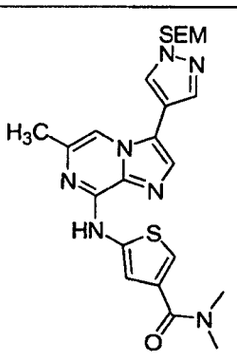
EXAMPLE 45

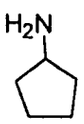
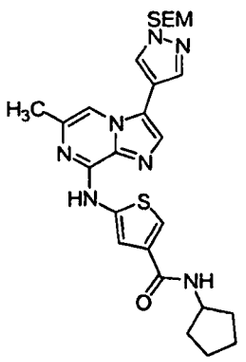
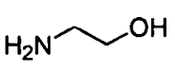
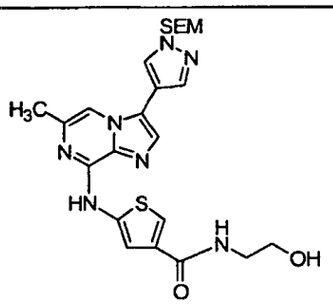
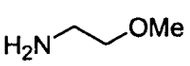
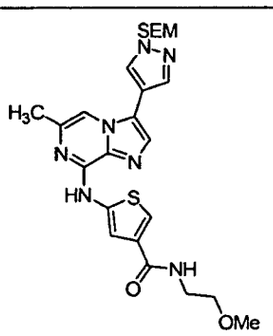
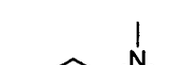
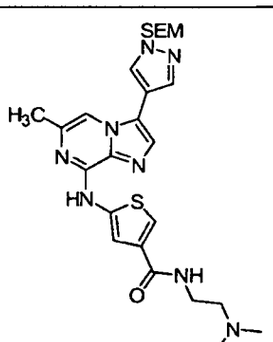


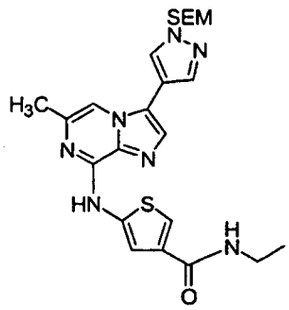
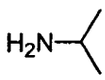
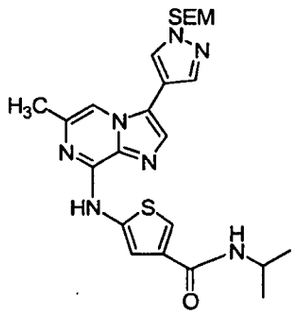
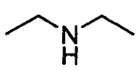
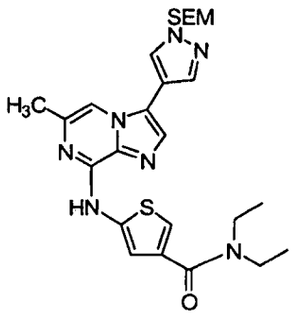
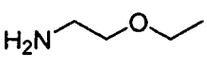
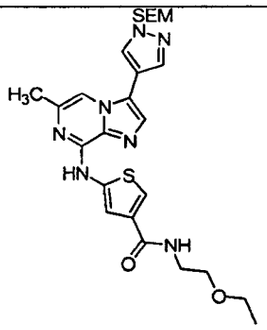
A solution of the carboxylic acid (prepared in Example 4) (0.054 g, 0.115 mmol) in DMF (3 mL) was treated with amine (0.03 mL, 0.262 mmol), NMM (0.07 mL, 0.637 mmol) and then HATU (0.141 g, 0.372 mmol). The reaction was stirred at room temperature for 16 hr. Water (15 mL) was added and the reaction was stirred for 10 minutes. The precipitated solid was collected via filtration to yield 0.038 g (60%) of the desired amide. ^{1}H NMR (400 MHz) $CDCl_3$ δ 9.13 (s, 1H), 7.86 (s, 1H), 7.80 (s, 3H), 7.54 (s, 1H), 7.41 (s, 1H), 7.31 (s, 1H), 7.08 (s, 3H), 5.83 (d, 1H), 5.53 (s, 2H), 3.93 (m, 1H), 3.67 (t, 2H), 2.44 (s, 3H), 1.70 (m, 10H), 0.96 (t, 2H), 0.00 (s, 9H). Mass calculated for formula $C_{27}H_{37}N_7O_2SSi$ 551.78; observed MH^+ (MS) 552.1 (m/z).

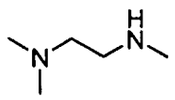
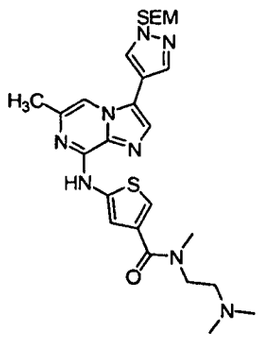
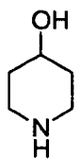
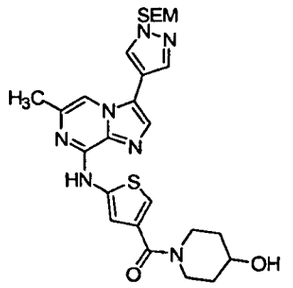
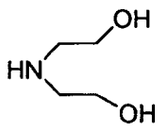
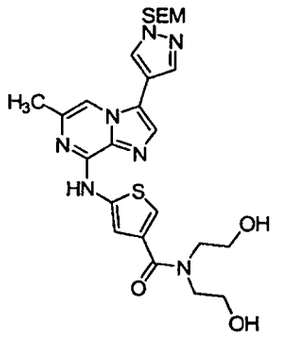
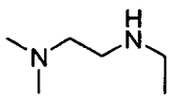
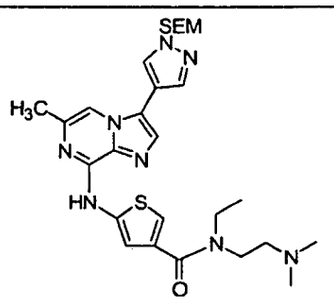
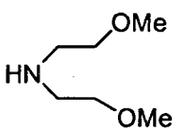
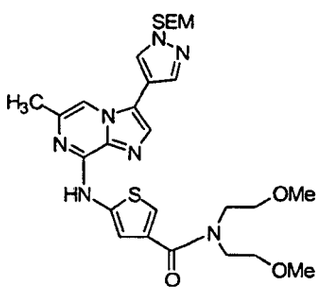
By essentially the same procedure set forth in Example 45, only substituting the amines shown in Column 2 of Table 7a (shown immediately below), the compounds in Column 3 were prepared:

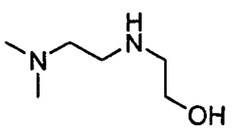
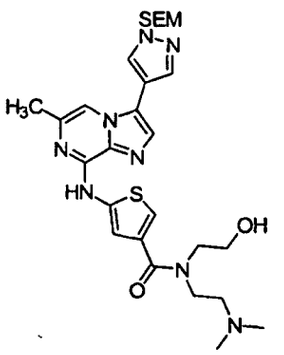
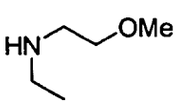
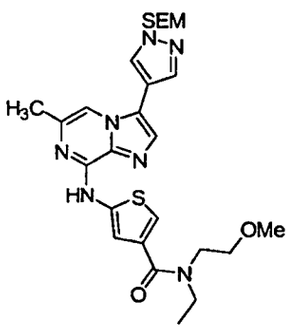
TABLE 7a

Example	Column 2	Column 3	MW	MH^+ m/z	LCMS MS t_R
45-1			523.7	524.1	
45-2			539.7	540.2	
45-3			552.8	553.3	
45-4			497.7	498.3	4.16

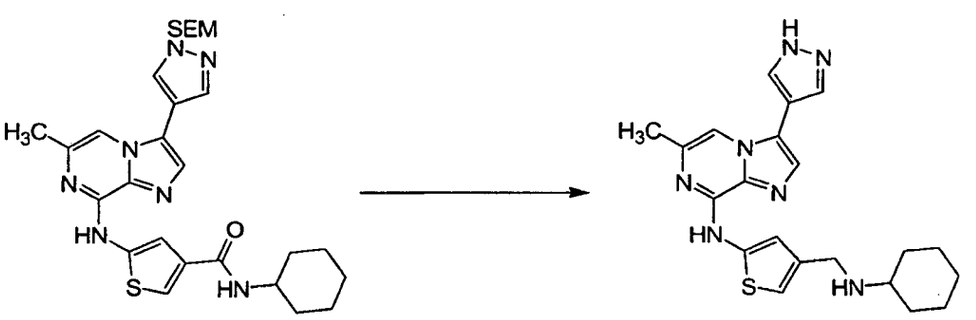
45-5			537.8	538.1	
45-6			513.7	514.3	
45-7			527.7	528.2	
45-8			540.8	541.2	

45-9			497.7	498.1	
45-10			511.7	512.1	
45-11			525.7	526.1	
45-12			541.7	542.2	

45-13			554.8	555.3	
45-14			553.8	554.2	
45-15			557.7	558.2	
45-16			568.8	569.2	
45-17			585.8	586.2	

45-18			584.8	585.2	
45-19			555.8	556.3	4.37

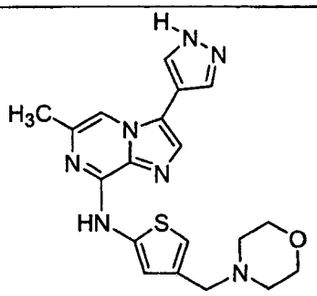
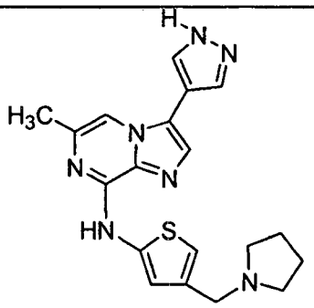
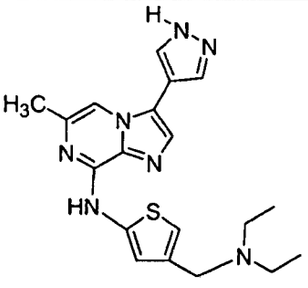
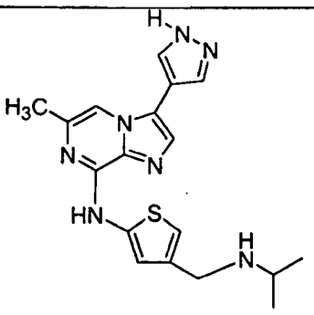
EXAMPLE 46

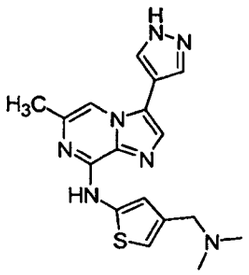
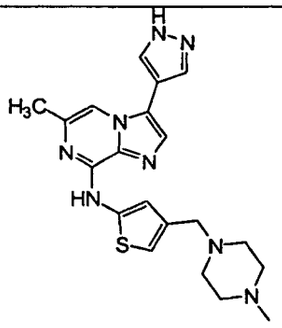
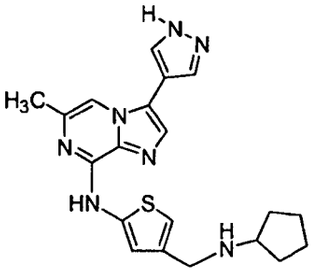
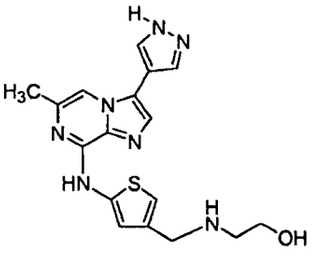
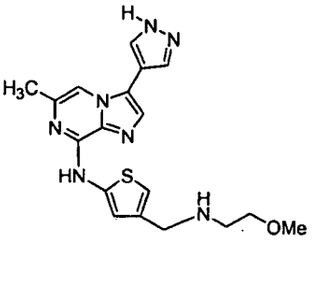


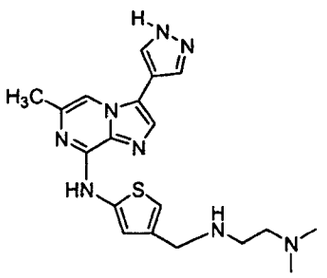
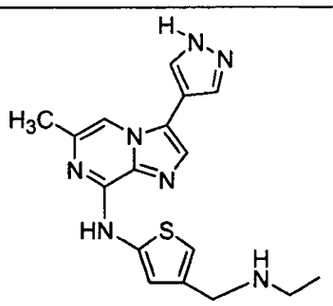
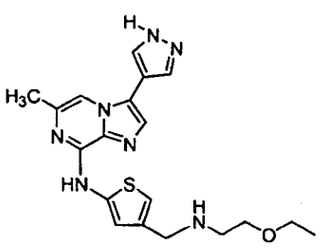
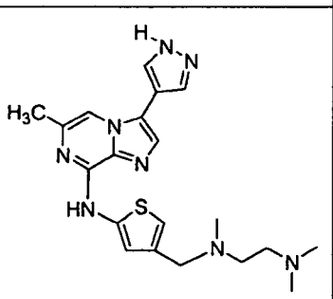
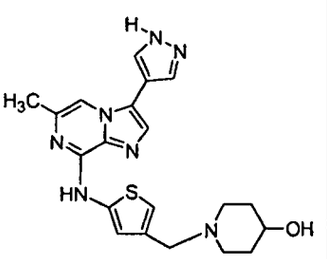
To a solution of the amide (0.038 g, 0.069 mmol) in dichloromethane (4 mL) was added lithium aluminum hydride (0.029 g, 0.775 mmol) and ethyl ether (0.8 mL). The reaction mixture was stirred at RT for 10 min then refluxed at 40° C for 5 hr. The reaction was monitored by mass spectrometry. Upon consumption of the starting amide, the reaction was cooled to RT and quenched with H_2O (2 mL). The reaction was diluted with DCM and filtered. The filtrate was washed with H_2O ($\leq$ 8 mL). The organic layer was concentrated to give 0.019 g (52 %) of the amine. The above amine in THF was further treated with 4 N HCl/dioxane at 60 °C for 1 hr. Upon cooling to RT, Et_2O was added and the mixture was stirred for 10 min. The precipitated solid was collected giving 13.9 mg (96 % yield) of the desired amine.

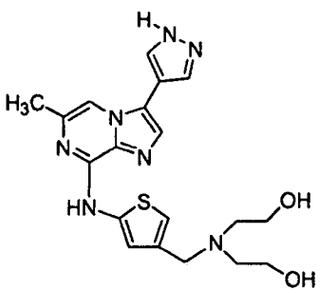
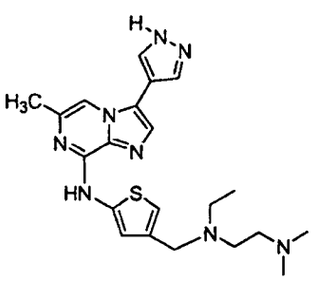
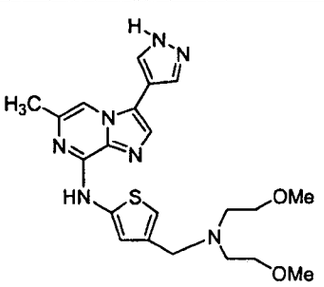
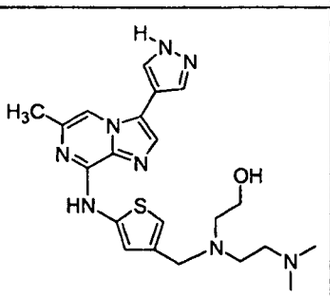
By essentially the same procedure set forth in Example 46, the following compounds shown in Column 2 of Table 7 (shown immediately below) were prepared:

TABLE 7

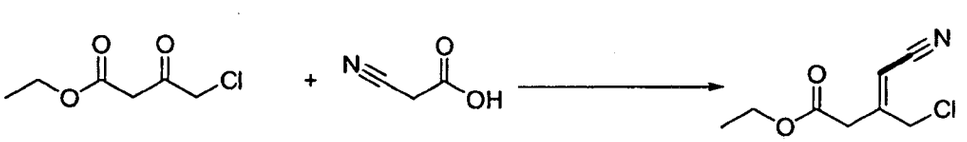
Example	Column 2	MW	LCMS MH^+ m/z	LCMS MS t_R
46-1		395.5	396.2	2.06
46-2		379.5	381.2	2.12
46-3		381.5	382.2	2.03
46-4		367.5	368.2	1.95

46-5		353.4	354.2	1.97
46-6		408.5	409.2	1.77
46-7		393.5	394.2	2.06
46-8		369.4	370.2	1.76
46-9		383.5	384.2	1.78

46-10		396.5	397.2	1.52
46-11		353.4	354.2	1.79
46-12		397.5	398.2	1.93
46-13		410.5	411.2	1.76
46-14		409.5	410.2	1.94

46-15		413.5	414.2	1.87
46-16		424.6	425.2	1.80
46-17		441.6	442.2	2.23
46-18		440.6	441.2	1.78

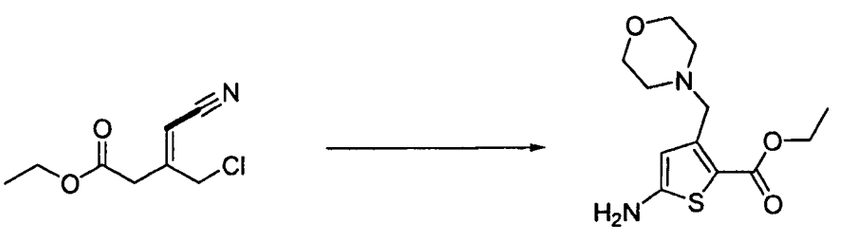
EXAMPLE 47



Ethyl 4-chloro-3-oxobutanoate (14.15 g, 86 mmol), cyanoacetic acid (8.00 g, 86 mmol), NH_4OAc (1.32 g, 17.2 mmol), AcOH (2.46 mL, 43 mmol), and benzene (40 mL) was stirred overnight at reflux with a Dean-Stark trap. The mixture was cooled to room temperature,

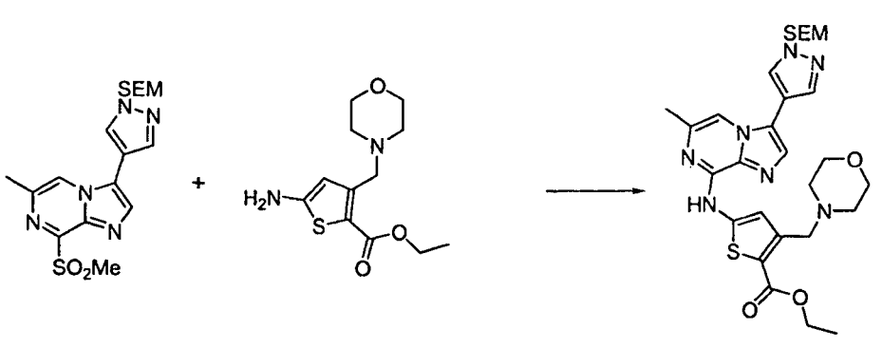
diluted with EtOAc, washed with sat. $NaHCO_3$, brine, dried with Na_2SO_4, and concentrated to afford crude product 1 (9.29g, 58%). HPLC-MS t_R =1.67 Min (UV $_{254nm}$). Mass calculated for M+ 187.0, observed LC/MS m/z 188.1(M+H).

EXAMPLE 48



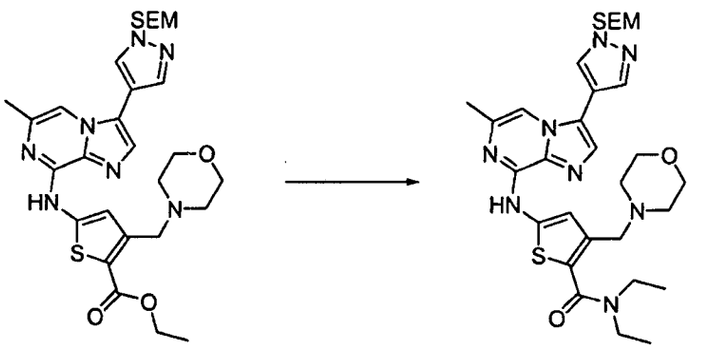
Morpholine (580 µL, 6.65 mmol) was added dropwise to a mixture of ethyl 3-(chloromethyl)-4-cyanobut-3-enoate (622 mg, 3.33 mmol) and S-flakes (116 mg, 3.63mmol) in EtOH (5 mL). The reaction stirred at room temperature overnight. The mixture was concentrated. The mixture was diluted with EtOAc, washed with brine, dried with Na_2SO_4, and concentrated to afford crude product. Purification by Prep-LC afforded the title compound (182 mg, 20%). HPLC-MS t_R = 0.80 Min (UV $_{254nm}$). Mass calculated for M+ 270.1, observed LC/MS m/z 271.1(M+H).

EXAMPLE 49



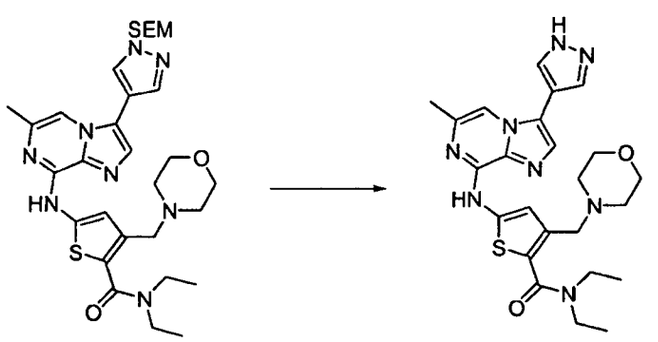
A solution of ethyl 5-amino-3-(morpholinomethyl)thiophene-2-carboxylate (61.0 mg, 0.225 mmol) and sulfone (71.0 mg, 0.173 mmol) in DMF (2 mL) was treated with NaH (60% dispersion in oil, 20.9 mg, 0.521 mmol) at room temperature. The mixture was stirred at room temperature until LCMS indicate the reaction was complete. The reaction mixture was diluted with EtOAc, washed with sat NH_4Cl, dried with Na_2SO_4, and concentrated to afford title compound. HPLC-MS t_R = 1.79 Min (UV $_{254nm}$). Mass calculated for M+ 597.2, observed LC/MS m/z 598.3(M+H).

EXAMPLE 50



A solution of *i*-PrMgCl in THF (0.78 μL, 1.56 mmol) was added dropwise to a solution of crude compound from example 49 (104.2 mg, 0.173 mmol) and diethylamine (91 μL, 0.782 mmol) in THF (3 mL) at –20°C. The mixture was slowly warmed up to room temperature and stirred at this temperature until LCMS indicate the reaction was complete. The reaction mixture was cooled to 0°C and quenched with Sat. NH_4Cl. The reaction mixture was extracted with EtOAc and the organic layer was dried with Na_2SO_4 and concentrated to afford crude product 4. HPLC-MS t_R = 1.81 Min (UV $_{254nm}$). Mass calculated for M+ 624.3, observed LC/MS m/z 625.3(M+H).

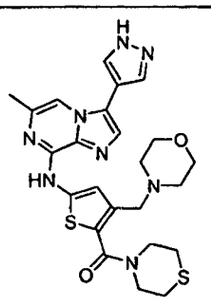
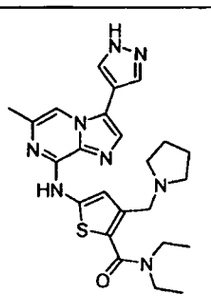
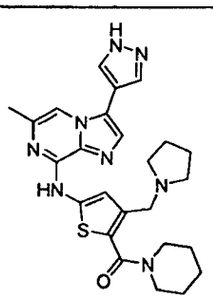
EXAMPLE 51



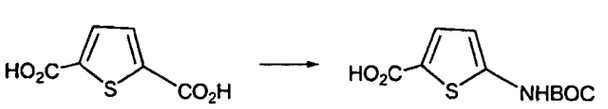
4N HCl in dioxane (1mL) was added to crude compound 4 (17mg, 0.027 mmol) at 0°C. The mixture was warmed to room temperature and stirred at this temperature until LCMS indicate the reaction was complete. Concentration and purification by Prep-LC and conversion to a hydrochloric salt afforded the title compound. HPLC-MS t_R = 1.14 Min (UV $_{254nm}$). Mass calculated for M+ 494.2, observed LC/MS m/z 495.2(M+H).

By essentially the same procedure, compounds given in Column 2 of Table 8 (shown immediately below) can be prepared.

Table 8

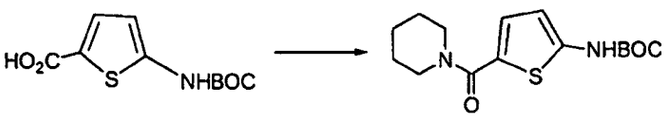
Example	Column 2	MW	LCMS MH^+ m/z	LCMS MS t_R
51-1		524.2	525.2	1.328
51-2		478.2	479.2	1.355
51-3		490.2	491.2	1.099

EXAMPLE 52



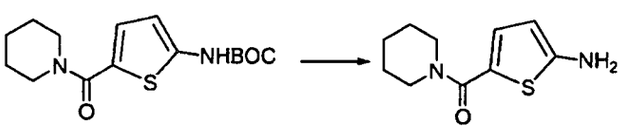
A solution of thiophene-2,5-dicarboxylic acid (2.73 g, 15.84 mmol), diphenylphosphoryl azide (3.41 mL g, 15.84 mmol) and triethylamine (4.4 mL, 31.68 mmol) in tert-butanol (80 mL) was heated at refluxing 5h. The reaction mixture was cooled to room temperature and then concentrated to afford the crude title compound. HPLC-MS t_R =1.52 Min (UV $_{254nm}$). Mass calculated for M+ 243.0, observed LC/MS m/z 244.1(M+H).

EXAMPLE 53



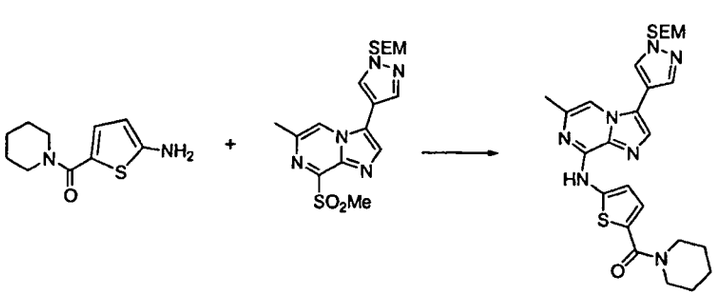
Et_3N (1261.6 μL, 9.05 mmol) was added at 0°C to a mixture of 5-tert-Butoxycarbonylamino-thiophene-2-carboxylic acid (550 mg, 2.26mmol), EDCI (1086 mg, 5.65 mmol) , and piperidine (447 μL, 4.52 mmol) in DMF (6ml). The reaction mixture was warmed up to room temperature and stirred at this temperature overnight. The mixture was diluted with EtOAc, washed with brine (2X), dried over Na_2SO_4 and concentrated to afford crude residue. Purification by Biotage afforded compound 2 (368 mg, 53%). HPLC-MS t_R =1.89 Min (UV $_{254nm}$). Mass calculated for M+ 310.1, observed LC/MS m/z 311.2(M+H). HPLC-MS t_R =2.4 Min (UV $_{254nm}$).

EXAMPLE 54



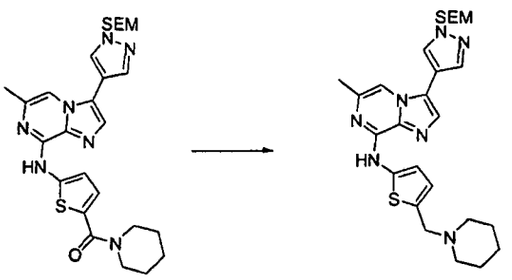
Compound from Example 53 (90 mg, 0.29 mmol) was stirred in 20% TFA / CH_2Cl_2 solution (5 mL) at room temperature for 1.5 hrs. The reaction mixture was concentrated to afford compound 3. The crude product was used without further purification. HPLC-MS t_R =1.16 Min (UV $_{254nm}$). Mass calculated for M+210.0, observed LC/MS m/z 211.1(M+H).

EXAMPLE 55



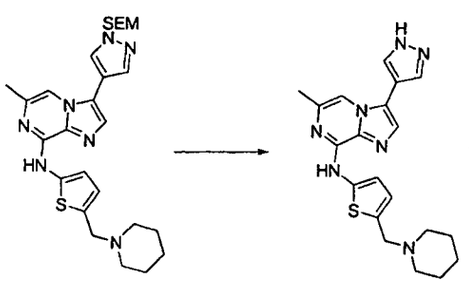
A solution of crude material from Example 54 and sulfone (98.0 mg, 0.241 mmol) in DMF (2 mL) was treated with NaH (60% dispersion in oil, 29.0 mg, 0.725 mmol) at room temperature. The mixture was stirred until LCMS indicate the reaction was complete. The reaction mixture was diluted with EtOAc, washed with sat NH_4Cl, dried with Na_2SO_4, and concentrated to afford crude product 4. Purification by Biotage afforded the title compound (82 mg, 63%). HPLC-MS t_R = 2.30 Min (UV $_{254nm}$). Mass calculated for M+ 537.2, observed LC/MS m/z 538.2(M+H).

EXAMPLE 56



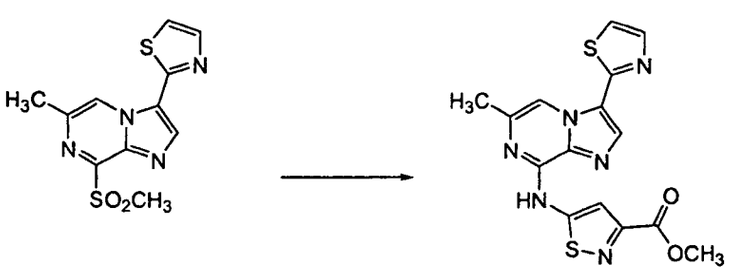
To a solution of the amide (47.6 mg, 0.089 mmol) in dichloromethane (5 mL) was added lithium aluminum hydride (39.9 mg, 1.0 mmol) and ethyl ether (1 mL). The reaction mixture was stirred at room temperature for 10 min then refluxed at 40° C until LCMS indicate the reaction was complete. The reaction was cooled to room temperature and quenched with H_2O (0.5 mL). The reaction was diluted with dichloromethane, dried over Na_2SO_4 and concentrated to afford crude title compound. HPLC-MS t_R = 1.52 Min (UV $_{254nm}$). Mass calculated for M+ 523.2, observed LC/MS m/z 524.2 (M+H).

EXAMPLE 57



4N HCl in dioxane (2mL) was added to crude compound from example 56 at 0°C. The mixture was warmed to room temperature and stirred at this temperature until LCMS indicate the reaction was complete. Concentration afforded crude title compound. Purification by Prep-LC and conversion to a hydrochloric salt afforded the title compound. HPLC-MS t_R = 0.91 Min (UV $_{254nm}$). Mass calculated for M+ 393.1, observed LC/MS m/z 394.1 (M+H).

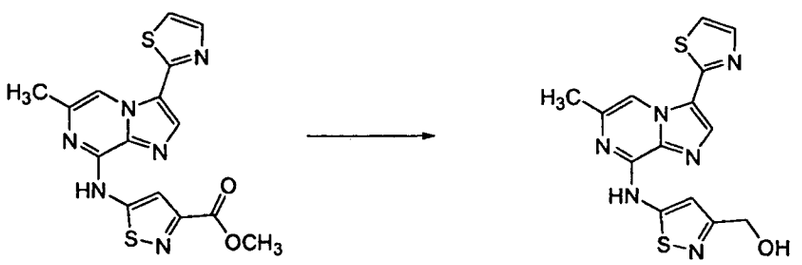
EXAMPLE 58



To a solution of 8-methanesulfonyl-6-methyl-3-thiazol-2-yl-imidazo [1, 2-a] pyrazine (0.070 g; 0.24 mmol) and 5-amino-3-carbomethoxy-isothiazole (0.039g; 0.25 mmol) in

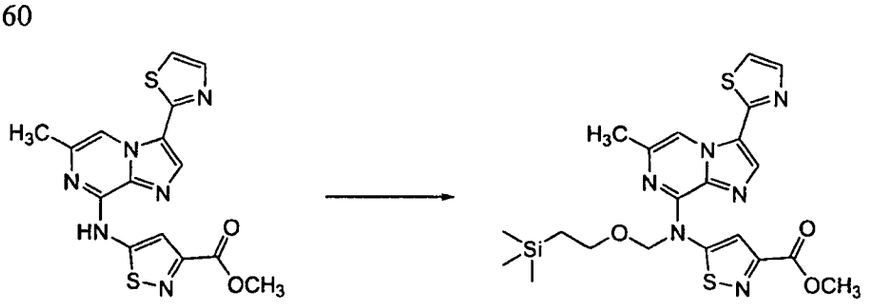
dimethyl formamide (DMF; 0.8 mL) was added sodium hydride (NaH; 60% in oil; 0.024 g). The reaction mixture was stirred at room temperature for 0.5 hr and then quenched with saturated aqueous solution of ammonium chloride (NH_4Cl). Diluted with more water and filtered. The filter cake was washed with water and hexanes. The filter cake was dried in vacuo to obtain the title compound as yellow solid (0.078 g; 87%). ^1H NMR (400 MHz, DMSO-d_6): 8.85 (s, 1H), 8.42 (s, 1H), 8.1 (s, 1H), 7.9 (s, 1H), 7.65 (s, 1H), 3.85 (s, 3H) 2.5 (s, 3H). HPLC-MS t_R = 4.35 (UV_{254nm}). Mass Calc. for $C_{15}H_{12}N_6O_2S_2$ 372.04; obsd MH^+ (LCMS) 373.2 (m/z).

EXAMPLE 59



A solution of lithium triethylborohydride (Super Hydride; 1M in THF; 0.32 mL) was added dropwise to a solution of the methyl ester (0.03 g; 0.08 mmol) in dry THF (0.8 mL). After stirring at room temperature for 1.5 hr, the reaction mixture was quenched with saturated aqueous NH_4Cl solution (8 mL) and diluted with water. Small amount of the precipitated yellow solid was filtered and washed with water and ether. The solid was dried *in vacuo* to obtain ~10 mg (36%) of the alcohol. ^1H NMR (400 MHz, DMSO-d_6): 8.8 (s, 1H), 8.4 (s, 1H), 8.1 (s, 1H), 7.9 (s, 1H), 7.2 (s, 1H), 5.4 (t, 1H). 4.5 (d, 2H), 2.5 (s, 3H). HPLC-MS t_R = 2.98 (UV_{254nm}). Mass Calc. for $C_{14}H_{12}N_6OS_2$ 344.05; obsd MH^+ (LCMS) 345.2 (m/z).

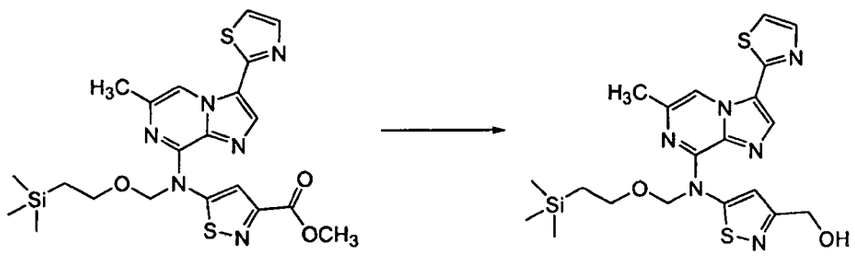
EXAMPLE 60



A solution of ester (0.113 g; 0.3 mmol) in DMF (1.5 mL) was treated with NaH (60% in oil; 0.03 g; 0.76 mmol) followed by 2-(Trimethylsilyl) ethoxymethyl chloride (SEM-Cl; 0.1 mL; 0.61 mmol). The reaction mixture was stirred at room temperature for 3 hr and quenched with saturated aqueous NH_4Cl and water. The precipitated yellow solid was collected by filtration, washed with water and dried. The title compound was obtained as yellow solid

(0.142 g; 92%). ^{1}H NMR (400 MHz, CDCl3): 9.1 (s, 1H), 8.1 (s, 1H), 7.98 (s, 1H), 7.8 (s, 1H), 7.4 (s, 1H), 6.65 (s, 2H), 4.0 (s, 3H), 3.78 (t, 2H), 2.65 (s, 3H), 1.0 (t, 2H), 0.0 (s, 9H). HPLC-MS t_R = 5.98 (UV_{254nm}). Mass Calc. for $C_{21}H_{26}N_6O_3S_2Si$ 502.13; obsd MH^+ (LCMS) 503.3 (m/z).

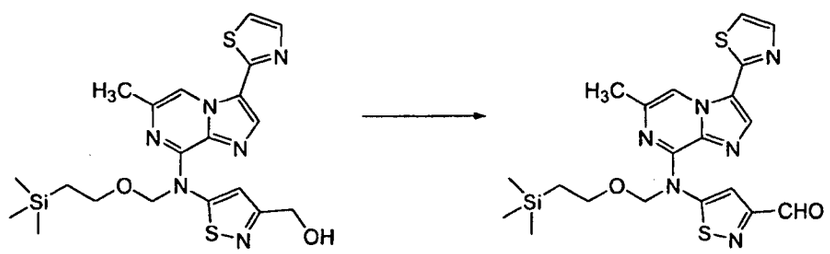
EXAMPLE 61



A solution of lithium triethylborohydride (Super Hydride; 1M in THF; 1 mL) was added dropwise to a solution of the methyl ester 2 in dry THF. After stirring at room temperature for 1 hr, the reaction mixture was quenched with saturated aqueous NH_4Cl solution (8 mL) and saturated aqueous solution of Rochelle salt. The organic product was extracted with dichloromethane (CH_2Cl_2), washed with water and brine. Concentration in *vacuo* gave ~120 mg (100%) of the alcohol.

HPLC-MS t_R = 4.22 (UV_{254nm}). Mass Calc. for $C_{20}H_{26}N_6O_2S_2Si$ 474.13; obsd MH^+ (LCMS) 475.3 (m/z).

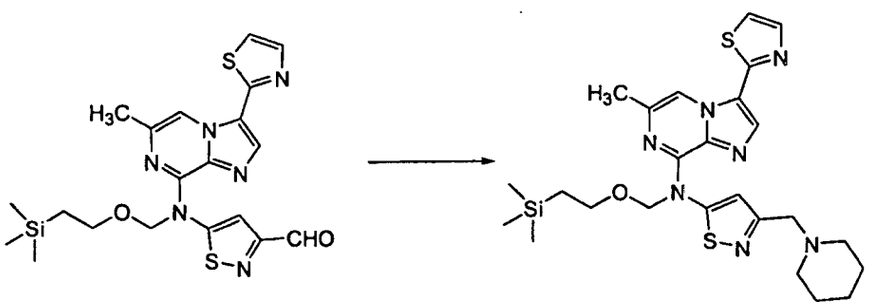
EXAMPLE 62



Dess-Martin periodinane (0.147 g; 0.35 mmol) was added to a solution of alcohol (0.11 g; 0.23 mmol) in dry THF and stirred at room temperature for 40 minutes. The reaction mixture was diluted with 30 mL of CH_2Cl_2, washed with saturated sodium bicarbonate ($NaHCO_3$) solution, water and dried. Concentration furnished a yellow solid which was re-dissolved in CH_2Cl_2 and filtered. The filtrate was concentrated to obtain 120 mg of crude title compound as a yellow solid which was used as is in the next step. ^{1}H NMR (400 MHz, CDCl3): 10 (s, 1H), 9.1 (s, 1H), 8.1 (s, 1H), 7.98 (s, 1H), 7.78 (s, 1H), 7.4 (s, 1H), 6.6 (s, 2H),

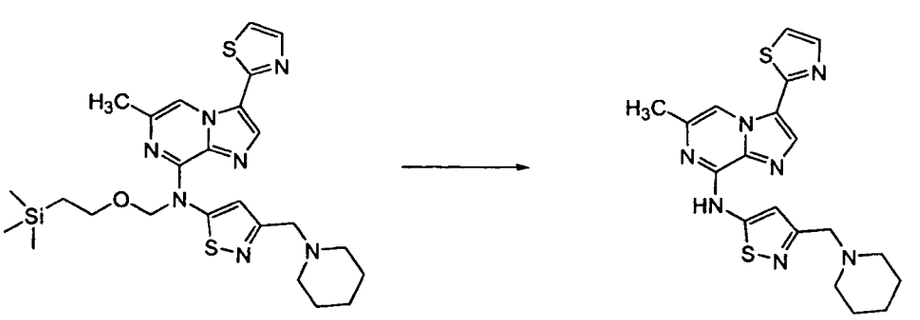
3.78 (t, 2H), 2.65 (s, 3H), 1.0 (t, 2H), 0.0 (s, 9H). HPLC-MS t_R = 6.14 (UV_{254nm}). Mass Calc. for $C_{20}H_{24}N_6O_2S_2Si$ 472.12; obsd MH^+ (LCMS) 473.3 (m/z).

EXAMPLE 63



A solution of aldehyde (0.05 g; 0.1 mmol) and piperidine (0.05 mL; 0.5 mmol) in CH_2Cl_2 (1 mL) was treated with glacial acetic acid (AcOH; 1 drop) and stirred at room temperature (RT) for 3 hr. Solid sodium borohydride ($NaBH_4$; 0.016 g; 0.42 mmol) was added and the reaction mixture was cooled in an ice/brine bath (-5°C) and methanol (0.2 mL) was added dropwise. After stirring at low temperature for 30 minutes, the reaction was quenched with saturated NH_4Cl and extracted into CH_2Cl_2. The organic extract was washed with saturated NH_4Cl, water and brine. Removal of solvent gave the crude product which was purified by preparative thin layer chromatography (Prep TLC) using CH_2Cl_2 with 4% CH_3OH and 1% ammonium hydroxide. The title compound was isolated as yellow film (25 mg; 45%). ^1H NMR (400 MHz, CDCl3): 9.1 (s, 1H), 8.1 (s, 1H), 7.98 (s, 1H), 7.4 (s, 1H),7.3 (s, 1H), 6.6 (s, 2H), 3.8 (t, 2H), 3.6 (s, 2H), 2.65 (s, 3H), 2.5 (br-s, 4H),1.7 (br-s, 4H), 1.45 (br-s, 2H), 0.98 (t, 2H), 0.0 (s, 9H). HPLC-MS t_R = 3.82 (UV_{254nm}). Mass Calc. for $C_{25}H_{35}N_7OS_2Si$ 541.21; obsd MH^+ (LCMS) 542.3 (m/z).

EXAMPLE 64

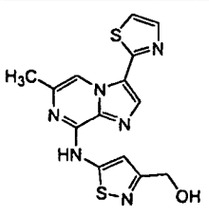
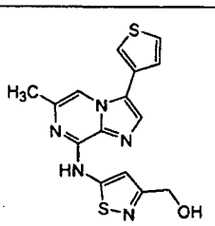
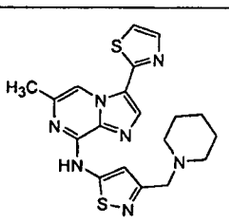
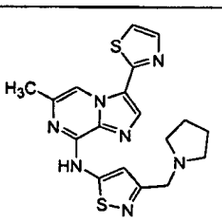


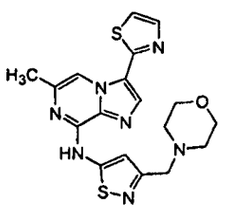
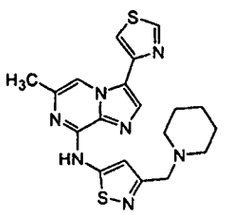
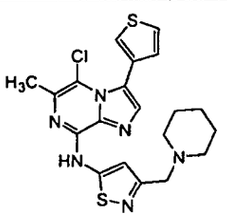
A solution of compound from Example 63 (0.013 g; 0.02 mmol) in 0.5 mL of THF was treated with HCl in dioxane (4M; 0.5 mL) and placed in an oil bath at 70°C. After heating for 30 min, a precipitate formed which dissolved upon adding 0.5 mL of methanol. The reaction mixture was heated at a bath temperature of 70°C for an additional 1 hr. The contents of the

reaction were cooled to RT and all the volatiles were removed on a rotary evaporator. The residue was suspended in THF and triturated with ether. The precipitate was collected by filtration, washed with ~ 10 mL of ether and dried in air (0.5 hr) and in *vacuo* (16 hr) to furnish 10 mg (93%) of the title compound as a yellow solid. ^{1}H NMR (400 MHz, CD_3OD): 9.0 (s, 1H), 8.3 (s, 1H), 8.05 (s, 1H), 7.7 (s, 1H), 7.25 (s, 1H), 4.4 (s, 2H), 3.6 (d, 2H), 3.1 (t, 2H), 2.6 (s, 3H), 2.0 (d, 2H), 1.85 (t, 4H), 1.6 (t, 1H). HPLC-MS t_R = 2.96 (UV_{254nm}). Mass Calc. for $C_{19}H_{21}N_7S_2$ 411.13; obsd MH^+ (LCMS) 412.2 (m/z).

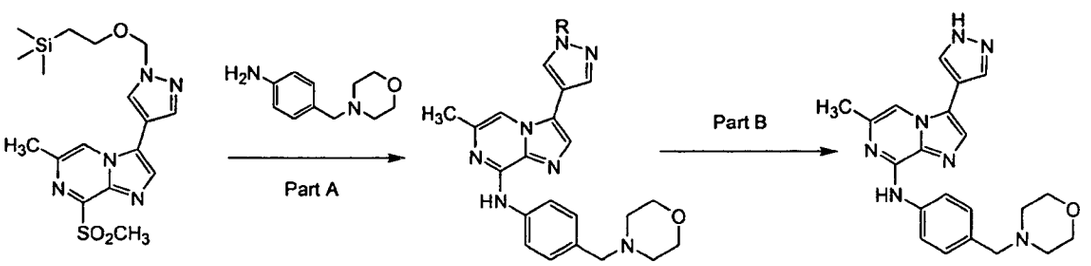
Compounds in the Table 9 (shown immediately below) were prepared as per the above-described examples:

Table 9

Example	Structure	MW	LCMS MH^+ (m/z)	HPLC MS t_R
59-1		344.05	345.2	2.98
59-2		343.06	344.2	2.78
64-1		411.13	412.2	2.96
64-2		397.11	398.2	3.11

64-3		413.11	414.2	2.86
64-4		411.13	412.2	2.99
64-5		444.09	445.2	3.29

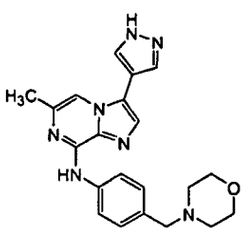
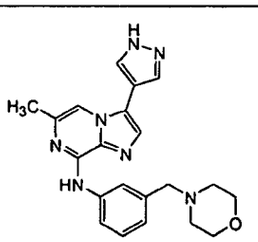
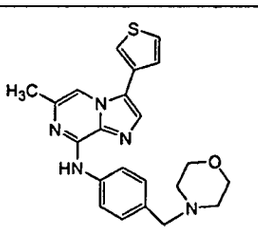
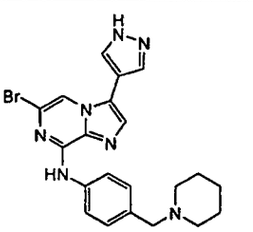
EXAMPLE 65

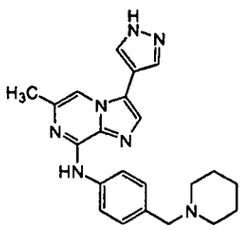
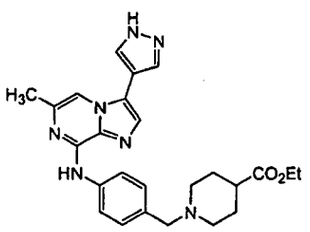
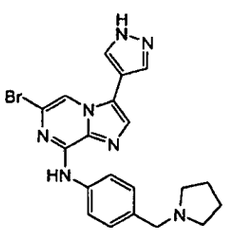
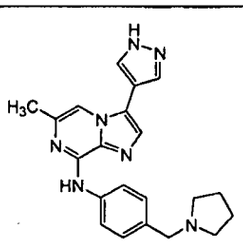
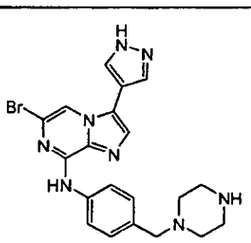
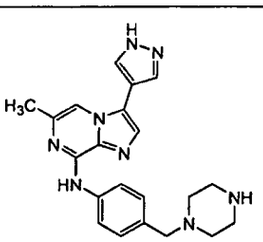


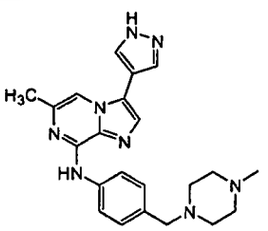
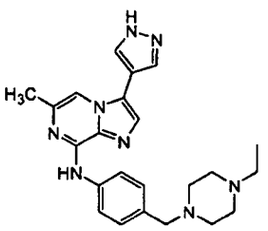
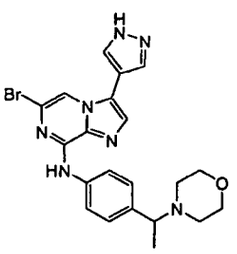
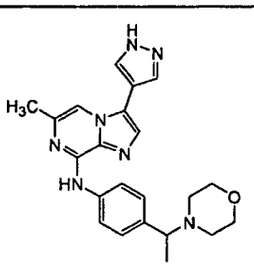
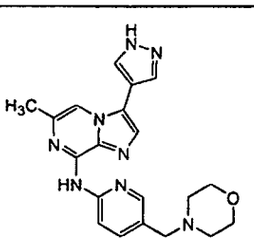
Part A: Lithium hexamethyldisilazide (1M in THF; 0.18 mL) was added to an amber solution of 4-morpholin-4-ylmethyl phenylamine (0.013g; 0.068 mmol) and 8-methanesulfonyl-6-methyl-3-[1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-pyrazol-4-yl]-imidazo[1, 2-*a*]pyrazine (0.025g; 0.061 mmol) in 2 mL of THF at RT resulting in a burgundy solution. After stirring at RT for 20 minutes, the reaction mixture was quenched with saturated aqueous NH_4Cl solution. The contents were diluted with ethyl acetate and washed with water and brine. The crude material from the organic extract was purified by prep TLC (5% methanol-CH_2Cl_2) to obtain the title compound as pale yellow oil (0.025 g; 80%). ^1H NMR (400 MHz, CDCl3): 8 (s, 1H), 7.9 (d, 2H), 7.85 (s, 1H), 7.8 (s, 1H), 7.5 (s, 1H), 7.4 (s, 1H), 7.35 (d, 2H), 5.55 (s, 2H), 3.75 (br-s, 4H), 3.7 (t, 2H), 3.5 (br-s, 2H), 2.5 (br-s, 2H), 2.4 (s, 3H), 1.6 (br-s, 2H), 0.95 (t, 2H), 0.0 (s, 9H). HPLC-MS t_R = 3.05 (UV_{254nm}). Mass Calc. for $C_{27}H_{37}N_7O_2Si$ 519.27; obsd MH^+ (LCMS) 520.3 (m/z).

Part B: The compound from Part A (0.025g; 0.048 mmol) was suspended in dry THF and treated with HCl in dioxane (4M; 1 mL) and heated in an oil bath set to 70°C for 15 minutes when a white precipitate was formed. Methanol was added to dissolve some of the solid and the reaction mixture was continued to be heated for 45 minutes more. After cooling to RT, the volatiles were removed on the rotary evaporator. The residue was suspended in THF and the precipitated solid was collected by filtration, washed with ether and dried in *vacuo* overnight. The title compound was isolated as a beige solid (14 mg; 78%). All the analogues in Table 10 were similarly prepared.

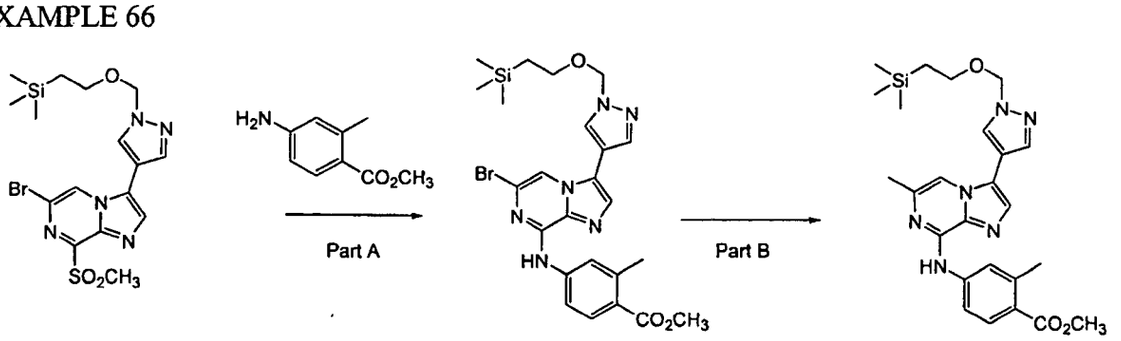
Table 10

Example	Structure	MW	LCMS MH^+ (m/z)	HPLC MS t_R
65-1		389.19	390.2	1.7
65-2		389.19	390.2	1.76
65-3		405.16	406.2	2.38
65-4		451.11	452.2	2.51

65-5		387.22	388.2	1.85
65-6		459.24	460.3	2.03
65-7		437.1	438.2	2.38
65-8		373.2	374.2	1.65
65-11		452.11	453.3	1.93
65-12		388.21	389.2	1.59

65-13		402.23	403.2	1.51
65-14		416.24	417.2	1.54
65-15		467.1	468.3	2.27
65-16		403.21	404.2	1.9
65-17		390.19	391.2	1.36

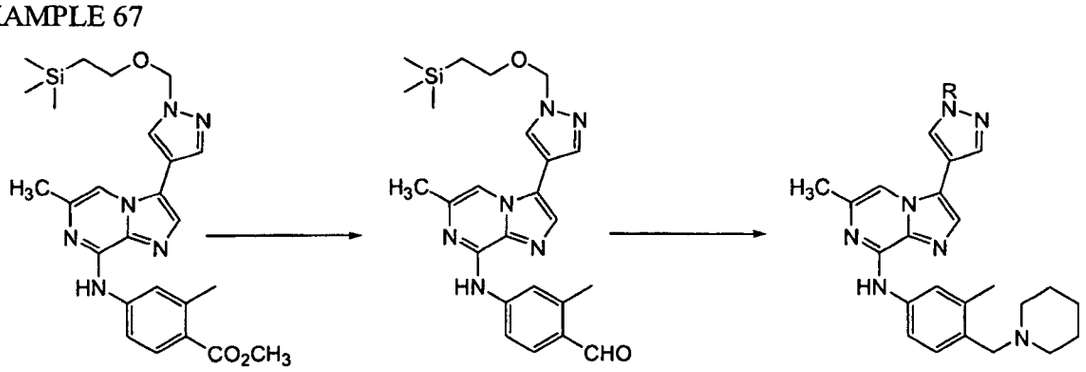
EXAMPLE 66



Part A: A solution of 4-Amino-2-methyl-benzoic acid methyl ester (0.33 g; 2 mmol; prepared from commercially available 4-nitro-2-methyl-benzoic acid) and 8-methanesulfonyl-6-bromo-3-[1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-pyrazol-4-yl]-imidazo[1, 2-*a*]pyrazine (0.472 g; 1.0 mmol) was treated with LiHMDS (1M in THF; 2 mL) at RT. The resulting burgundy solution was stirred at RT for 20 minutes and then quenched with saturated aqueous NH_4Cl solution. Standard work up as described for Example 65 and flash silicagel chromatography (25% EtOAc in CH_2Cl_2) provided the title compound as pale yellow foam (0.48 g; 86%). NMR (400 MHz, CDCl3): 8.18 (s, 1H), 8 (d, 1H), 7.9 (s, 1H), 7.85 (d, 1H), 7.78 (s, 1H), 7.7 (s, 1H), 7.62 (s, 1H), 7.58 (s, 1H), 5.5 (s, 2H), 3.9 (s, 3H), 3.65 (t, 2H), 2.6 (s, 3H), 0.98 (t, 2H), 0.0 (s, 9H). Mass Calc. for $C_{24}H_{29}BrN_6O_3Si$ 556.13; Obsd MH^+ (CI-MS) 557 / 559 (m/z).

Part B: A solution of compound from Part A (0.48 g; 0.86 mmol) in 2 mL of dry THF was treated with a solution of dimethyl zinc (2M; 4 mL) dropwise. After the effervescence ceased, solid $Pd(PPh_3)_4$ was added and the reaction was flushed with nitrogen, fitted with a reflux condenser and heated in an oil bath at 65-70°C. After 0.5 hr, the reaction mixture had turned from yellow orange to deep red and after 4 more hours, it had become an opaque black. TLC (25% EtOAc- CH_2Cl_2) indicated the formation of a slightly more polar spot. The reaction was cooled to RT, quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc. Flash silicagel chromatography of the crude material gave the 6-methyl title compound as yellow solid (0.38 g; 90%). NMR (400 MHz, CDCl3): 8.1 (s, 1H), 8 (d, 1H), 7.9 (d, 1H), 7.85 (s, 1H), 7.8 (s, 1H), 7.7 (s, 1H), 7.58 (s, 1H), 7.4 (s, 1H), 5.5 (s, 2H), 3.9 (s, 3H), 3.65 (t, 2H), 2.65 (s, 3H), 2.4 (s, 3H), 0.98 (t, 2H), 0.0 (s, 9H). Mass Calc. for $C_{25}H_{32}N_6O_3Si$ 492.23; Obsd MH^+ (CI-MS) 493.11 (m/z).

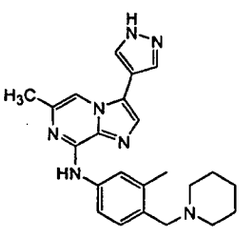
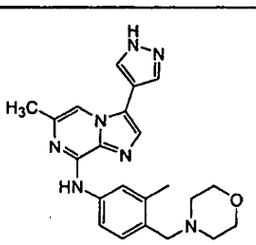
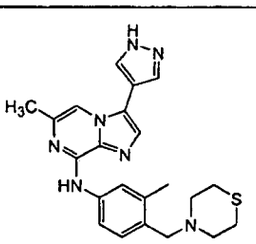
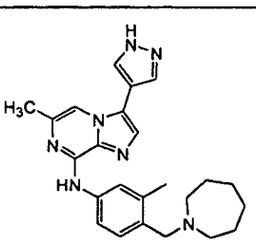
EXAMPLE 67



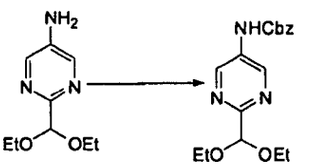
Part A: Ester was first reduced to the alcohol using $LiBEt_3H$ in THF at RT and subsequently oxidized using Dess-Marin periodinane to the aldehyde as described previously. The reductive amination of aldehyde with various secondary amines was carried out provided SEM-protected

title compound. Removal of the SEM protecting group was carried out under conditions described previously. In a similar manner, other tertiary amines listed in Table 11 (shown immediately below) were also prepared by the similar reaction scheme with the corresponding secondary amines followed by removal of the SEM protecting group.

Table 11

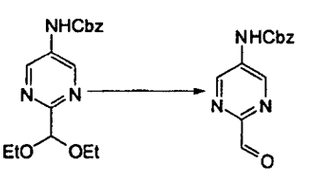
Example	Structure	MW	LCMS MH^+ (m/z)	HPLC MS t_R
67-1		401.23	402.2	1.87
67-2		403.21	404.2	1.71
67-3		419.19	420.2	1.95
67-4		415.25	416.2	2.0

EXAMPLE 68



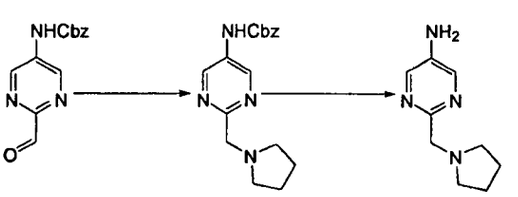
The substrate (1 g, 5.07 mmol) was dissolved in THF:H_2O (12 mL, 1:1, v/v) and treated with K_2CO_3 (1.4 g, 10.15 mmol) at room temperature. Then benzyl chloroformate (0.79 ml, 5.58 mmol) in THF (2 mL) was slowly added. The mixture was stirred for 16 h. It was diluted with ethyl acetate (25 mL). The two layers were separated, and the aqueous layer was extracted with ethyl acetate (2 × 25 mL). The combined organic layer was washed with brine (1 × 30 mL), dried (Na_2SO_4), filtered and evaporated under reduced pressure to give the crude product which was purified by column chromatography (SiO_2) eluting ethyl acetate-hexane.

EXAMPLE 69



The substrate acetal (1.2 g, 3.64 g) was dissolved in acetone (20 mL), and treated with 1N aqueous HCl (2 mL) at room temperature, and the mixture was stirred for 7 h. Then acetone was evaporated off, and the residue was diluted with saturated aqueous $NaHCO_3$ (30 mL). The aqueous layer was extracted with ethyl acetate (2 × 30 mL). The combined organic layer was washed with brine (1 × 30 mL), dried (Na_2SO_4), filtered and evaporated under reduced pressure to give the crude product as solid which was used in the next step without any further purification.

EXAMPLE 70

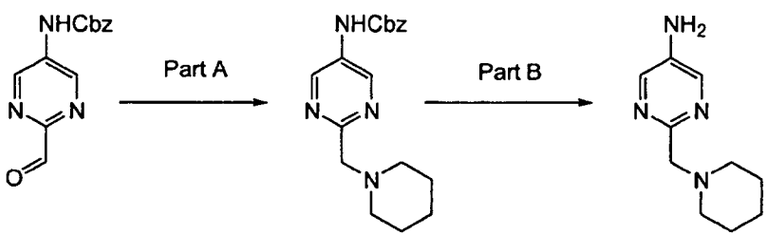


The substrate (1 eq.), amine (4 eq.), catalytic AcOH, $NaB(OAc)_3H$ (2 eq.) in 1,2-dichloroethane was stirred at room temperature for 2 h. Then sodium borohydride (3 eq.) was added and the mixture was stirred for 30 min at which point LC-MS analysis indicate complete consumption of starting material to product. Then the reaction was quenched with 2N aqueous

NaOH, and the mixture was stirred vigorously until two clear layer separated. The organic layer was washed with water, brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure to give the product.

The crude product was hydrogenated in ethyl acetate using 10% Pd/C at 1 atmosphere hydrogen pressure. The catalyst was filtered off, and solvent was evaporated under reduce pressure to give the crude product.

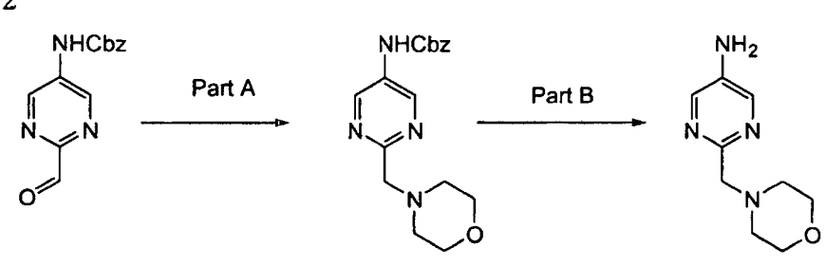
EXAMPLE 71



Part A: The substrate (1 eq.), amine (4 eq.), catalytic AcOH, $NaB(OAc)_3H$ in 1,2-dichloroethane was stirred at room temperature for 2 h. Then sodium borohydride (3 eq.) was added and the mixture was stirred for 30 min at which point LC-MS analysis indicate complete consumption of starting material to product. Then the reaction was quenched with 2N aqueous NaOH, and the mixture was stirred vigorously until two clear layer separated. The organic layer was washed with water, brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure to give the product.

Part B: The crude product was hydrogenated in ethyl acetate using 10% Pd/C at 1 atmosphere hydrogen pressure. The catalyst was filtered off, and solvent was evaporated under reduce pressure to give the crude product.

EXAMPLE 72

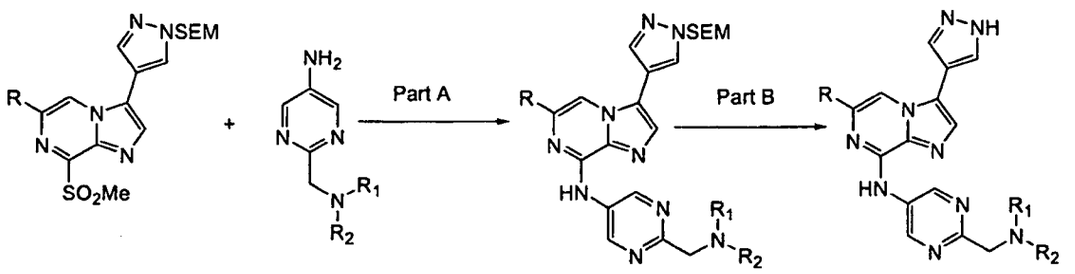


Part A: The substrate (1 eq.), amine (4 eq.), catalytic AcOH, $NaB(OAc)_3H$ in 1,2-dichloroethane was stirred at room temperature for 2 h. Then sodium borohydride (3 eq.) was added and the mixture was stirred for 30 min at which point LC-MS analysis indicate complete consumption of starting material to product. Then the reaction was quenched with 2N aqueous NaOH, and the mixture was stirred vigorously until two clear layer separated. The organic

layer was washed with water, brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure to give the product.

Part B: The crude product was hydrogenated in ethyl acetate using 10% Pd/C at 1 atmosphere hydrogen pressure. The catalyst was filtered off, and solvent was evaporated under reduce pressure to give the crude product.

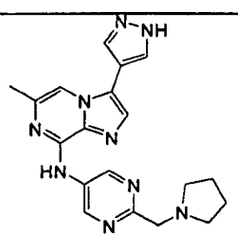
EXAMPLE 73

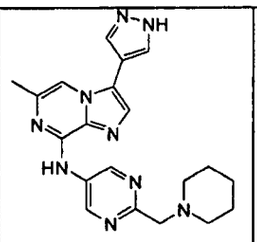
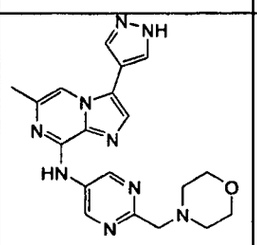
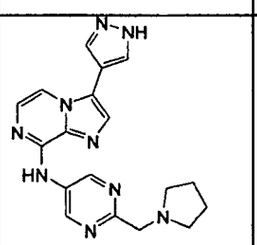
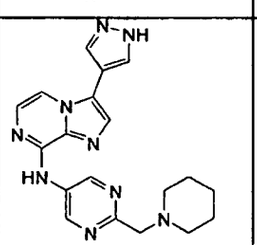
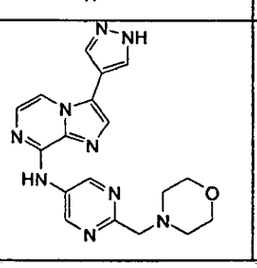


Part A: The substrate (1 eq.) and amine (1.5-2 eq.) was dissolved in DMSO under argon, and treated with NaH (5 eq., 60% dispersion in oil). After 30 min, LC-MS analysis indicated complete consumption of starting material. The reaction was quenched by addition of saturated aqueous NH_4Cl-acetonitrile (1:1, v/v). The two layers were separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure to give the crude product.

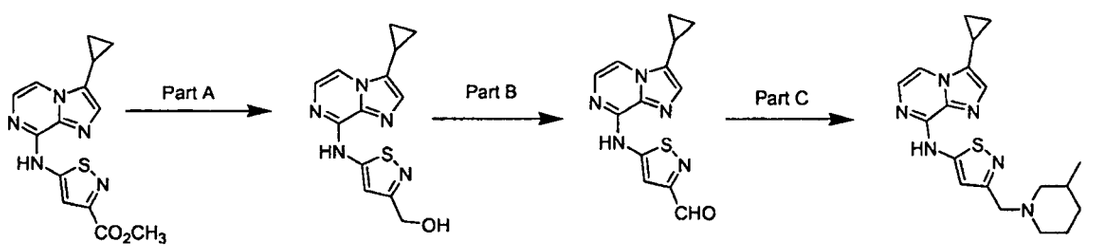
Part B: The substrate was dissolved in 4N HCl in dioxane, and stirred at room temperature for 30 min. The solvent was then evaporated, and the residue was purified by Prep-LC. Conversion to hydrochloride salt afforded the product as solid. The compounds in Table 12 (shown immediately below) were prepared accordingly:

Table 12

Example	Column	MW	LCMS MH^+ m/z	HPLC MS t_R
73-1		375.4	376.1	0.83

73-2		389.4	390.2	1.05
73-3		391.4	392.1	0.78
73-4		361.4	362.2	0.74
73-5		375.4	376.2	0.85
73-6		377.4	378.3	0.87

EXAMPLE 74



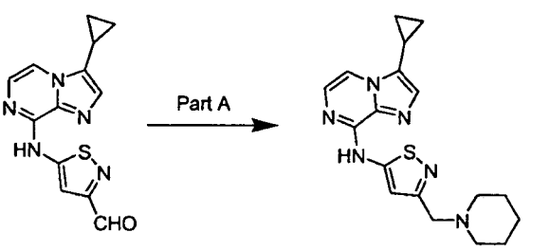
Part A: By essentially the same procedure as described for Example 1 and 13.

Part B: To a solution of compound from Example 74, Part A (0.16 g, 0.57 mmol) in THF (20 mL) and water (0.025 mL) was added Dess-Martin periodinane (3 equivalents). The resulting solution was stirred at rt for 1.5h at which time LC-MS analysis indicated the reaction was

complete. The reaction mixture was diluted with dichloromethane (75 mL), washed with water, dried (sodium sulfate) and concentrated. Purification by column chromatography (SiO_2 10% methanol / DCM) afforded the title compound as a yellow solid 0.08 g (49%). HPLC-MS t_R = 1.59 Min (UV $_{254nm}$). Mass calculated for formula C13H11N5OS 285.07, observed LC/MS m/z 286.1 (M+H).

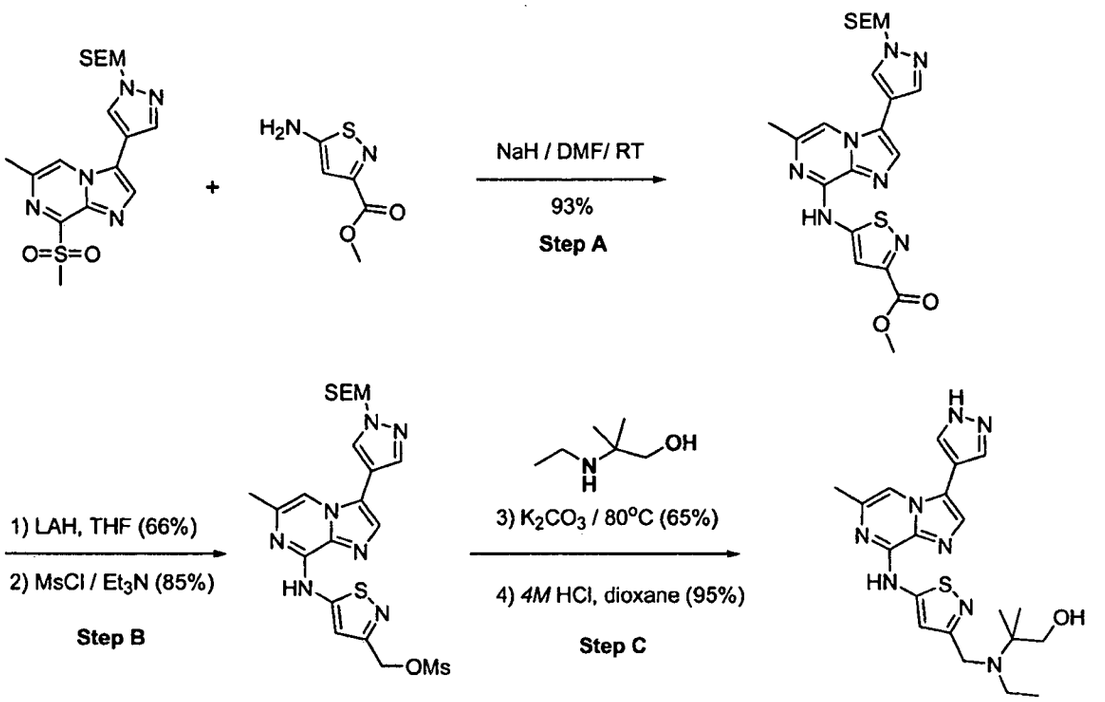
Part C: To a solution of compound from Part B (30 mg, 0.105 mmol, 1 equivalent), 3-methylpiperidine (10 equivalents) in dichloromethane:methanol (5:1) (3 ml) was added acetic acid (1 drop). The resulting solution was stirred at rt for 30 minutes, and then sodium borohydride (8 equivalents) added to the reaction. The reaction mixture was stirred at rt for 1 hour at which time LC-MS analysis indicated the reaction was complete. The reaction was quenched with sat. aq. sodium bicarbonate and then extracted with dichloromethane (x2). The combined organic layer was dried (sodium sulfate) and concentrated. Purification by Prep-LC and conversion to a hydrochloric salt afforded the title compound. HPLC-MS t_R = 3.73 Min (UV $_{254nm}$). Mass calculated for formula $C_{19}H_{24}N_6S$ 368.18, observed LC/MS m/z 369.2 (M+H).

EXAMPLE 75



Part A: To a solution of compound 1 (30 mg, 0.105 mmol, 1 equivalent), piperidine (10 equivalents) in dichloromethane:methanol (5:1) (3 ml) was added acetic acid (1 drop). The resulting solution was stirred at rt for 30 minutes, and then sodium borohydride (8 equivalents) added to the reaction. The reaction mixture was stirred at rt for 1 h at which time LC-MS analysis indicated the reaction was complete. The reaction was quenched with sat. aq. sodium bicarbonate and then extracted with dichloromethane (x2). The combined organic layer was dried (sodium sulfate) and concentrated. Purification by Prep-LC and conversion to a hydrochloric salt afforded compound 2. HPLC-MS t_R = 3.47 Min (UV $_{254nm}$). Mass calculated for formula $C_{18}H_{22}N_6S$ 354.16, observed LC/MS m/z 355.1 (M+H).

EXAMPLE 76:



Step A: Sodium hydride (60% dispersion in mineral oil, 6.68 g, 3.40 equiv) was slowly added in one portion to a stirring mixture of compound sulfone (20.0 g, 1.00 equiv) and aminoisothiazole (11.5 g, 1.20 equiv, as HCl salt) in DMF (490 mL) at room temperature (with aid of a room temperature water bath). Reaction was allowed to stir for 1 hour at which time HPLC analysis indicated the reaction was complete. The reaction was carefully quenched with saturated aqueous sodium bicarbonate (200 mL) and then diluted with water (1L). This mixture was stirred for 20 minutes at room temperature, and then the resulting precipitate was collected by filtration, washed with water (200 mL), and dried under high vacuum for 16 hours. The resulting waxy solid was dissolved in 1.8 L of 1:1 chloroform : methanol, dried over sodium sulfate, filtered, and concentrated under reduced pressure to give the title compound (22.3 g, 93%) as a dark yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.3 (bs, 1H), 8.60 (s, 1H), 8.10 (s, 1H), 7.88 (s, 2H), 7.59 (s, 1H), 5.51 (s, 2H), 3.85 (s, 3H), 3.63 (d, J = 8 Hz, 2H), 2.48 (s, 3H), 0.88 (d, J = 8 Hz, 2H), -0.026 (s, 9H). Mass calculated for formula $C_{21}H_{27}N_7O_3SSi$ 485.63; observed MH^+ (MS) 486.6 (m/z).

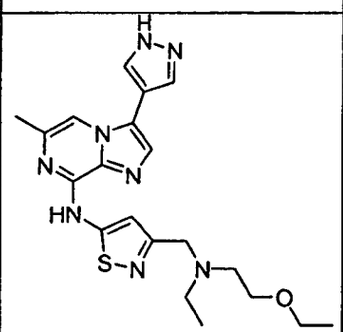
Step B: A mixture of compound from Step A (4.27g, 3.73 mmol) was dissolved in 180 mL of THF. The resulting solution was cooled to 0 °C and $LiAlH_4$ powder (2.6 g, 68.5 mmol) was carefully added. The cooling bath was removed and the reaction was stirred at RT under a N_2 atmosphere for 1.5 hr. The reaction was cooled to 0 °C and carefully quenched by the

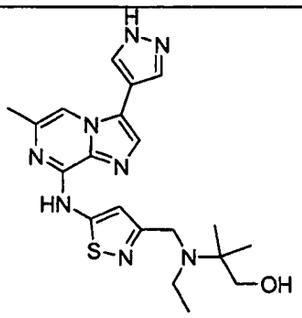
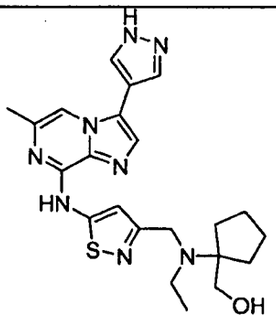
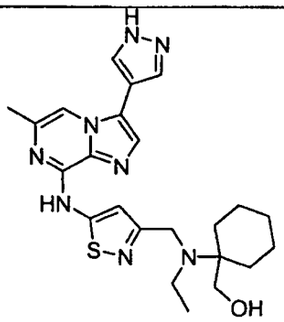
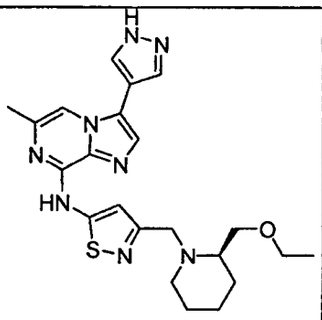
sequential addition of 2.6 mL of H_2O; 2.6 mL of 15 % NaOH (aq); 7.8 mL H_2O. After stirring for 10 min, the reaction was filtered through a very thin pad of Celite (rinsing with THF, EtOAc and DCM). Concentration of the filtrate yielded a light yellow solid. Pure alcohol (2.66 g, 66 % yield) was obtained via triturating with MeOH and used directly in the next step.

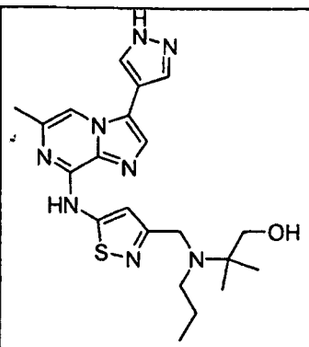
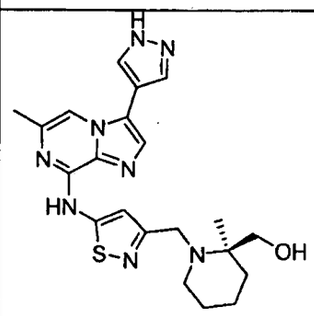
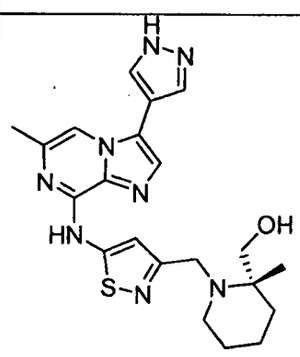
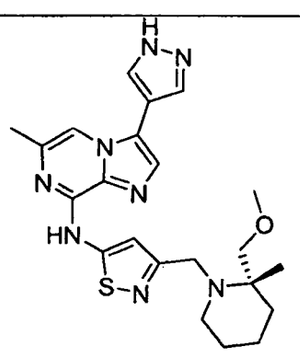
Step C: A mixture of compound from Step B (2.40 g, 4.49 mmol), amine (1.57 g, 13.46 mmol), and NaI (63.0 mg, 0.449 mmol) in 45 mL of THF was heated at 80 °C for 12 h. It was diluted with 200 mL of CH_2Cl_2, and washed with 100 mL of saturated aqueous $NaHCO_3$ solution, then with brine (100 mL). The solvent was removed under vacuum. The residue was purified by flash chromatography eluting with 5% to 10% MeOH/CH_2Cl_2 to give 1.68 g of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.49 (brs, 1H), 7.89 (s, 1H), 7.82 (s, 1H), 7.60 (s, 1H), 7.49 (s, 1H), 6.86 (s, 1H), 5.54 (s, 2H), 3.79 (brs, 3H), 3.67 (t, J = 8.3 Hz, 2H), 3.36 (s, 2H), 2.65-2.80 (m, 2H), 2.50 (s, 3H), 1.11 (s, 6H), 1.02(t, J = 7.1 Hz, 2H), 0.96 (t, J = 8.2 Hz, 2H), 0.01 (s, 9H). To a solution of Sem-protected compound (2.0 g, 3.6 mmol) in 36 mL of MeOH/CH_2Cl_2 (1:1) stirred at 80 °C, was added 36 mL of 4 N HCl in dioxane. The reaction was stirred at 80 °C for 30 min. After it was cooled to the room temperature, 120 mL of ether was added. The solid was collected by filtration, washed with ether and dried under vacuum to give 2.0 g of the title compound as its HCl salt form. Mass calculated for formula $C_{20}H_{26}N_8OS$ 426.2; observed MH^+ (LCMS) 427.2 (m/z).

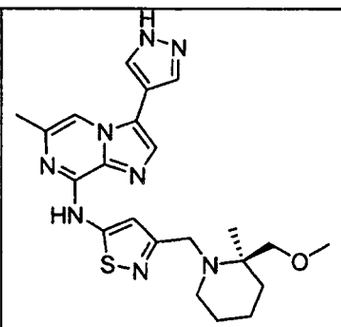
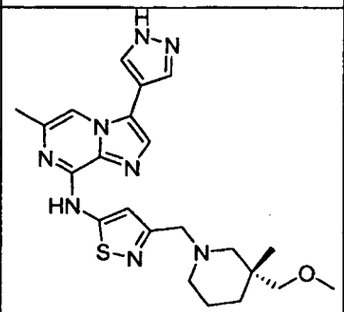
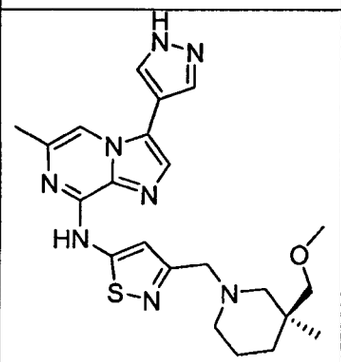
Using essentially the same procedures as described for Example 76, the following compounds in Table 13 (shown immediately below) were prepared.

Table 13

Example	Column 2	EM	LCMS MH^+ m/z	HPLC MS t_R
76-1		426.2	427.2	2.28

76-2		426.2	427.2	2.21
76-3		452.2	453.2	2.26
76-4		466.3	467.3	2.48
76-5		452.2	453.2	2.35

76-6		440.2	441.2	2.39
76-7		438.1	439.1	1.81
76-8		438.1	439.1	1.03
76-9		452.2	453.3	1.48

76-10		452.2	453.1	1.48
76-11		452.2	453.3	1.35
76-12		452.2	453.2	1.36

Example 76-1: ^{1}H NMR (400 MHz, CD_3OD) δ 8.24 (s, 1H), 8.23 (s, 2H), 8.07 (s, 1H), 7.35 (s, 1H), 4.57 (d, J = 12.8 Hz, 2H), 3.81 (t, J = 4.8, 2H), 3.57 (q, J = 14.0, 6.8 Hz, 2H), 3.52 (m, 2H), 3.41 (m, 2H), 2.60 (s, 3H), 1.38 (t, J = 7.2 Hz, 3H), 1.21 (t, J = 6.8 Hz, 3H). HPLC-MS t_R = 2.28 min (UV $_{254nm}$). Mass calculated for formula $C_{20}H_{26}N_8OS$ 426.2; observed MH^+ (LCMS) 427.2 (m/z).

Example 76-2: ^{1}H NMR (400 MHz, CD_3OD) δ 8.31 (s, 1H), 8.29 (s, 2H), 7.32 (s, 1H), 4.88 (d, 1H), 4.46 (d, J = 16.1 Hz, 1H), 3.82 (d, J = 12.3 Hz, 1H), 3.71 (d, J = 12.3 Hz, 1H), 3.64 (m, 1H), 2.65 (s, 3H), 1.42 (s, 3H), 1.40 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H). HPLC-MS t_R = 2.26 min (UV $_{254nm}$).

Example 76-3: ^{1}H NMR (400 MHz, CD_3OD) δ 8.16 (s, 2H), 8.13 (s, 1H), 7.99 (s, 1H), 7.25 (s, 1H), 4.72 (d, J = 15.6 Hz, 1H), 4.53 (t, J = 15.6, 1H), 3.66 (s, 2H), 3.61 (m, 1H), 3.40 (m, 1H),

2.57 (s, 3H), 1.33-0.95 (8H), 1.17 (t, J = 6.8 Hz, 3H). HPLC-MS t_R = 2.26 min (UV $_{254nm}$). Mass calculated for formula $C_{20}H_{26}N_8OS$ 452.2; observed MH^+ (LCMS) 453.2 (m/z).

Example 76-4: ^{1}H NMR (400 MHz, CD_3OD) δ 8.16 (s, 2H), 8.15 (s, 1H), 8.00 (s, 1H), 7.21 (s, 1H), 4.95 (d, J = 16.0 Hz, 1H), 4.35 (d, J = 16.8 Hz, 1H), 4.07 (d, J = 12.4 Hz 1H), 3.82 (d, J = 12.8 Hz 1H), 3.52 (m, 2H), 2.57 (s, 3H), 1.96-1.58 (10H), 1.26 (t, J = 6.8 Hz, 3H). HPLC-MS t_R = 2.48 min (UV $_{254nm}$). Mass calculated for formula $C_{20}H_{26}N_8OS$ 466.3; observed MH^+ (LCMS) 467.3 (m/z).

Example 76-5: ^{1}H NMR (400 MHz, CD_3OD) δ 8.28 (s, 1H), 8.25 (s, 2H), 8.10 (s, 1H), 7.39 (s, 1H), 4.65 (d, J = 14.0 Hz, 1H), 4.52 (d, J = 10.8 Hz, 1H), 4.24 (d, J = 14.0 Hz 1H), 3.85 (d, J = 18.0 Hz 1H), 3.65-3.44 (4H), 2.65 (s, 3H), 1.97-1.58 (6H), 1.29 (t, J = 7.2 Hz, 3H). HPLC-MS t_R = 2.35 min (UV $_{254nm}$). Mass calculated for formula $C_{20}H_{26}N_8OS$ 452.2; observed MH^+ (LCMS) 453.2 (m/z).

Example 76-6 ^{1}H NMR (400 MHz, CD_3OD) δ 8.21 (s, 3H), 8.03 (s, 1H), 7.23 (s, 1H), 4.38 (d, J = 5.6 Hz, 1H), 3.79 (d, J = 5.4 Hz, 1H), 3.63 (d, J = 12.4 Hz 1H), 3.53 (m, 1H), 3.10 (m, 1H), 2.58 (s, 3H), 1.34 (s, 6H), 0.87 (t, J = 6.2 Hz, 3H). HPLC-MS t_R = 2.39 min (UV $_{254nm}$). Mass calculated for formula $C_{20}H_{26}N_8OS$ 440.2; observed MH^+ (LCMS) 441.2 (m/z).

Example 76-7: ^{1}H-NMR (400 MHz, CD_3OD) δ 8.33 m (3H), 8.15 s (1H), 7.41 s (1H), 4.80 (d, 2H), 4.15 (d, 2H), 4.06 (d, 2H), 3.62 (d, 2H), 3.58 (m, 1H), 2.68 (d, 3H), 2.21 (m, 1H), 1.81 (m , 6H) and 1.45 (s, 3H). HPLC-MS t_R =1.80Min (UV $_{254nm}$). Mass calculated for formula C21H26N8OS 438.55, observed LC/MS m/z 439.1 (M+H).

Example 76-8: ^{1}H-NMR (400 MHz, DMSO-d_6) δ 12.73 bs (1H), 9.2 bs (1H), 8.28 s (2H), 8.09 s (1H), 8.08 s (1H), 7.36 s (1H), 4.71 m (1H), 4.05 m (1H), 3.82 m (1H), 3.63 m (1H), 3.25 m (2H), 1.97 m (1H), 1.65 m (6H) and 1.30 s (3H).

Example 76-9: ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.28 (1H), 8.25 (2H), 8.08 (1 H), 7.32 (1 H), 4.71 (1 H), 4.08 (1 H), 3.84 (1 H), 3.52 (3 H), 3.46 (1 H), 2.63 (3 H), 2.17 (2 H), 1.87-1.73 (6 H), 1.45 (3 H).

Example 76-10: ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.28 (1H), 8.25 (2H), 8.08 (1 H), 7.32 (1 H), 4.71 (1 H), 4.08 (1 H), 3.84 (1 H), 3.52 (3 H), 3.46 (1 H), 2.63 (3 H), 2.17 (2 H), 1.87-1.73 (6 H), 1.45 (3 H).

Example 76-11: ^{1}HNMR (400 MHz, CD_3OD) δ 8.20 (s, 2H), 8.14 (s, 1H), 8.03 (s, 1H), 7.25 (s, 1H), 4.48 (d, 1H), 4.37 (d, 1H), 3.46 (s, 3H), 2.91-3.60 (m, 6H), 2.62 (s, 3H), 1.40 – 1.89 (m, 4H), 0.92 (s, 3H).

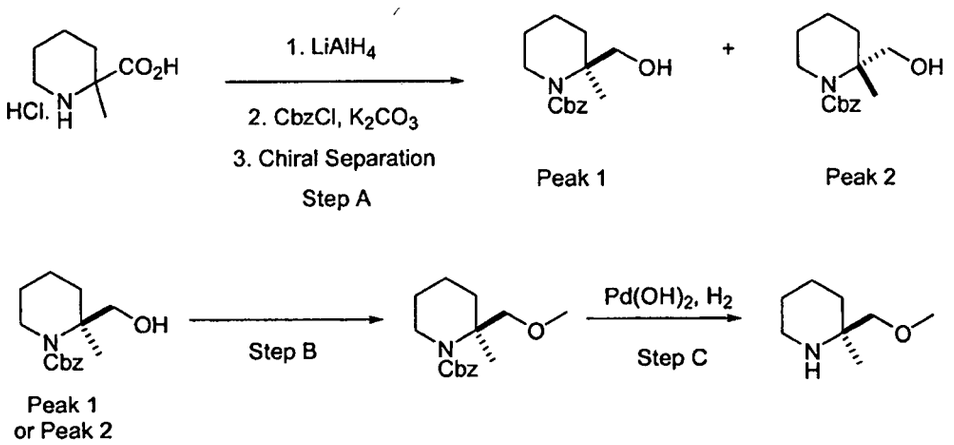
Example 76-12: ^{1}HNMR (400 MHz, CD_3OD) δ 8.20 (s, 2H), 8.14 (s, 1H), 8.03 (s, 1H), 7.25 (s, 1H), 4.48 (d, 1H), 4.37 (d, 1H), 3.46 (s, 3H), 2.91-3.60 (m, 6H), 2.62 (s, 3H), 1.40 – 1.89 (m, 4H), 0.92 (s, 3H).

EXAMPLE 77



A mixture of iodoethane (52.5 g, 336.5 mmol) and 2-amino-2-methyl-1-propanol (30.0 g, 336.5 mmol) was stirred at 60 °C for 15 min. It was diluted with 500 mL of ether, and basified by adding 5 N aqueous NaOH until it reaches pH =10. The organic layer was separated. The aqueous layer was extracted with ether (500 mL X 3). The combined organic was washed sequentially with 100 mL of water, and 100 mL of brine, then dried over anhydrous Na_2SO_4. The solvent was removed to provide 20 g of the crude product, which was purified by recrystallization in 150 mL of hexanes to give 13 g of a white solid. The solid was further purified by sublimation under reduced pressure to give 12 g of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.28 (s, 2H), 2.54 (qt, J = 7.1 Hz, 2H), 1.09 (t, J = 7.0 Hz, 3H), 1.07 (s, 6H).

EXAMPLE 78



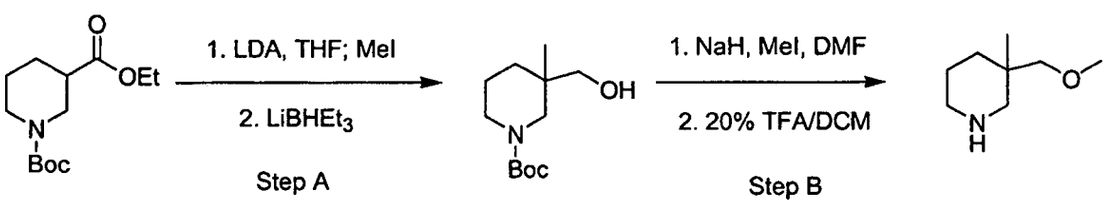
Step A: The substrate (10 g) was suspended in THF (200 mL). Then lithium aluminum hydride solution (110 mL, 2M in THF) was slowly added. The mixture was stirred at room temperature for 12 h. The solution was cooled to 0 °C, and saturated aqueous Na_2SO_4 (200 mL) was slowly added. The mixture was filtered through Celite, and filter cake was washed with ethyl acetate (400 mL). The organic layer was washed with water (200 mL) and brine (200 mL). The organic layer was dried (anhydrous Na_2SO_4), filtered and evaporated to give the amino alcohol (6.9g). The amino alcohol (6.9 g) was dissolved in THF (80 mL) and water (80 mL) at room temperature. The potassium carbonate (14.76 g) was added. Then benzyl chloroformate (8.28 mL) in THF (40 mL) was added dropwise. The mixture was stirred at room temperature for 30 min. Solvent was evaporated off under reduced pressure, and ethyl acetate (100 mL) was added. Two layers were separated, and the aqueous layer was extracted with ethyl acetate (2 × 100 mL). The combined organic layer was washed with brine (200 mL), dried (Na_2SO_4), filtered and evaporated under reduced pressure to give the crude product which was purified by column chromatography. The racemic aminoalcohol was chirally separated by SFC HPCL method. Then enatiomers corresponding to peak 1 and peak 2 were separately taken forward to prepare the corresponding building blocks.

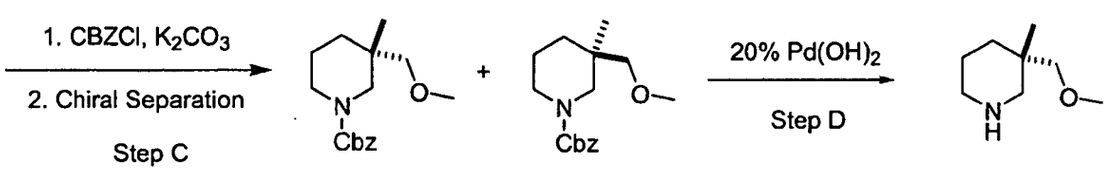
Step B: The alcohol from Step A (1.936 g) was dissolved in dichloromethane (80 mL), and treated with proton sponge (8.32 g) at room temperature. Then trimethyloxonium tetrafluoroborate (5.69 g) was added. The mixture was stirred for 1 h. The reaction was quenched with saturated aqueous ammonium chloride solution (100 mL). The two layers were separated, and the aqueous layer was extracted with dichloromethane (2 × 100 mL). The combined organic layer was washed sequentially with hydrochloric acid (200 mL, 1 N), saturated sodium bicarbonate solution (200 mL), brine (200 mL), dried (Na_2SO_4), filtered and

evaporated under reduced pressure to give the crude product which was purified by column chromatography.

Step C: The enantiomerically pure methyl ether from Step B in EtOH was treated with $Pd(OH)_2$ on carbon (20% wt) and stirred in hydrogen atmosphere at atmospheric pressure at room temperature for 2 h. The mixture was filtered off, and the filtrate was evaporated under reduced pressure to give the amine.

EXAMPLE 79





Step A: At -78°C, ester (6359 mg, 24.7 mmol) in THF (50ml) was added dropwise to LDA (1.8 M in THF, 27.5 ml, 49.4 mmol) in THF (200ml). The reaction mixture was slowly warmed up to room temperature and stirred at that temperature overnight. The reaction was cooled to 0°C and quenched with saturated NH_4Cl solution. The mixture was diluted with H_2O and extracted with EtOAc (x2). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated. Purification by column chromatography afforded the title compound (6221 mg, 93%). LCMS t_R =2.27 Min. Mass calculated for, M+ 271.1, observed LC/MS m/z 216.1 ($M+H-C_4H_8$). To a solution of ester (4659 mg, 17.2 mmol) in THF (300 ml) was added $LiBHEt_3$ (69 ml, 1M in THF). The reaction was stirred at room temperature for 30 min. It was quenched by adding saturated NH_4Cl. The mixture was extracted with CH_2Cl_2. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated. Purification by column chromatography afforded the title compound (3032mg, 77%). LCMS t_R =1.82 Min. Mass calculated for, M+ 229.1, observed LC/MS m/z 174.1 ($M+H-C_4H_8$).

Step B: NaH (1324 mg, 60% dispersion in mineral oil, 33.1 mmol) was added portion wise to a mixture of compound from Step A and MeI (3.3 ml, 52.9 mmol) in DMF (66 mL) at 0°C. The reaction mixture was slowly warmed up to room temperature and stirred at that temperature overnight. The reaction was cooled to 0°C and quenched with saturated NH_4Cl solution. The

mixture was diluted with H_2O and extracted with EtOAc (x2). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated. Purification by column chromatography afforded the title compound (2633 mg, 82%). LCMS t_R =2.32 Min. Mass calculated for, M+ 243.1, observed LC/MS m/z 188.1 (M+H-C_4H_8). A solution of compound 4 (901 mg, 3.71 mmol) was stirred in 20 % TFA in CH_2Cl_2 (20 mL) at 0°C for 30 min and then room temperature for 15 min. The reaction mixture was concentrated. The crude residue was used for example without further purification. LCMS t_R =0.26 Min. Mass calculated for, M+ 143.1, observed LC/MS m/z 144.1 (M+H).

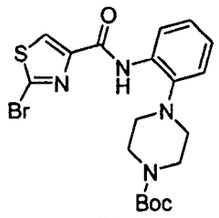
Step C: CbzCl (604 µl, 4.08 mmol) in THF (1 ml) was added to a mixture of compound from Step B and K_2CO3 (1125 mg, 8.15 mmol) in THF (20 ml) and H_2O (20 ml) at 0°C. After stirring at room temperature for 30 min, the reaction mixture was extracted with EtOAc (x2). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated. Purification by column chromatography afforded the title compound (965mg, 94%). LCMS t_R =2.28 Min (UV_{254nm}). Mass calculated for, M+ 277.1, observed LC/MS m/z 278.1 (M+H). The title amines were chirally separated utilizing a Gilson GX-281 liquid handling system with HPLC capabilities. Separation was accomplished with the following conditions: Chiral Technologies Chiral PAK AD column (5 x 50 cm; 20 µ); flow = 50 mL/min; 7.5% isopropanol in hexanes (isocratic); observed at 210 nm.

Step D: The enatiomerically pure isomers from Step C were dissolved in (1mmol, 277 mg) in EtOH (6 ml) was mixed with 20% $Pd(OH)_2$ (51mg) and stirred under H_2 balloon at room temperature for 2h. Filtration through celite and concentration afforded the title compound, which was used for next step without further purification. LCMS t_R =0.26 Min. Mass calculated for, M+ 143.1, observed LC/MS m/z 144.1 (M+H).

The synthesis of the compounds in paragraph (j), as reported in U.S. provisional patent application, Serial No. 60/855421, is shown below:

Example 1

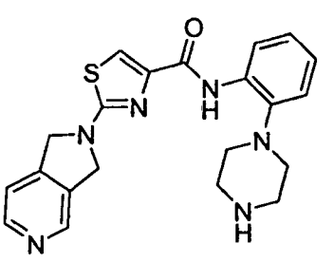
Preparation of Intermediate Compound JA



JA

To a solution of 2-bromo-thiazole-4-carboxylic acid (2.0 mmol, 0.42 g), *N,N*-diisopropylethylamine (3.0 mmol, 0.52 mL) and HATU (2.0 mmol, 0.76 g) in DMF (10 mL) was added 4-(2-aminophenyl)-piperazine-1-carboxylic acid *tert*-butyl ester (2.0 mmol, 0.56 g). The reaction mixture was stirred at 80 °C for 3 h, and then concentrated *in vacuo*. The resulting residue was purified using flash column chromatography on silica gel (eluent: Hexane:EtOAc (4.5:1)) to provide Compound JA as a yellow solid (0.67 g , 72%). ^{1}H NMR (400 MHz, $CDCl_3$) □ 10.38 (s, 1H), 8.49 (dd, J = 8.0, 1.2 Hz, 1H), 8.14 (s, 1H), 7.23–7.10 (m, 3 H), 3.72 (br s, 4H), 2.89-2.87 (m, 4H), 1.50 (s, 9H). HPLC-MS RT= 2.39 min, mass calculated for formula $C_{19}H_{23}BrN_4O_3S$ 466.07, observed LCMS m/z 467.05 (M+H).

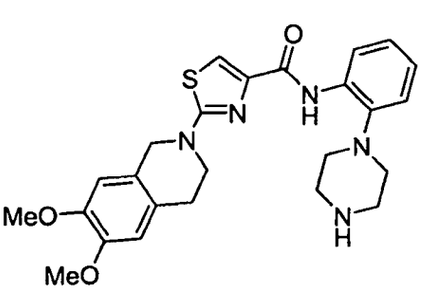
Example 2
Preparation of Compound 1



1

A solution of Compound JA (0.050 mmol, 23 mg), *N,N*-diisopropylethylamine (0.20 mmol, 35 □L) and 2,3-dihydro-1*H*-pyrrolo[3,4-c]pyridine (0.1 mmol) in DMF (1 mL) was irradiated using microwave for 15 minutes at a temperature of 180 °C. The reaction mixture was then concentrated *in vacuo*, and to the resulting residue was added TFA (0.5 mL). The resulting solution was allowed to stir at room temperature for 10 minutes and was then concentrated *in vacuo*. The resulting residue was purified using reverse phase HPLC to provide Compound **1**.

Example 3
Preparation of Compound 2

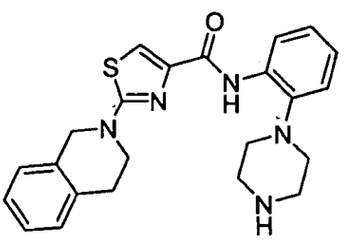


2

Using the method described in Example 2 and substituting 6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline for 2,3-dihydro-1*H*-pyrrolo[3,4-c]pyridine, Compound **2** was prepared.

Example 4

Preparation of Compound 3

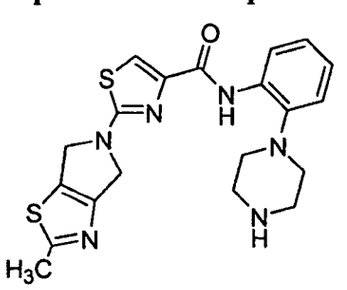


3

Using the method described in Example 2 and substituting 1,2,3,4-tetrahydro-isoquinoline for 2,3-dihydro-1*H*-pyrrolo[3,4-c]pyridine, Compound **3** was prepared.

Example 5

Preparation of Compound 4

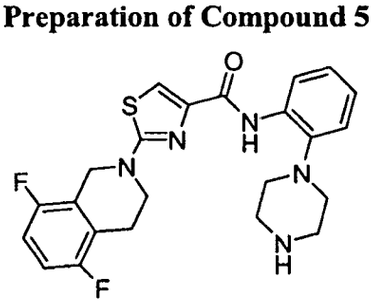


4

Using the method described in Example 2 and substituting 2-methyl-5,6-dihydro-4*H*-pyrrolo[3,4-d]thiazole for 2,3-dihydro-1*H*-pyrrolo[3,4-c]pyridine, Compound **4** was prepared.

Example 6

Preparation of Compound 5

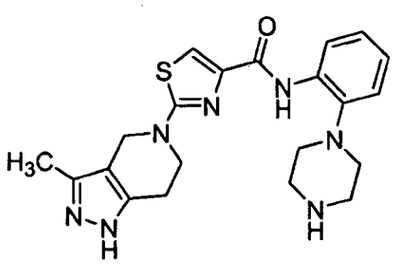


5

Using the method described in Example 2 and substituting 5,8-difluoro-1,2,3,4-tetrahydro-isoquinoline for 2,3-dihydro-1*H*-pyrrolo[3,4-c]pyridine, Compound **5** was prepared.

Example 7

Preparation of Compound 6

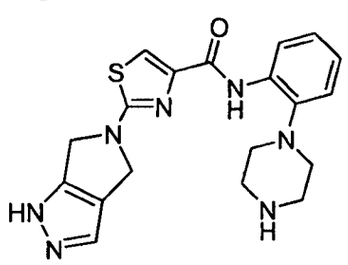


6

Using the method described in Example 2 and substituting 3-methyl-4,5,6,7-tetrahydro-1*H*-pyrazolo[4,3-c]pyridine for 2,3-dihydro-1*H*-pyrrolo[3,4-c]pyridine, Compound **6** was prepared.

Example 8

Preparation of Compound 7

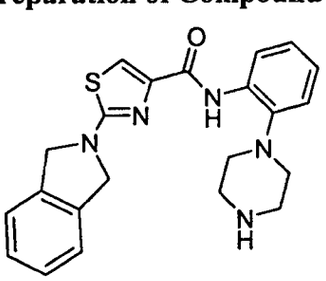


7

Using the method described in Example 2 and substituting 1,4,5,6-tetrahydro-pyrrolo[3,4-c]pyrazole for 2,3-dihydro-1*H*-pyrrolo[3,4-c]pyridine, Compound **7** was prepared.

Example 9

Preparation of Compound 8

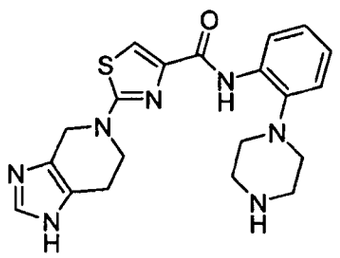


8

Using the method described in Example 2 and substituting 2,3-dihydro-1*H*-isoindole for 2,3-dihydro-1*H*-pyrrolo[3,4-c]pyridine, Compound **8** was prepared.

Example 10

Preparation of Compound 9

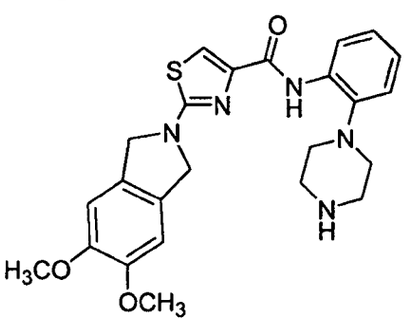


9

Using the method described in Example 2 and substituting 4,5,6,7-tetrahydro-1*H*-imidazo[4,5-c]pyridine for 2,3-dihydro-1*H*-pyrrolo[3,4-c]pyridine, Compound **9** was prepared.

Example 11

Preparation of Compound 10

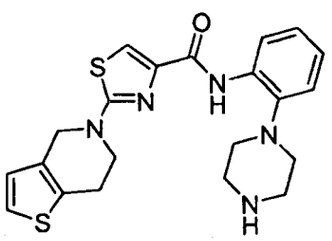


10

Using the method described in Example 2 and substituting 5,6-dimethoxy-2,3-dihydro-1*H*-isoindole for 2,3-dihydro-1*H*-pyrrolo[3,4-c]pyridine, Compound **10** was prepared.

Example 12

Preparation of Compound 11

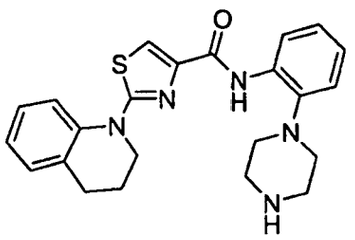


11

Using the method described in Example 2 and substituting 4,5,6,7-tetrahydro-1*H*-thieno[3,2-c]pyridine for 2,3-dihydro-1*H*-pyrrolo[3,4-c]pyridine, Compound **11** was prepared.

Example 13

Preparation of Compound 12

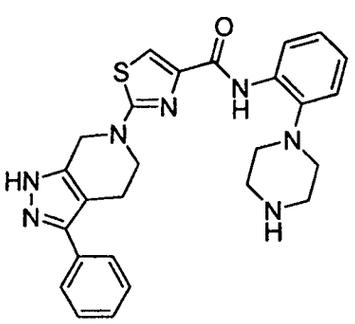


12

Using the method described in Example 2 and substituting 1,2,3,4-tetrahydroquinoline for 2,3-dihydro-1*H*-pyrrolo[3,4-c]pyridine, Compound **12** was prepared.

Example 14

Preparation of Compound 13

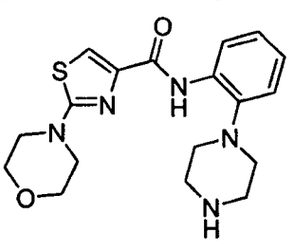


13

Using the method described in Example 2 and substituting 3-phenyl-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-c]pyridine for 2,3-dihydro-1*H*-pyrrolo[3,4-c]pyridine, Compound **13** was prepared.

Example 15

Preparation of Compound 14



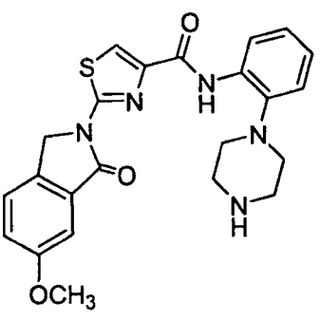
14

A tube containing a stir bar was charged with a solution of Compound JA (0.050 mmol, 23 mg), $Pd_2(DBA)_3$ (5.0 □mol, 4.6 mg), and X-Phos (0.010 mmol, 4.8 mg) in dioxane (1 mL).

K_3PO_4 (0.10 mmol, 21 mg) was added to the solution and the resulting reaction was put under a nitrogen atmosphere. Morpholine (8.7 mg, 0.10 mmol) was added to the reaction mixture via a syringe under a N_2 atmosphere. The tube put into an oil bath at 100 °C and the reaction was allowed to stir at this temperature for about 15 hours, then cooled to room temperature. The reaction mixture was then diluted with acetonitrile (5 mL), the resulting solution was centrifuged for about 2 hours at a speed of about 1000 rpm, and the supernatant was collected and concentrated *in vacuo*. To the resulting residue was added TFA (0.5 mL) and the resulting solution was allowed to stand for 10 minutes, then concentrated *in vacuo*. The resulting residue was purified using reverse phase HPLC to provide Compound **14**.

Example 16

Preparation of Compound 15

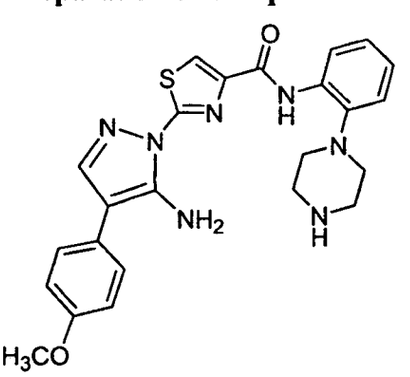


15

Using the method described in Example 15 and substituting 6-methoxy-2,3-dihydro-isoindol-1-one for morpholine, Compound **15** was prepared.

Example 17

Preparation of Compound 16



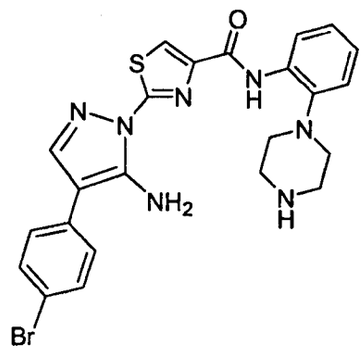
16

A tube containing a stir bar was charged with a solution of 4-(4-methoxy-phenyl)-2*H*-pyrazol-3-ylamine (0.10 mmol), $Pd_2(DBA)_3$ (5.0 □mol, 4.6 mg), Xantphos (0.010 mmol, 5.8

mg) and Compound JA (0.050 mmol, 23 mg) in dioxane (1 mL). To the solution was then added K_3PO_4 (0.10 mmol, 21 mg) and the reaction tube was flushed with N_2 then sealed tightly. The resulting reaction was heated to 100 °C and allowed to stir at this temperature for about 15 hours, then cooled to room temperature. The reaction mixture was then diluted with acetonitrile (5 mL), the resulting solution was centrifuged for about 2 hours at a speed of about 1000 rpm, and the supernatant was collected and concentrated *in vacuo*. To the resulting residue was added TFA (0.5 mL) and the resulting solution was allowed to stand for 10 minutes, then concentrated *in vacuo*. The resulting residue was purified using reverse phase HPLC to provide Compound **16**.

Example 18

Preparation of Compound 17

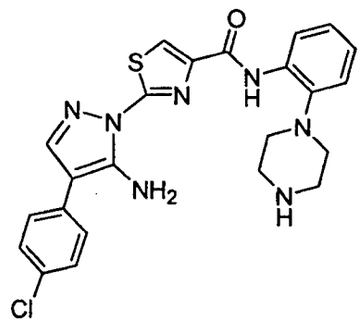


17

Using the method described in Example 17 and substituting 4-(4-bromo-phenyl)-2*H*-pyrazol-3-ylamine for 4-(4-methoxy-phenyl)-2*H*-pyrazol-3-ylamine, Compound **17** was prepared.

Example 19

Preparation of Compound 18

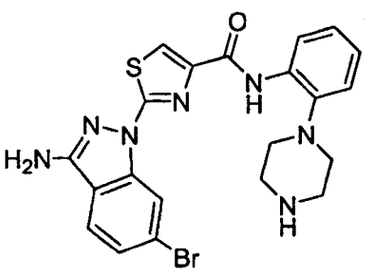


18

Using the method described in Example 17 and substituting 4-(4-chloro-phenyl)-2*H*-pyrazol-3-ylamine for 4-(4-methoxy-phenyl)-2*H*-pyrazol-3-ylamine, Compound **18** was prepared.

Example 20

Preparation of Compound 19

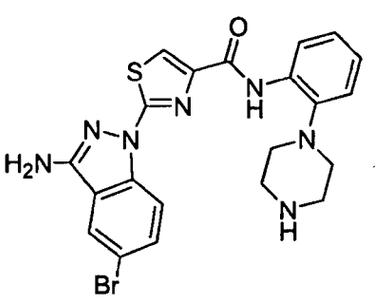


19

Using the method described in Example 17 and substituting 6-bromo-1*H*-indazol-3-ylamine for 4-(4-methoxy-phenyl)-2*H*-pyrazol-3-ylamine, Compound **19** was prepared.

Example 21

Preparation of Compound 20

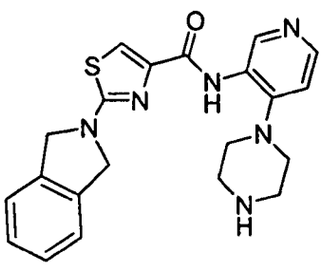


20

Using the method described in Example 17 and substituting 5-bromo-1*H*-indazol-3-ylamine for 4-(4-methoxy-phenyl)-2*H*-pyrazol-3-ylamine, Compound **20** was prepared.

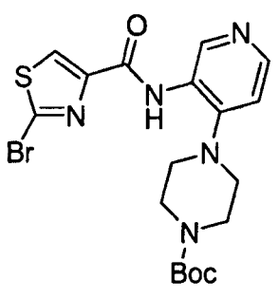
Example 22

Preparation of Compound 21



21

Step 1 – Synthesis of Intermediate Compound B



B

A solution of 4-chloro-3-nitro-pyridine (2.0 mmol, 0.32 g), triethylamine (3.0 mmol, 0.42 mL) and piperazine-1-carboxylic acid *tert*-butyl ester (2.5 mmol, 0.47 g) in dioxane (2 mL) was irradiated using microwave for 8 minutes at a temperature of 150 °C. The solution was then cooled to room temperature and concentrated *in vacuo* and the resulting residue was purified using flash column chromatography on silica gel (eluent: ethyl acetate) to provide 4-(3-nitro-pyridin-4-yl)-piperazine-1-carboxylic acid *tert*-butyl ester as a yellow solid (633 mg, quantitative yield). ^{1}H NMR (400 MHz, $CDCl_3$) □ 8.87 (s, 1H), 8.40 (d, J = 5.6 Hz, 1H), 6.87 (d, J = 6.0 Hz, 1H), 3.68-3.56 (m, 4H), 3.32-3.18 (m, 4H), 1.48 (s, 9H).

The 4-(3-nitro-pyridin-4-yl)-piperazine-1-carboxylic acid *tert*-butyl ester (633 mg) was then diluted with MeOH/EtOAc (1:1, 10 mL) and to the resulting solution was added Pd on carbon (5% Pd). The resulting reaction mixture was stirred under a hydrogen atmosphere at room temperature for about 15 hours. The reaction mixture was filtered through a pad of celite and the filtrate was concentrated in vacuo to provide 4-(3-amino-pyridin-4-yl)-piperazine-1-carboxylic acid *tert*-butyl ester as a solid form. HPLC-MS RT= 1.10 min, mass calculated for formula $C_{14}H_{22}N_4O_2$ 278.17, observed LCMS m/z 279.28 (M+H).

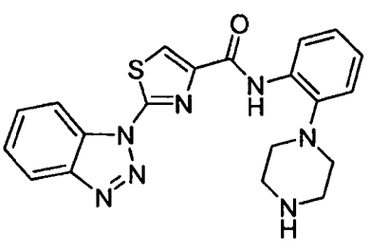
To a solution of 2-bromo-thiazole-4-carboxylic acid (0.78 mmol, 0.16 g), *N,N*-diisopropylethylamine (1.5 mmol, 0.26 mL) and HATU (0.78 mmol, 0.30 g) in DMF (10 mL) was added 4-(3-amino-pyridin-4-yl)-piperazine-1-carboxylic acid *tert*-butyl ester (0.78 mmol, 0.22 g). The reaction mixture was heated to 80 °C and allowed to stir at this temperature for about 15 hours, after which time the reaction mixture was cooled to room temperature and concentrated *in vacuo*. The resulting crude residue was purified using flash column chromatography on silica gel (eluent: ethyl acetate) to provide Compound **B** as a yellow solid. HPLC-MS RT= 1.40 min, mass calculated for formula $C_{18}H_{22}BrN_5O_3S$ 467.06, observed LCMS m/z 468.05 (M+H).

Step 2 – Synthesis of Compound 21

Using the method described in Example 2 and substituting Compound **B** for Compound **A**, and 2,3-dihydro-1*H*-isoindole for 2,3-dihydro-1*H*-pyrrolo[3,4-c]pyridine, Compound **21** was prepared.

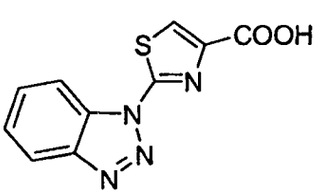
Example 23

Preparation of Compound 22



22

Step 1 – Synthesis of Compound C



C

Benzotriazole (1.20 mmol, 143 mg), K_3PO_4 (1.5 mmol, 0.32 g), $Pd_2(DBA)_3$ (40.0 □mol, 36.6 mg), X-Phos (0.12 mmol, 57 mg) and 2-bromo-thiazole-5-carboxylic acid ethyl ester (1.00 mmol, 236 mg) were loaded into a Schlenk tube containing a stir bar. The Schlenk tube was capped with a rubber septum, evacuated and put under a nitrogen atmosphere. Toluene (2 mL) was added through the septum via a syringe, then the tube was sealed with a

Teflon screw cap under a flow of nitrogen, and put into an oil bath at 100 °C. The reaction was heated to 100 °C and allowed to stir at this temperature for about 15 hours, after which time, the reaction mixture was cooled to room temperature and filtered through a pad of celite. The filtrate was concentrated in vacuo and the resulting residue was purified using flash column chromatography on silica gel (eluent: Hexane/EtOAc (6:1)) to provide 2-benzotriazol-1-yl-thiazole-4-carboxylic acid ethyl ester as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) □ 8.57 (d, J = 8.4 Hz, 1H), 8.14 (d, J = 8.0 Hz, 1H), 8.06 (s, 1H), 7.73–7.68 (m, 1H), 7.54–7.49 (m, 1H), 4.46 (q, J = 7.2 Hz, 2H), 1.45 (t, J = 7.2 Hz, 3H).

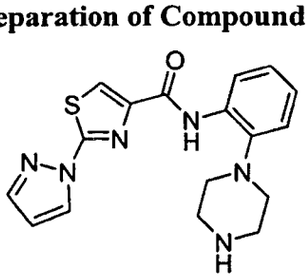
2-benzotriazol-1-yl-thiazole-4-carboxylic acid ethyl ester was diluted with concentrated aqueous hydrochloric acid and the resulting solution was heated to reflux and allowed to stir at this temperature for about 15 hours. The reaction mixture was then cooled to room temperature and lyophilized to provide Compound **C** as an ammonium chloride salt.

Step 2 – Synthesis of Compound 22

To a solution of 2-benzotriazol-1-yl-thiazole-4-carboxylic acid (0.050 mmol, 14 mg), *N,N*-diisopropylethylamine (0.25 mmol, 44 □L) and HATU (0.050 mmol, 19 mg) in DMF (0.5 mL) was added 4-(2-aminophenyl)-piperazine-1-carboxylic acid *tert*-butyl ester (0.10 mmol, 28 mg). The reaction mixture was heated to 80 °C and allowed to stir at this temperature for about 15 hours, after which time the reaction mixture was cooled to room temperature and concentrated *in vacuo*. To the resulting solid residue was added TFA (0.5 mL) and the resulting solution was allowed to stand for 10 minutes, then was concentrated *in vacuo*. The resulting residue was purified using reverse phase HPLC to provide Compound **22**.

Example 24

Preparation of Compound 23

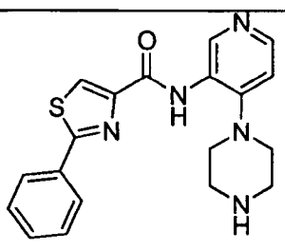
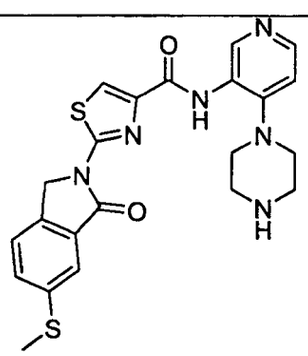


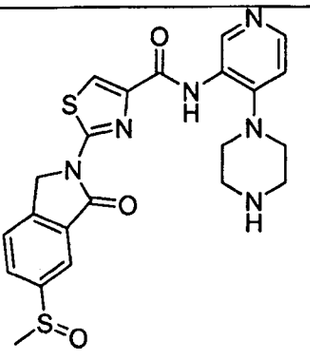
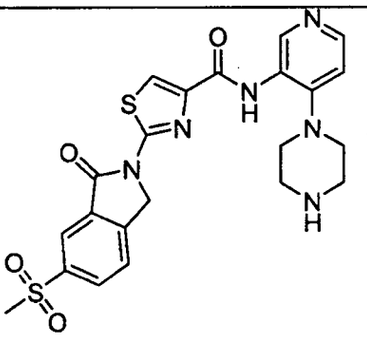
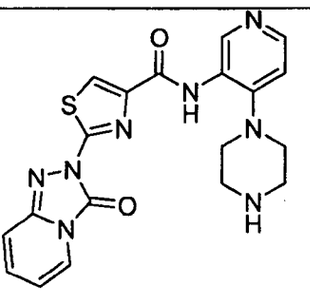
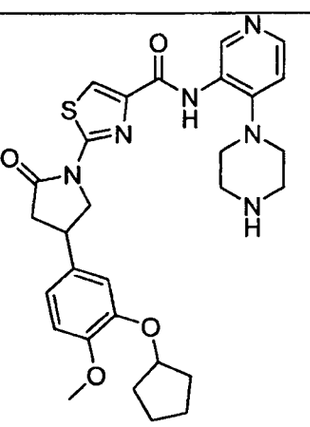
23

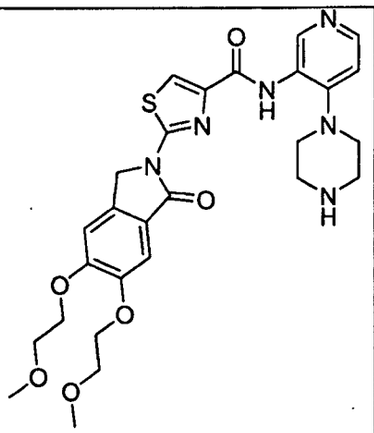
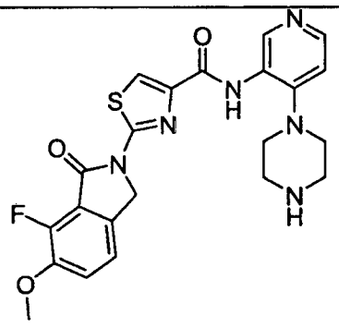
In 20 mL vial containing a stir bar (vial 1) is charged with a solution of 4-{2-[(2-bromo-thiazole-4-carbonyl)-amino]-phenyl}-piperazine-1-carboxylic acid tert-butyl ester acid (107 μmol, 50 mg) and 1,4-dioxane (1 mL). A second 20 mL vial containing a stir bar (vial 2) is charged with a solution of pyrazole (4 eq, 428 μmol, 29.1 mg) and 1,-4 dioxane (2 mL). To

the solution in vial 2 is added NaH (60% dispersion in mineral oil, 4 eq, 428 μmol, 17.2 mg). The resulting reaction is allowed to stir for 15 minutes, then is added to the solution in vial 1. Vial 1 is sealed and the resulting reaction inside vial 1 is heated to 100° C and allowed to stir at this temperature for about 18 hours. LC/MS analysis confirmed disappearance of the starting material and the reaction mixture was concentrated *in vacuo*. The resulting crude residue was diluted with dichloromethane (2 mL), filtered through celite and the filtrate was purified using flash column chromatography on silica gel (eluent: gradient from 100% hexanes to 60% ethyl acetate in hexanes) provided an intermediate white solid product. ^{1}H NMR (400 MHz, CD_3CN) □10.35-10.25 (br s, 1H), 8.49-8.46 (dd, J = 8, 1.6 Hz, 1H), 8.39-8.37 (d, J = 2.8 Hz, 1H), 8.04 (s, 1H), 7.84–7.83 (d, J = 1.6 Hz, 1H), 7.30-7.27 (dd, J = 8, 1.6 Hz, 1H), 7.25-7.20 (td, J = 8, 1.6 Hz, 1H), 7.18-7.13 (td, J = 8, 1.6 Hz, 1H), 3.70-3.63 (br t, J = 4.8 Hz, 4H), 2.91-2.86 (m, J = 4.8 Hz, 4H), 1.48 (s, 9H). The intermediate white solid product was diluted with a 9:1 solution of TFA:H_2O (2 mL). The resultant solution was shaken for 2 hours at room temperature and the reaction mixture was concentrated in vacuo. The resulting residue was purified using reverse-phase HPLC and lyophilized with aqueous HCl (1 M) to provide Compound **23** as a dihydrochloride salt (15.43 mg).

The following illustrative compounds of the invention were prepared using this method with appropriate reactants:

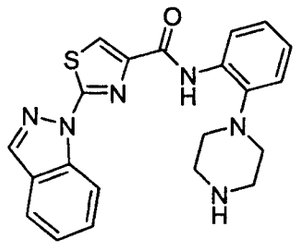
No.	*Structure*	*LCMS MH^+ m/z*	*HPLC MS t_R*
118		366.21	1.74
204		467.23	2.13

242		483.11	1.48
243		499.08	1.26
267		445.69 (M+Na)	0.749
269		563.26	2.71

293		569.37	2.07
333		469.22	1.92

Example 25

Preparation of Compound 24

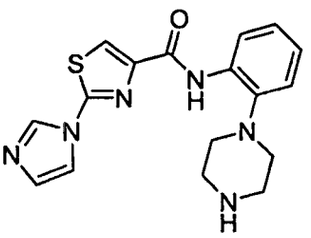


24

Using the method described in Example 24 and substituting indazole for pyrazole, Compound **24** was prepared as a dihydrochloride salt.

Example 26

Preparation of Compound 25

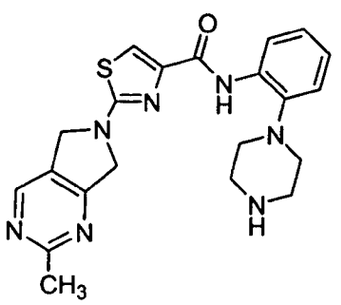


25

Using the method described in Example 24 and substituting imidazole for pyrazole, Compound **25** was prepared as a dihydrochloride salt.

Example 27

Preparation of Compound 26

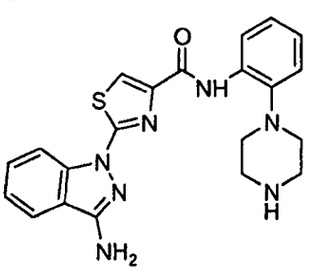


26

Using the method described in Example 24 and substituting 2-methyl-6,7-dihydro-5*H*-pyrrolo[3,4-d]pyrimidine dihydrochloride for pyrazole, Compound **26** was prepared as a dihydrochloride salt.

Example 28

Preparation of Compound 27



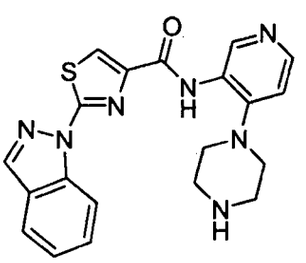
27

A 20 mL vial containing a stir bar was charged with 4-{2-[(2-bromo-thiazole-4-carbonyl)-amino]-phenyl}-piperazine-1-carboxylic acid tert-butyl ester (107 μmol, 50 mg), $Pd_2(DBA)_3$ (0.05 eq, 5.4 μmol, 4.9 mg), Xant-Phos (0.1 eq, 10.7 μmol, 6.2 mg), K_3PO_4 (2 eq, 214 μmol, 45.5 mg), 3-aminoindazole (2 eq, 214 μmol, 28.5 mg) and toluene (3 mL). The vial was flushed with argon, capped and sealed and then put in an oil bath at 140 °C. The reaction was

then allowed to stir at this temperature for about 18 hours. LC/MS confirms the presence of 2 products. The reaction mixture was concentrated *in vacuo* and the resulting residue was diluted with dichloromethane (2 mL) and filtered through celite. The filtrate was then purified using reverse-phase HPLC and the 2 separated products were characterized using LC/MS (the first product had a retention time = 5.76 min, and m+1=520.24; the second product has a retention time = 5.99 minutes, and m+1=520.35). The second product was diluted with a 9:1 mixture of TFA:H_2O (2 mL) and the resulting solution was shaken for 2 hours at room temperature. The reaction mixture was concentrated *in vacuo* and the resulting residue was purified using reverse-phase HPLC and lyophilized with aqueous HCl (1M) to provide Compound **27** as a dihydrochloride salt.

Example 29

Preparation of Compound 28

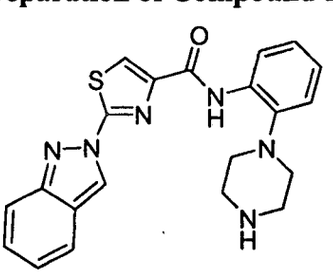


28

Using the method described in Example 24 and substituting 4-{3-[(2-Bromo-thiazole-4-carbonyl)-amino]-pyridin-4-yl}-1-Boc-piperazine for 4-{2-[(2-bromo-thiazole-4-carbonyl)-amino]-phenyl}-piperazine-1-carboxylic acid tert-butyl ester acid and indazole for pyrazole, Compound **28** was prepared as a dihydrochloride salt.

Example 30

Preparation of Compound 29

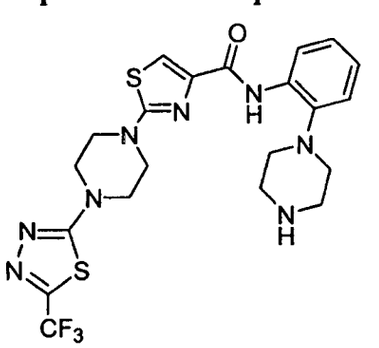


A 20 mL vial containing a stir bar (vial 1) was charged with a solution of 4-{2-[(2-bromo-thiazole-4-carbonyl)-amino]-phenyl}-piperazine-1-carboxylic acid tert-butyl ester acid

(321 μmol, 150 mg). To this is added 2 mL 1,4-dioxane. A second 20 mL vial containing a stir bar (vial 2) was charged with a solution of indazole (3 eq, 963 μmol, 114 mg) and 4 mL 1,4-dioxane. To the solution in vial 2 was then added NaH (60% dispersion in mineral oil, 3 eq, 963 μmol, 38.5 mg). The resulting reaction was allowed to stir at room temperature for about 15 minutes, then the reaction mixture was added to the solution in vial 1. Vial 1 was then sealed, placed in an oil bath at 100 °C and the reaction mixture was allowed to stir at this temperature for about 5 hours. The reaction mixture was then concentrated *in vacuo* and the resulting residue was diluted with dichloromethane (2 mL) and filtered through celite. The resulting residue was purified using flash column chromatography on silica gel (eluent: gradient from 100% hexanes to 70% ethyl acetate in hexanes) provided a product which was collected and diluted with a 9:1 mixture of TFA:H_2O (3 mL) and the resulting solution was allowed to stir for 2 hours at room temperature. concentrated *in vacuo* and the resulting residue was purified by reverse-phase HPLC and shown to contain two products. The first product has a retention time of 3.73 minutes with a visible mass of m+1=405.23. This product was lyophilized with aqueous HCl to provide Compound **29** as a dihydrochloride salt (12.45 mg).

Example 31

Preparation of Compound 30



30

A 2 mL microwave vial was charged with a solution of 4-{2-[(2-bromo-thiazole-4-carbonyl)-amino]-phenyl}-piperazine-1-carboxylic acid tert-butyl ester (107 μmol, 50 mg) in acetonitrile (2 mL). To this solution was added a solution of 1-(5-Trifluoromethyl-[1,3,4]thiadiazol-2-yl)-piperazine (160 μmol, 38 mg) in DIEA (160 μmol, 28 μL) and the resulting reaction was microwaved at 180° C for about 15 minutes. The reaction mixture was then concentrated *in vacuo* and the resulting residue was diluted with a 9:1 mixture of TFA:H_2O (2 mL) and the resulting solution was shaken for about 2 hours at room temperature.

The reaction mixture was then concentrated *in vacuo* and the resulting residue was purified using reverse-phase HPLC and lyophilized with aqueous HCl to provide Compound **30** as a dihydrochloride salt (53.34 mg).

LCMS data and HPLC retention times for Illustrative Anilinopiperazine Derivatives are provided in the table below, wherein the compound numbers in Table 1 correspond to the compound numbering in the specification.

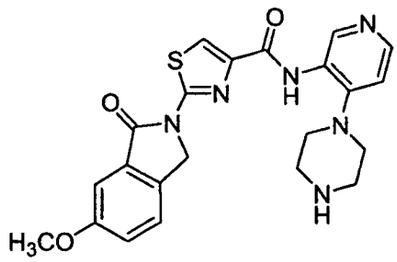
Compound	Observed LCMS *m/z* (M+H)	HPLC-MS retention time (min)
1	407.28	2.56
2	480.33	4.06
3	420.40	4.24
4	427.23	3.72
5	456.29	4.37
6	424.28	2.93
7	396.29	3.27
8	406.26	4.13
9	410.29	2.36
10	466.26	3.91
11	426.26	4.11
12	420.27	4.21
13	486.22	3.82
14	374.25	3.28
15	450.12	3.72
16	476.32	3.75
17	524.26	4.11
18	480.32	4.05
19	498.22	3.84
20	498.25	3.81
21	407.28	2.70
22	406.21	3.48
23	355.33	3.20
24	405.28	3.89

25	355.27	2.31
26	422.27	3.28
27	420.10	3.45
28	406.12	2.31
29	405.23	3.73
30	525.21	3.85
31	487.5	NA

NA = not available

Example 32

Preparation of Compound 45

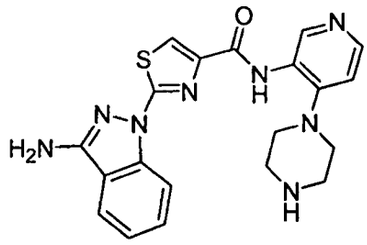


45

Using the method described in Example 24 and substituting 4-{3-[(2-Bromo-thiazole-4-carbonyl)-amino]-pyridin-4-yl}-1-Boc-piperazine for 4-{2-[(2-bromo-thiazole-4-carbonyl)-amino]-phenyl}-piperazine-1-carboxylic acid tert-butyl ester acid (compound B)and 6-methoxy-2,3-dihydro-isoindol-1-one, Compound **45** was prepared as a dihydrochloride salt.

Example 33

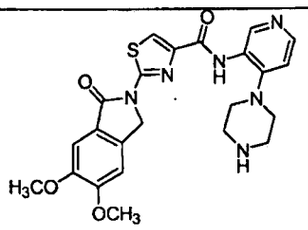
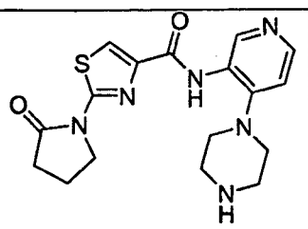
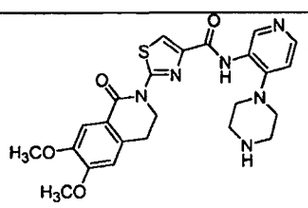
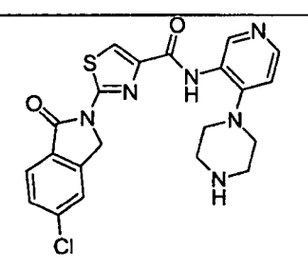
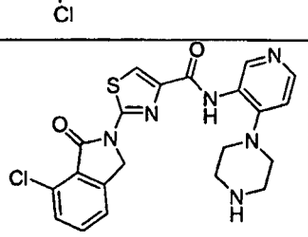
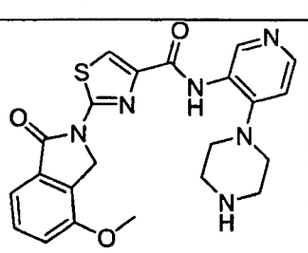
Preparation of Compound 43

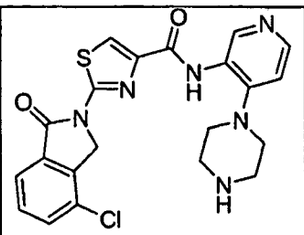
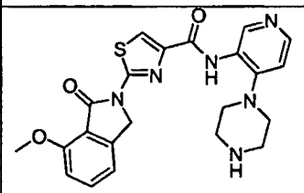
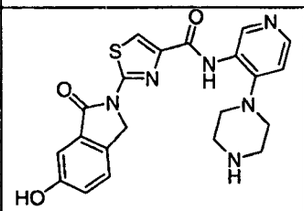
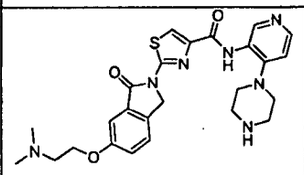
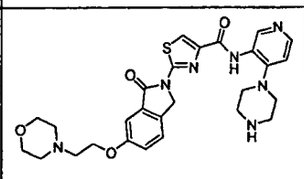
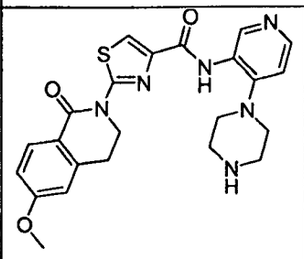
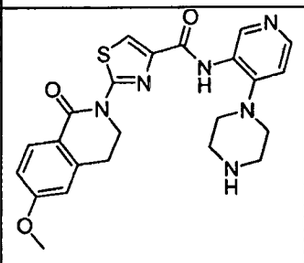


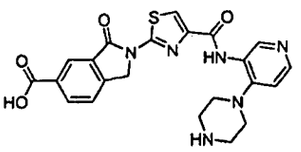
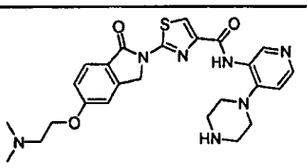
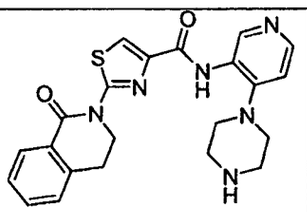
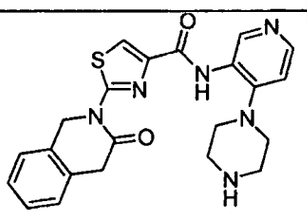
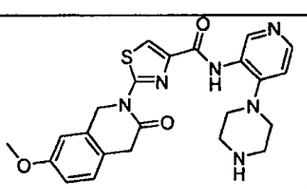
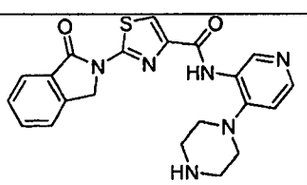
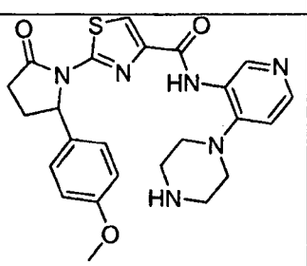
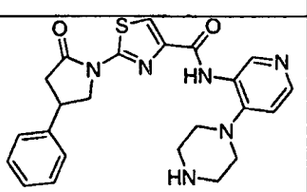
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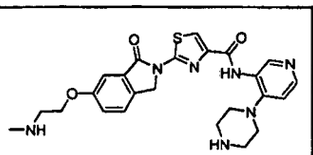
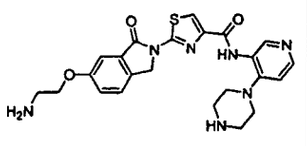
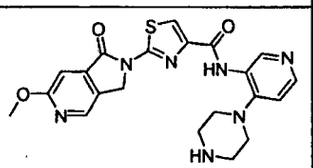
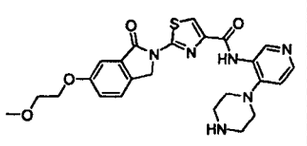
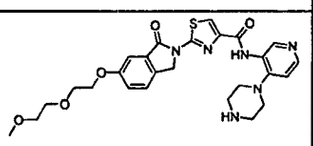
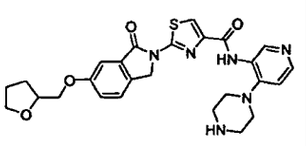
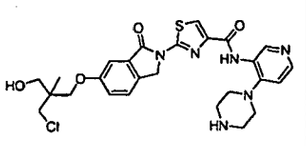
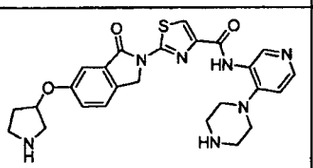
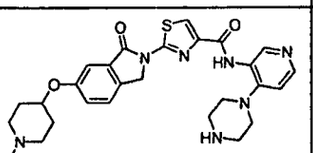
Using the method described in Example 24 and substituting 4-{3-[(2-Bromo-thiazole-4-carbonyl)-amino]-pyridin-4-yl}-1-Boc-piperazine for 4-{2-[(2-bromo-thiazole-4-carbonyl)-amino]-phenyl}-piperazine-1-carboxylic acid tert-butyl ester acid and 3-amino indazole, Compound **43** was prepared as a trihydrochloride salt.

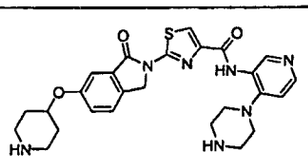
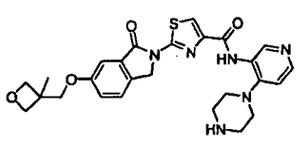
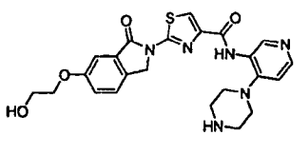
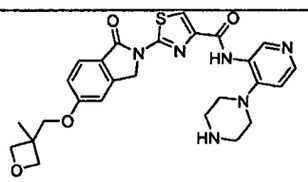
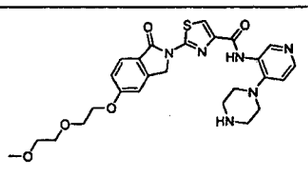
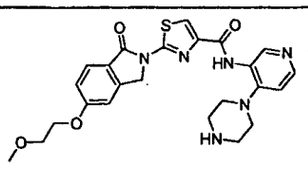
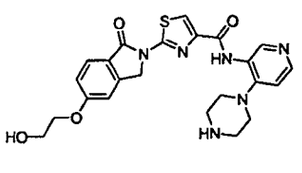
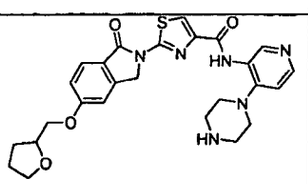
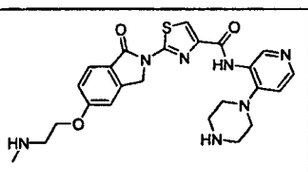
Using the same procedure and the appropriate reactants, the following compounds were prepared.

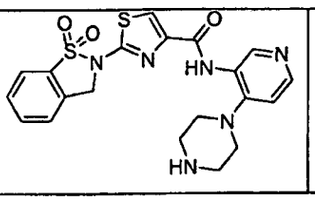
No.	Structure	MS m/z (M+H)	HPLC MS t_R
84		481.1	1.04
96		373.1	0.60
99		495.1	0.92
100		455.0	0.98
106		455.0	0.97
107		451.1	1.06

108		**455.0**	**0.95**
109		**451.1**	**0.88**
115		**437.1**	**0.74**
116		**508.1**	**0.65**
119		**550.2**	**0.66**
121		**465.1**	**1.00**
86		**465.1**	**1.00**

138		**465.0**	**0.72**
139		**508.1**	**0.69**
147		**435.1**	**0.98**
149		**435.1**	**0.98**
150		**465.1**	**1.00**
164		**421.1**	**0.88**
165		**479.1**	**0.93**
169		**449.2**	**0.97**

186		494.1	0.63
187		480.0	0.62
188		452.1	0.88
190		495.1	0.92
191		539.2	0.93
192		521.2	1.00
196		557.2	0.97
197		506.2	0.65
198		534.2	0.86

199		520.2	0.68
200		521.2	1.03
205		481.1	0.93
234		521.2	1.01
235		539.2	0.94
236		495.1	0.92
237		481.1	0.90
238		521.2	1.01
263		494.1	0.64

287		457.1	0.81

Example 34

Preparation of intermediate compound **34C**



34A **34B** **34C**

Into a solution of 2-Methyl-5-methylsulfanyl-benzoic acid (250mg, 1.37mmol) in 12mL (1:1 benzene/methanol) mixture was added 2.74mmol of (Trimethylsilyl)diazomethane. Reaction was stirred for 1.5 hours. Solvent was removed to yield **34A** (2-Methyl-5-methylsulfanyl-benzoic acid methyl ester) as yellow oil which was used as is in subsequent step.

Into solution of **34A** (1.034g, 5.27mmol) in 15 mL of carbon tetrachloride was added *N*-Bromosuccinimide (0.685g, 3.85mmol) and benzoyl peroxide (46.63mg, 0.19mmol). The reaction mixture was refluxed at 80 °C for 6 hours. Mixture was cooled and precipitate removed via filtration. Organic layer collected was concentrated under vacuo. Resulting crude compound **34B** was dissolved in 7N NH_3 in methanol (20mL) and heated to 85 °C in a sealed vessel for about 15 hours. Solvent was removed and crude was purified on flash silica column using ethyl acetate/hexane solvent system to provide 158 mg of compound **34A** as a white powder. NMR (H^1) □ 2.51(3H), 4.30(2 H), 7.45-7.47(m,3H).

Example 35

Preparation of intermediate compound **35A**

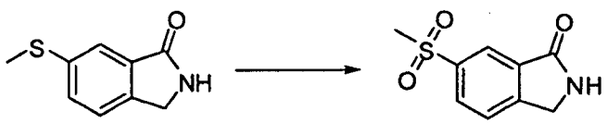


34C **35A**

To solution of compound **34C** (40mg, 0.223mmol) in 5 mL dichloromethane was added 3-chloroperoxybenzoic acid (55mg, 0.223mmol) and the reaction was stirred at room temperature for 3 hours. The reaction mixture was then cooled in an ice bath and the precipitated formed was removed via filtration. The filtrated was washed with water, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to provide compound **35A**, which was used without further purification. NMR of crude indicate a shift of S-CH3 peak from 2.51 to 2.84ppm

Example 36

Preparation of intermediate compound **36A**

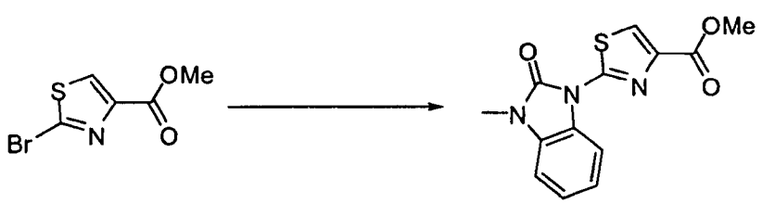


35A **36A**

Using the method described in Example 35, compound **35A** was converted to compound **36A**.

Example 37

Preparation of Intermediate Compound **37A**

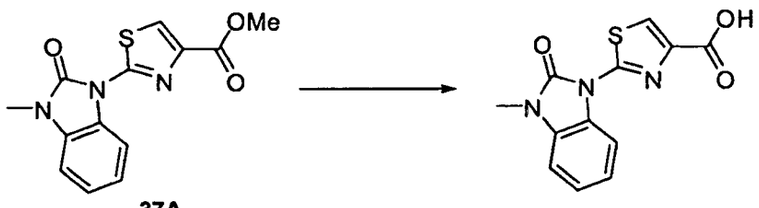


37A

To a solution of 2-bromo-4-carbomethoxythiazole (1.5 g, 6.78 mmol) in dioxane (80 mL) at room temperature was added 1-methyl-2-benzimidazolone (1.0 g, 6.78 mmol) followed by CuI (0.13 g, 0.68 mmol), K_2CO_3 (1.0 g, 7.47 mmol), trans-*N*, *N*-dimethylcyclohexane (0.21 mL, 1.35 mmol). The mixture was degassed under house vacuum and filled with N_2 six times and heated to 90 °C. The mixture was stirred for 12 hours, cooled to rt, and concentrated under reduced pressure. The crude product was purified using flash chromatography using a 20:1 mixture of CH_2Cl_2/MeOH to provide 1.8 g (92% yield) of the title compound as an off-white solid. LC-MS [M+H] = 290.2; 98% purity.

Example 38

Preparation of Intermediate Compound **38A**

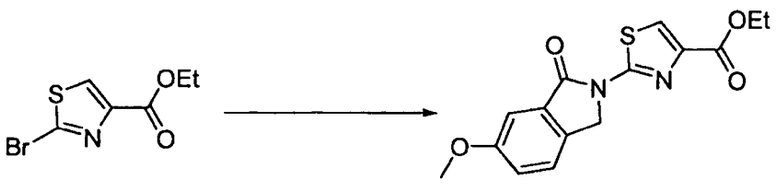


37A **38A**

To a solution of compound **37A** (0.18 g, 0.59 mmol) in THF (1.5 mL) at 0 °C was added dropwise a 1M solution of LiOH (1.18 mL). The resulting reaction was allowed to warm to room temperature and allowed to stir for 12 hours. The mixture was concentrated under reduced pressure and taken up in H_2O (2 mL). The mixture was treated with concentrated HCl until pH = 4 was attained. The mixture was concentrated under reduced pressure to provide compound **38A** (0.15 g, 92% yield) as an orange solid which was used without further purification. LC-MS [M+H] = 276.2; 96% purity

Example 39

Preparation of Intermediate Compound **39A**

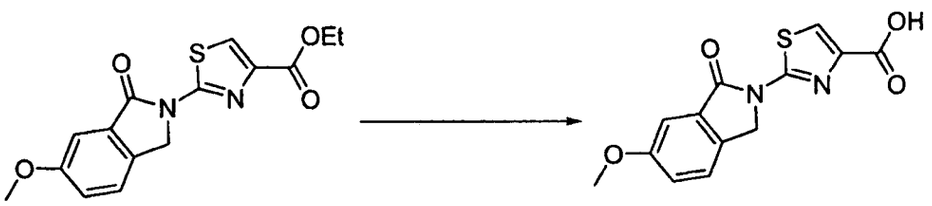


39A

To a pressure tube charged with 2-bromo-4-carboethoxythiazole (2.5 g, 10.6 mmol) and a stir bar was added 6-methoxyisoindolin-1-one (2.1 g, 12.7 mmol), K_3PO_4 (4.9 g, 23.3 mmol), $Pd_2(dba)_3$ (0.58 g, 0.64 mmol), Xant-Phos (0.62g, 1.1 mmol). Dioxane (20 mL) was added and N_2 was bubbled thru the solution for 10 min before the vessel was capped. The mixture stirred at 105 °C for 12h and was cooled to rt. The mixture was filtered thru a pad of Celite and was washed with CH_2Cl_2/MeOH (20:1; 2 x 10 mL). The resulting filtrate was concentrated under reduced pressure and place under high vacuum. The crude product was purified using flash chromatography using a gradient from CH_2Cl_2 to 97:3 CH_2Cl_2/acetone to provide 3.1 g (91% yield) of compound **39A** as a brown solid. LC-MS [M+H] = 400.2; 98% purity.

Example 40

Preparation of Intermediate Compound **40A**

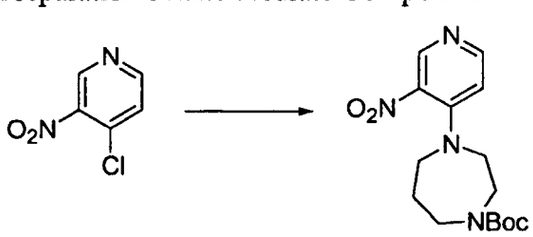


39A **40A**

To a solution of the compound **39A** (0.67 g, 2.1 mmol) in THF/MeOH/H_2O (2:2:1;12.5 mL total) at room temperature was added LiOH·H_2O (97 mg, 2.3 mmol) in one portion. The resulting solution was stirred at 40 °C for 12, cooled to rt, and concentrated under reduced pressure. The crude material and taken up in H_2O (20 mL) and was treated with concentrated HCl until pH 3 was attained. The mixture was concentrated under reduced pressure to provide 0.58 g (95 % yield) of compound **40A** a pale white solid which was used without further purification. MS [M+H] = 290.9

Example 41

Preparation of Intermediate Compound **41A**



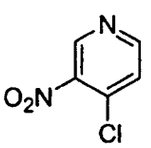
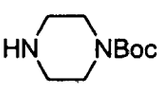
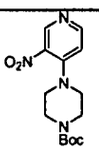
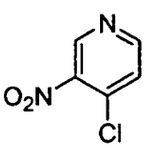
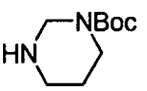
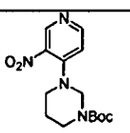
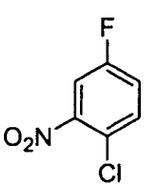
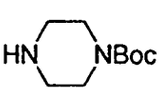
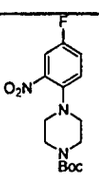
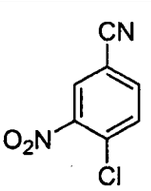
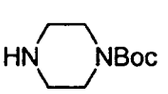
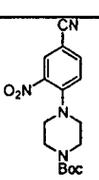
41A

To a solution of 4-chloro-3-nitropyridine (2.0 g, 12.5 mmol) in dioxane (25 mL) was added DIPEA (3.2 mL, 18.7 mmol) followed by Boc-homopiperazine (3.0 g, 15.0 mmol). The resulting mixture was stirred at 110 oC for 12 hours, cooled to rt, and concentrated to dryness. The mixture was partitioned between sat. aq $NaHCO_3$ (4 mL) and CH_2Cl_2 (15 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 15 mL) and the organic layers were combined. The organic layer was washed with brine (1 x 4 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified using flash chromatography using a 50:1 mixture of CH_2Cl_2/MeOH as eluent to provide 3.7g (93% yield) of compound **41A** as a yellow solid. LC-MS [M+H] = 323.2; 98% purity.

Example 42

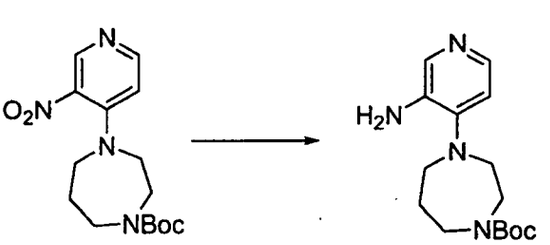
Preparation of Intermediate Compounds **42A-42D**

Intermediate compounds 42A-42D, shown in the table below, were prepared by reacting the indicated chloro derivatives with the indicated amines according to the method described in Example 41.

Chloro derivative	*Amine*	*Product*	*1. Yield (%)* **2. LC-MS (M+H)**
		 **42A**	1. 98 2. 309.2
		 **42B**	1. 80 2. 309.2
		 **42C**	1. 94 2. 326.1
		 **42D**	1. 98 2. 333.2

Example 43

Preparation of Intermediate Compound **43A**



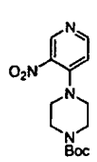
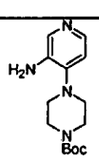
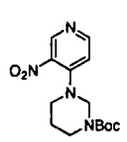
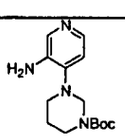
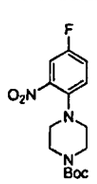
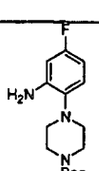
41A **43A**

To a mixture of compound **41A** (3.5 g, 11.1 mmol) in MeOH/EtOAc (1:1; 100 mL) at room temperature was added 5% Pd/C (1.2 g). The resulting mixture was degassed and filled with N_2 and finally with H_2 (balloon). The mixture was stirred for 12h at room temperature and was purged to N_2. The reaction mixture was filtered through a pad of Celite which was washed with the MeOH/EtOAc (1:1; 3 x 25 mL). The resultant filtrate was concentrated under reduced pressure and placed under high vacuum to provide 3.2 g (99% yield) of compound **43A** as a yellow semisolid. LC-MS [M+H] = 293.2; 87% purity. This material was used without further purification.

Example 44

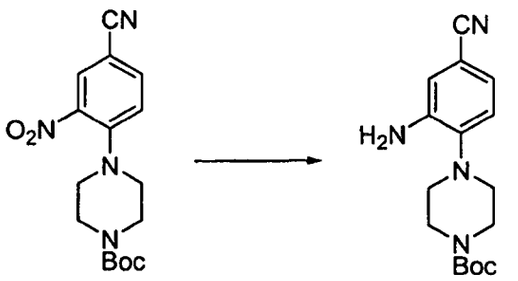
Preparation of Intermediate Compounds **44A-44C**

Following the method described in Example 43, the indicated nitro derivatives were converted to the corresponding amino derivatives 44A-44C.

Nitro derivative	**Product**	**1. Yield (%) 2. LC-MS (M+H)**
	 **44A**	1. 98 2. 309.2
	 **44B**	1. 80 2. 309.2
	 **44C**	1. 94 2. 326.1

Example 45

Preparation of Intermediate Compound **45A**

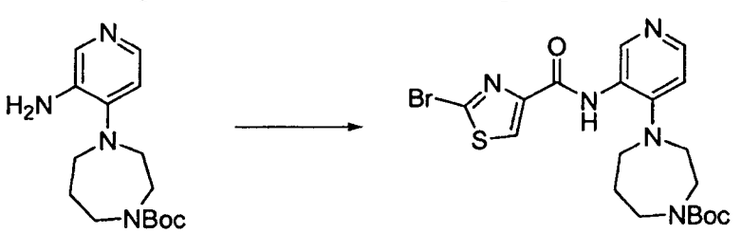


42D **45A**

To a mixture of compound **42D** (0.5 g, 1.5 mmol) in THF (15 mL) at room temperature was added ammonium formate (0.95 g, 15.1 mmol) followed by 10% Pd/C (50 mg). The resulting mixture heated to 65 °C, stirred for 30 min, and was cooled to rt. The reaction mixture was filtered through a pad of Celite which was washed with the EtOH (2 x 5 mL) and CH_2Cl_2 (2 x 5 mL). The resultant filtrate was concentrated under reduced pressure and placed under high vacuum to provide 0.46 g (99% yield) of compound **45A** as a yellow semisolid. LC-MS [M+H] = 303.2; 99% purity. This material was used without further purification.

Example 46

Preparation of Intermediate Compound **46A**



43A **46A**

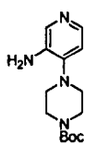
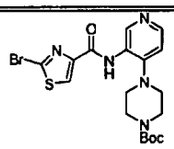
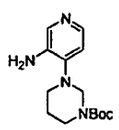
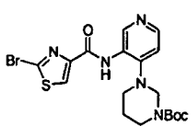
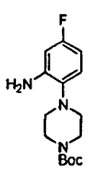
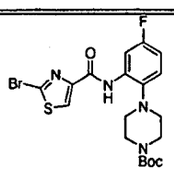
To a solution of compound **43A** (1.1 g, 5.2 mmol) in DMF (10 mL) was added *N,N*-diisopropylethylamine (2.7 ml, 15.4 mmol) and HATU (2.2 g, 5.6 mmol) in DMF (10 mL) was added aniline (1.5 g, 5.2 mmol) from Preparative Example 10. The reaction mixture was stirred at room temperature for 72 h and then concentrated *in vacuo*. The crude residue was taken up in EtOAc (50 mL) and sat. aq $NaHCO_3$ (2 mL) was added. The layers were separated and the organic layer was washed with sat. aq. $NaHCO_3$ (1 x 2 mL) and brine (1 x 2 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified using preparative thin-layer chromatography using a 40:1 mixture

of CH_2Cl_2/MeOH as eluent to provide 1.9 g (75% yield) of compound **46A** as a light yellow solid as the title compound. LC-MS [M+H] = 483.2; 89% purity.

Example 47

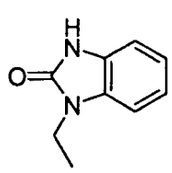
Preparation of Intermediate Compounds **47A-47C**

Following the method described in Example 46, utilizing 2-bromo-thiazole-4-carboxylic acid and the indicated amines, intermediate compounds 47A-47C were made.

Amine	Product	1. Yield (%) 2. LC-MS (M+H)
	 **47A**	1. 63 2. 470.3
	 **47B**	1. 35 2. 470.3
	 **47C**	1. 67 2. 470.3

Example 48

Preparation of Intermediate Compound **48A**

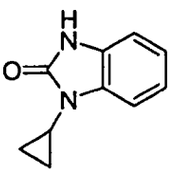


48A

Compound **48A** was prepared using the method described in US Patent Publication No. 2007/0072928.

Example 49

Preparation of Intermediate Compound **49A**

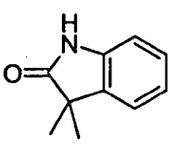


49A

Compound **49A** was prepared using the method described in US Patent Publication No. 2007/0072928.

Example 50

Preparation of Intermediate Compound **50A**

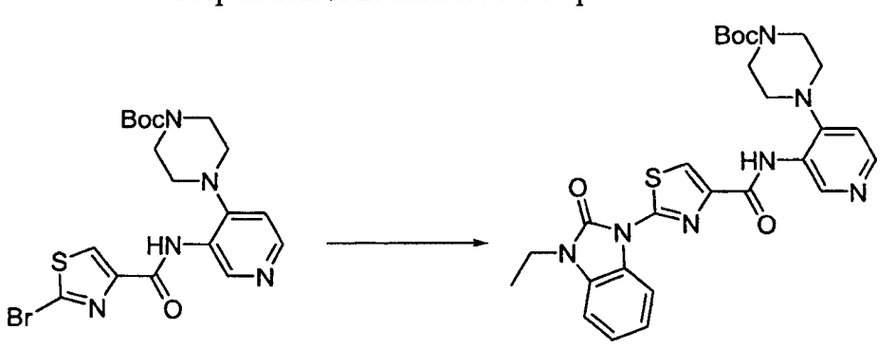


50A

Compound **50A** was prepared using the method described in *J. Med. Chem.* **1986**, *29*, 1832.

Example 51

Preparation of Intermediate Compound **51A**



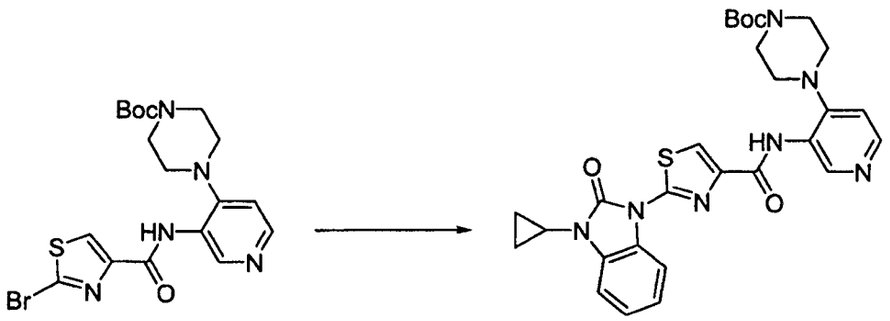
47A **51A**

To a solution of the compound **47A** (0.35 g, 0.75 mmol) was added compound **48A** (0.12 g, 0.75 mmol), CuI (14 mg, 0.075 mmol), K_2CO_3 (114 mg, 0.83 mmol), and trans-N, N-dimethylcyclohexane (23 □L, 0.15 mmol). The mixture was degassed under house vacuum and filled with N_2 six times and heated to 90 °C. The mixture was stirred for 12 hours, cooled to rt, and concentrated under reduced pressure. The crude product was taken up in EtOAc (2 mL) and filtered. The resultant solid was washed with EtOAc (2 x 2 mL) and H_2O (2 x 2 mL),

then dried under high vacuum to provide 0.25 g (61% yield) of compound **51A** as a tan solid. MS (M+H) = 550.2.

Example 52

Preparation of Intermediate Compound **52A**

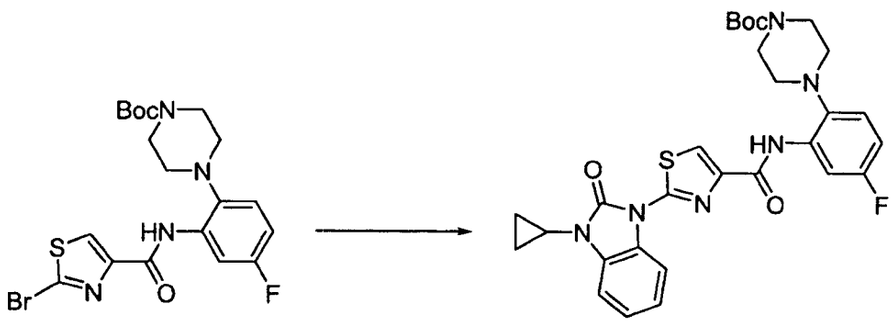


47A **52A**

Compound **47A** (0.35 g, 0.75 mmol) was reacted with compound **49A** (0.12 g, 0.75 mmol) according to the method described in Example 51 to provide 0.28 g (66% yield) of compound **52A** as a light yellow solid. MS (M+H) = 562.3.

Example 53

Preparation of Intermediate Compound **53A**

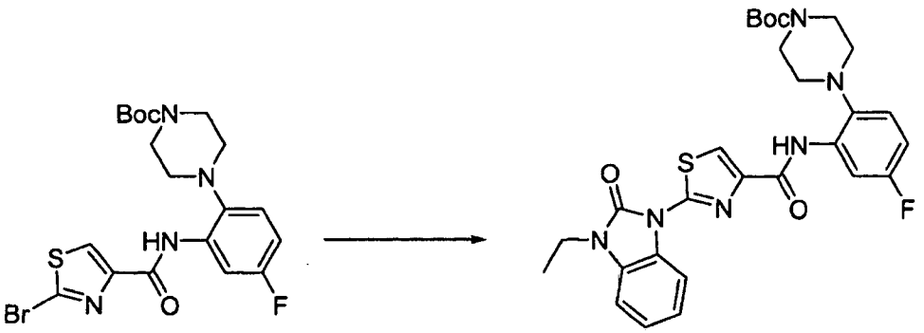


47C **53A**

Compound **47C** (0.35 g, 0.72 mmol) was reacted with compound **49A** (0.13 g, 0.72 mmol) according to the method described in Example 51 to provide 0.28 g (66% yield) of compound **53A** as a gray solid. MS (M+H) = 579.1.

Example 54

Preparation of Intermediate Compound **54A**

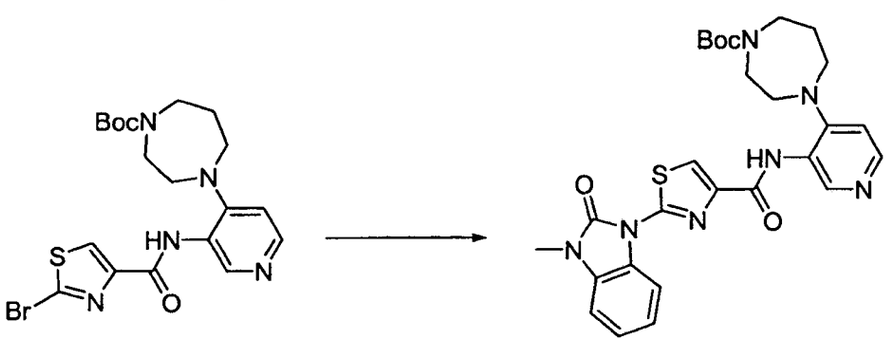


47C **54A**

Compound **47C** (0.35 g, 0.72 mmol) was reacted with compound **48A** (0.12 g, 0.72 mmol) according to the method described in Example 51 to provide 0.29 g (71% yield) of compound **54A** as an orange solid. MS (M+H) = 567.1.

Example 55

Preparation of Intermediate Compound **55A**

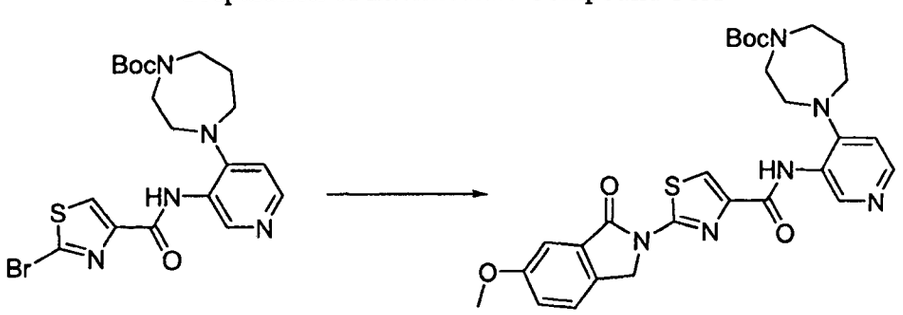


46A **55A**

Compound **46A** (0.10 g, 0.21 mmol)was reacted with 1-methyl-2-benzimidazolone (31 mg, 0.21 mmol) according to the method described in Example 51 to provide 0.11 g (95% yield) of compound **55A** as an orange solid. LC-MS [M+H] = 550.3; 99% purity.

Example 56

Preparation of Intermediate Compound **56A**

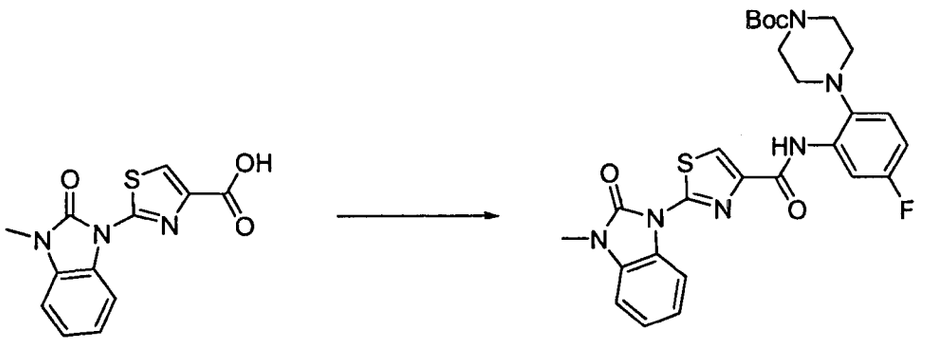


46A **56A**

Compound **46A** (0.25 g, 0.52 mmol) was reacted 6-methoxyisoindolin-1-one (93 mg, 0.57 mmol) according to the method described in Example 51 to provide 0.28 g (96% yield) of compound **56A** as an orange solid. LC-MS [M+H] = 565.3; 80% purity.

Example 57

Preparation of Intermediate Compound **57A**

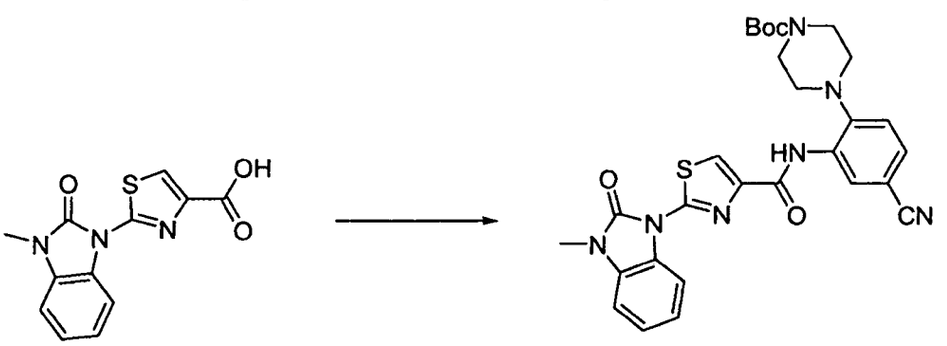


38A **57A**

Compound **38A** (0.15 g, 0.55 mmol) was reacted with compound **44C** (0.12 g, 0.72 mmol) according to the method described in Example 58 below to provide 0.29 g (71% yield) of compound **57A** as an orange solid. MS (M+H) = 567.1.

Example 58

Preparation of Intermediate Compound **58A**



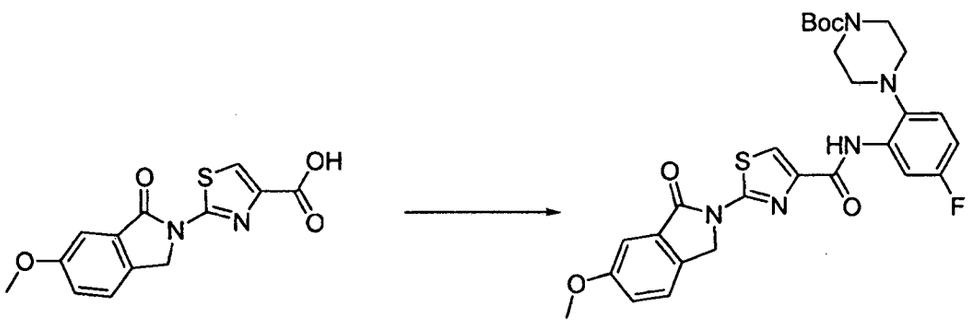
38A **58A**

To a solution of compound **38A** (0.10 g, 0.36 mmol) in CH_2Cl_2 (4 mL) at room temperature was added oxalyl chloride (61 □L, 0.72 mmol) followed by DMF (3 drops). The mixture was stirred for 1 h whereupon an addition portion of oxalyl chloride (61 □L, 0.72 mmol) and DMF (3 drops) were added. After an additional 1 hours, the mixture was concentrated under reduced pressure and redissolved in CH_2Cl_2 (3 mL). DIPEA (0.19 mL, 1.1 mmol) was added followed by addition of compound **45A** (0.12 g, 0.42 mmol) and the

mixture was stirred for 12 hours. The reaction mixture was concentrated to dryness and was partitioned between sat. aq $NaHCO_3$ (3 mL) and CH_2Cl_2 (10 mL). The layers were separated, the aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL), and the organic layers were combined. The organic layer was washed with brine (1 x 4 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified using flash chromatography using a 50:1 mixture of CH_2Cl_2/MeOH as eluent to provide 0.10 (50% yield) of compound **58A** as a yellow semisolid. MS [M+H] = 560.2.

Example 59

Preparation of Intermediate Compound **59A**

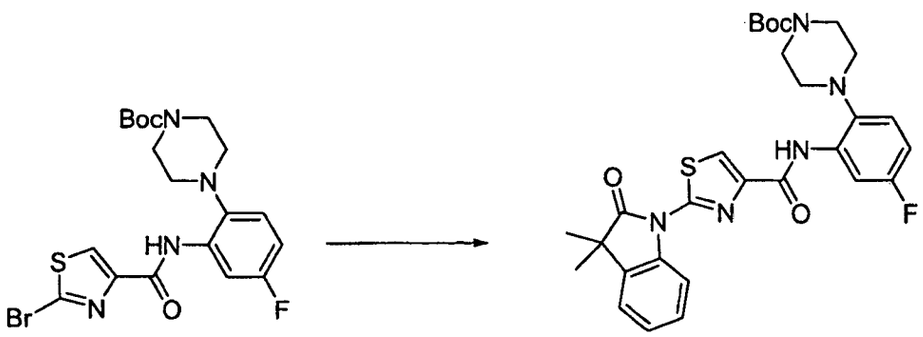


40A **59A**

To a solution of compound **40A** (0.15 g, 0.52 mmol) in DMF (2 mL) was added compound **44C** (0.17 g, 0.57 mmol), followed by *N*-methylmorpholine (0.17 mL, 1.56 mmol) and PyBop (0.54 g, 1.1 mmol). The resulting mixture was stirred for 72 h at room temperature and concentrated under reduced pressure. The crude residue was taken up in EtOAc (8 mL) and sat. aq $NaHCO_3$ (3 mL) was added. The layers were separated and the aqueous layer was extracted with EtOAc (2 x 8 mL). The organic layers were combined and washed with brine (1 x 5 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified using preparative thin-layer chromatography using a 2:1 mixture of hexanes/EtOAc as eluent to provide 40 mg (14% yield) of compound **59A** a light yellow solid. LC-MS [M+H] = 568.3; 89% purity.

Example 60

Preparation of Intermediate Compound **60A**

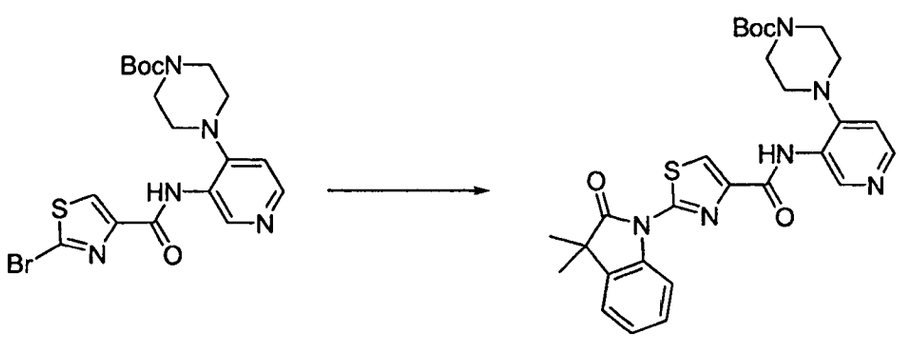


47C **60A**

To a solution of compound **47C** (0.30 g, 0.61 mmol) was added compound **50A** (98 mg, 0.61 mmol), CuI (58 mg, 0.31 mmol), K_3PO_4 (263 mg, 1.24 mmol), and 1,2-*trans*-diamino cyclohexane (73 □L, 0.61 mmol). The mixture was diluted with dioxane (4 mL) and degassed under house vacuum and filled with N_2 six times. The reaction mixture was heated to 100 °C, stirred for 12 hours, cooled to rt, and concentrated under reduced pressure. The crude product was taken up in a 20:1 mixture of CH_2Cl_2/MeOH (5 mL), filtered and concentrated under reduced pressure. The residue from the filtrate was purified using preparative thin-layer chromatography using a 3:1 mixture of hexanes/EtOAc as eluent to provide 125 mg (36% yield) of compound **60A** as an off-white solid. LC-MS [M+H] = 566.3; 98% purity.

Example 61

Preparation of Intermediate Compound **61A**

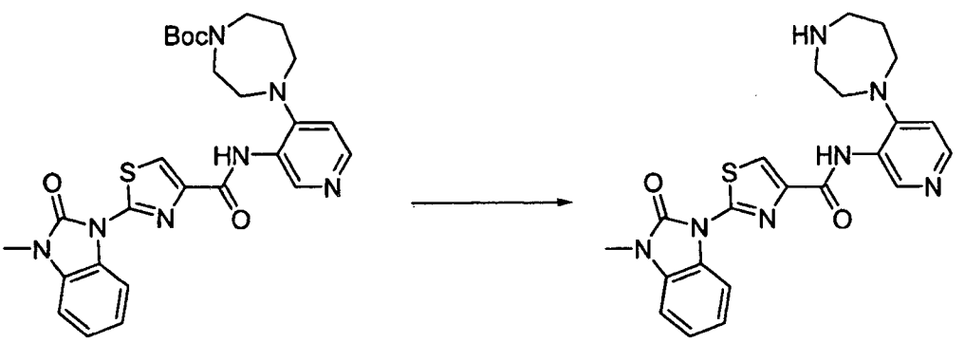


47A **61A**

Using the method described in Example 60, compound **47A** (0.35 g, 0.75 mmol) was reacted with compound **50A** (0.12 g, 0.75 mmol) to provide 0.15 g (36% yield) of compound **61A** as a brown solid. LC-MS [M+H] = 549.3; 90% purity.

Example 62

Preparation of Compound **258**



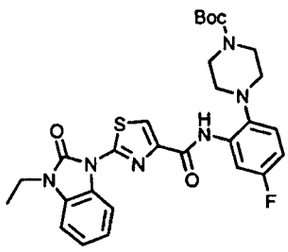
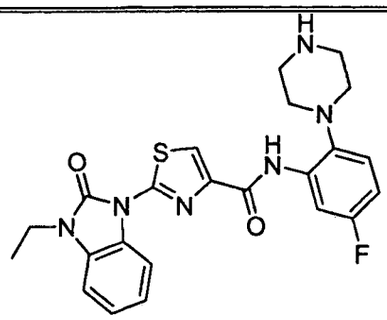
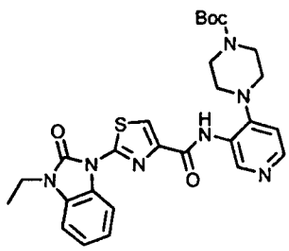
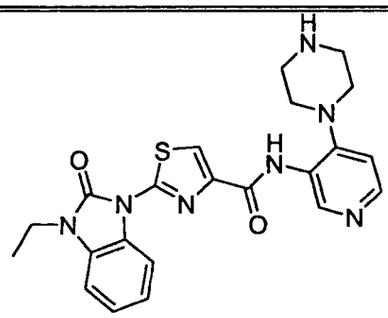
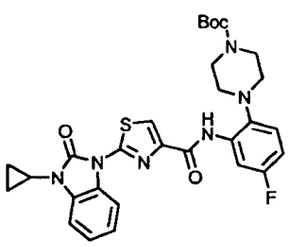
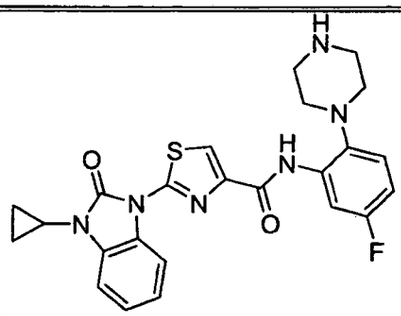
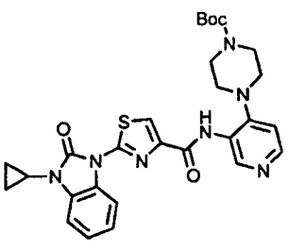
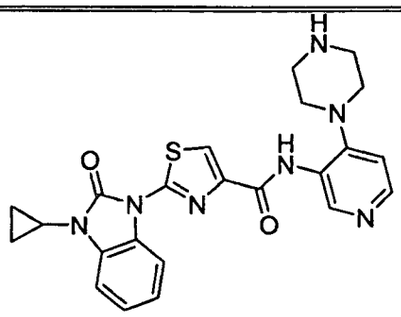
55A **258**

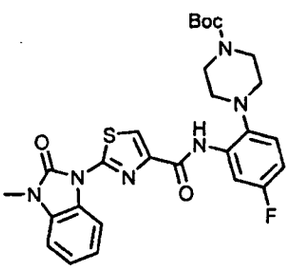
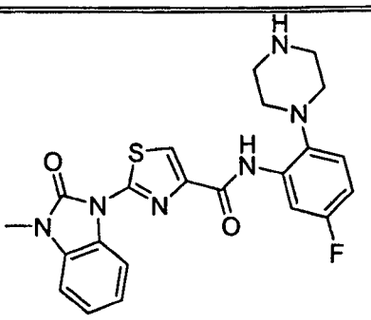
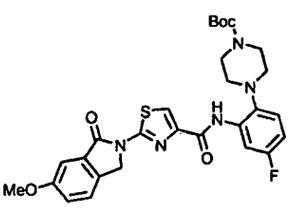
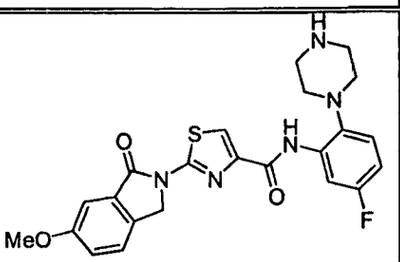
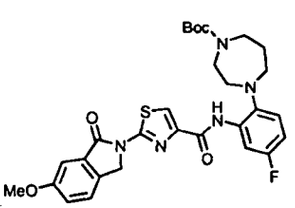
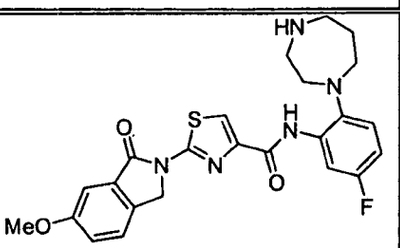
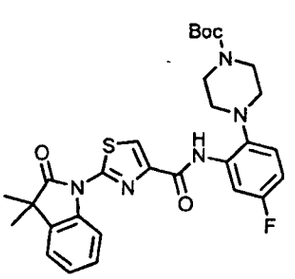
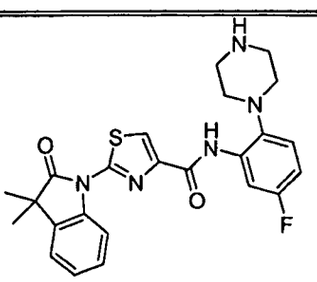
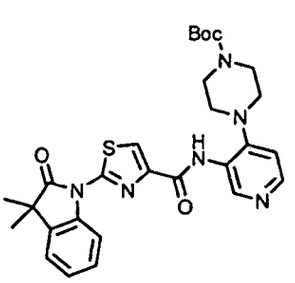
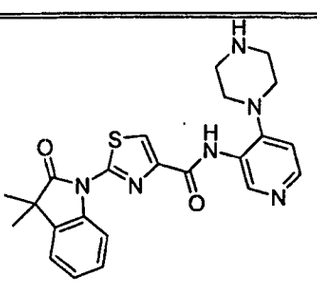
To a solution of compound **55A** (42 mg, 0.08 mmol) in CH_2Cl_2 (3 mL) at room temperature was added TFA (1 mL). The mixture was stirred for 3 hours at room temperature and was concentrated under reduced pressure. The crude product was taken up in 7M NH_3 in MeOH (5 mL), stirred for 2 hours, and concentrated under reduced pressure. The crude product was purified using preparative thin-layer chromatography using a 12:1 mixture of CH_2Cl_2/MeOH (7M NH_3) as eluent to provide 29 mg (85% yield) of compound **258** as a pale yellow solid. mp 152-155 °C, LC-MS [M+H] = 450.1; 95% purity.

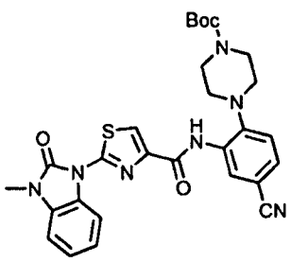
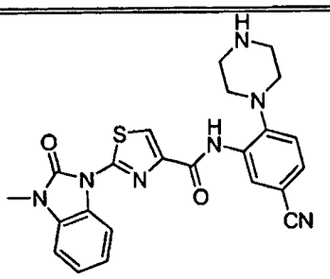
Example 63

Preparation of Compounds **229-232**, **239**, **256**, **288**, **301** and **313**

Using the methods described in Examples 60 and 62, and utilizing the Boc adducts indicated, the following illustrative compounds of the invention were made.

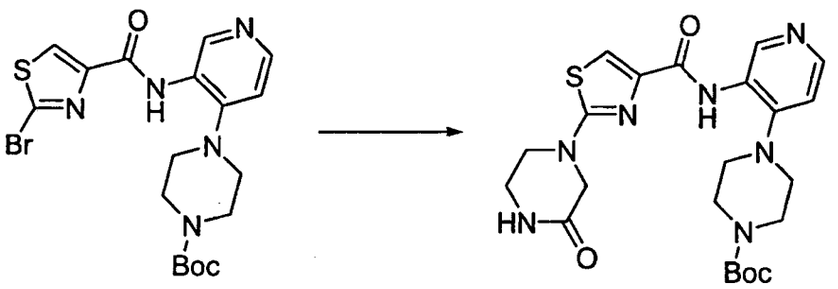
Boc adduct	Product	1.Yield (%) 2. LC-MS 3. mp (°C)
	 **255**	1. 90 2. 467.3 3. 242-244
	 **239**	1. 73 2. 450.2 3. 172-175
	 **256**	1. 92 2. 479.3 3. 220-223
	 **229**	1. 67 2. 462.3 3. 180-183

	 **232**	1. 62 2. 453.2 3. 140-142
	 **230**	1. 86 2. 468.3 3. 168-171
	 **231**	1. 90 2. 465.3 3. 133-135
	 **301**	1. 87 2. 466.3 3. 167-170
	 **313**	1. 92 2. 449.2 3. 200-205

	 **288**	1. 57 2. 460.2 3. 168-171

Example 64

Preparation of Compound **64A**

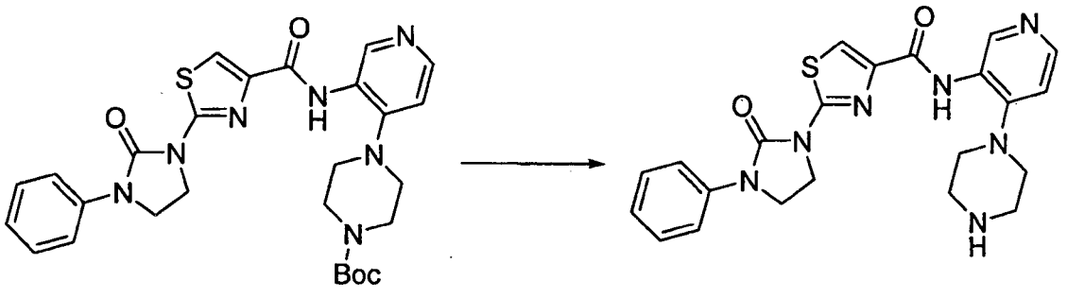


47A **64A**

Using the methods described in Examples 60 and 62, compound **47A** (0.15 g, 0.32 mmol) was reacted with piperazin-2-one (96 mg, 0.96 mmol) in dioxane (2 mL) to provide 84 mg (54% yield) of compound **64A** as a light yellow solid. LC-MS [M+H] = 488.3; 98% purity.

Example 65

Preparation of Compound **112**

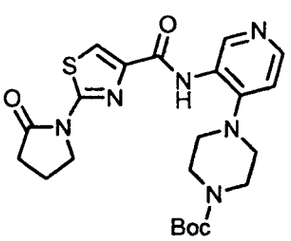
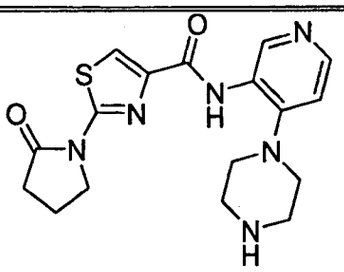
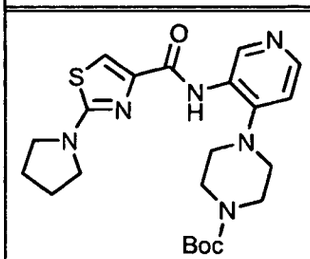
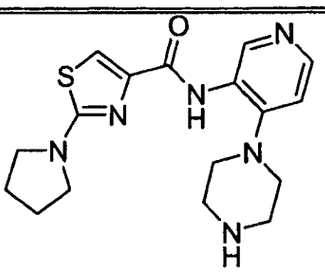
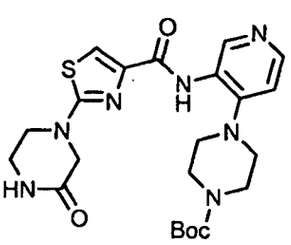
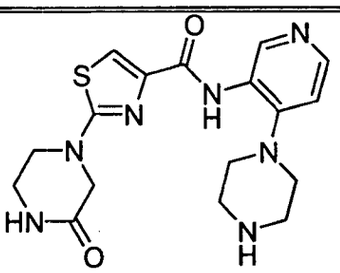


65A **112**

To a solution of compound **65A** (0.13 g, 0.22 mmol) in CH_2Cl_2 (3 mL) at room temperature was added TFA (1 mL). The mixture was stirred for 2 hours at room temperature and was concentrated under reduced pressure. The crude product was taken up in 2M ammonia in MeOH (3 mL), stirred for 2 hours, then concentrated under reduced pressure. The

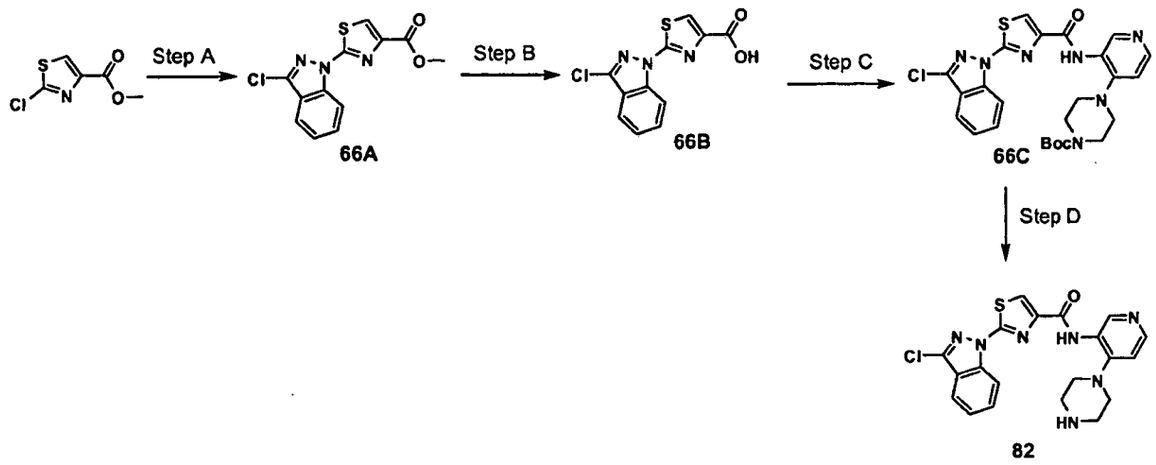
crude product was purified using preparative thin-layer chromatography using a 11:1 mixture of CH_2Cl_2/MeOH (7M NH_3) as eluent to provide 63 mg (64% yield) of compound **112** a pale yellow solid. mp 116-118 °C, LC-MS [M+H] = 450.2; 95% purity.

Using the method described above, the indicated Boc adducts were deprotected to provide illustrative compounds 96, 101 and 111 shown in the table below.

Boc adduct	**Product**	1.Yield (%) 2. LC-MS 3. mp (°C)
	 **96**	1. 45 2. 373.2 3. 122-124
	 **101**	1. 71 2. 359.2 3. 179-181
	 **111**	1. 77 2. 388.2 3. 215-218

Example 66

Preparation of Compound **82**



Step A:

3-Chloroindazole (305 mg, 2.0 mmol) and 2-chlorothiazole (355 mg, 2.0 mmol) were taken up in DMF (20 mL). NaH (80 mg, 60% in oil, 2.0 mmol) was added carefully and the resulting mixture was heated to 60 °C and stirred for 3 hours. After cooling to room temperature, NH_4Cl (aq.) was added carefully and the resulting solution was extracted with EtOAc (60 mL x 3). The organics was dried over Na_2SO_4, concentrated under vacuum, and purified using flash column chromatography on silica gel (EtOAc/Hexane = 30:70) to provide compound **66A** (503 mg) as brown solid. HPLC-MS t_R = 2.24 min ($UV_{254\ nm}$); mass calculated for formula $C_{12}H_8ClN_3O_2S$ 293.0, observed LCMS m/z 294.0 (M+H).

Step B:

Compound **66A** (503 mg, 1.7 mmol) was diluted with THF (10 mL) and to the resulting solution was added LiOH (1N, 3.0 mL). The mixture was stirred at room temperature for about 15 hours. The solvent was removed under vacuum, and the residue obtained was diluted with H_2O (5 mL). 1N HCl was added to adjust the pH to 5 and the solid formed was collected by filtration, then washed with water and air-dried to provide compound **66B**, which was used in the next step without further purification. HPLC-MS t_R = 1.71 min ($UV_{254\ nm}$); mass calculated for formula $C_{11}H_6ClN_3O_2S$ 279.0, observed LCMS m/z 280.0 (M+H).

Step C:

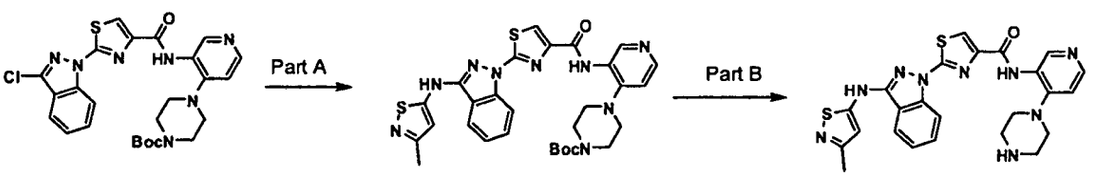
Compound **66C** was synthesized from compound **66B** using the method described in Example 59. HPLC-MS t_R = 1.75 min ($UV_{254\ nm}$); mass calculated for formula $C_{25}H_{26}ClN_7O_3S$ 539.2, observed LCMS m/z 540.1 (M+H).

Step D:

Compound **82** was prepared from compound **66C** using the method described in Example 62. HPLC-MS t_R = 1.10 min ($UV_{254\ nm}$); mass calculated for formula $C_{20}H_{18}ClN_7OS$ 439.1, observed LCMS m/z 440.0 (M+H).

Example 67

Preparation of Compound **78**



66C **67A** **78**

Step A:

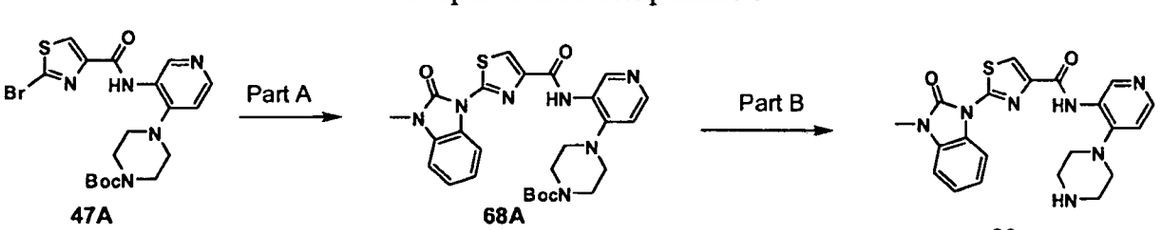
To a 25 ml round bottom flask charged with compound **66C** (270 mg, 0.5 mmol), isothiazole HCl salt (300 mg, 2.0 mmol), $Pd_2(dba)_3$ (45 mg, 0.05 mmol), 2-di-t-butylphosphino-2',4',6'-tri-i-propyl-1,1-biphenyl (42 mg, 0.1 mmol) and K_3PO_4 (616 mg, 3.0 mmol) was added toluene (10 mL). The mixture was thoroughly degassed by alternately connected the flask to vacuum and Argon. This resulting mixture was then heated to 90 °C and stirred for about 15 hours, then was diluted by EtOAc (40 mL) and washed with brine. After concentration, the residue obtained was purified using Preparative liquid chromatography to provide compound **67A**. HPLC-MS t_R = 1.49 min ($UV_{254\ nm}$); mass calculated for formula $C_{29}H_{31}N_9O_3S_2$ 617.2, observed LCMS m/z 618.1 (M+H).

Step B:

Compound **78** was prepared by removing the Boc protecting group from compound **67A** using the method described in Example 62. HPLC-MS t_R = 0.97 min ($UV_{254\ nm}$); mass calculated for formula $C_{24}H_{23}N_9OS_2$ 517.1, observed LCMS m/z 518.1 (M+H).

Example 68

Preparation of Compound **90**



47A **68A** **90**

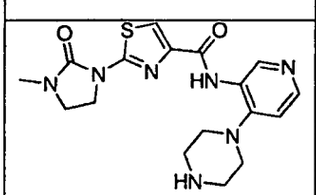
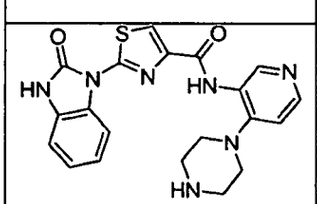
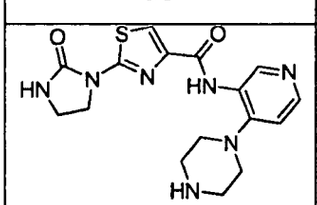
Step A:

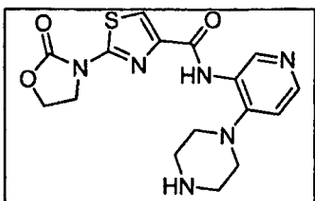
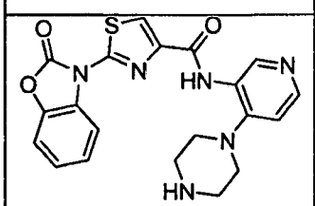
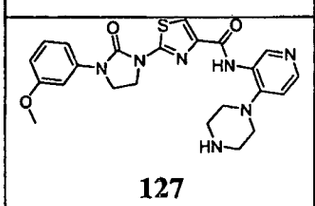
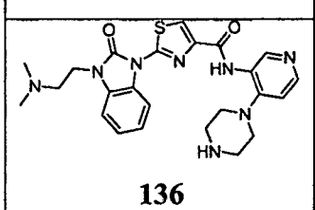
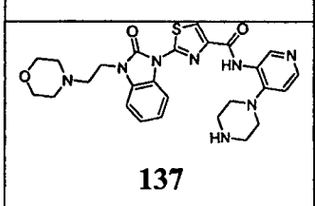
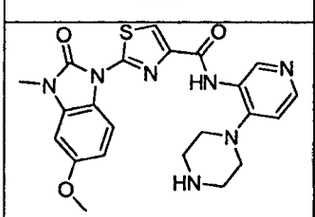
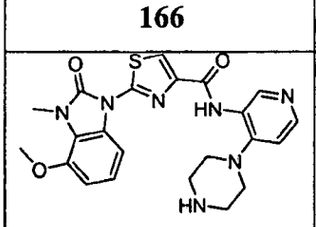
To a 25 mL round bottom flask charged with compound **47A** (100 mg, 0.22 mmol), benzimidazolone (45 mg, 0.3 mmol), CuI (10 mg, 0.05 mmol), trans-1,2-dimethylaminocyclohexane (13 mg, 0.1) and K_2CO_3 (51 mg, 0.3 mmol) was added dioxane (10 mL). The mixture was thoroughly degassed by alternately connected the flask to vacuum and Argon. This resulting mixture was then heated at 80 °C for about 15 hours. After cooling to room temperature, the solvent was removed under vacuum. The residue obtained was diluted with H_2O (5 mL) and the crude solid compound **68A** was collected by filtration and used directly in the next step without further purification. HPLC-MS t_R = 1.42 min ($UV_{254\ nm}$); mass calculated for formula $C_{26}H_{29}N_7O_4S$ 535.2, observed LCMS m/z 536.2 (M+H).

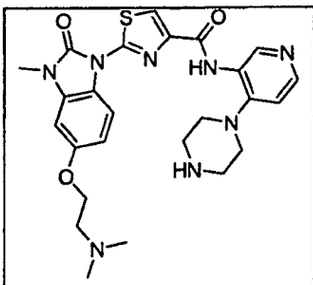
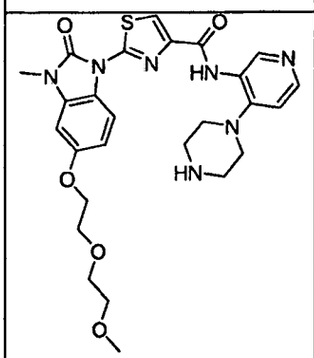
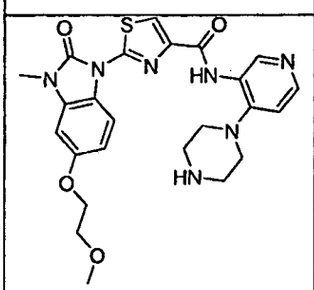
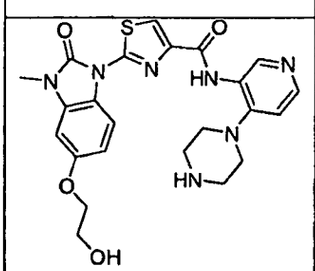
Step B:

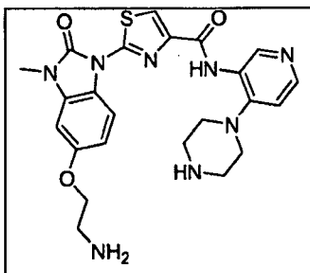
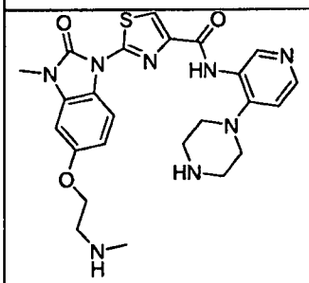
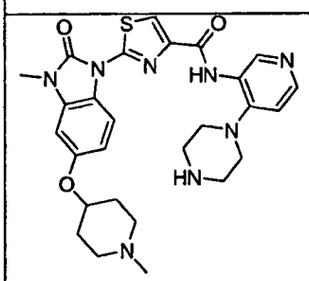
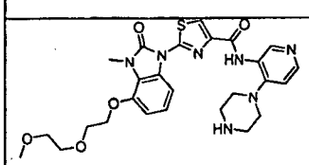
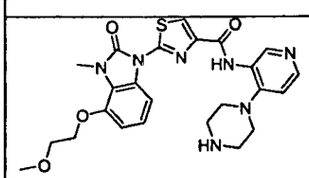
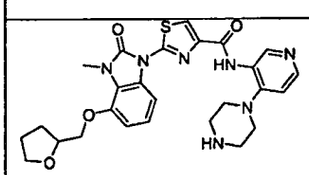
Compound **90** was prepared by removing the Boc protecting group from compound **68A** using the method described in Example 62. HPLC-MS t_R = 0.83 min ($UV_{254\ nm}$); mass calculated for formula $C_{21}H_{21}N_7O_2S$ 435.1, observed LCMS m/z 436.1 (M+H).

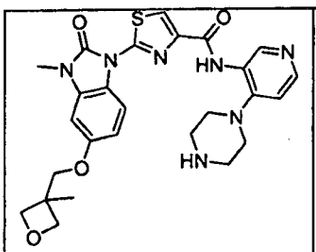
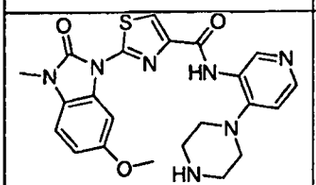
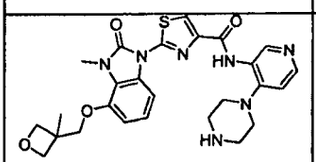
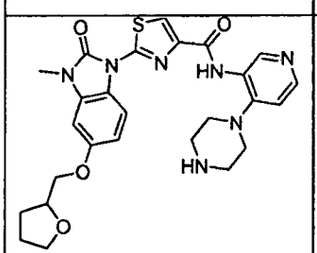
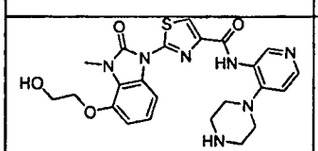
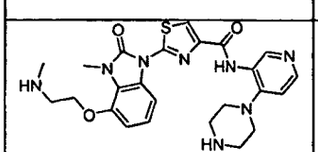
Using the method described in Steps A and B above, and using the appropriate coupling partners in Step A, the following illustrative compounds were made.

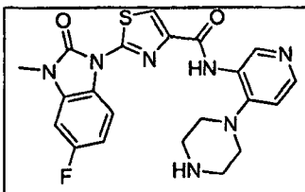
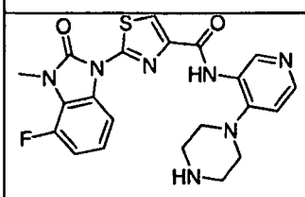
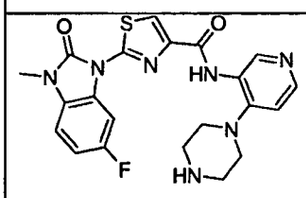
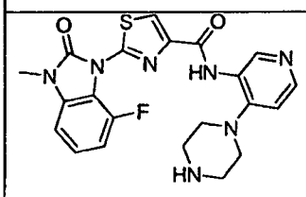
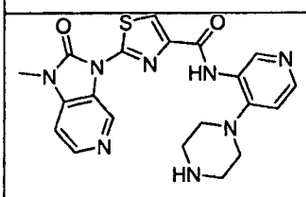
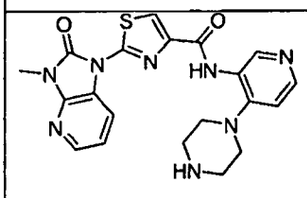
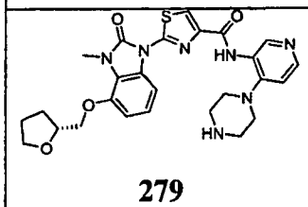
Compound	MS m/z (M+H)	HPLC MS t_R
 **89**	**388.1**	**0.74**
 **93**	**422.1**	**0.71**
 **97**	**374.2**	**0.47**

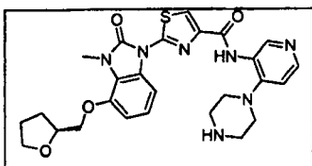
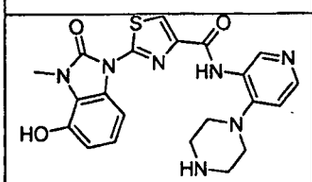
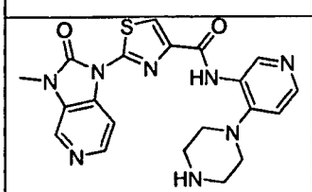
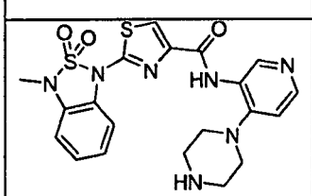
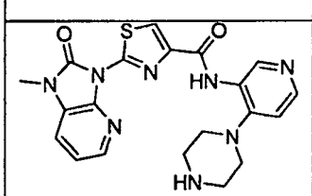
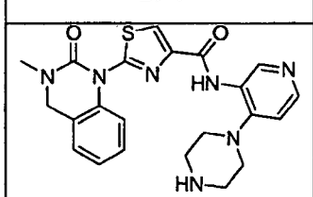
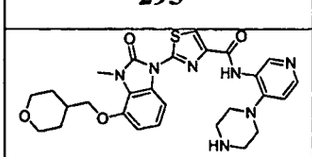
 **98**	**375.1**	**0.55**
 **120**	**423.1**	**0.88**
 **127**	**480.1**	**1.00**
 **136**	**493.1**	**0.58**
 **137**	**535.1**	**0.61**
 **166**	**466.1**	**0.86**
 **185**	**466.1**	**0.97**

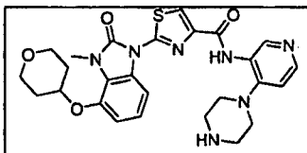
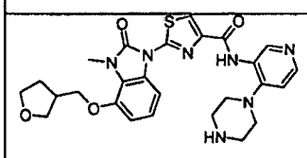
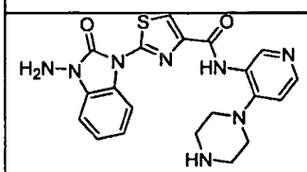
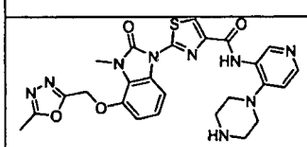
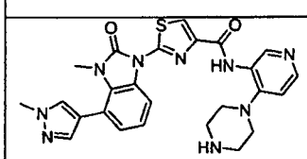
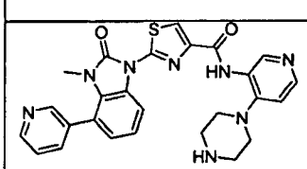
 **189**	**523.1**	**0.63**
 **194**	**554.2**	**0.93**
 **195**	**510.1**	**0.90**
 **206**	**496.2**	**0.97**

 **207**	**495.1**	**0.68**
 **208**	**509.2**	**0.69**
 **222**	**549.2**	**0.75**
 **223**	**554.2**	**1.15**
 **224**	**510.2**	**1.13**
 **225**	**536.2**	**1.21**

 **226**	**536.2**	**1.17**
 **228**	**466.1**	**0.91**
 **259**	**536.3**	**0.98**
 **260**	**536.2**	**1.23**
 **261**	**496.1**	**0.90**
 **262**	**509.2**	**0.67**

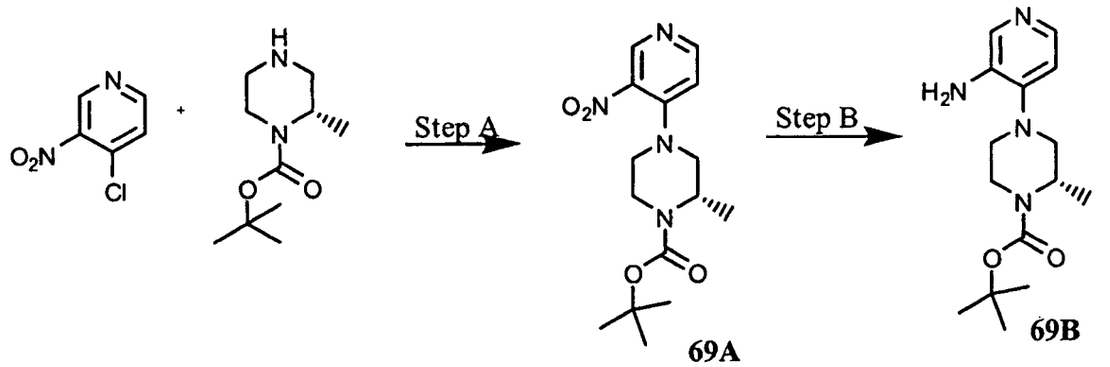
 **264**	**454.1**	**1.02**
 **270**	**454.1**	**0.93**
 **273**	**454.1**	**1.02**
 **274**	**454.1**	**1.02**
 **275**	**437.2**	**0.64**
 **278**	**437.2**	**0.93**
 **279**	**536.2**	**1.22**

 **280**	**536.2**	**1.25**
 **286**	**452.2**	**1.12**
 **289**	**437.1**	**0.19**
 **290**	**472.1**	**0.94**
 **294**	**437.0**	**0.92**
 **295**	**450.1**	**1.06**
 **32**	**550.2**	**1.09**

 **299**	**536.2**	**1.06**
 **300**	**536.2**	**1.06**
 **329**	**437.1**	**0.72**
 **330**	**548.2**	**1.11**
 **331**	**516.1**	**0.93**
 **332**	**513.1**	**0.92**

Example 69

Preparation of Compound **69B**



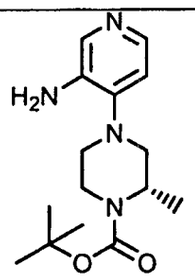
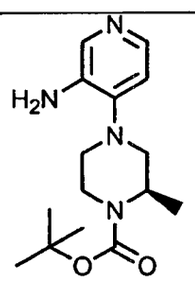
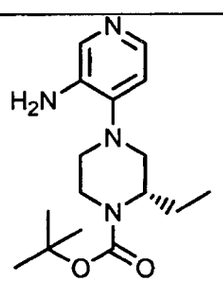
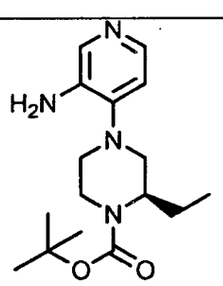
Step A:

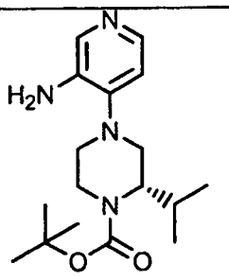
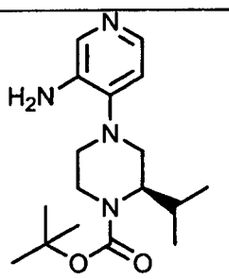
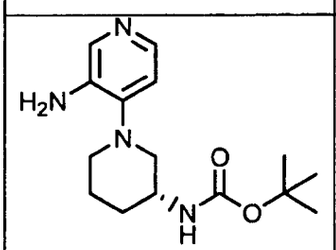
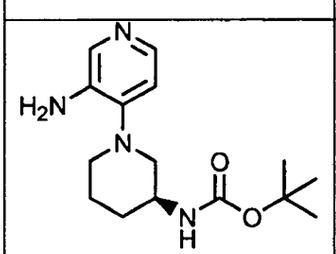
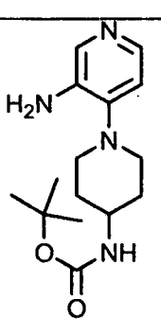
A solution of 4-chloro-3-nitro-pyridine (2.0 mmol, 0.32 g), diethylisopropyl amine (3.0 mmol, 0.52 mL) and 2(s)-methyl-piperazine-1-carboxylic acid *tert*-butyl ester (2.5 mmol, 0.50 g) in dioxane (2 mL) was irradiated using microwave for 20 minutes at a temperature of 120 °C. The reaction mixture was concentrated *in vacuo*, and the resulting residue was purified using flash column chromatography on silica gel (eluent: ethyl acetate) to provide compound **69A** as a yellow solid in quantitative yield. HPLC-MS RT= 1.42 min, mass calculated for formula $C_{15}H_{22}N_4O_4$ 322.16, observed LCMS m/z 323.1 (M+H).

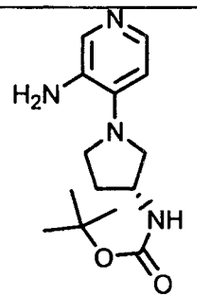
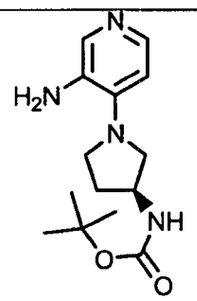
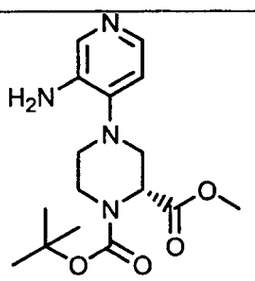
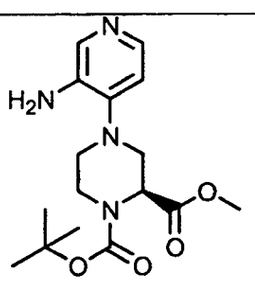
Step B:

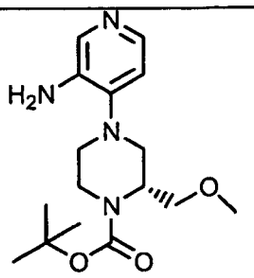
To a solution of compound **69A** (600 mg) in Ethanol/EtOAc (1:1, 10 mL) was added Pd on carbon (5% Pd). The reaction mixture was stirred under a hydrogen atmosphere at room temperature for about 15 hours, then filtered through a pad of celite. The filtrate was concentrated. *in vacuo* to provide Compound **69B** as a solid. HPLC-MS RT= 1.10 min, mass calculated for formula $C_{15}H_{24}N_4O_2$ 292.19, observed LCMS m/z 293.20 (M+H).

Using the methods described in Steps A and B above, and using the appropriate reactants, the following intermediate compounds were made:

Compound	M+H Observed	Retention Time
 **69C**	293.2	1.10
 **69D**	293.2	1.10
 **69E**	307.3	1.0
 **69F**	307.3	1.0

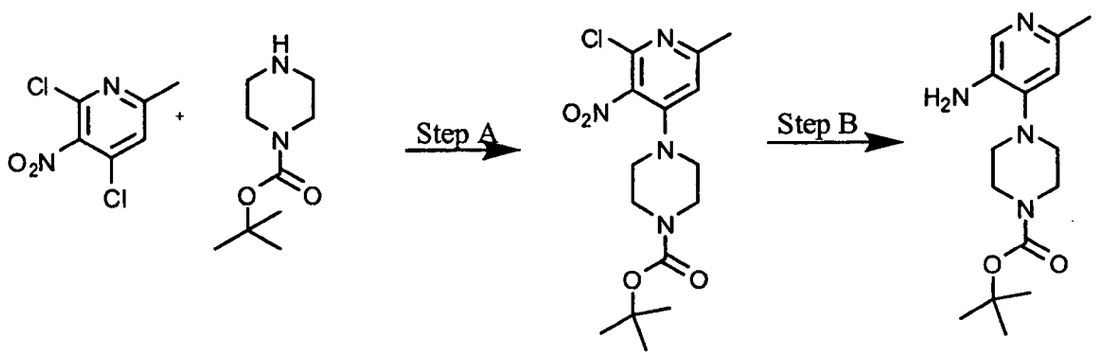
 **69G**	321.2	1.15
 **69H**	321.2	1.15
 **69J**	293.2	0.09
 **69K**	293.2	0.09
 **69L**	293.3	1.0

 **69M**	279.1	0.85
 **69N**	279.1	0.85
 **69P**	337.12	0.95
 **69Q**	337.12	0.95

 **69R**	323.2	1.05

Example 70

Preparation of Compound **70B**



70A **70B**

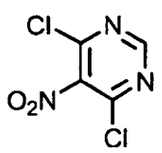
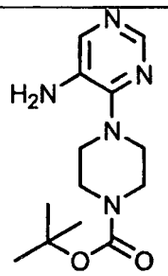
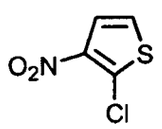
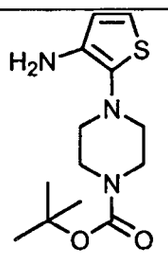
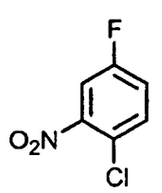
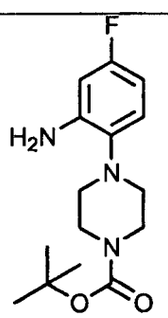
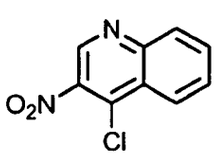
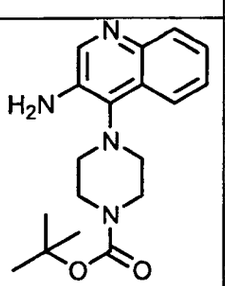
Step A:

A solution of 2,4-dichloro-6-methyl-3-nitro-pyridine (2.0 mmol, 0.42 g), diethylisopropyl amine (3.0 mmol, 0.52 mL) and piperazine-1-carboxylic acid *tert*-butyl ester (2. mmol, 0.372 g) in dichloromethane (5 mL) was stirred at room temperature for 12 hours. The reaction mixture was concentrated *in vacuo*, and the resulting residue was purified using flash column chromatography on silica gel (eluent: Hexane and ethyl acetate) to provide compound **70A** as a yellow solid in quantitative yield. HPLC-MS RT= 2.1 min, mass calculated for formula $C_{15}H_{21}ClN_4O_4$ 356.13, observed LCMS m/z 357.1 (M+H).

Step B:

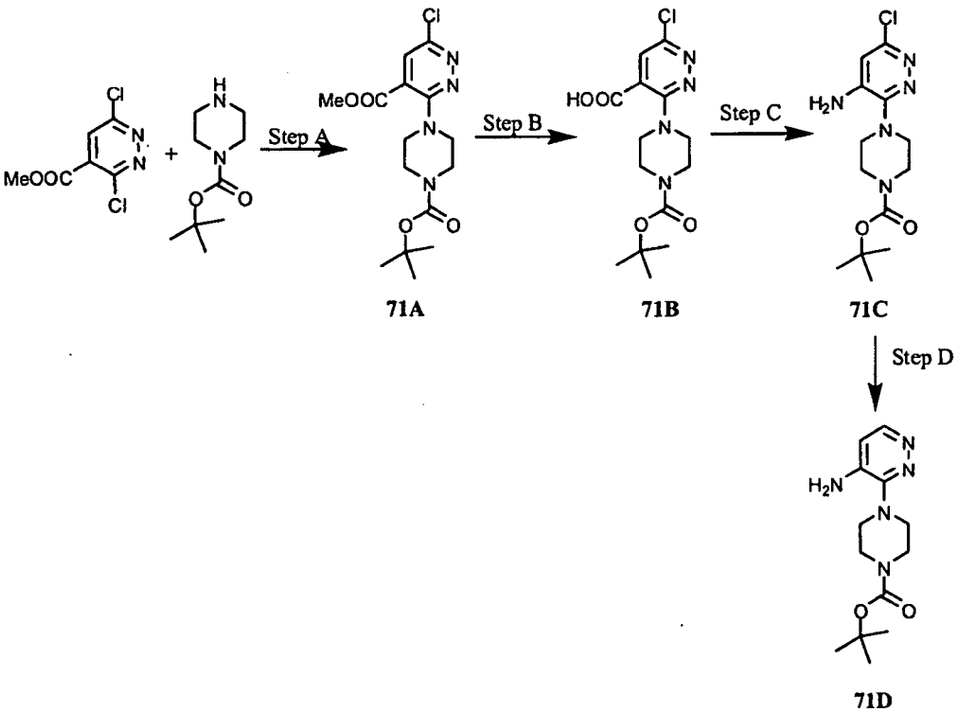
To a solution of compound **70A** (600 mg) in Ethanol/EtOAc (1:1, 10 mL) was added Pd on carbon (5% Pd). The reaction mixture was stirred under a hydrogen atmosphere at 40psi for about 15 hours, then filtered through a pad of celite. The filtrate was concentrated. *in vacuo* to provide Compound **70B** as a solid. HPLC-MS RT= 1.10 min, mass calculated for formula $C_{15}H_{24}N_4O_2$ 292.19, observed LCMS m/z 293.20 (M+H).

Using the methods described in Steps A and B above, and using the appropriate reactants, the following intermediate compounds were made:

Starting material	Product	M+H Observed	Retention Time
	 **70C**	**280.3**	**0.9**
	 **70D**	**284.1**	**1.5**
	 **70E**	**296.2**	**2.0**
	 **70F**	**329.2**	**1.2**

Example 71

Preparation of Compound **71D**



Step A:

A solution of 3,6-dichloro pyridazine-4-carboxylic acid methyl ester (2.0 mmol, 0.41 g), diethylisopropyl amine (3.0 mmol, 0.52 mL) and piperazine-1-carboxylic acid *tert*-butyl ester (2 mmol, 0.37 g) in dioxane (2 mL) was irradiated using microwave for 20 minutes at a temperature of 80 °C. The reaction mixture was concentrated *in vacuo*, and the resulting residue was purified using flash column chromatography on silica gel (eluent: ethyl acetate) to provide compound **71A** as a yellow solid in quantitative yield. HPLC-MS RT= 1.9 min, mass calculated for formula $C_{15}H_{21}ClN_4O_4$ 356.13, observed LCMS m/z 357.1 (M+H).

Step B:

To a solution of compound **71A** (2.0 mmol. .714 g) in 4 ml of THF was added 1N. LiOH solution in water 4 mL and stirred for about 15 hours at room temperature. THF is removed and acidified to pH to 2. Aqueous layer is extracted with ethyl acetate, washed with brine, dried over anhydrous sodium sulfate. Filtered and concentrated to get compound **71B**. HPLC-MS RT= 1.3 min, mass calculated for formula $C_{14}H_{19}ClN_4O_4$ 342.11, observed LCMS m/z 343.1 (M+H).

Step C:

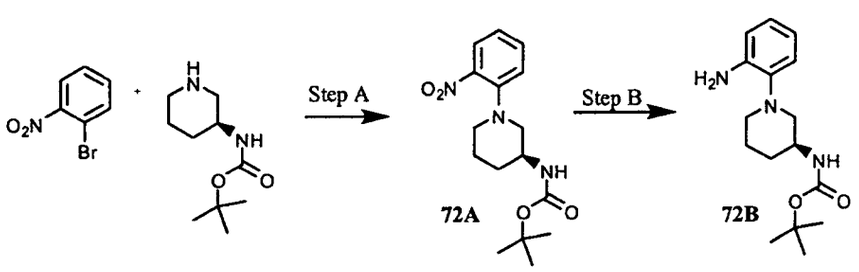
To a solution of Compound **71B** (1 mmol, 0.34 g.) in DMF (5mL) was added DPPA (1 mmol, 0.275 g.) and triethylamine (1.1 mmol, 0.16 mL) and stirred under Ar for 4 hours then added 1 ml of water and heated to 65^{0}C for 1 hour. Cooled to room temperature and pH was adjusted to 9 by adding potassium carbonate. Extracted with Ethyl acetate, washed with brine, dried over sodium sulfate, filtered and concentrated to obtain compound **71C**. HPLC-MS RT= 1.35 min, mass calculated for formula $C_{13}H_{20}ClN_5O_2$ 313.13, observed LCMS m/z 314.2 (M+H).

Step D:

To a solution of compound **71C** (150 mg) in Ethanol/EtOAc (1:1, 10 mL) was added Pd on carbon (5% Pd). The reaction mixture was stirred under a hydrogen atmosphere at 40 psi for about 15 hours, then filtered through a pad of celite. The filtrate was concentrated. *in vacuo* to provide Compound **71D** as a solid. HPLC-MS RT= 1.0 min, mass calculated for formula $C_{13}H_{21}N5O_2$ 279.17, observed LCMS m/z 280.30 (M+H).

Example 72

Preparation of Compound **72B**



Step A:

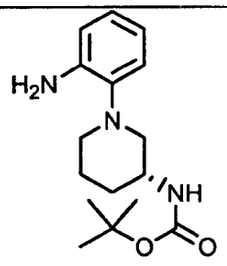
A solution of 1-bromo-2-nitro-benzene (2.0 mmol, 0.4 g), diethylisopropyl amine (3.0 mmol, 0.52 mL) and Compound (2.5 mmol, 0.50 g) in dimethylacetamide (2 mL) was irradiated using microwave for 30 minutes at a temperature of 200 °C. The reaction mixture was concentrated *in vacuo*, and the resulting residue was purified using flash column chromatography on silica gel (eluent: ethyl acetate) to provide compound **72A** as a solid. HPLC-MS RT= 2.15 min, mass calculated for formula $C_{16}H_{23}N_3O_4$ 321.17, observed LCMS m/z 322.2 (M+H).

Step B:

To a solution of compound **72A** (400 mg) in Ethanol/EtOAc (1:1, 10 mL) was added Pd on carbon (5% Pd). The reaction mixture was stirred under a hydrogen atmosphere at room

temperature for about 15 hours, then filtered through a pad of celite. The filtrate was concentrated *in vacuo* to provide Compound **72B** as a solid. HPLC-MS RT= 1.70 min, mass calculated for formula $C_{16}H_{25}N3O_2$ 291.19, observed LCMS m/z 292.20 (M+H).

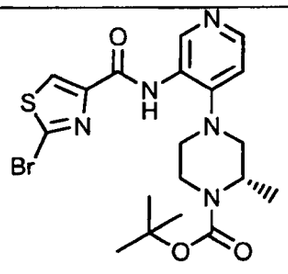
Using the methods described in Steps A and B above, and utilizing the enantiomer of compound **72B**, the following intermediate compound was made:

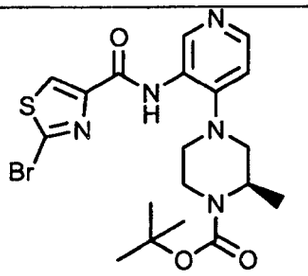
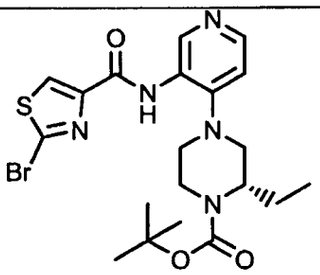
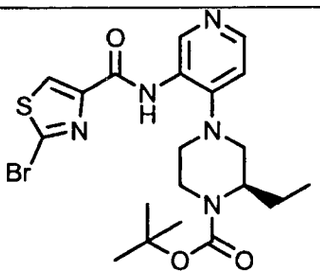
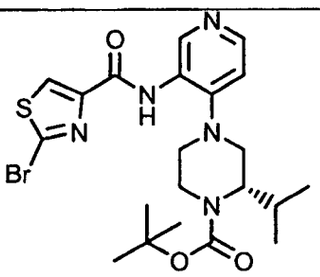
Compound	M+H Observed	Retention Time
 **72C**	292.20	1.70

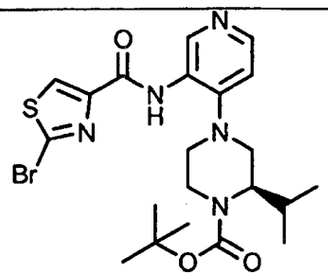
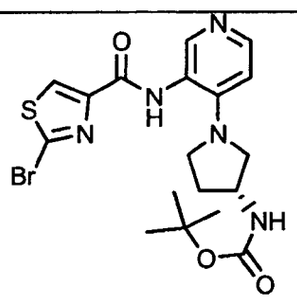
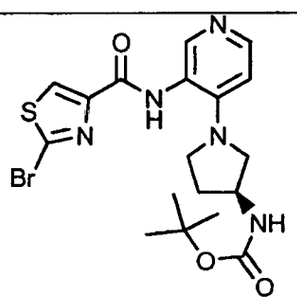
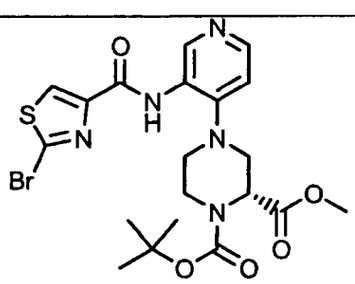
Example 73

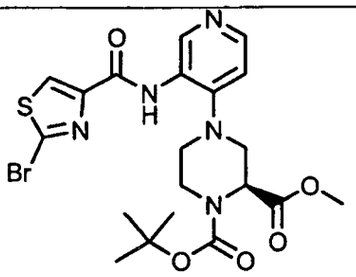
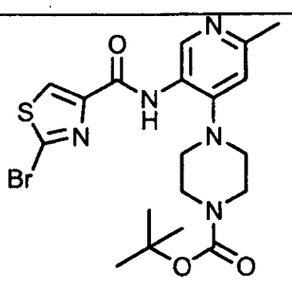
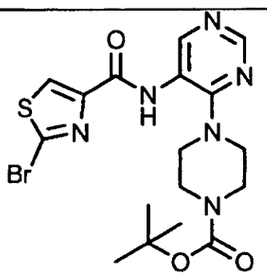
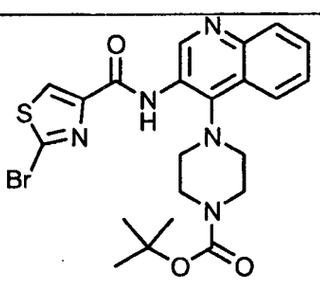
Preparation of Intermediate Compounds **73A-73Q**

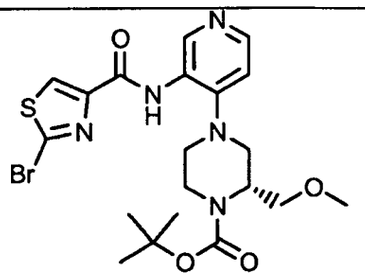
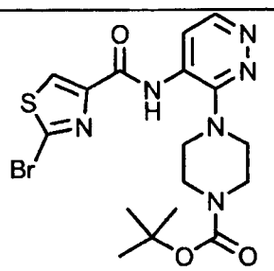
Using the methods described in Example 46 above, and using the appropriate reactants, the following intermediate compounds were made:

Compound	M+H Observed
 **73A**	482.1

 **73B**	482.1
 **73C**	496.1
 **73D**	496.1
 **73E**	510.1

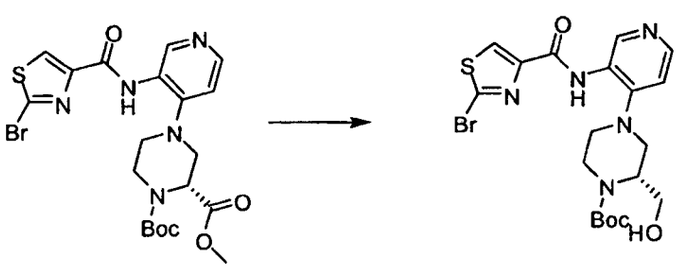
 **73F**	510.1
 **73G**	468.1
 **73H**	468.1
 **73J**	526.1

 **73K**	526.1
 **73L**	**482.1**
 **73M**	**469.1**
 **73N**	518.1

 73P	512.1
 73Q	469.1

Example 74

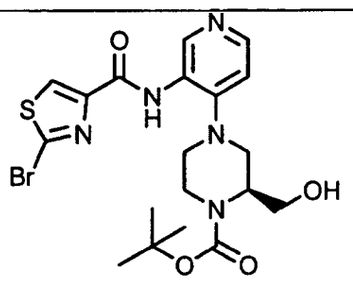
Preparation of Compound **74A**



73J **74A**

To a solution of compound **73J** (0.2 mmol, 0.1 g.) in Ethanol 2 mL added sodium borohydride (0.8 mmol, 0.03 g.) and stirred for about 15 hours. Water is added and extracted with ethylacetate . Ethylacetate layer is washed with water, brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to provide product **75A**. HPLC-MS RT= 1.10 min, mass calculated for formula $C_{19}H_{24}BrN_5O_4S$ 497.07, observed LCMS m/z 498.1 (M+H).

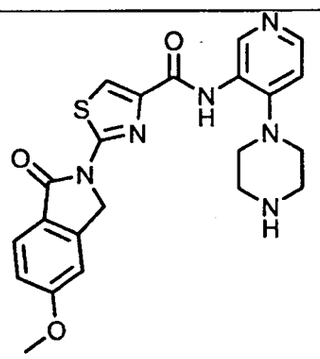
Using this procedure, compound **74B** was synthesized from compound **73K**.

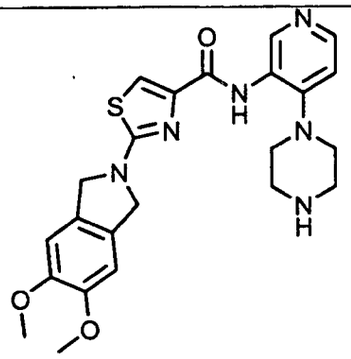
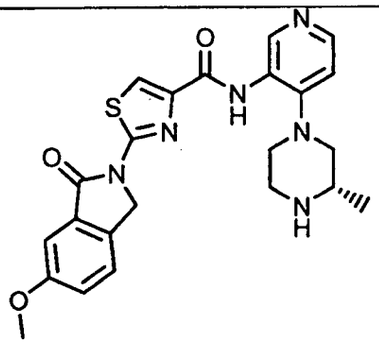
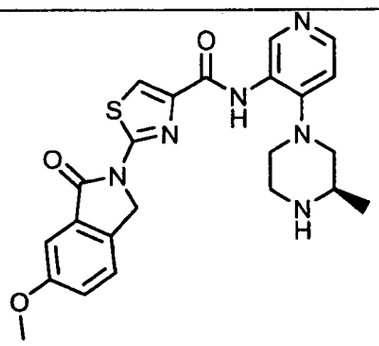
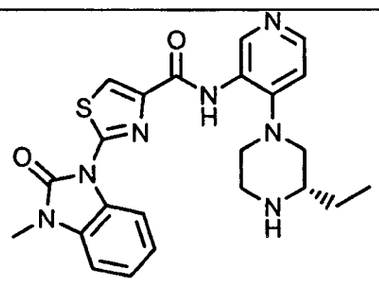
Compound	M+H Observed
 **74B**	498.31

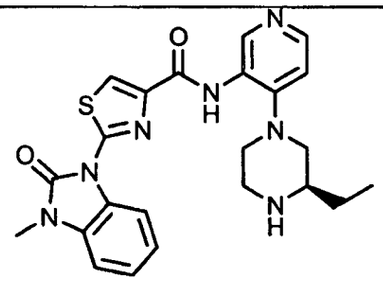
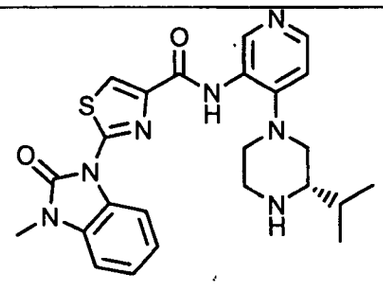
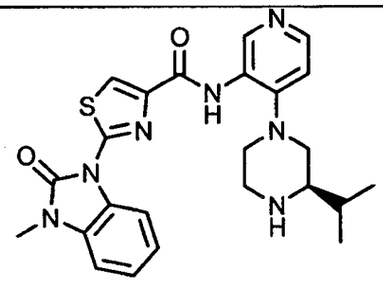
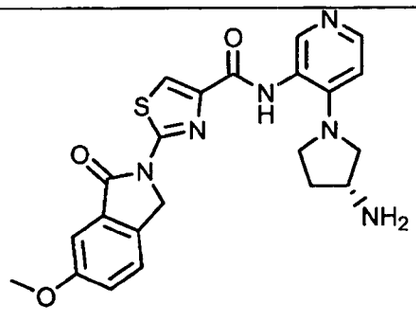
Example 75

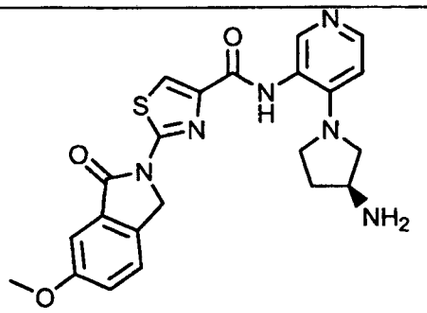
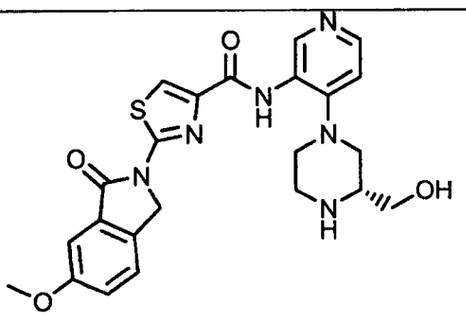
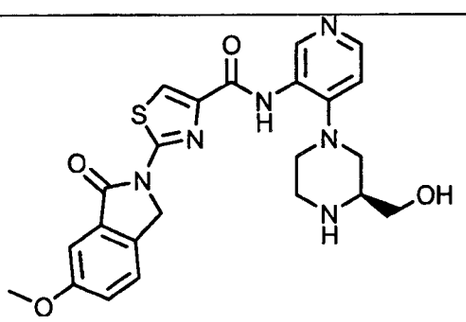
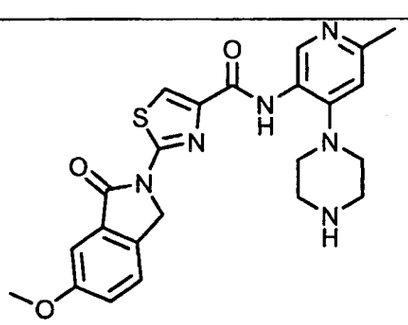
Preparation of Compounds **65, 71, 75, 81, 83, 86, 87, 151-153, 201, 202, 240, 241, 257, 317, 320-322** and **324**

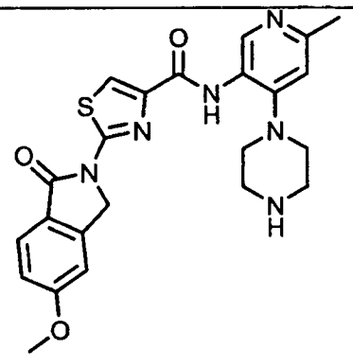
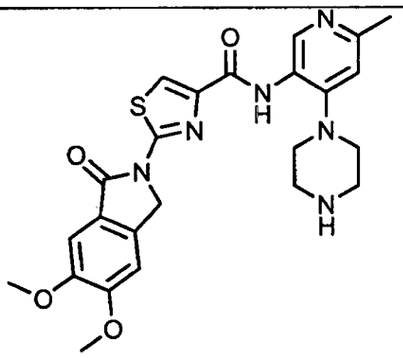
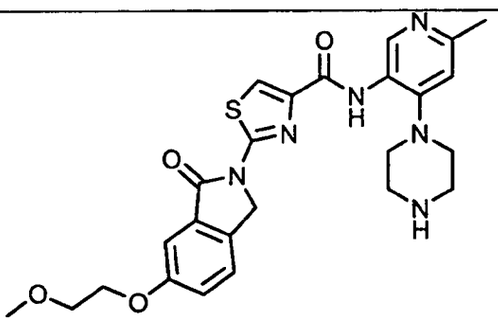
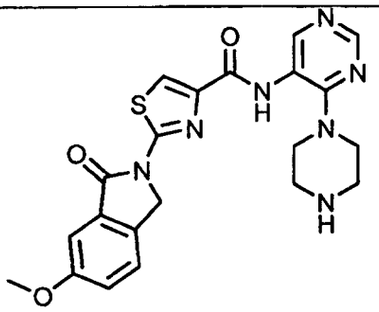
The compounds depicted below were made using the method described in Example 51 and utilizing the appropriate reactants.

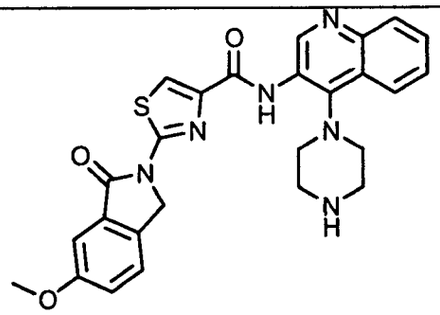
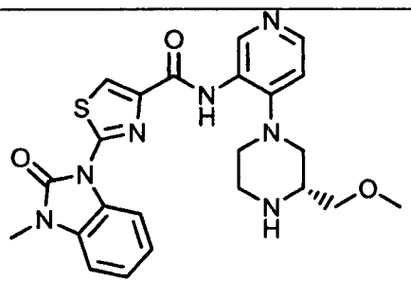
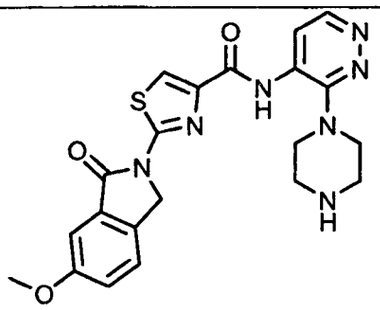
Compound	M+H Observed	Retention Time
 **83**	451.14	2.07

 **65**	467.2	0.5
 **202**	465.1	0.75
 **201**	465.1	0.8
 **320**	464.17	1.81

 **324**	464.17	1.92
 **322**	478.19	1.93
 **321**	478.19	1.86
 **153**	451.1	2.1

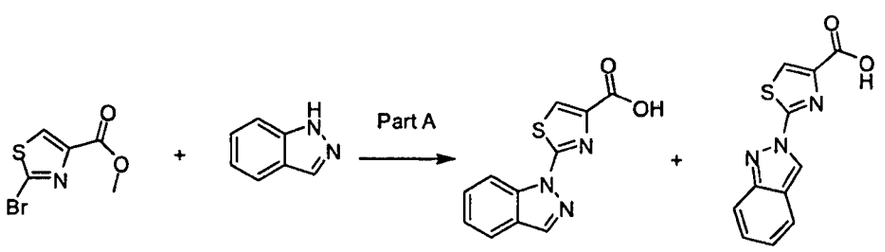
 **152**	451.1	2.1
 **241**	481.15	1.71
 **240**	481.15	1.74
 **81**	**465.16**	**2.14**

 **86**	**465.16**	**1.93**
 **87**	**495.17**	**1.99**
 **257**	**509.19**	**2.10**
 **71**	**452.1**	**2.45**

 **75**	501.16	2.14
 **317**	**480.17**	**1.78**
 **151**	**452.15**	**2.76**

Example 76

Preparation of Compound **76A** and **76B**



76A **76B**

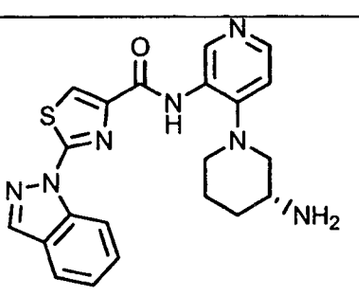
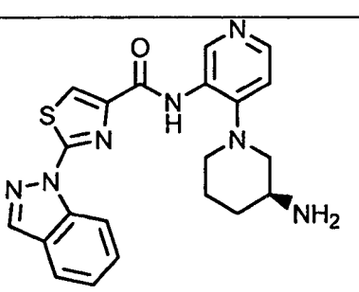
To a suspension of NaH (60% dispersion in oil, 10 mmol, 0.48 g.) in anhydrous dioxane (5 mL) was added a solution of indazole (10 mmol, 1.18 g) in dioxane (5 mL) and the resulting reaction was allowed to stir for 30 minutes. A solution of 2-bromo-thiazole-4-carboxylic acid

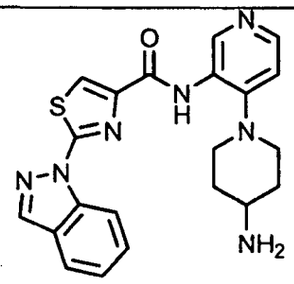
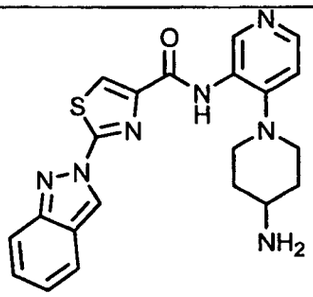
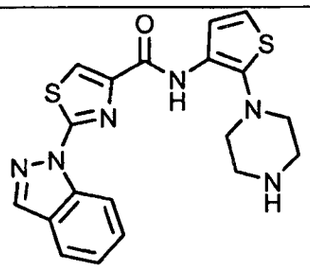
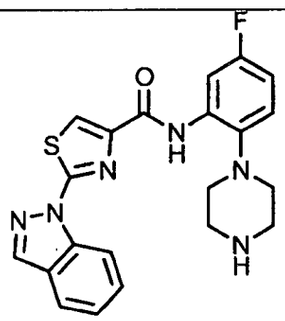
methyl ester (10.0 mmol, 2.22 g) in dioxane (5 mL) was then added dropwise and the reaction mixture was heated to 100^{0}C for 4 hrs. The reaction mixture was cooled to room temperature, quenched with water, and the solution was adjusted to pH 2 using 1N HCl. The resulting basic solution was extracted with ethyl acetate and the organic phase was washed with water and brine, dried over anhydrous sodium sulfate, then filtered and concentrated. LCMS of the resulting residue showed two peaks for the acid indicating the formation of two regioisomers (Compounds **76A** and **76B**). HPLC-MS RT= 1.35 and 1.45 min, mass calculated for formula $C_{11}H_7N_3O_2S$ 245.03, observed LCMS m/z 246.1 (M+H).

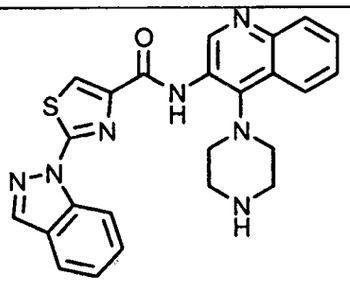
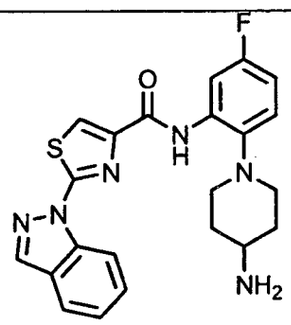
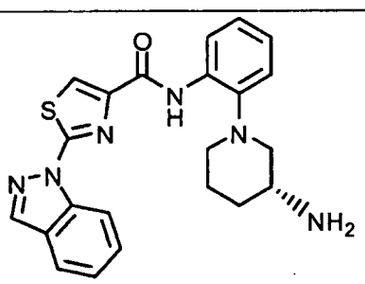
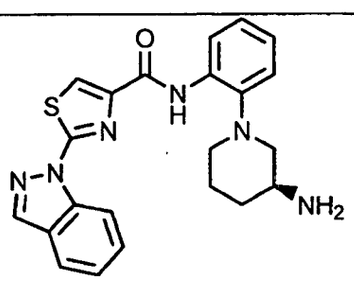
Example 77

Preparation of Compounds **33, 40, 53, 59, 60, 76, 173, 176** and **179**

The compounds depicted below were made by reacting compound **76A** or **76B** with the appropriate coupling partner using the method described in Steps C and D of Example 66.

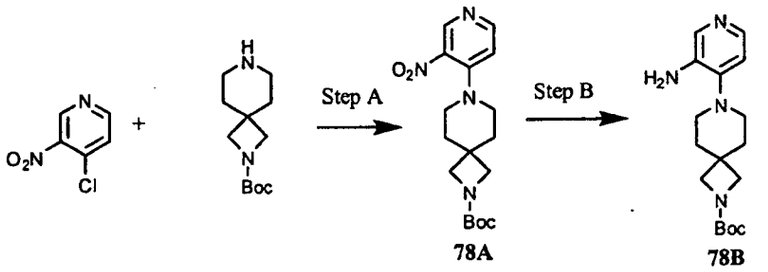
Compound	M+H Observed	Retention Time
 **173**	420.1	**2.07**
 **171**	420.1	2.07

 **59**	420.15	2.22
 **60**	420.15	2.16
 **33**	**411.09**	**3.34**
 **40**	**423.1**	**3.75**

 **76**	456.15	2.31
 **53**	**437.2**	**4.0**
 **179**	**419.15**	**3.57**
 **176**	**419.15**	**3.54**

Example 78

Preparation of Compound **78B**



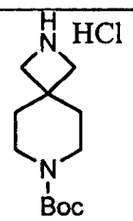
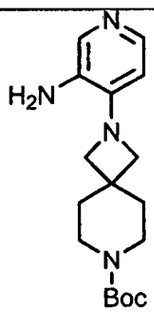
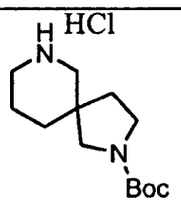
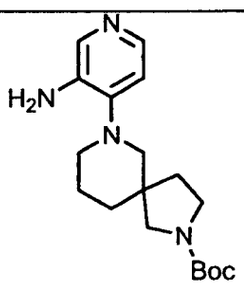
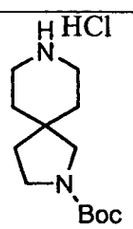
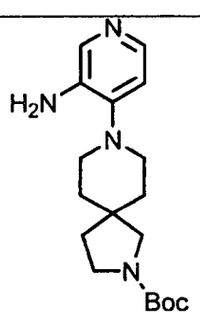
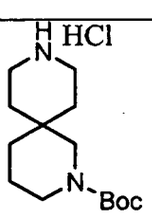
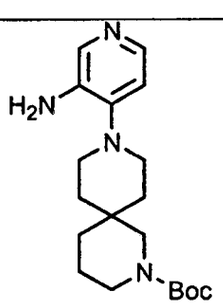
Step A:

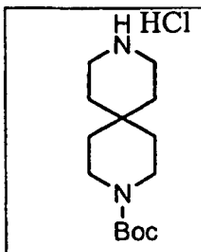
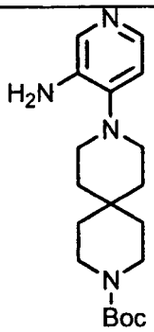
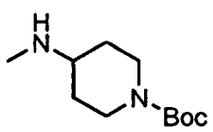
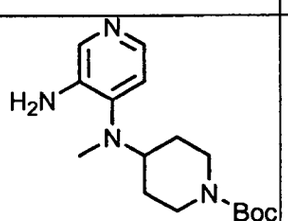
To a vial were added 4-chloro-3-nitro pyridine (2 mmol) and spirocyclic amine (2 mmol). The starting materials were dissolved in 4 mL of dichloromethane followed by the addition of DIPEA (6 mmol). The reaction was stirred at 60° for about 15 hours, then the reaction mixture was concentrated and using preparative liquid chromatography (0-5% methanol in ethyl acetate) to provide compound **78A**. Recovered 1.6 mmol (80%) of 274. Mass calculated for formula $C_{17}H_{24}N_4O_4$ 348.18, observed LCMS m/z 348.20 (M+H).

Step B:

To a round-bottom flask was added a solution of compound **78A** in ethyl acetate. Next, Pd/C was added to the mixture. The flask was sealed with a septum and evacuated. The mixture was hydrogenated using a balloon for about 15 hours. Product was confirmed by LCMS. The Pd/C was filtered off using Celite and the filtrate was concentrated *in vacuo* to provide compound **78B** in quantitative yield. Mass calculated for formula $C_{17}H_{26}N_4O_2$ 318.21, observed LCMS m/z 319.20 (M+H). LCMS calculated for 275: 318.21.

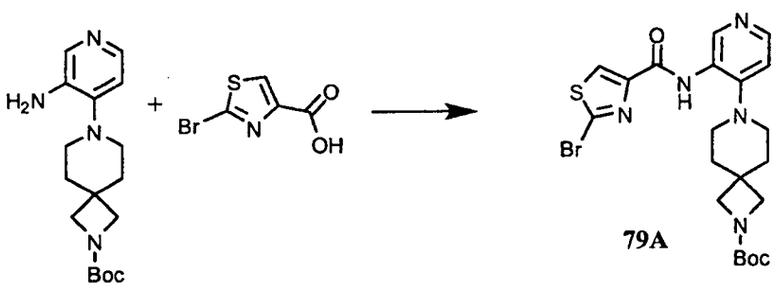
Using the methods described in Steps A and B above, and using the appropriate reactants, the following intermediate compounds were made:

Starting Material	Product	M+1	Retention time (min)
	 **78C**	319.2	0.95
	 **78D**	333.2	1.11
	 **78E**	333.3	1.21
	 **78F**	347.2	1.12

	 **78G**	347.2	1.05
	 **78H**	307.3	0.99

Example 79

Preparation of Compound **79A**

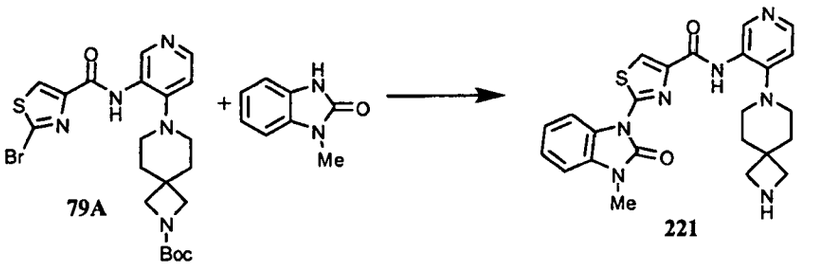


78B **79A**

To a solution of 2-bromo thiazole-5 carboxylic acid (0.57 mmol) and HATU (0.68 mmol) in 1 mL of DMF, was added DIPEA (3 equivalents, 1.6 mmol) and the resulting reaction was stirred for 10 minutes at room temperature. To the reaction mixture was then added a solution of compound **78B** (0.57 mmol) in 0.5mL of DMF and the resulting reaction was stirred at room temperature for an additional 2 hours. The reaction mixture was then concentrated *in vacuo* and the residue obtained was purified using preparative liquid chromatography (5-10% methanol in dichloromethane) to provide 0.54 mmol (95%) of compound **79A**.

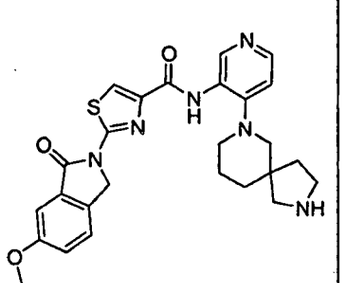
Example 80

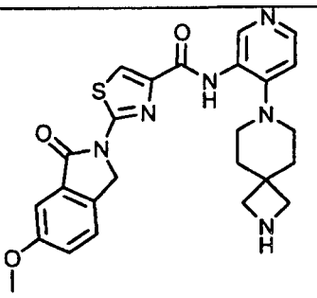
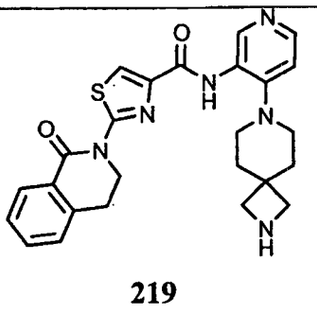
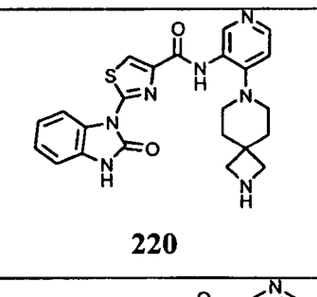
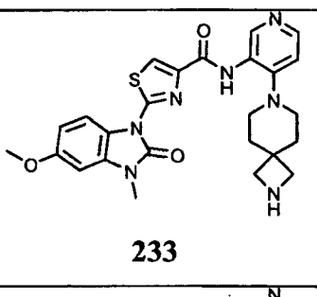
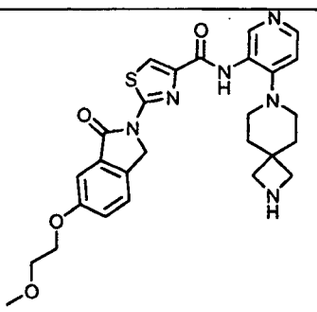
Preparation of Compound **221**

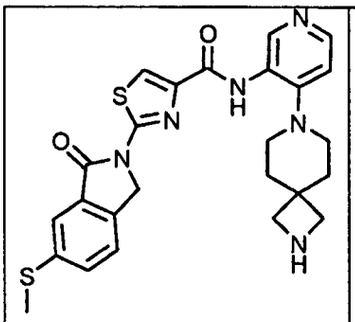
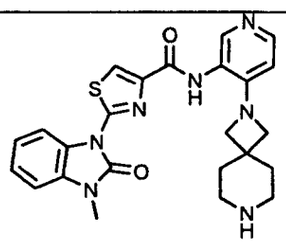
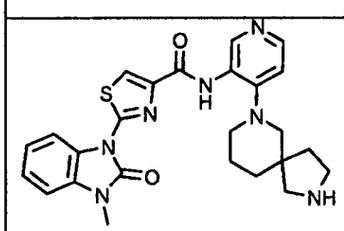
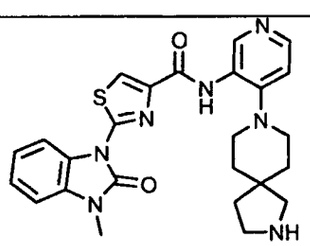
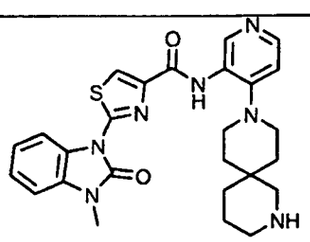


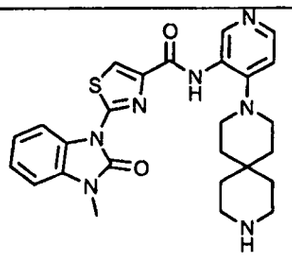
Compound **79A** (0.15 mmol), 1-methyl-1,3-dihydro-benzimidazole-2-one (0.1 mmol), Pd_2dba_3 (0.01 mmol), Xantphos (0.02 mmol), and K_3PO_4 (0.3 mmol) were placed in vial and diluted with dioxane (1 mL). The resulting solution was degassed and flushed with argon, then capped, and sonicated. The reaction was heated to 90 °C and allowed to stir at this temperature for 2 hours, then the reaction mixture was cooled to room temperature and diluted with ethyl acetate. The organic layer was sequentially washed with saturated $NaHCO_3$ (aq), brine, and water. The organic layer was then dried with sodium sulfate, filtered and concentrated *in vacuo* and the crude residue obtained was purified using preparative liquid chromatography (5-10% methanol in dichloromethane). The product obtained was then lyophilized and the solid material obtained was treated with excess 2M HCl in dioxane to provide compound **221**.

Using the method described above, the following illustrative compounds were made:

Compound	M+(m/z)	M+H	Retention time (minutes)
 **77**	504.20	505.20	2.75

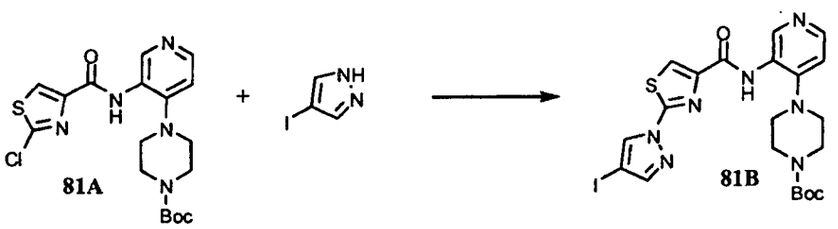
 **170**	490.18	491.2	2.60
 **219**	474.18	475.2	2.19
 **220**	461.16	462.1	1.84
 **233**	505.19	506.1	2.26
 **268**	534.21	535.2	2.66

 **276**	506.16	507.1	2.48
 **309**	475.18	476.1	1.75
 **315**	489.19	490.1	2.31
 **316**	489.19	490.1	2.39
 **319**	503.21	504.3	2.18

 **323**	503.21	504.3	2.15

Example 81

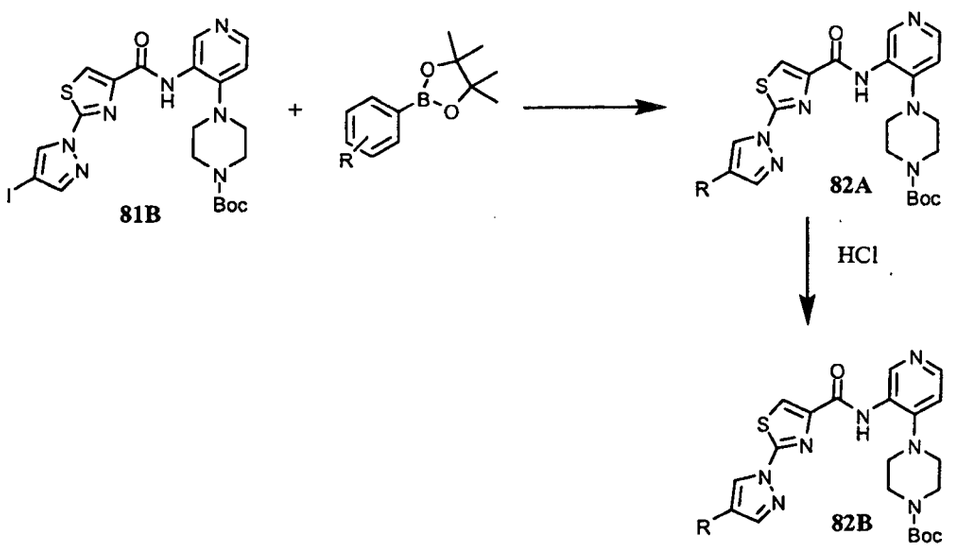
Preparation of Compound **81B**



Using the method described in Example 24, compound **81A** was reacted with 4-iodopyrazole to prepare compound **81B**. Mass calculated for formula $C_{21}H_{24}N_7O_2SI$ 581.0, observed LCMS m/z 582.20 (M+H).

Example 82

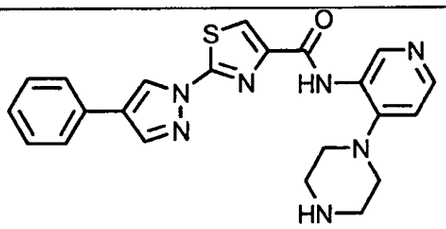
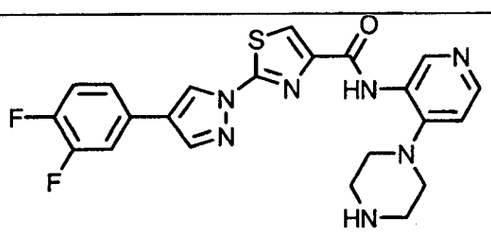
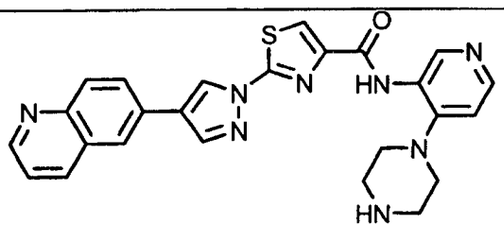
Preparation of Compounds **62, 63, 66, 70, 272, 277** and **283**

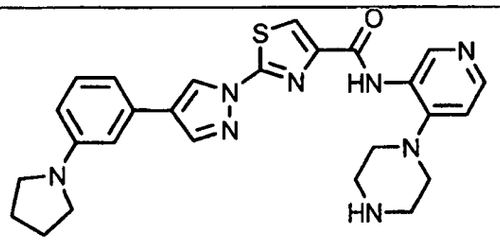
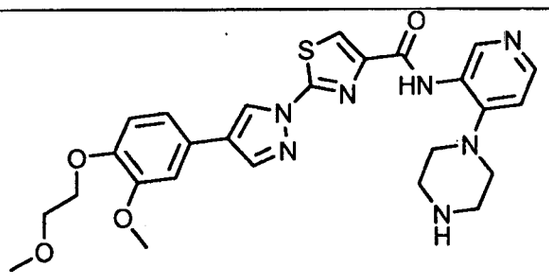
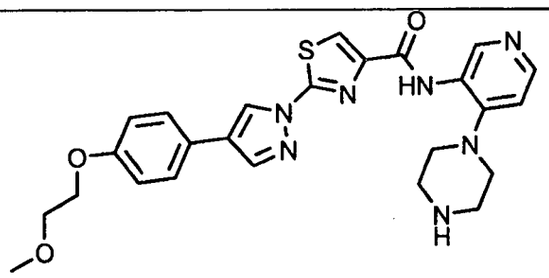
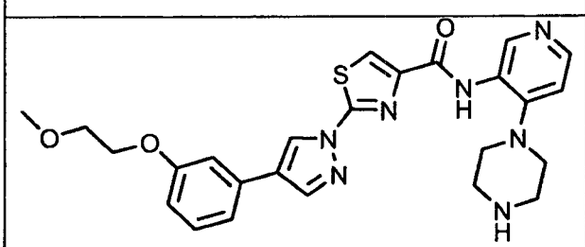


General Procedure:

Compound **81B** (0.30 mmol), a representative boronic acid or ester (0.34 mmol), $Pd(dppf)Cl_2$ (0.034 mmol), and K_3PO_4 (0.9 mmol) are dissolved in 2 mL of dioxane and 300 □L of water. The resulting solution is degassed and flushed with argon, then heated to 90 °C and allowed to stir at this temperature for about 2 hours. The reaction is then diluted with ethyl acetate and the organic phase is washed sequentially with saturated aqueous $NaHCO_3$ and water. The organic layer is then dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue obtained can be purified using preparative HPLC to provide a compound of formula 82A, which is subsequently lyophilized and the purified product is then treated with 4N HCl to remove the Boc group and afforded the desired product **82B**.

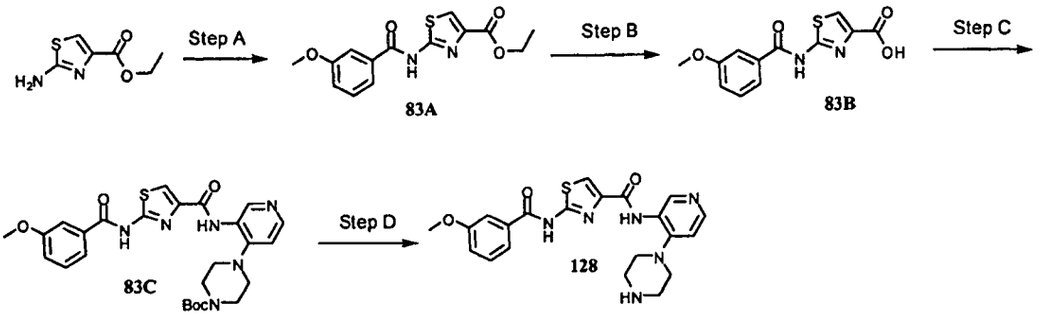
Using this method, the following illustrative compounds were made.

Compound	M+H Observed	Ret time (min)
 **62**	432.15	2.60
 **63**	468.1	2.49
 **66**	483.1	1.69

 **70**	501.2	2.63
 **272**	536.2	2.86
 **277**	506.2	2.96
 **283**	506.2	2.95

Example 83

Preparation of Compound **128**



Step A:

To the mixture of Methyl-2-amino-4-carboxylate (634 mg, 3.69 mmol), DIEA (0.7 mL, 4.0 mmol) and 3-methoxybenzoic acid (561 mg, 3.69 mmol) in DMF (10 mL) was added HATU (1.52 g, 4.0 mmol). The resulting mixture was stirred at room temperature for about 15 hours and water (60 mL) was added. The solid precipitated out was collected with filtration and washed with water, dried under air. The crude product **83A** was used in the next step directly without any further purification. HPLC-MS t_R = 1.71 min ($UV_{254\ nm}$); mass calculated for formula $C_{14}H_{14}N_2O_4S$ 306.1, observed LCMS m/z 307.1 (M+H).

Step B:

The compound **83B** was prepared by hydrolyzing compound **83A** using the method described in Example 50 above. HPLC-MS t_R = 1.45 min ($UV_{254\ nm}$); mass calculated for formula $C_{12}H_{10}N_2O_4S$ 278.0, observed LCMS m/z 279.1 (M+H).

Step C:

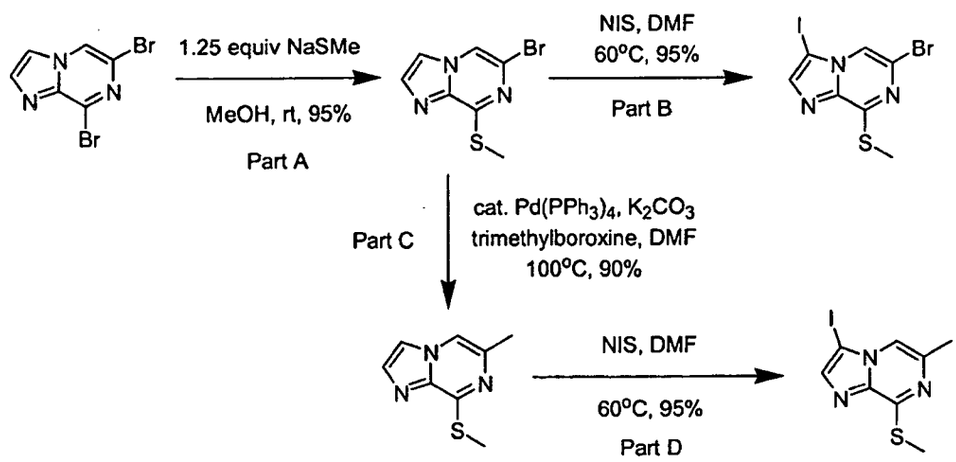
Compound **83C** was prepared by reacting compound **83B** with the appropriate coupling partner according to the method described in Example 58 above. HPLC-MS t_R = 1.50 min ($UV_{254\ nm}$); mass calculated for formula $C_{26}H_{30}N_6O_5S$ 538.2, observed LCMS m/z 539.2 (M+H).

Step D:

Compound **128** was prepared by deprotecting compound **83C** using the method described in Example 62 above. HPLC-MS t_R = 0.94 min ($UV_{254\ nm}$); mass calculated for formula $C_{21}H_{22}N_6O_3S$ 438.1, observed LCMS m/z 439.1 (M+H).

The synthesis of compounds (k) from U.S. provisional patent application, Docket No. OC06760L01 filed of even date herewith, is described below:

EXAMPLE 1



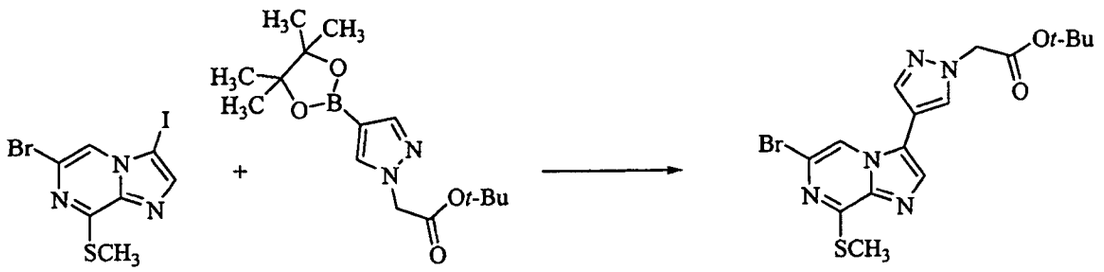
Part A: The title compound was prepared according to US20060106023 (A1).

Part B: To a solution of compound from Example 1, Part A (2.00 g, 8.19 mmol) in DMF (50 mL) was added N-iodosuccinimide (1.84 g, 8.19 mmol). The reaction mixture was stirred at 60C for 16 hours. The mixture was cooled to 25C and concentrated. The residue was dissolved in DCM with a small amount of methanol and then loaded on the column. Purification by column chromatography (SiO_2, 40% ethyl acetate/hexanes) afforded compound as a white solid 2.30 g (76%). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.3 (s, 1H), 7.8 (s, 1H), 2.6 (s, 3H). HPLC-MS t_R = 1.87 Min (UV $_{254nm}$). Mass calculated for formula C7H5BrIN3S 370.01, observed LC/MS m/z 370.9 (M+H).

Part C: A suspension of bromide from Part A (45.6 g), Pd(PPh3)4 (10.8 g), potassium carbonate (77.4 g), trimethylboroxine (46.9 g) and potassium carbonate (77.4 g) in DMF (410 mL) was heated overnight under nitrogen at 105C. After cooling, the mixture was diluted with ethyl acetate (1 L), washed with brine (2 x 500 mL), dried (magnesium sulfate), filtered, concentrated and purified by chromatography on silica gel. The title compound was obtained as a pale yellow solid (21.4 g, 64%).

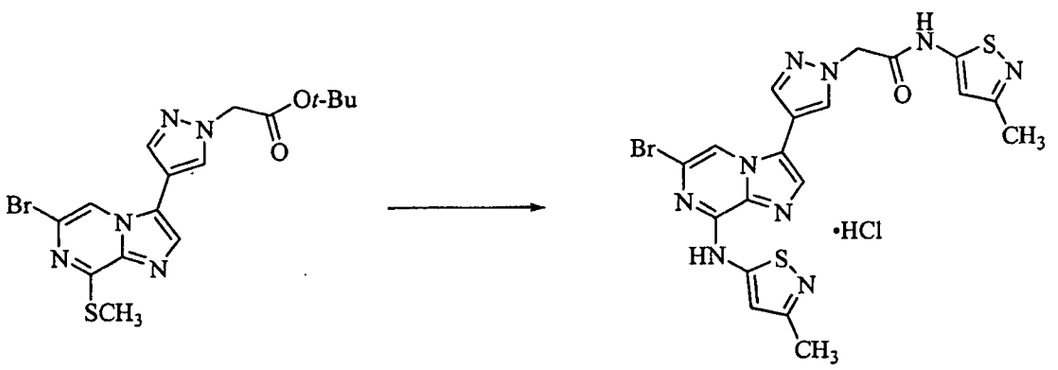
Part D: To a DMF (400 mL) solution of compound from Example 1, Part C (21.8 g) was added N-iodosuccinimide (26.9 g) and the resulting mixture was heated overnight at 60C. The mixture was concentrated and water (400 mL) was added. After stirring 1 hr at rt, saturated sodium carbonate was added (250 mL) and subsequently stirred an additional 30 min at rt. The mixture was filtered, washed with water, methanol (100 mL) and the filter cake was dried overnight under vacuum. A brown solid was obtained (31.4 g, 87%).

EXAMPLE 2



A solution of *tert*-butyl 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)acetate (318 mg, 1.03 mmol) in 1,4-dioxane (3 mL) and water (0.30 mL) was added to an argon degassed mixture of compound from Example 1, Part B (292 mg, 0.79 mmol), $Pd(dppf)Cl_2$ (58 mg, 0.079 mmol) and potassium phosphate (503 mg, 2.37 mmol). The reaction was heated to 40 °C and allowed to stir for 12 hours. The reaction was cooled to room temperature, filtered through Celite eluting with ethyl acetate then concentrated to dryness. Purification of the crude residue by flash chromatography (SiO_2, 12 g; 5% to 40% ethyl acetate in hexanes) afforded the title compound as a light brown solid 244 mg (73%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.81 (s, 1H), 7.80 (s, 1H), 7.65 (s, 1H), 4.94 (s, 2H), 2.68 (s, 3H), 1.51 (s, 9H).

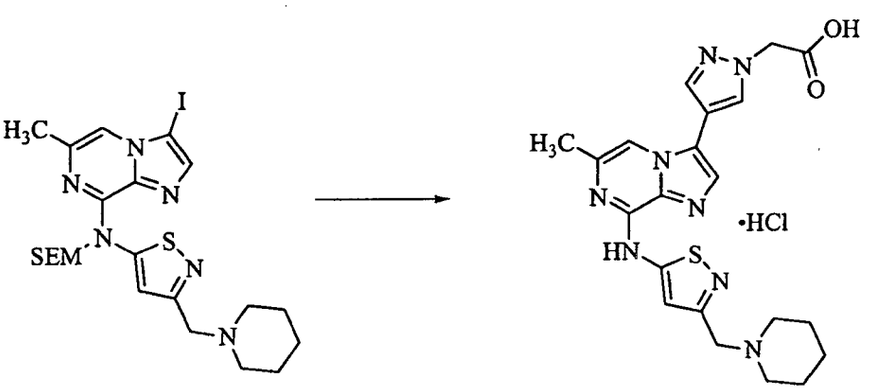
EXAMPLE 3



3-Chloroperoxybenzoic acid (204 mg, 1.18 mmol) was added to a room temperature solution of ester from Example 2 (244 mg, 0.58 mmol) in methylene chloride (3 mL). The reaction was allowed to stir for 1 hour. Upon completion, the reaction was concentrated to dryness then taken up into ethyl acetate (50 mL). The solution was washed with saturated aqueous sodium bicarbonate solution (50 mL) and brine (2 × 50 mL) then dried (sodium sulfate), filtered and concentrated to dryness to give 220 mg of crude sulfoxide. The crude sulfoxide (220 mg, 0.48 mmol) in dimethylsulfoxide (2.5 mL) was added to a premixed solution of sodium hydride (106 mg, 1.45 mmol) and 2-amino-4-methylisothiazole (78 mg,

0.68 mmol) in dimethylsulfoxide (2.5 mL). The reaction was stirred for 20 minutes then quenched with saturated aqueous ammonium chloride (50 mL). The aqueous layer was extracted with diethyl ether (2 × 50 mL) and ethyl acetate (2 × 50 mL). The combined organic layers were washed with brine (2 × 50 mL), dried (sodium sulfate), filtered and concentrated to dryness. Purification of the resultant residue by flash chromatography (SiO_2, 12 g; 5% to 40 % ethyl acetate in methylene chloride) and then on prep-HPLC afforded the title compound as a yellow solid 2 mg (0.8%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (s, 1H), 8.32 (s, 1H), 8.02 (s, 1H), 7.93 (s, 1H), 7.17 (s, 1H), 6.90 (s, 1H), 5.37 (s, 2H), 2.63 (s, 3H), 2.46 (s, 3H). HPLC t_R = 4.62 min (UV $_{254nm}$). Mass calculated for formula $C_{19}H_{16}BrN_9OS_2$ 529.01; observed MH^+ (APCI MS) 531.1 (m/z).

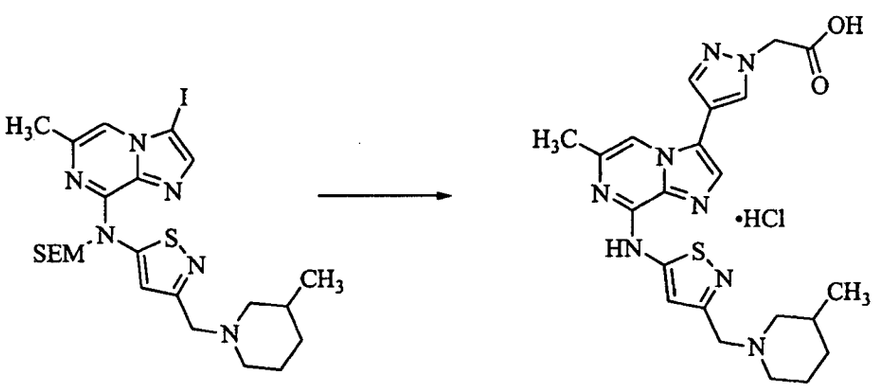
EXAMPLE 4



A solution of *tert*-butyl 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)acetate (135 mg, 0.44 mmol) in 1,4-dioxane (3 mL) and water (0.30 mL) was added to a nitrogen flushed mixture of iodide (200 mg, 0.34 mmol), $Pd(dppf)Cl_2$ (25 mg, 0.034 mmol) and potassium phosphate (216 mg, 1.02 mmol). The reaction mixture was heated to 90 °C and allowed to stir for 12 hours. Upon completion, the reaction was allowed to cool to room temperature and then was concentrated to dryness. Purification of the resultant residue by flash chromatography (SiO_2; 12 g; 10% to 80% ethyl acetate in methylene chloride) afforded the desired coupled intermediate. Trifluoroacetic acid (1 mL) was added to a room temperature solution of the desired coupled ester (80 mg, 0.125 mmol) in methylene chloride (3 mL). The reaction was stirred for 12 hours then concentrated to dryness. Purification of the resultant residue by prep-HPLC afforded the title compound as a yellow solid 40 mg (45%). ^{1}H NMR (300 MHz, CD_3OD) δ 8.34 (s, 1H), 8.26 (s, 1H), 8.08 (s, 1H), 8.01 (s, 1H), 7.36 (s, 1H), 5.15 (s, 2H), 4.43 (s, 2H), 3.17-2.99 (m, 2H), 2.71-2.55 (m, 2H), 2.64 (s, 3H), 2.06-1.71

(m, 5H), 1.65-1.46 (m, 1H). HPLC t_R = 3.82 min (UV $_{254nm}$). Mass calculated for formula $C_{21}H_{24}N_8O_2S$ 452.17; observed MH^+ (ESI MS) 453.1 (m/z).

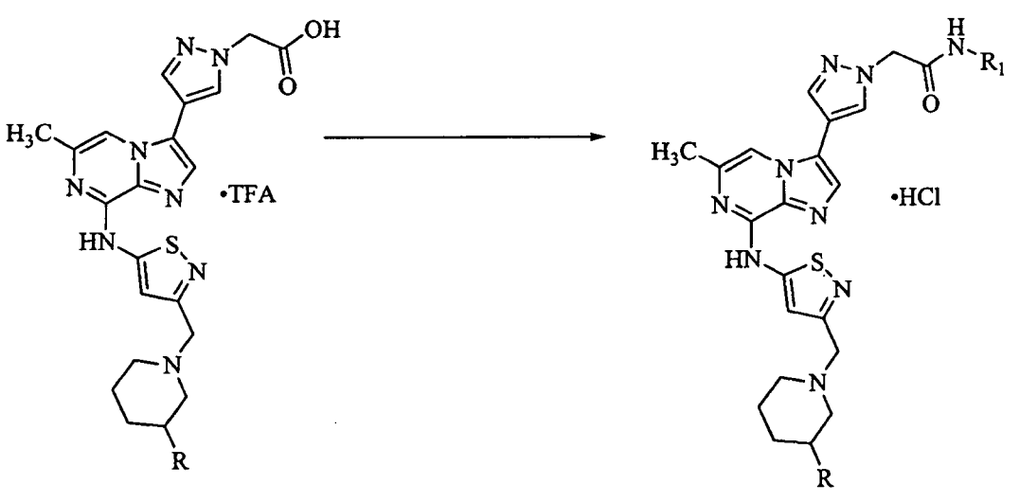
EXAMPLE 5



Example 5 was prepared in a similar manner to Example 4. ^1H NMR (300 MHz, CD_3OD) δ 8.34 (s, 1H), 8.26 (s, 1H), 8.08 (s, 1H), 8.01 (s, 1H), 7.36 (s, 1H), 5.15 (s, 2H), 4.43 (s, 2H), 3.17-2.99 (m, 2H), 2.71-2.55 (m, 2H), 2.64 (s, 3H), 2.06-1.71 (m, 5H), 1.65-1.46 (m, 1H). HPLC t_R = 3.82 min (UV $_{254nm}$). Mass calculated for formula $C_{21}H_{24}N_8O_2S$ 452.17; observed MH^+ (ESI MS) 453.1 (m/z).

EXAMPLE 6

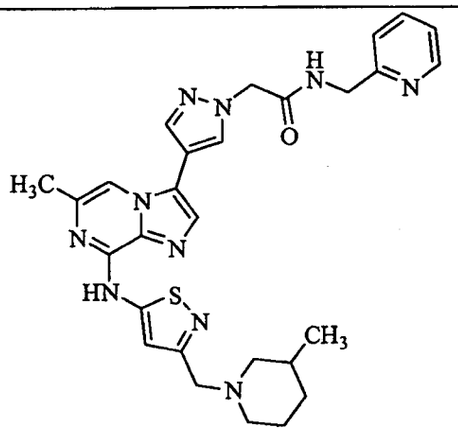
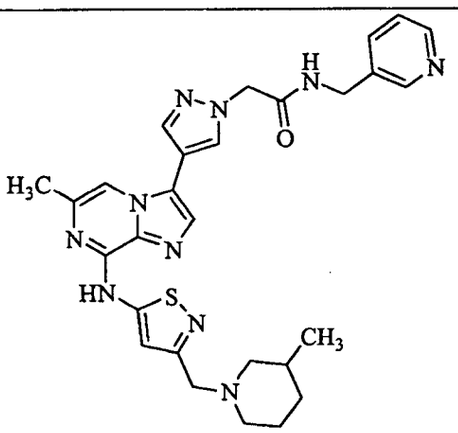
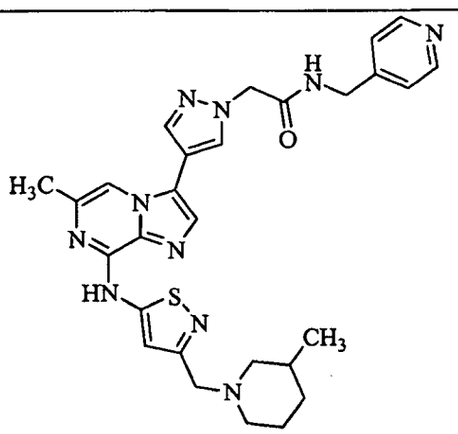
The compounds shown in column 2 of Table 1 (shown immediately below) were prepared as follows:

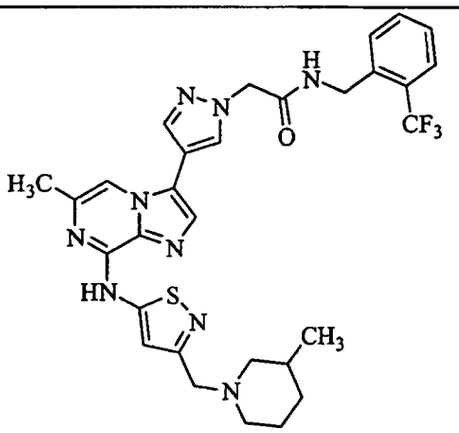
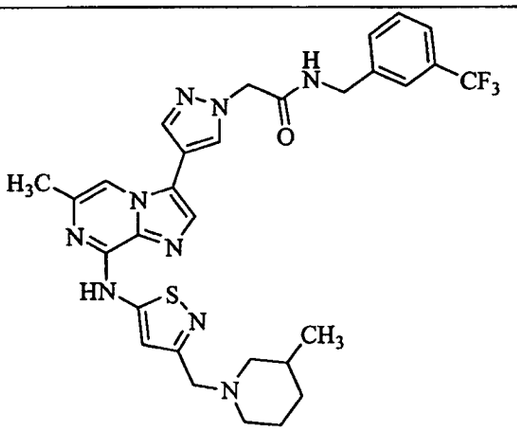
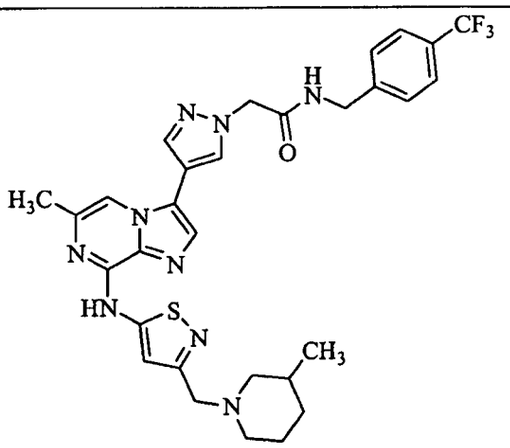


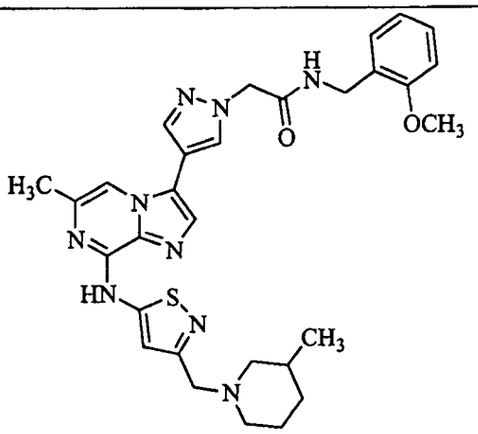
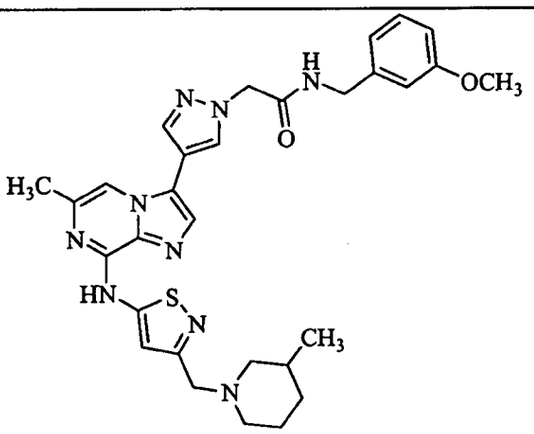
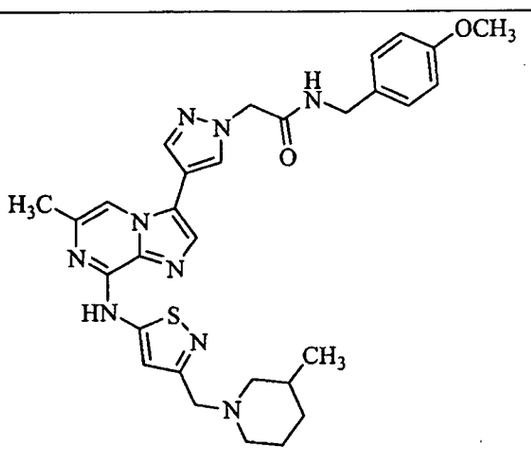
A mixture of acid (1 equivalent), the respective amine (1.5 equivalents), HATU (1.5 equivalents), and diisopropylethylamine (3 equivalents) in anhydrous DMF (500 μL) was stirred at room temperature for 2 hours. The reaction was then concentrated under reduced

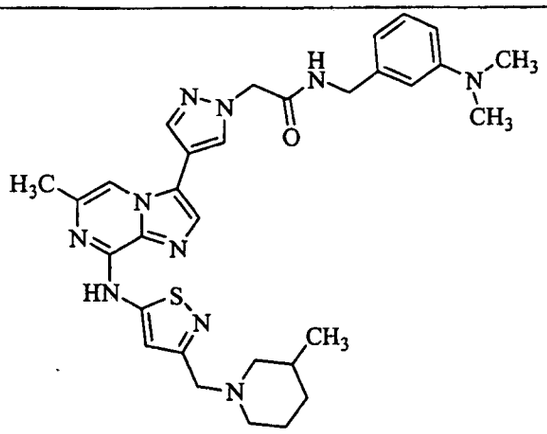
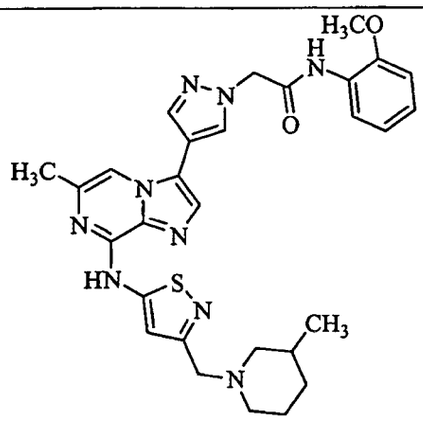
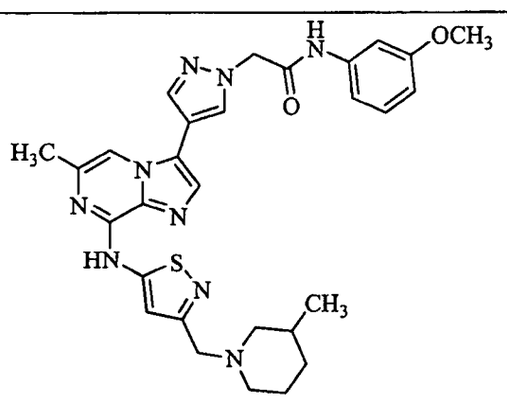
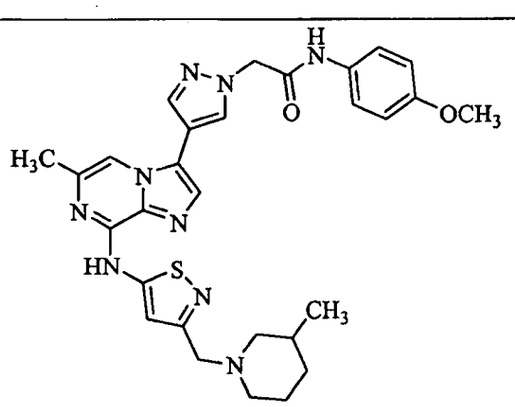
pressure, purified by preparative HPLC and conversion to the hydrochloride salt afforded compounds shown in Column 2 of Table 1(shown immediately below):

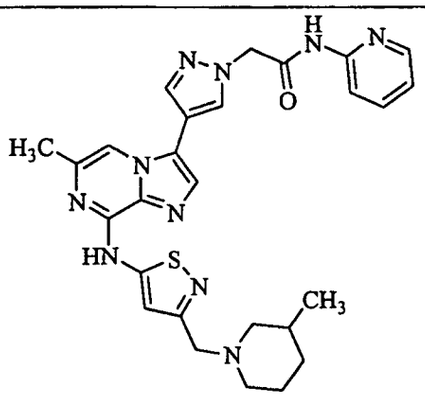
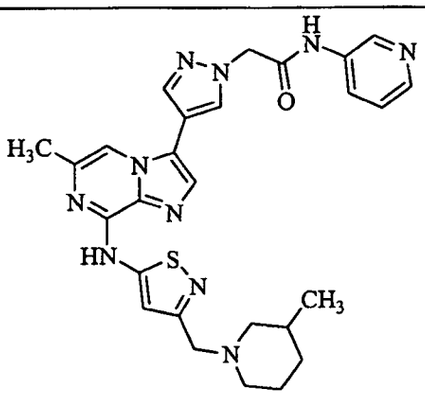
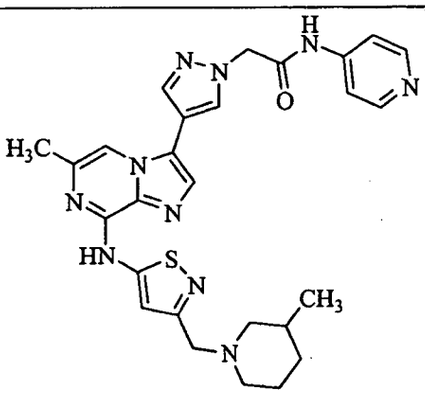
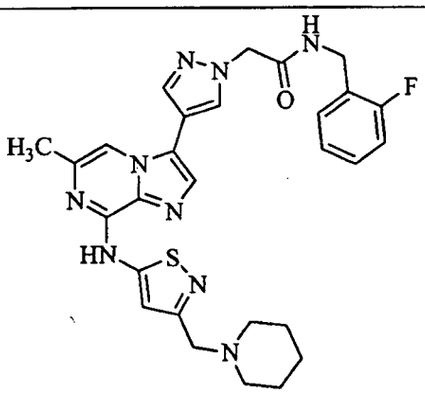
Table 1

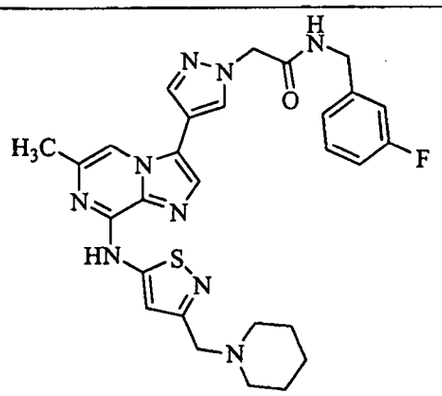
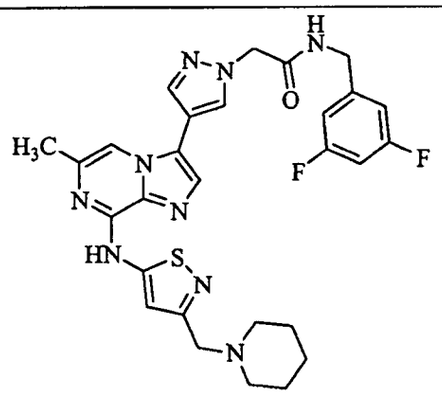
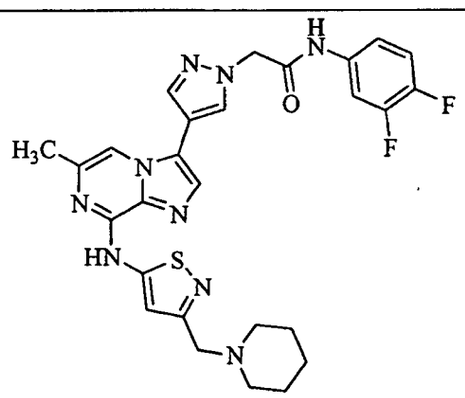
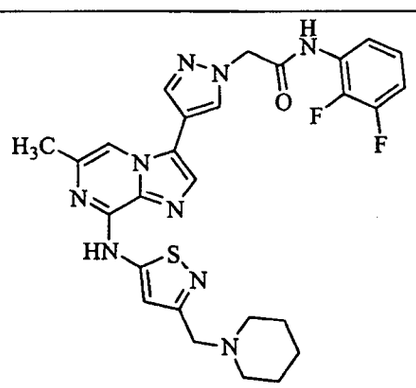
Example	Column 2	MW	MS MH^+ m/z	HPLC t_R
6-1		556.2	557.4	3.51
6-2		556.2	557.2	3.48
6-3		556.2	557.3	3.48

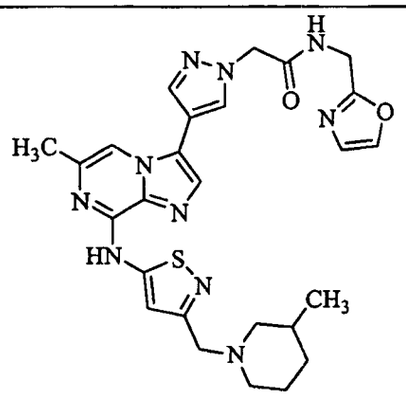
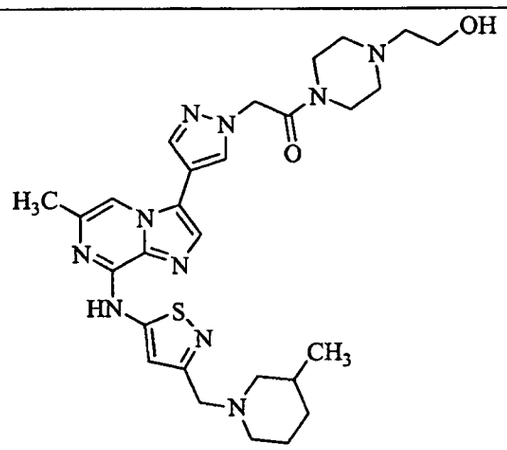
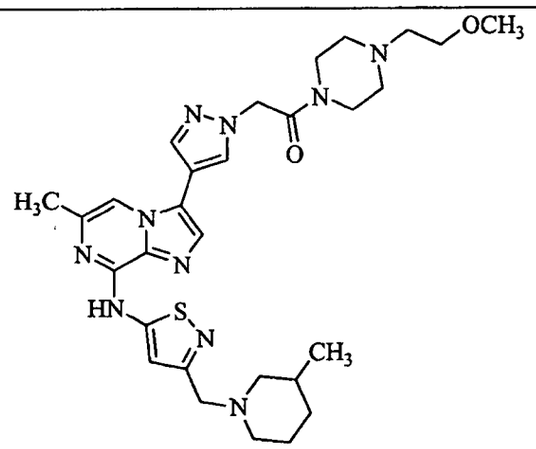
6-4		623.2	624.6	5.34
6-5		623.2	624.6	5.35
6-6		623.2	624.5	5.39

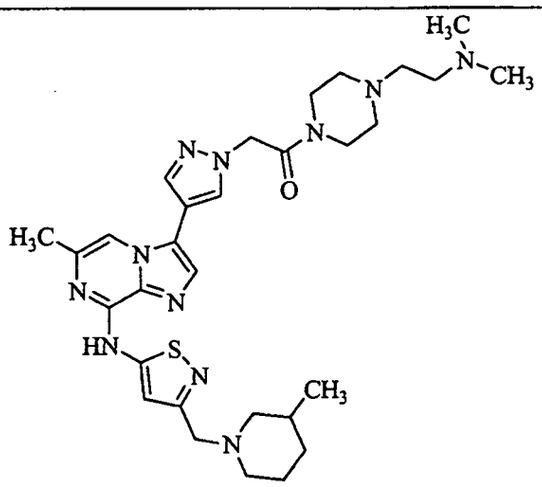
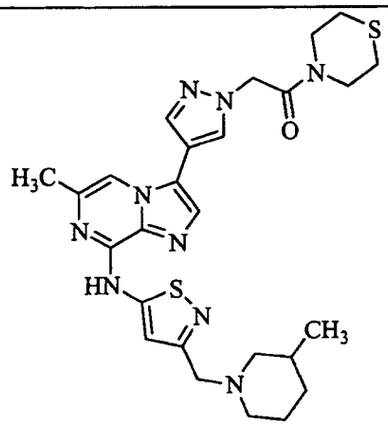
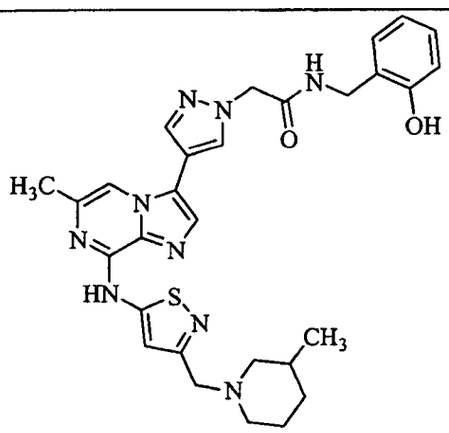
6-7		585.2	586.9	4.96
6-8		585.2	586.3	4.85
6-9		585.2	586.2	4.82

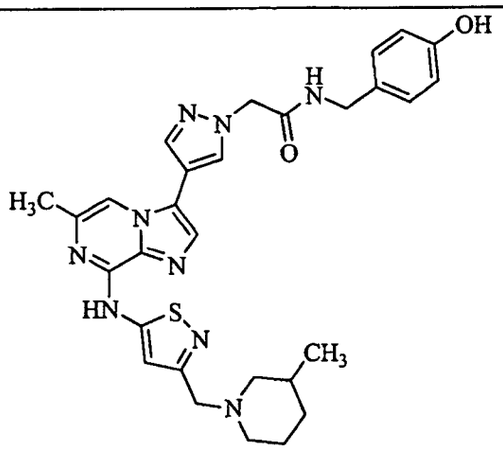
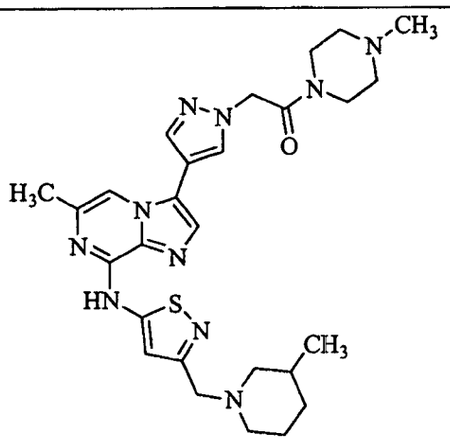
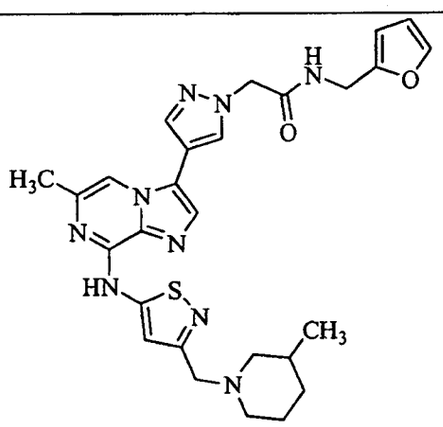
6-10		598.3	599.8	3.71
6-11		571.2	572.4	5.12
6-12		571.2	572.4	4.98
6-13		571.2	572.5	4.87

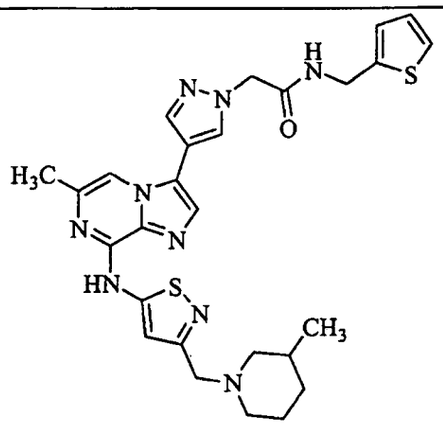
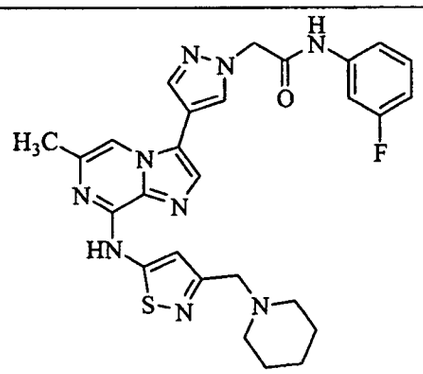
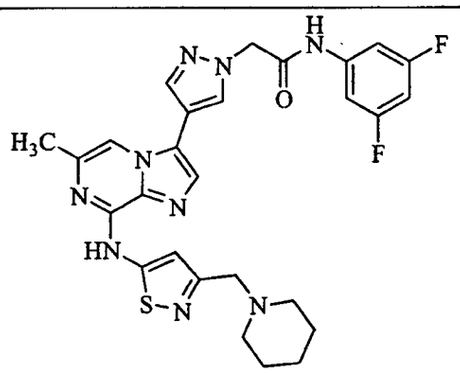
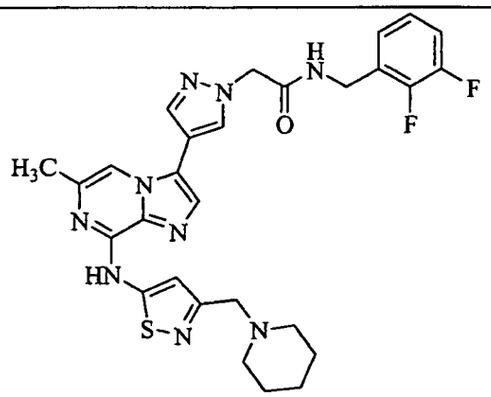
6-14		542.2	543.7	3.93
6-15		542.2	543.6	3.60
6-16		542.2	543.6	3.67
6-17		559.6	260.2	5.10

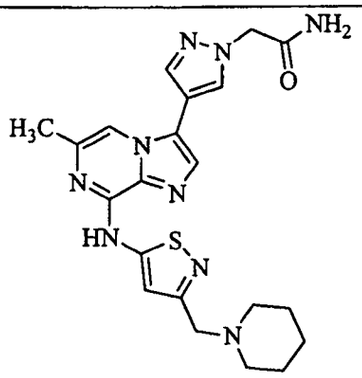
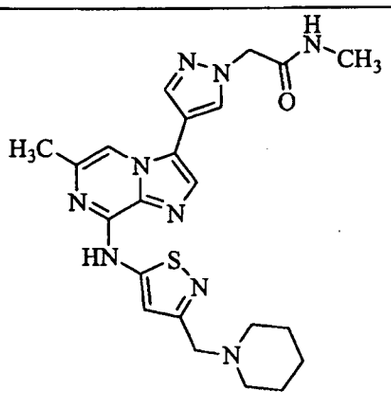
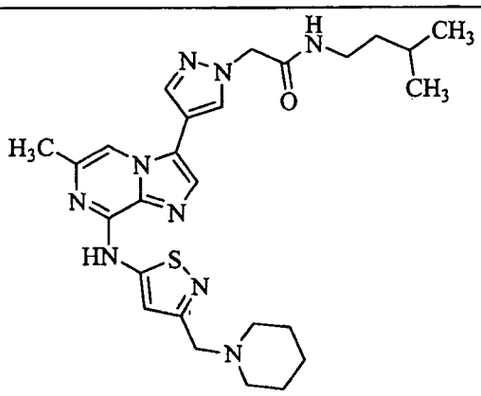
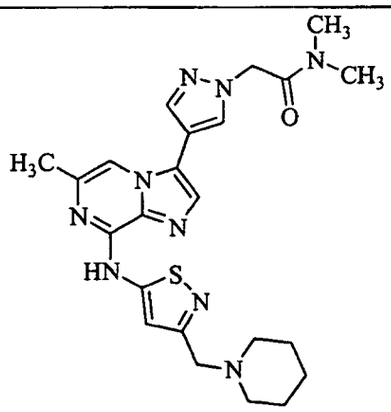
6-18		559.6	560.3	5.13
6-19		577.6	578.9	5.26
6-20		563.6	564.7	5.43
6-21		563.6	564.7	5.34

6-22		546.6	547.6	3.96
6-23		578.7	579.8	3.39
6-24		592.7	593.9	3.52

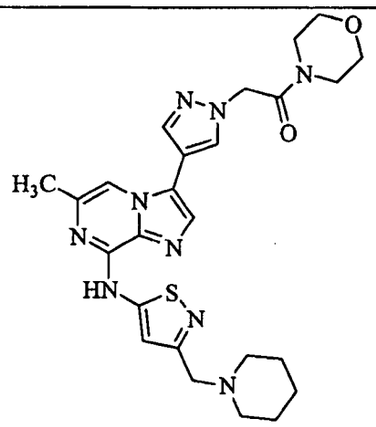
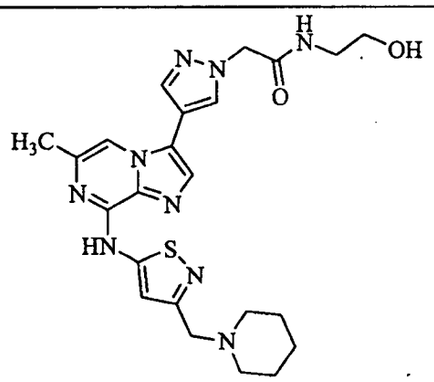
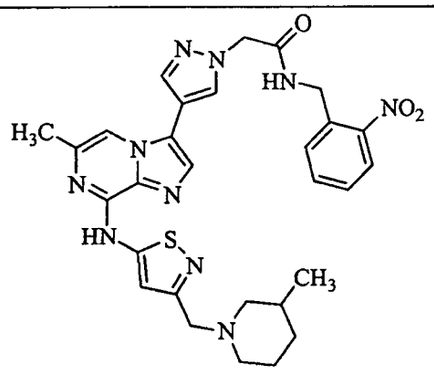
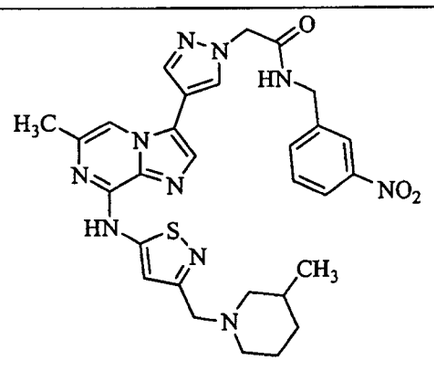
6-25		605.8	606.8	3.35
6-26		551.7	552.8	4.47
6-27		571.7	572.5	4.59

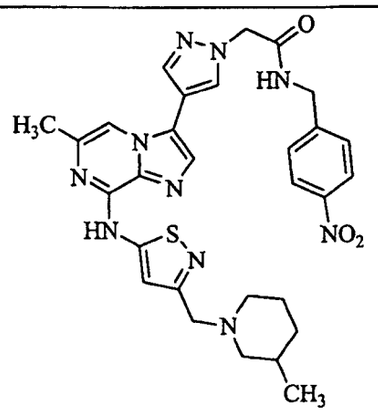
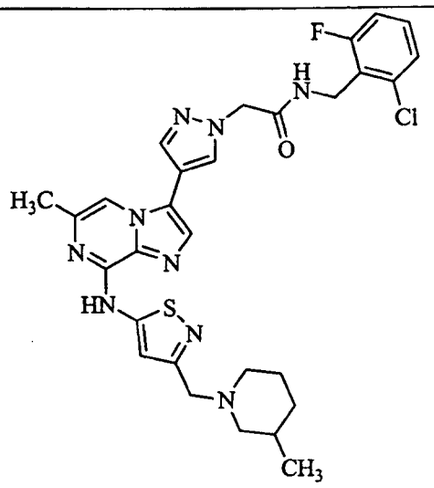
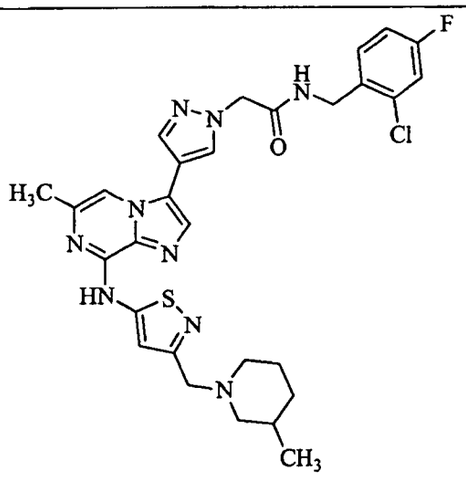
6-28		571.7	572.4	4.26
6-29		548.7	549.8	3.45
6-30		545.6	546.5	4.53

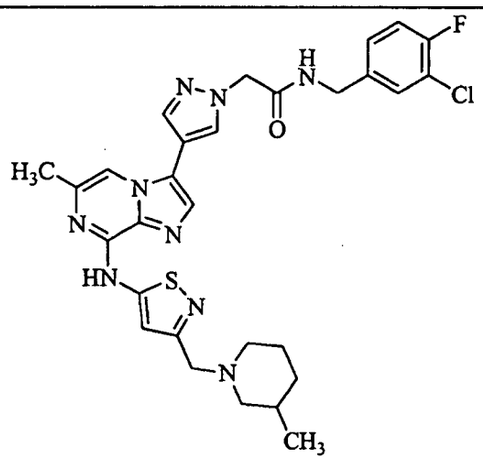
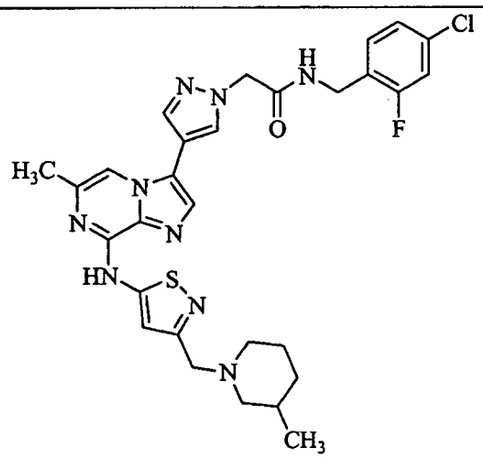
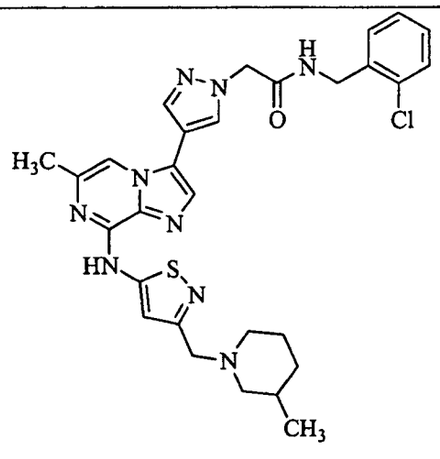
6-31		561.7	562.1	4.72
6-32		545.2	546.5	5.08
6-33		563.2	564.7	5.32
6-34		577.2	578.9	4.97

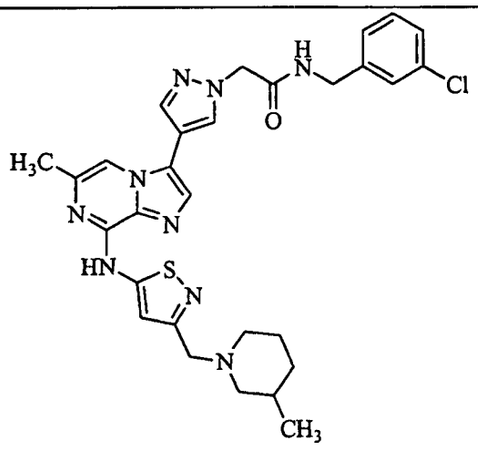
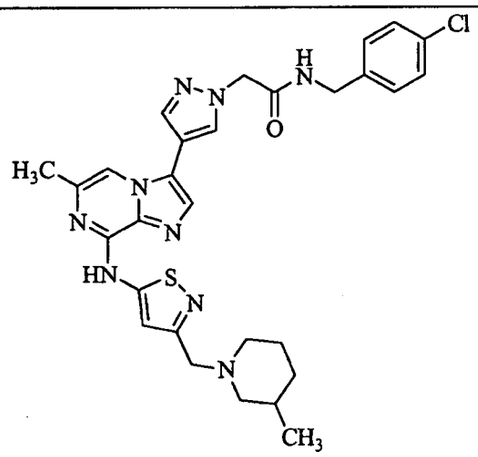
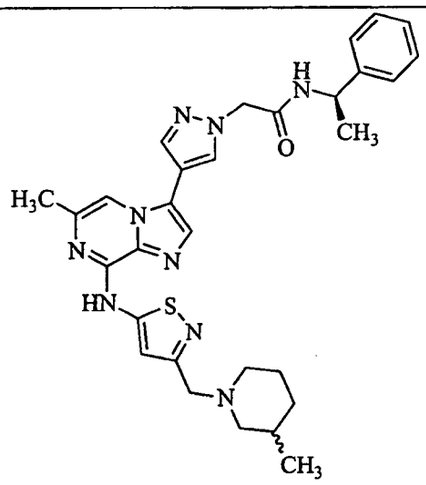
6-35		451.1	452.2	3.44
6-36		465.2	466.7	3.57
6-37		521.2	522.9	4.71
6-38		479.2	480.1	3.73

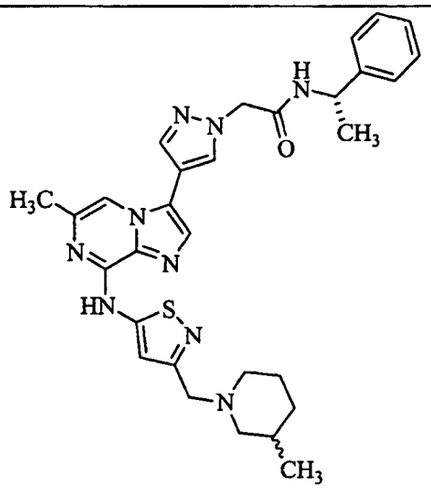
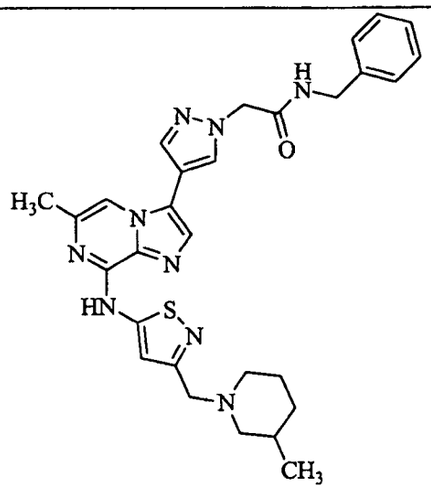
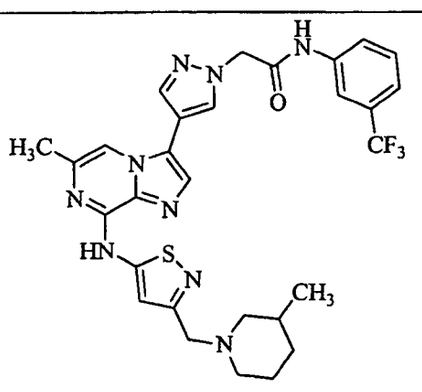
321

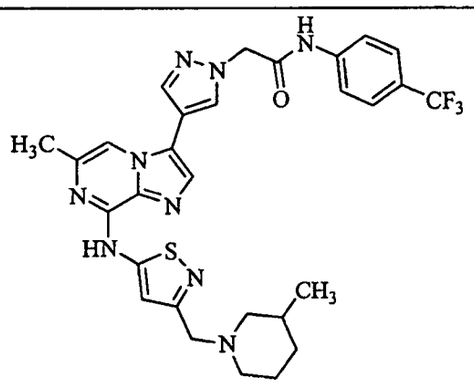
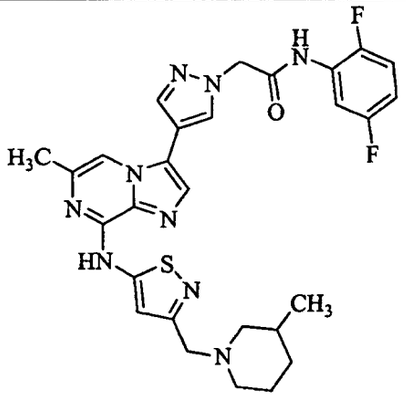
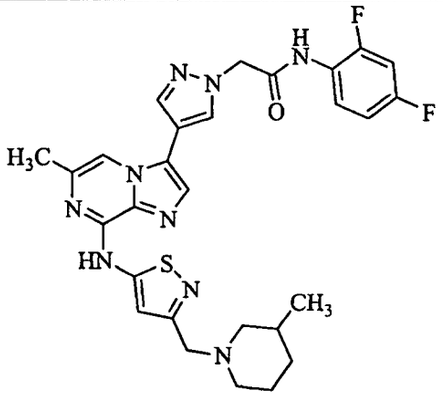
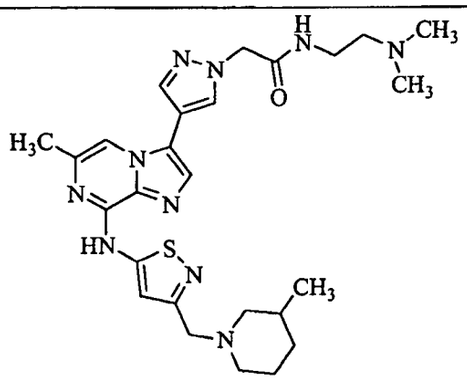
6-39		521.2	522.9	3.73
6-40		495.2	496.9	3.42
6-41		600.2	601.7	4.91
6-42		600.2	601.6	4.90

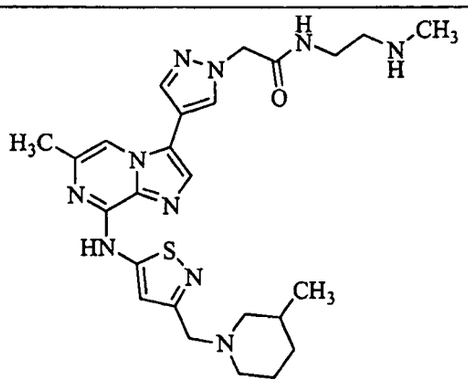
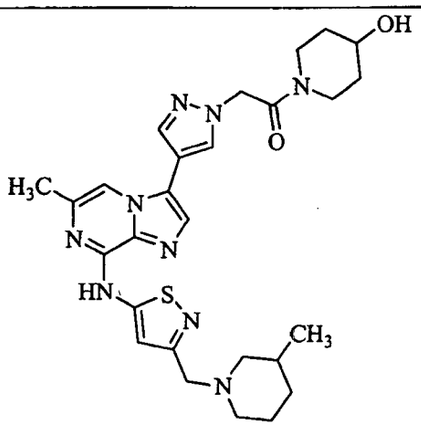
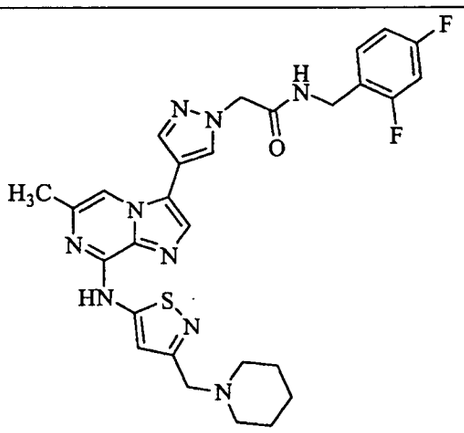
6-43		600.2	601.6	4.90
6-44		607.2	608.5	5.12
6-45		607.2	608.4	5.23

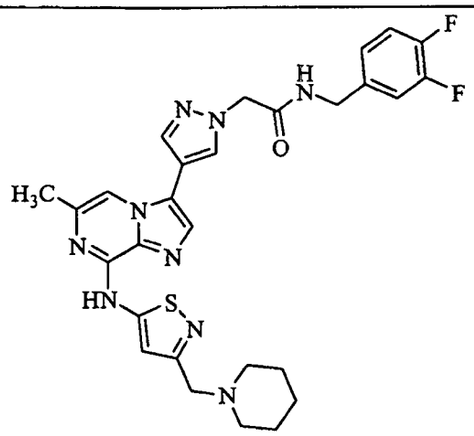
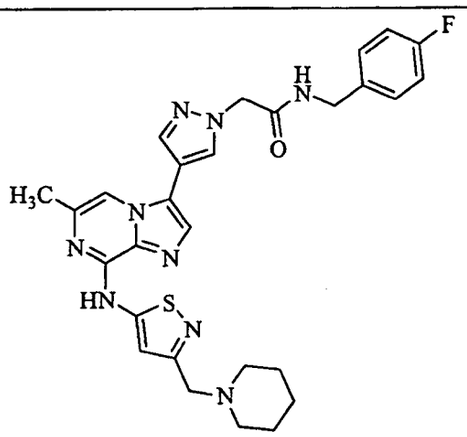
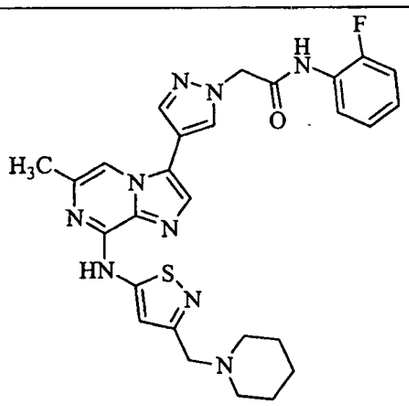
6-46		607.2	609.4	5.23
6-47		607.2	609.4	5.27
6-48		589.2	591.8	5.15

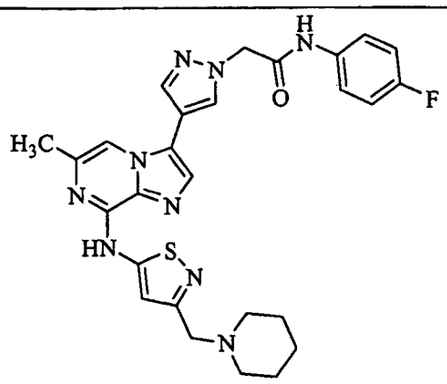
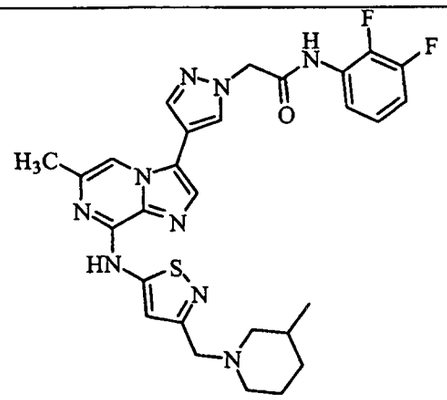
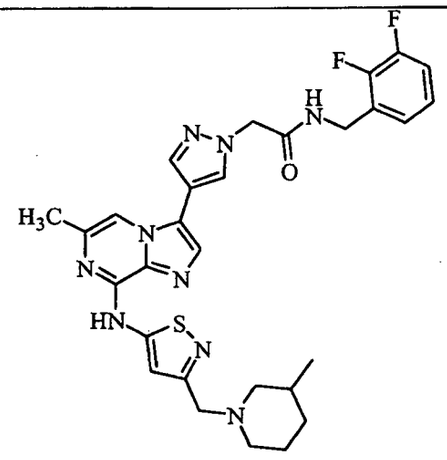
6-49		589.2	591.8	5.16
6-50		589.2	591.8	5.17
6-51		569.3	570.7	5.01

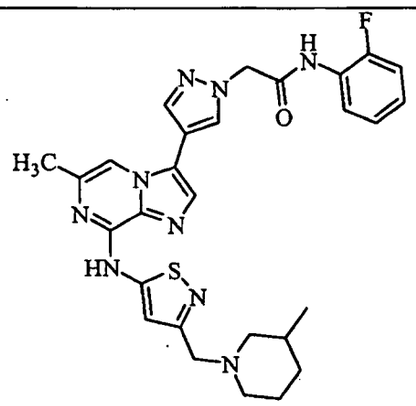
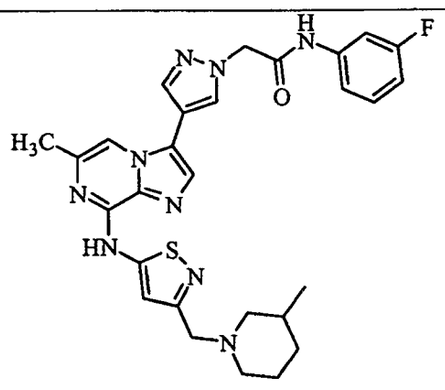
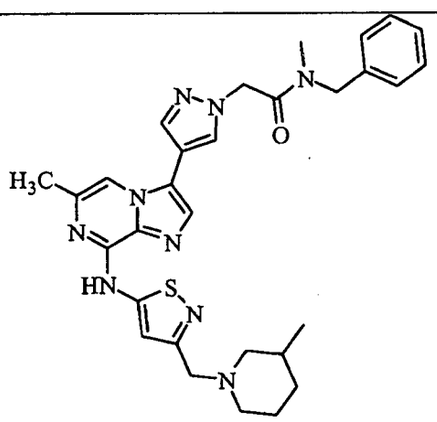
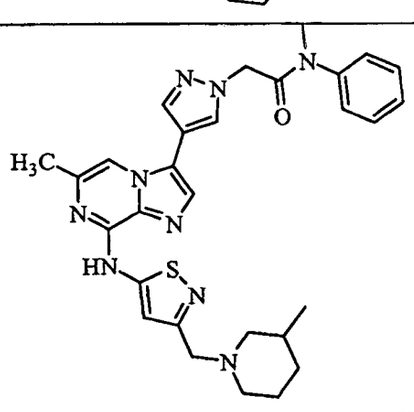
6-52		569.3	570.7	4.99
6-53		555.3	556.3	4.82
6-54		609.6	610.4	5.54

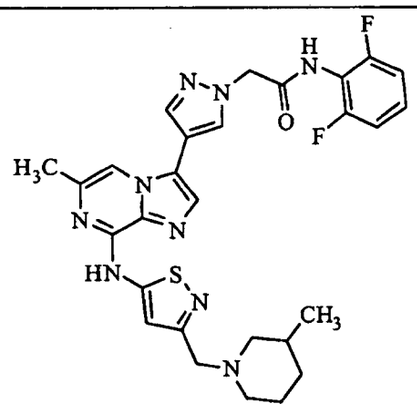
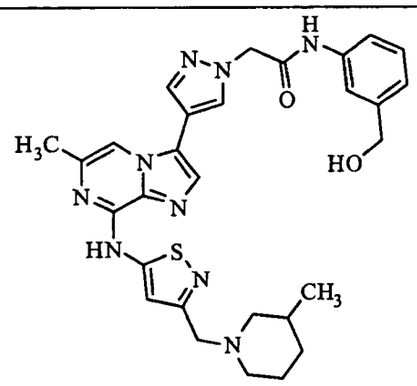
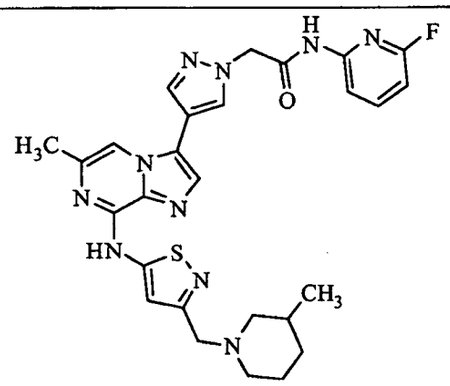
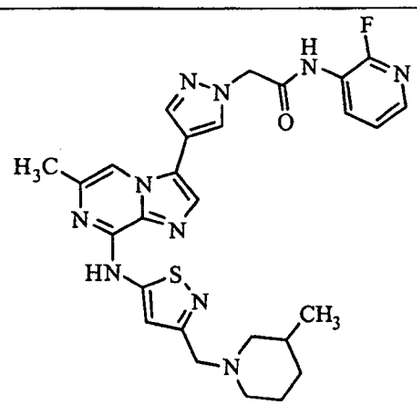
6-55		609.6	610.6	5.59
6-56		577.6	578.8	5.17
6-57		577.6	578.9	5.03
6-58		536.7	537.7	3.45

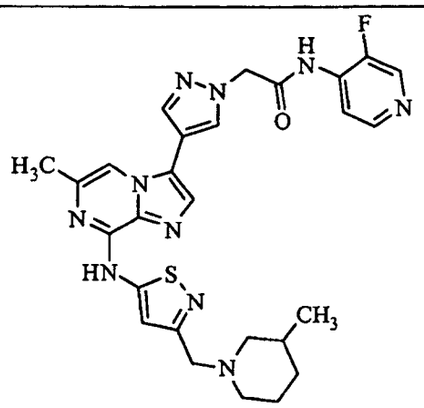
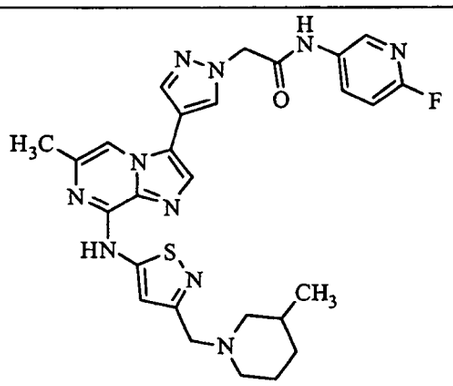
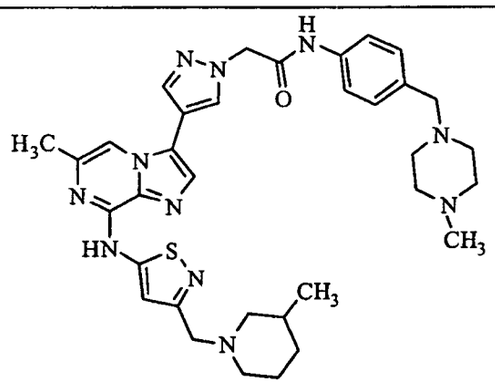
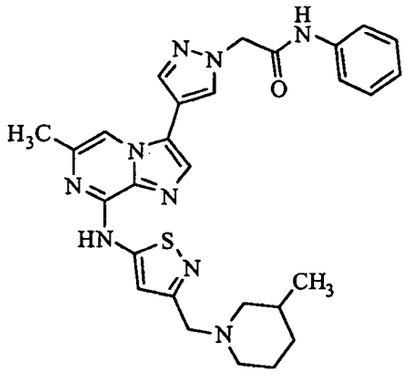
6-59		522.6	523.9	3.43
6-60		549.6	550.7	3.76
6-61		577.22	578.9	5.20

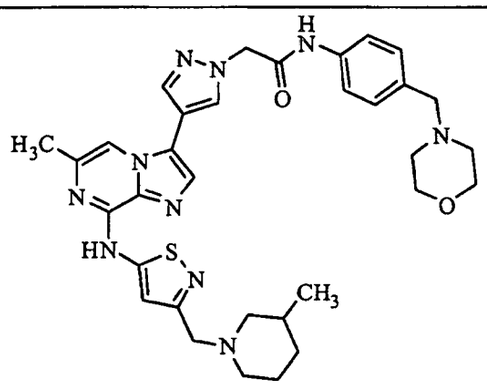
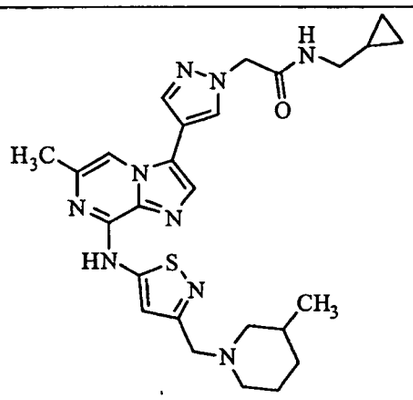
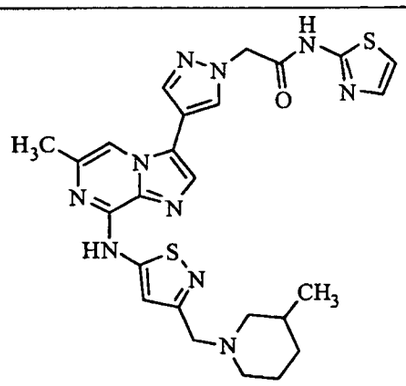
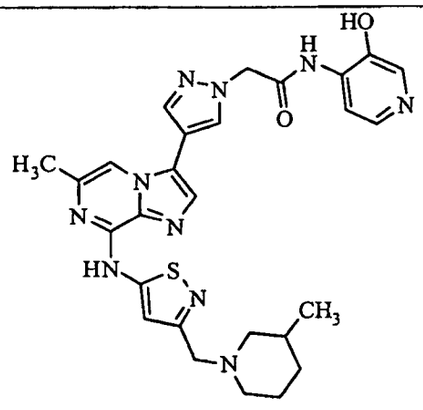
6-62		577.22	578.9	5.25
6-63		559.23	560.2	5.12
6-64		545.21	546.5	5.17

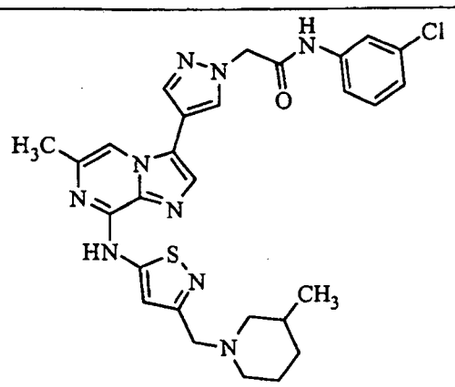
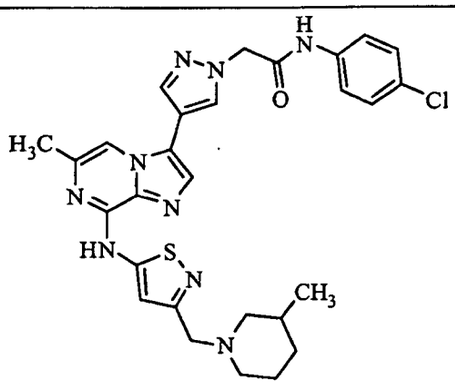
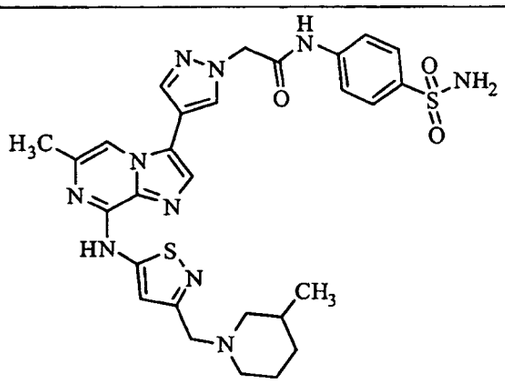
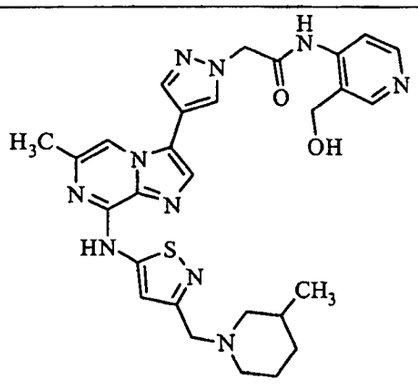
6-65		545.21	546.4	5.21
6-66		577.6	578.9	5.14
6-67		591.6	592.8	5.03

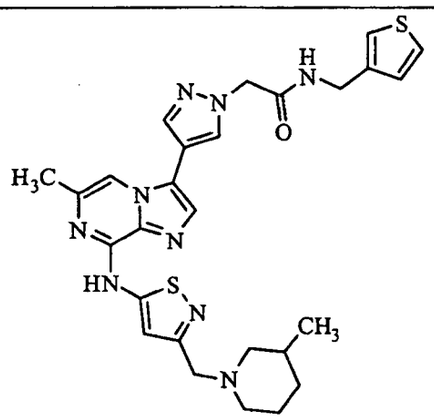
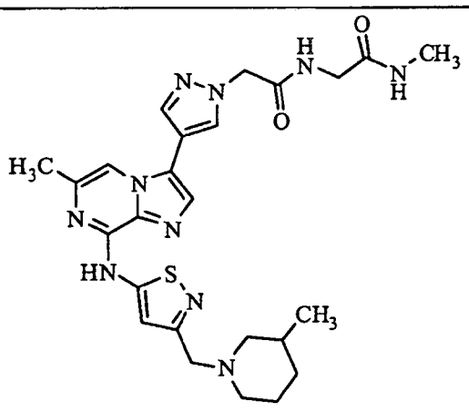
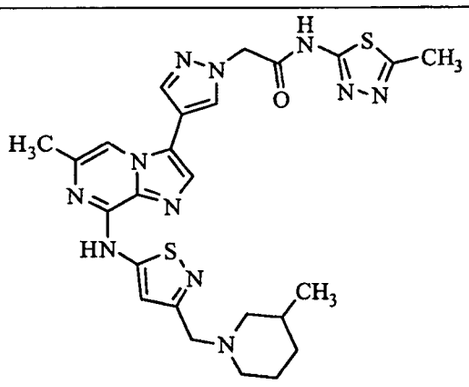
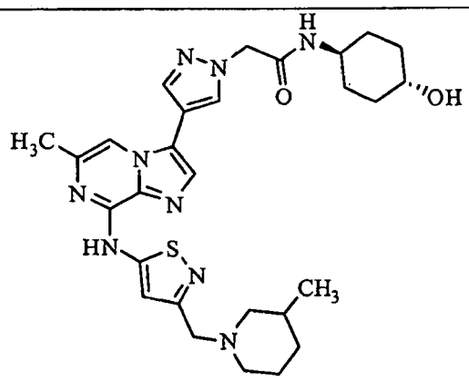
6-68		559.6	560.4	5.00
6-69		559.6	560.4	5.11
6-70		569.7	570.6	5.05
6-71		555.6	556.4	4.96

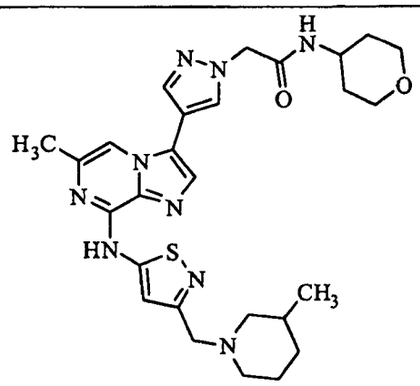
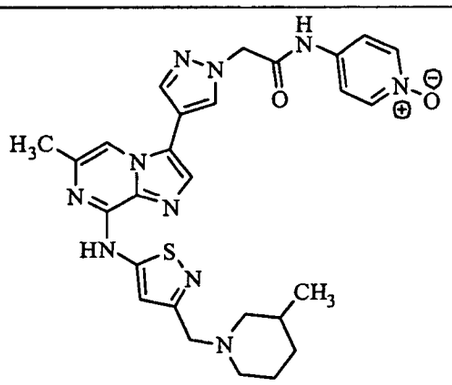
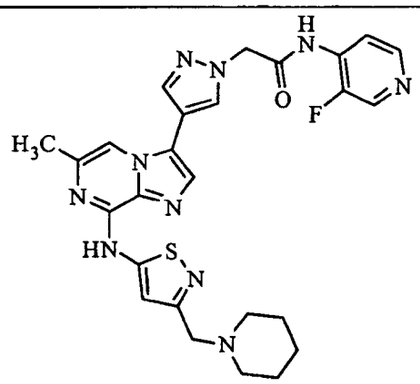
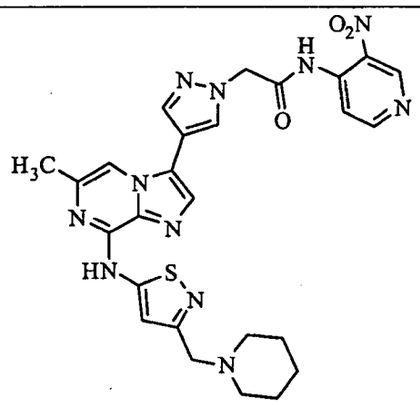
6-72		577.6	578.3	4.85
6-73		571.6	572.4	4.33
6-74		560.6	561.3	4.92
6-75		560.6	561.2	4.52

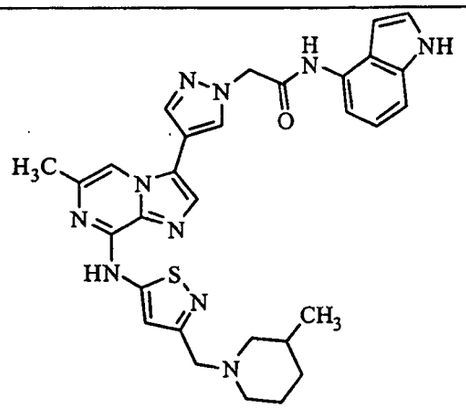
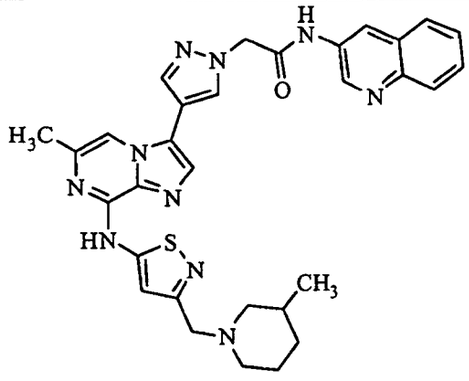
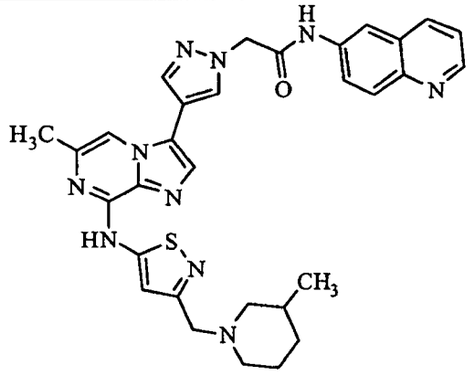
6-76		560.6	561.2	3.75
6-77		560.6	561.3	4.53
6-78		653.8	654.8	3.63
6-79		541.6	542.6	4.91

6-80		640.8	641.6	3.84
6-81		519.6	520.4	4.42
6-82		548.6	549.6	4.44
6-83		558.6	559.4	3.79

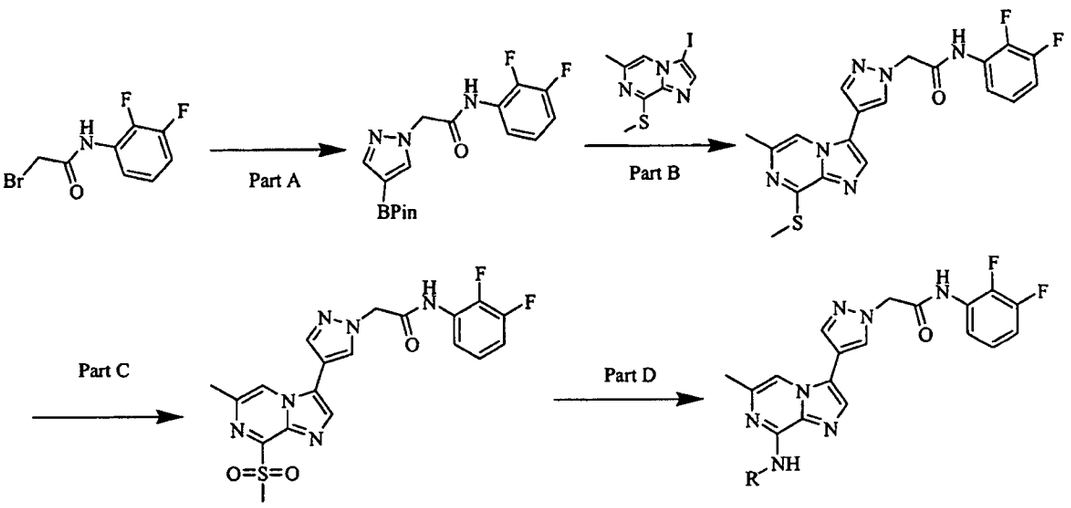
6-84		576.1	576.8	5.41
6-85		576.1	576.8	5.37
6-86		620.7	621.7	4.28
6-87		572.6	573.3	3.77

6-88		561.7	562.3	4.71
6-89		536.6	537.6	3.69
6-90		563.7	564.9	4.24
6-91		563.7	564.8	3.89

6-92		549.6	550.8	3.98
6-93		558.6	559.5	3.72
6-94		546.6	547.7	3.52
6-95		573.6	574.5	4.47

6-96		566.6	567.7	4.63
6-97		592.7	593.9	4.16
6-98		592.7	593.9	3.84

EXAMPLE 7



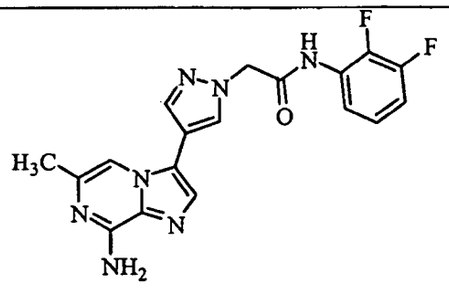
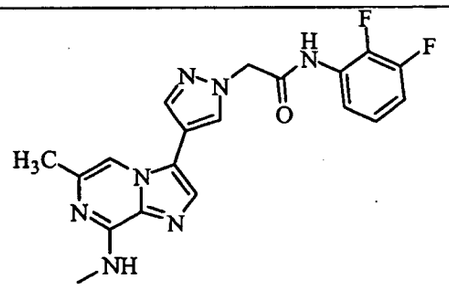
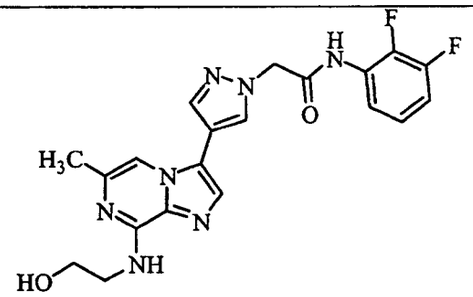
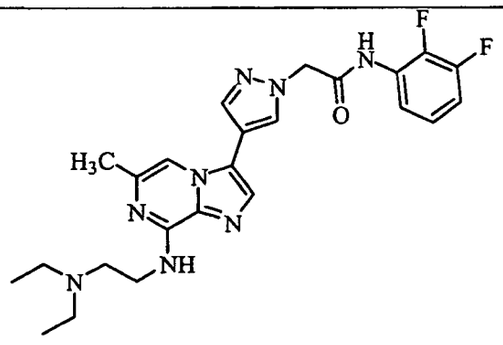
Part A: To a solution of 4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (2.2 g, 11.32) and bromide (2.83 g, 11.32 mmol) in DMA (5 mL) was added potassium carbonate (1.9 g, 13.6 mmol). The mixture was heated at 60C for 20 hr. To the reaction mixture was added half sat'd ammonium chloride and ethyl acetate. The organic phase was washed with water (2x), brine and dried (sodium sulfate). Concentration and purification by chromatography (50% ethyl acetate in hexanes) afforded the title compound as a pale yellow solid. (2.1 g, 51%). ^{1}H NMR (300 MHz, DMSO-d6) δ 10.3 (1H, br s), 7.95 (1H, s), 7.7-7.6 (1H, app t), 7.59 (1H, s), 7.1-7.2 (1H, m), 5.12 (s, 2H), 1.23 (s, 12H).

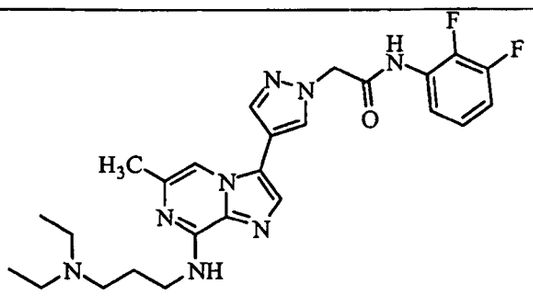
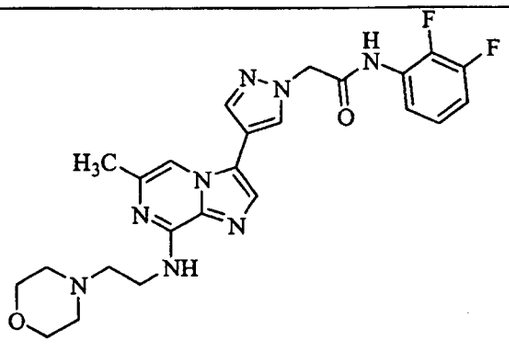
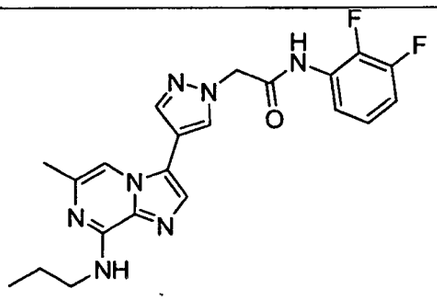
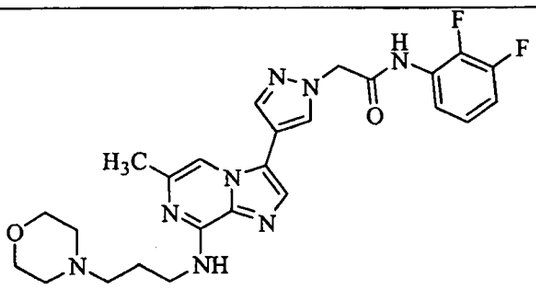
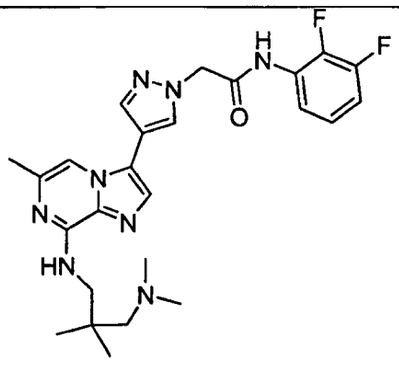
Part B: A mixture of Example 1, Part D (1.49 g), boronate from Example 7, Part A (2.13 g), PdCl2(dppf) (0.398 g), potassium phosphate (2.07 g), in DME (45 mL) and water (5 mL) was heated at 95C overnight. The reaction was allowed to cool, diluted with ethyl acetate and filtered through Celite. The filtrate was washed with water, brine and dried (sodium sulfate). Chromatography afforded the title compound.

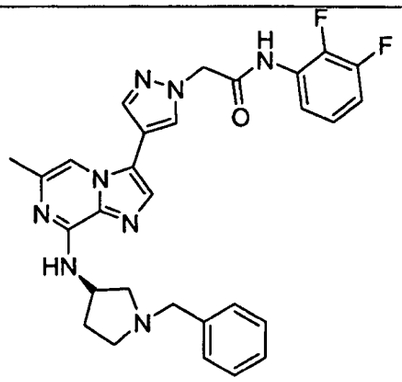
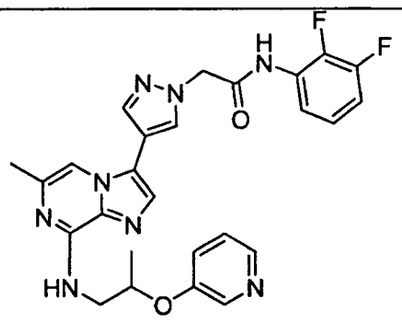
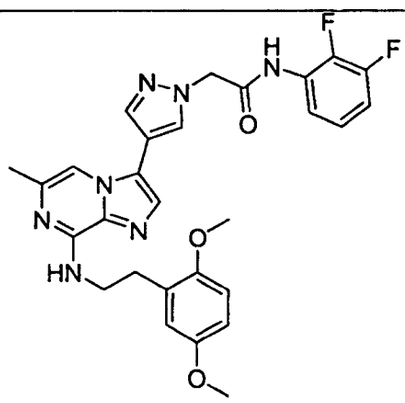
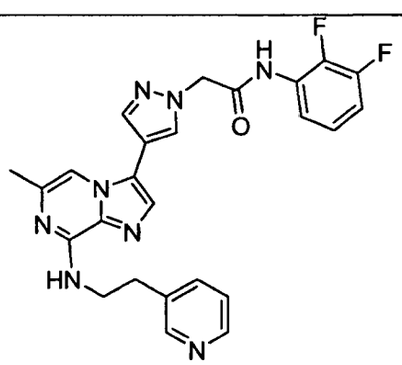
Part C: A solution of the compound from Example 7, Part B (260 mg) in THF (25 mL) at rt was added MCPBA (288 mg) in one portion. After 1 hr at rt, ethyl acetate was added and was washed with sat. sodium bicarbonate (2x), brine and dried (sodium sulfate). Concentration afforded the title compound that was used without further purification.

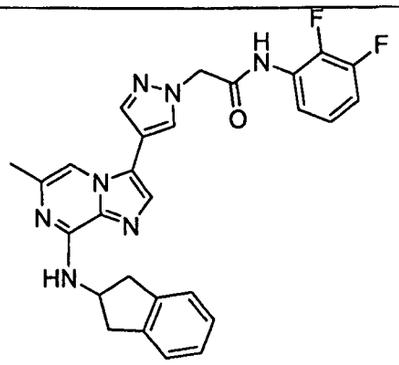
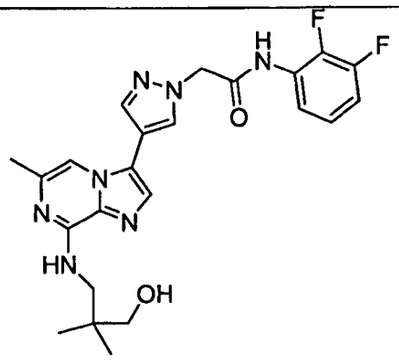
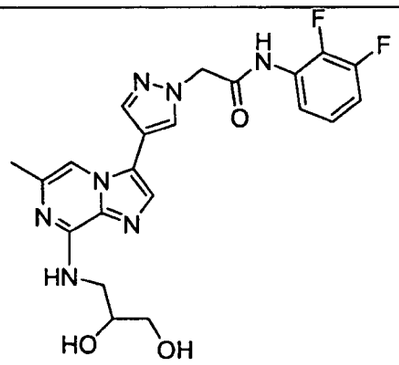
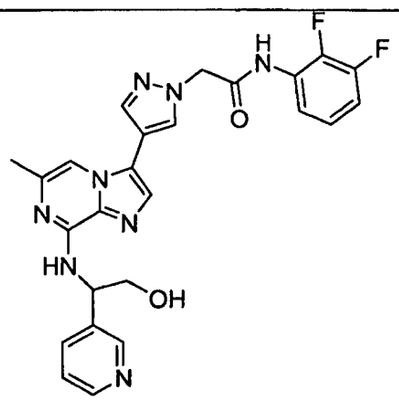
Part D: A solution of the compound from Example 7, Part C (1 equiv), amine (5 equiv), DIEA (5 equiv) in NMP was heated at 50C overnight. The reaction mixture was concentrated and purified by Prep-LC. Using this general procedure compounds listed in Table 2 (shown immediately below) were prepared.

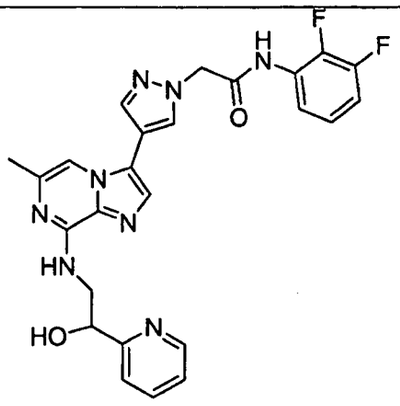
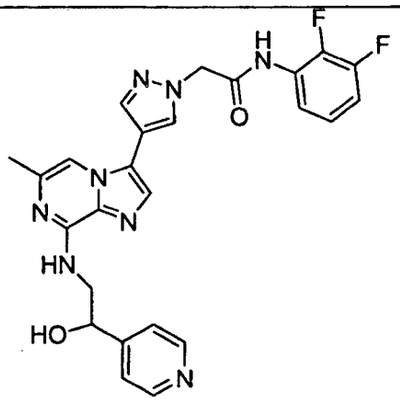
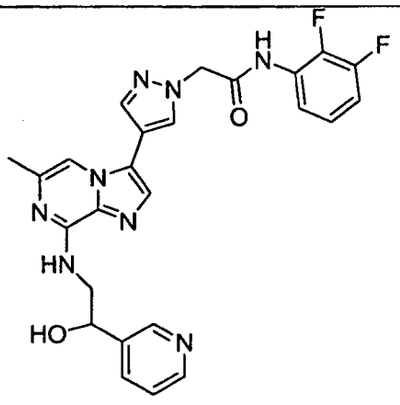
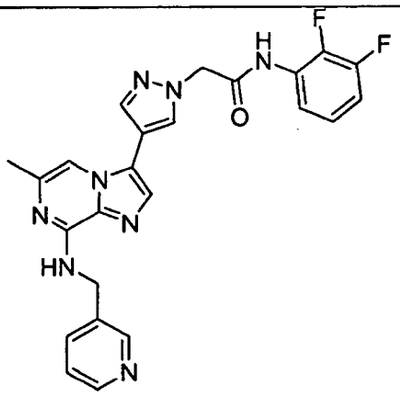
Table 2

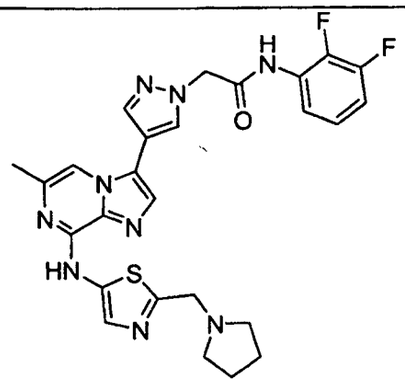
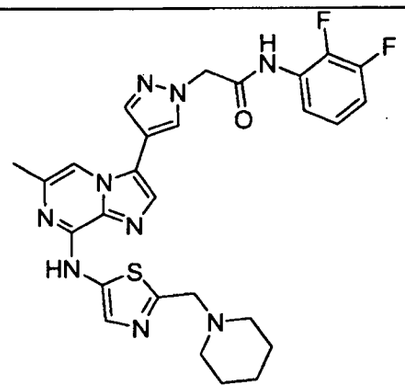
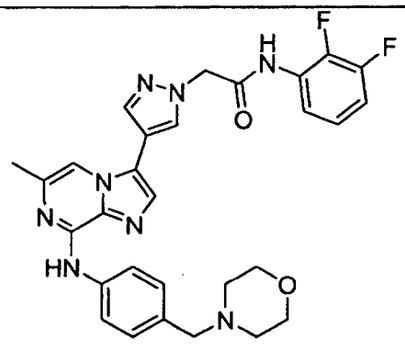
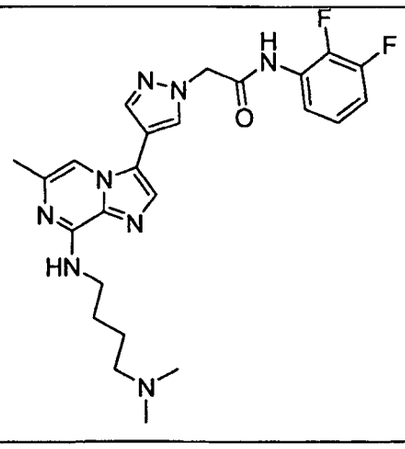
Example	Column 2	MW	MS MH^+ m/z	HPLC t_R
7-1		383.35	384.1	3.01
7-2		397.38	398.2	2.59
7-3		427.4	428.2	2.57
7-4		482.53	483.3	2.90

7-5		496.56	497.3	2.83
7-6		496.51	497.2	3.02
7-7		425.43	426.1	3.00
7-8		510.54	511.1	2.38
7-9		496.56	497.2	2.71

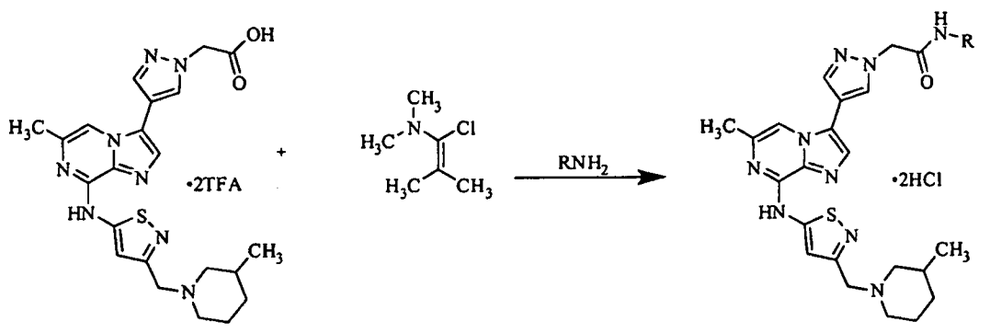
7-10		542.58	543.2	3.22
7-11		518.52	519.2	2.39
7-12		547.56	548.2	4.29
7-13		488.49	489.1	2.44

7-14		499.51	500.2	3.36
7-15		469.49	470.2	3.09
7-16		457.43	458.2	2.95
7-17		504.49	505.2	2.31

7-18		504.49	505.1	2.60
7-19		504.49	505.1	2.37
7-20		504.49	505.1	2.15
7-21		474.47	475.1	2.56

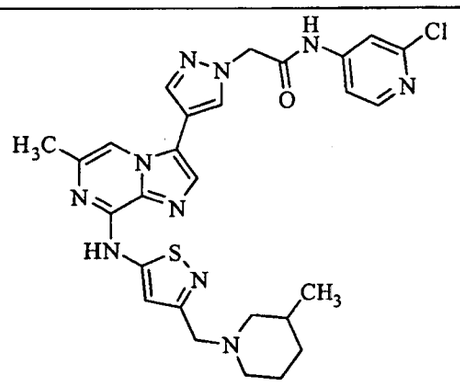
7-22		549.2	550.2	3.12
7-23		563.2	564.2	3.21
7-24		558.2	559.2	1.42
7-25		482.53	483.3	2.36

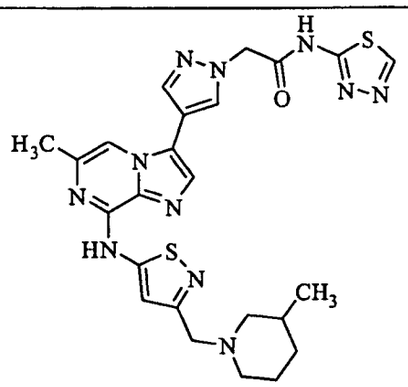
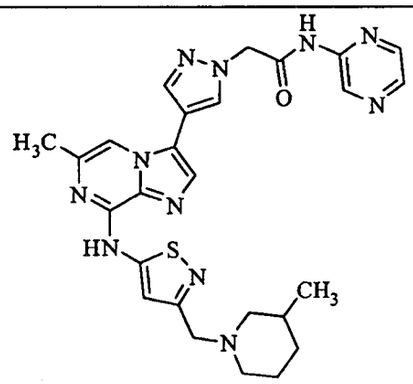
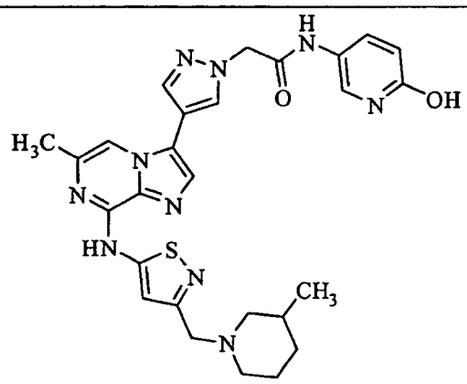
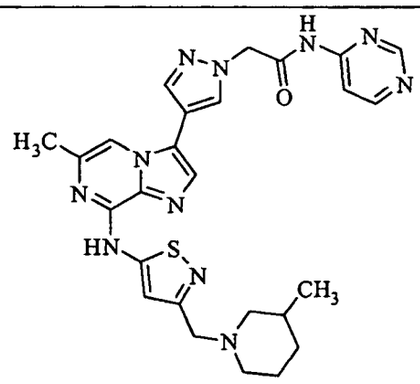
EXAMPLE 8

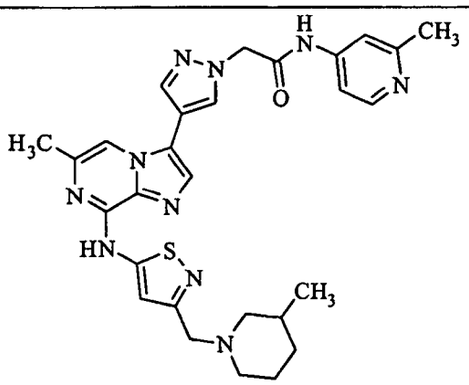


To a stirring suspension of carboxylic acid (1 equiv) in dichloromethane at 0 °C was added 1-chloro-N,N-2-trimethyl-1-propenylamine (5 equiv). After stirring for 1 hour the amine was added as a solution in dichloromethane or pyridine. When the reaction was deemed complete by HPLC analysis the mixture was concentrated under reduced pressure. Purification by prep-HPLC and conversion to the hydrochloride salt provided the compounds listed in Table 3(shown immediately below).

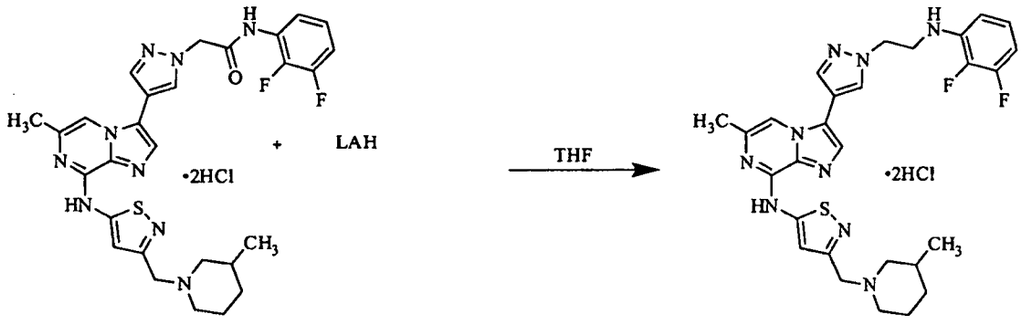
Table 3

Example	Column 2	MW	MS MH^+ m/z	HPLC t_R
8-1		577.1	587.0	4.64

8-2		549.6	550.9	4.11
8-3		543.6	544.6	4.15
8-4		558.6	559.4	3.73
8-5		543.6	544.5	6.99

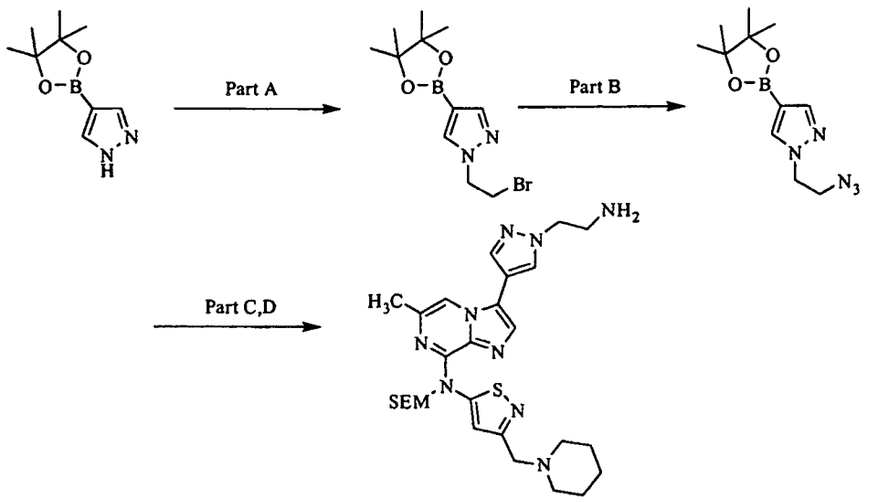
8-6		556.6	557.3	3.73

EXAMPLE 9



Lithium aluminum hydride (2 mg, 2.2 equiv) was added to a stirring suspension of amide (14 mg, 1 equiv) in THF (1 mL) at room temperature. HPLC analysis after 15 minutes showed no starting material so reaction was quenched with methanol, concentrated under reduced pressure, purified by prep-HPLC, and conversion to the hydrochloride salt afforded the title compound as a white solid 6.5 mg (47%)). ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.3 (s, 1H), 10.1 (bs, 1H), 8.41 (s, 1H), 8.03 (s, 1H), 7.89 (m, 2H), 7.30 (s, 1H), 6.97 (m, 1H), 6.55 (m, 2H), 4.39 (m, 4H), 3.67 (m, 2H), 3.39 (m, 2H), 2.80 (m, 2H), 2.48 (s, 3H), 1.79 (m, 4H), 1.05 (m, 1H), 0.89 (m, 3H). HPLC t_R = 5.58 min (UV $_{254nm}$). Mass calculated for formula $C_{28}H_{31}F_2N_9S$ 563.24; observed MH^+ (ESI MS) 564.8 (m/z).

EXAMPLE 10



Part A: Potassium hydroxide (1.45 g, 10.0 equiv) was added to a stirring solution of 4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (500 mg, 1.00 equiv) in DMSO (5 mL) at room temperature. After stirring for 1 hour, 1,2-dibromoethane (9.69 g, 20.0 equiv) was added. The reaction was stirred for 16 hours at which time TLC indicated no starting material remained so the reaction was quenched with water (10 mL) and extracted with ethyl acetate (3 x 15 mL). The combined organics were washed with brine (20 mL), dried over sodium sulfate, filtered, concentrated under reduced pressure, and purification by silica gel chromatography (12g SiO_2, dichloromethane to 5% methanol in dichloromethane) afforded the desired boronate as a yellow oil 350 mg (45%).

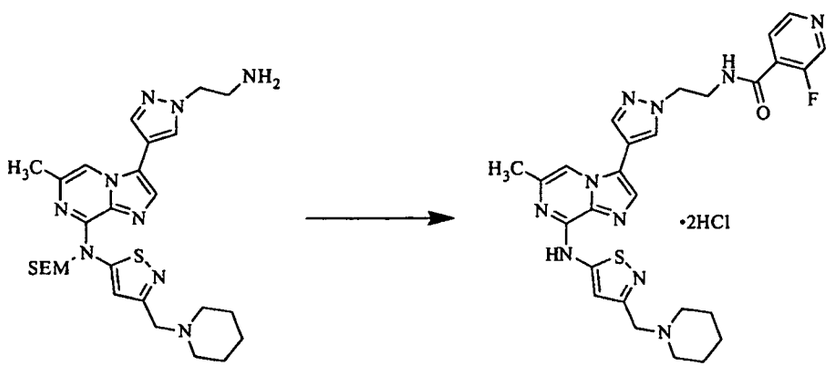
Part B: A mixture of the boronate from example 10 part A (250 mg, 1.00 equiv), sodium azide (108 mg, 2.00 equiv), and sodium iodide (124 mg, 1.00 equiv) in DMSO (2 mL) was stirred at 50 °C for 2 hours at which time TLC indicated no starting material remained. The reaction was allowed to cool to room temperature, then quenched with water (8 mL) and extracted with ethyl acetate (3 x 15 mL). The combined organics were washed with brine (15 mL), dried over sodium sulfate, filtered, concentrated under reduced pressure, and purification by silica gel chromatography (12g SiO_2, dichloromethane to 5% methanol in dichloromethane) afforded the desired boronate as a yellow solid 170 mg (78%).

Part C: To a mixture of aryl iodide from Part B (315 mg, 1.00 equiv), $PdCl_2$(dppf) (39 mg, 0.10 equiv), and potassium phosphate (228 mg, 2.00 equiv) under nitrogen was added a solution of the boronate from Part B (170 mg, 1.20 equiv) in 1,4-dioxane (1.5 mL), followed by water (0.15 mL). The mixture was stirred at 90 °C for 17 hours at which time TLC

indicated no starting material remained. The reaction was allowed to cool to room then diluted with ethyl acetate (8 mL) and washed with brine (10 mL), dried over sodium sulfate, filtered, concentrated under reduced pressure, and purification by silica gel chromatography (12g SiO_2, dichloromethane to 5% methanol in dichloromethane) afforded the desired azide as a brown solid 125 mg (39%).

Part D: To a stirring solution of azide from Part C (125 mg, 1.00 equiv) in 1,4-dioxane (2 mL) and water (0.2 mL) was added poly-styrene bound triphenylphosphine (84 mg, 1.20 equiv). The reaction was stirred at room temperature for 3 days at which time TLC indicated no starting material remained. The mixture was filtered, the mother liquor concentrated under reduced pressure, and the resulting residue purified by silica gel chromatography (12 g SiO_2, dichloromethane to 10% methanol in dichloromethane) affording the desired amine as a brown oil 77 mg (64%).

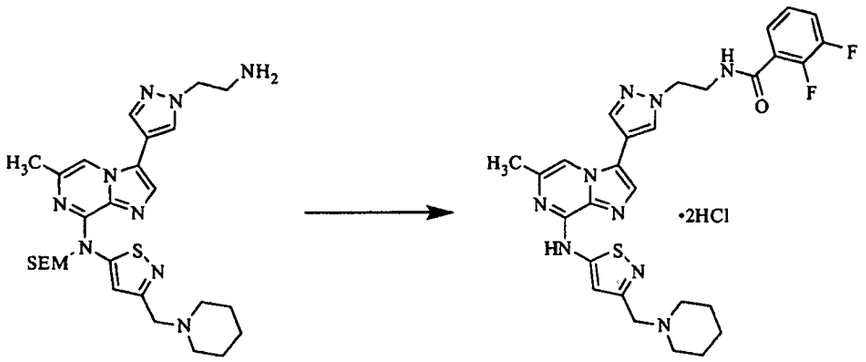
EXAMPLE 11



N-Methyl morpholine (14 mg, 2.00 equiv) was added to a stirring mixture of carboxylic acid (14 mg, 1.50 equiv) and HATU (39 mg, 1.50 equiv) in DMF (0.5 mL). After 30 minutes, the amine from example 10 (38.5 mg, 1.00 equiv) was added as a solution in DMF (0.5 mL). The mixture was stirred for 5 hours at which time HPLC indicated no starting material remained. The mixture was concentrated and the residue dissolved in 1,4-dioxane (1 mL). A solution on HCl in dioxane (1 mL, 4M in dioxane) was added and the mixture was sonicated for 1.5 hours at which time HPLC indicated no starting material remained. The mixture was concentrated under reduced pressure, purified by prep-HPLC, and conversion to the HCl salt afforded the desired compound as a yellow solid 6 mg (14%). ^{1}H NMR (300 MHz, CD_3OD) δ 8.90 (m, 1H), 8.72 (m, 1H), 8,36 (s, 1H), 8.24 (s, 1H), 8.01(m, 3H), 7.32 (s, 1H), 4.58 (m, 2H), 4.42 (s, 2H), 3.94 (m, 2H), 3.60 (m, 2H), 3.09 (m, 2H), 2.61 (s, 3H), 1.81 (m, 6H), 1.55 (m,

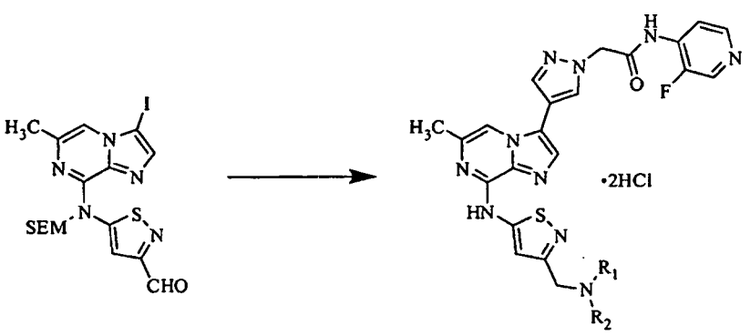
2H). HPLC t_R = 3.97 min (UV $_{254nm}$). Mass calculated for formula $C_{27}H_{29}FN_{10}OS$ 560.22; observed MH^+ (ESI MS) 561.3 (m/z).

EXAMPLE 12



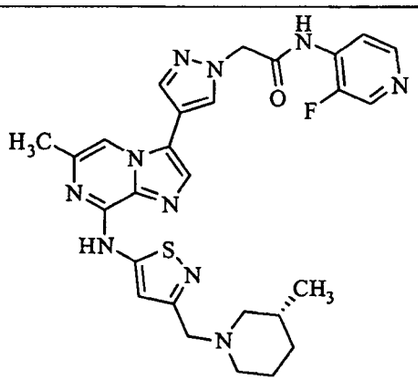
To a stirring solution of amine from example 10 (38.5 mg, 1.00 equiv) and triethylamine (14 mg, 2.00 equiv) in dichloromethane (0.75 mL) was added 2,3-difluorobenzoylchloride (13 mg, 1.10 equiv) dropwise. HPLC analysis after 4 hours showed no starting material so reaction was quenched with saturated aqueous sodium bicarbonate (2 mL) and then extracted with dichloromethane (3 x 1mL). The combined organics were concentrated and the resulting residue was dissolved in 1,4-dioxane (1 mL) and a solution on HCl in dioxane (1 mL, 4M in dioxane) was added and the mixture was sonicated for 1.5 hours at which time HPLC indicated no starting material remained. The mixture was concentrated under reduced pressure, purified by prep-HPLC, and conversion to the HCl salt afforded the desired compound as a yellow solid 5 mg (11%). ^{1}H NMR (300 MHz, CD_3OD) δ 8.34 (s, 1H), 8.21 (s, 1H), 8.06 (s, 1H), 7.92 (s, 1H), 7.44 (m, 2H), 7.36 (2, 1H), 7.20 (m, 1H), 4.56 (m, 2H), 4.41 (s, 2H), 3.92 (m, 2H), 3.59 (m, 2H), 3.08 (m, 2H), 2.59 (s, 3H), 1.78 (m, 6H). HPLC t_R = 4.61 min (UV $_{254nm}$). ass calculated for formula $C_{28}H_{29}F_2N_9OS$ 577.22; observed MH^+ (ESI MS) 578.8 (m/z).

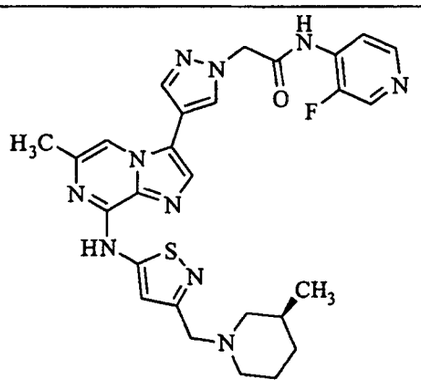
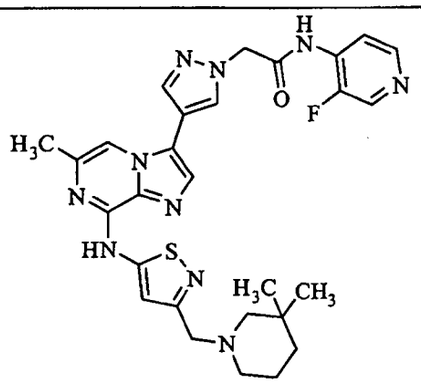
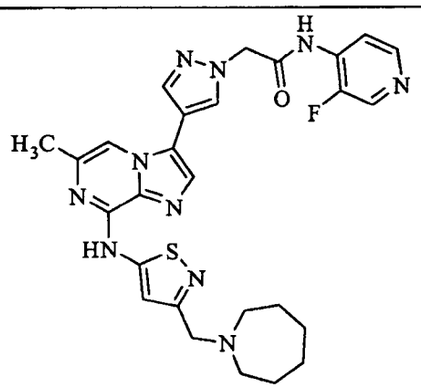
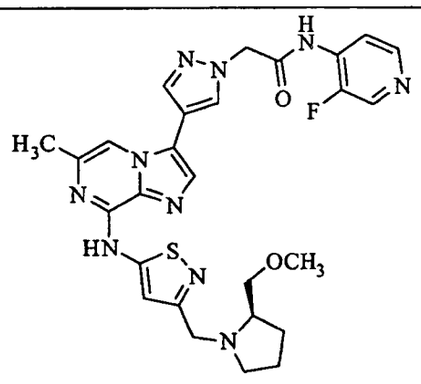
EXAMPLE 13

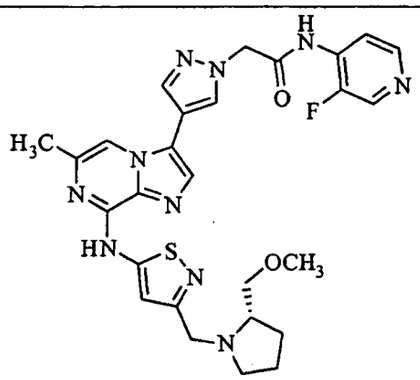
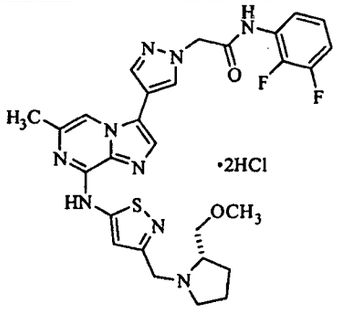
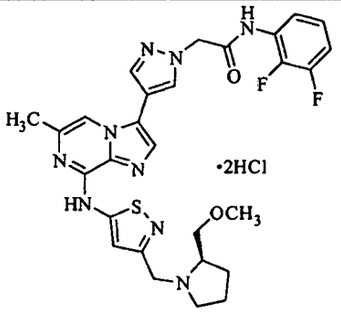


Sodium triacetoxyborohydride (1.50 equiv) was added to a stirring mixture of aldehyde (1.00 equiv), amine (1.20 equiv), and acetic acid (1.00 equiv) in 1,2-dichloroethane at room temperature. The mixture was stirred until no starting material remained as judged by TLC. The reaction was then quenched with 1N NaOH and extracted three times with chloroform. The combined organics were dried over sodium sulfate, filtered, and concentrated. The residue was then added as a solution in dioxane (1 equiv) to a mixture of boronate (1.50 equiv), $PdCl_2$(dppf) (0.10 equiv), and potassium phosphate (2.00 equiv) under nitrogen. Water was added and the mixture was stirred at 90 °C for 17 hours at which time HPLC indicated no starting material remained. The reaction was allowed to cool to room temperature the diluted with ethyl acetate, washed with water, dried over sodium sulfate, filtered, concentrated under reduced pressure, and purification by silica gel chromatography afforded the coupled product. This material was dissolved in 1,4-dioxane, HCl (4N in dioxane) was added and the mixture was sonicated until such time that HPLC indicated no starting material remained. The mixture was concentrated under reduced pressure, purified by prep-HPLC, and conversion to the hydrochloride salt afforded the title compounds as white solids in Table 4(shown immediately below):

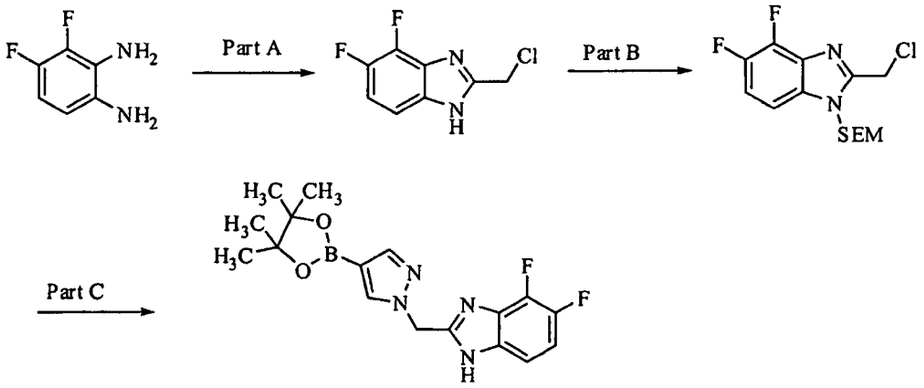
Table 4

Example	Column 2	MW	MS MH^+ m/z	HPLC t_R
13-1		560.6	561.4	3.75

13-2		560.6	561.3	3.78
13-3		574.6	575.6	3.97
13-4		560.6	561.4	3.76
13-5		576.6	578.2	3.63

13-6		576.6	578.2	3.62
13-7		593.7	594.7	5.13
13-8		593.7	594.7	5.15

EXAMPLE 14



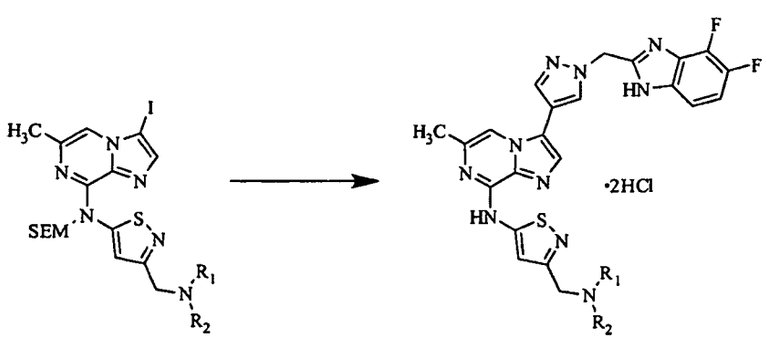
Part A: Chloroacetic acid (5.11 g, 1.3 equiv) was added to a stirring solution of 2-amino-3,4-difluoroaniline (6.00 g, 1 equiv) in 6 N hydrochloric acid (28 mL). After stirring for 18 hours

at 95 °C the reaction was cooled to room temperature, made basic with 10% aqueous potassium carbonate and extracted with ethyl acetate (850 mL). The organic layer was separated, dried over sodium sulfate, filtered, concentrated under reduced pressure, and purification by silica gel chromatography (120 g SiO_2, hexanes to 60% ethyl acetate in hexanes) afforded the desired benzimidazole as a pink solid 6.24 g (74%).

Part B: A mixture of the benzimidazole from example 14 part A (4.18 g, 1.00 equiv), potassium carbonate (8.53 g, 3.00 equiv) in DMF (50 mL) was stirred at room temperature for 5 minutes at which time 2-(trimethylsilyl)ethoxymethyl chloride (4.0 mL, 1.1 equiv) was added. After stirring at room temperature for 18 hours the reaction was quenched with a saturated aqueous solution of sodium bicarbonate (40 mL) and concentrated under reduced pressure to a residue. The residue was diluted with ethyl acetate (500 mL) and washed with water (150 mL), dried over sodium sulfate, filtered, concentrated under reduced pressure, and purification by silica gel chromatography (120 g SiO_2, hexanes to 50% of ethyl acetate in hexanes) afforded the desired benzimidazole as a brown oil 3.11 g (45%).

Part C: To a solution of 4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (1.65 g, 1 equiv), benzimidazole from Example 14 part B (3.11 g, 1.1 equiv) in DMA (57 mL) was added potassium carbonate (3.51 g, 3 equiv). The mixture was heated at 50 °C for 18 hours. The reaction mixture was poured into water (250 mL), extracted with ethyl acetate (500 mL), the organic layer washed with brine (250 mL), dried over sodium sulfate, filtered, concentrated under reduced pressure, and purification by silica gel chromatography (80 g SiO2, hexanes to 50% of ethyl acetate in hexanes) afforded the desired boronate as a off-white solid 2.67 g (64%).

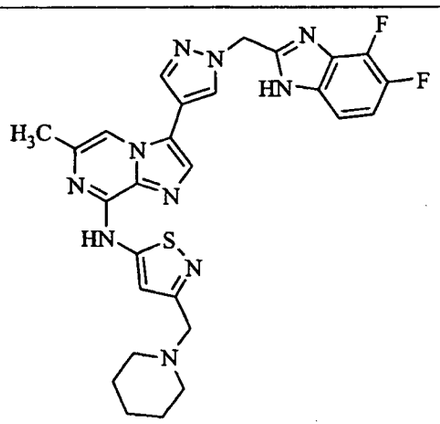
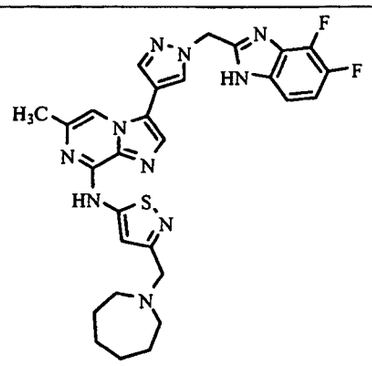
EXAMPLE 15



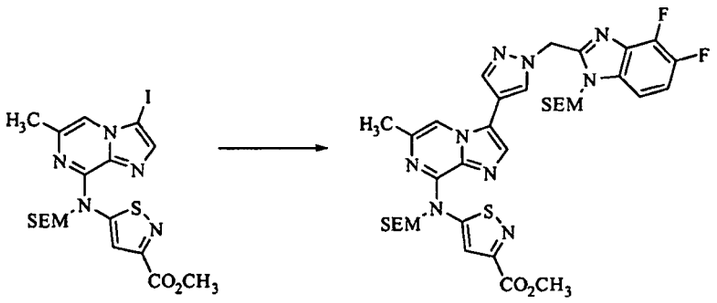
To a mixture of aryl iodide (100 mg, 1.00 equiv), $PdCl_2$(dppf) (12 mg, 0.10 equiv), and potassium phosphate (71 mg, 2.00 equiv) under nitrogen was added a solution of the boronate from Example 14 part C (123 mg, 1.20 equiv) in 1,4-dioxane (2.0 mL), followed by water (0.2

mL). The mixture was stirred at 90 °C for 18 hours at which time TLC indicated no starting material remained. The reaction was allowed to cool to room temperature, then diluted with ethyl acetate (100 mL) and washed with water (30mL), dried over sodium sulfate, filtered, concentrated under reduced pressure, and purification by silica gel chromatography (12 g SiO_2, dichloromethane to 10% methanol in dichloromethane) afforded the desired coupled product. This material was dissolved in 1,4-dioxane, HCl (4N in dioxane) was added and the mixture was sonicated until such time that HPLC indicated no starting material remained. The mixture was concentrated under reduced pressure, purified by prep-HPLC, and conversion to the hydrochloride salt afforded the title compounds as off-white solids in Table 5(shown immediately below):

Table 5

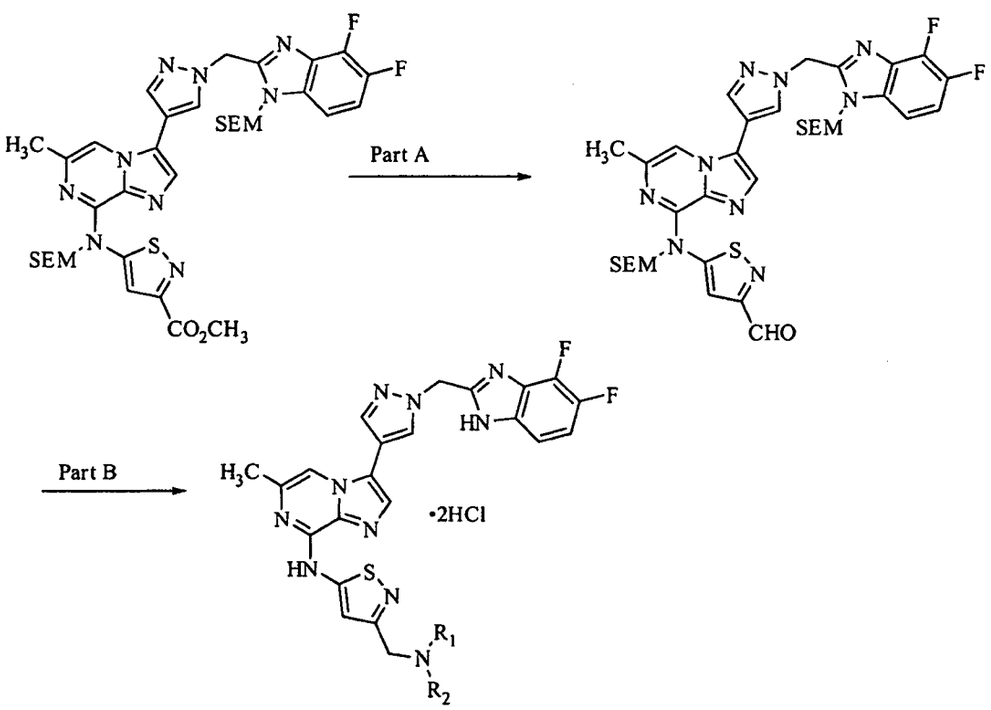
Example	Column 2	MW	MS MH^+ m/z	HPLC t_R
15-1		560.2	561.2	4.74
15-2		574.2	575.7	4.99

EXAMPLE 16



To a mixture of aryl iodide (2.15 g, 1.00 equiv), $PdCl_2(dppf)$ (288 mg, 0.10 equiv), and potassium phosphate (1.67 mg, 2.00 equiv) under nitrogen was added a solution of the boronate from Example 14 part C (2.51 g, 1.20 equiv) in 1,4-dioxane (47 mL), followed by water (4.7mL). The mixture was stirred at 90 °C for 3 hours at which time TLC indicated no starting material remained. The reaction was allowed to cool to room then diluted with ethyl acetate (700 mL) and washed with water (250 mL), dried over sodium sulfate, filtered, concentrated under reduced pressure, and purification by silica gel chromatography (120 g SiO_2, hexanes to 100% ethyl acetate) afforded the desired coupled product as a brown foam 2.04 g (66%).

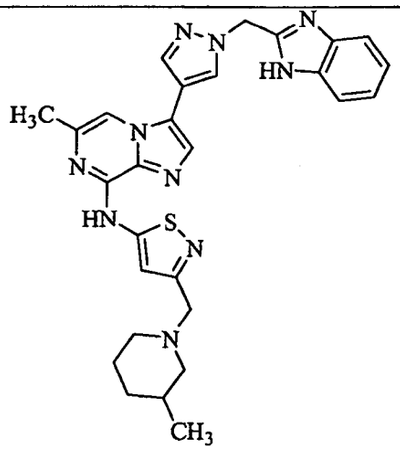
EXAMPLE 17

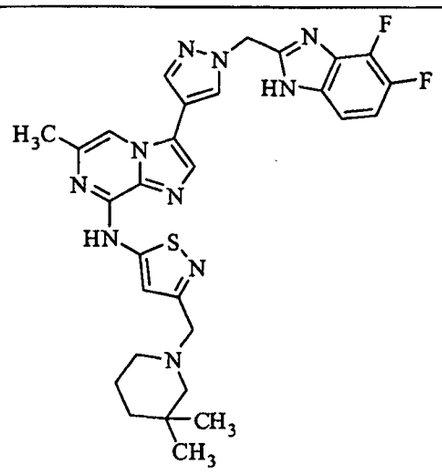
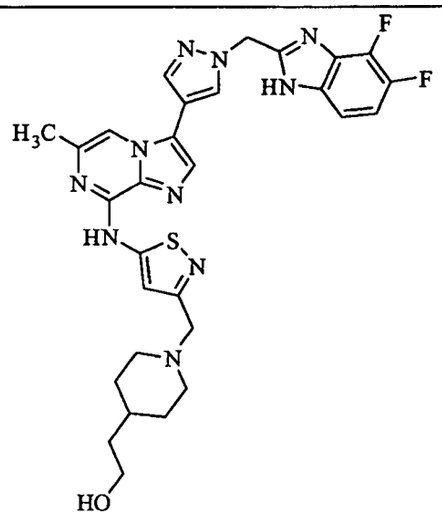
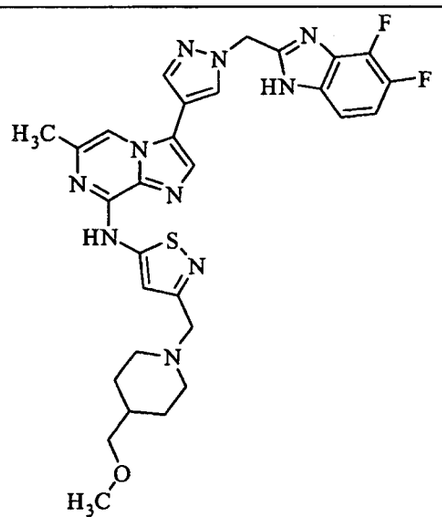


Part A: To a stirring solution of the coupled product from Example 16 (2.04 g, 1 equiv) in tetrahydrofuran (63 mL) at –78 °C was added DIBAL-H (1M in dichloromethane, 6.5 mL, 2.5 equiv) dropwise. The mixture was stirred at –78 °C for 5 hours at which time thin layer chromatography (30% ethyl acetate/hexanes) indicated the reaction was complete. The mixture was quickly poured into stirring saturated aqueous sodium potassium tartrate and stirred at room temperature for 14 hours. The mixture was extracted with ethyl acetate (500 mL), the organic layer separated, dried over sodium sulfate, filtered, and concentrated under reduced pressure affording the aldehyde as a brown foam 1.96 g (100%).

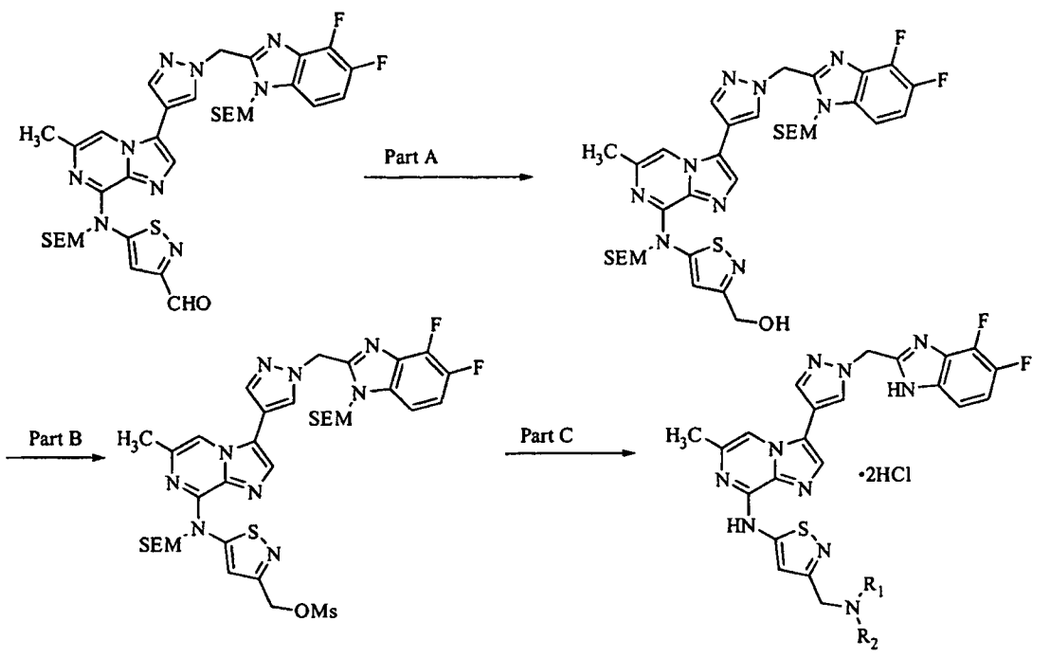
Part B: Sodium triacetoxyborohydride (1.50 equiv) was added to a stirring mixture of aldehyde (1.00 equiv), amine (1.20 equiv), and acetic acid (1.00 equiv) in 1,2-dichloroethane at room temperature. The mixture was stirred until no starting material remained as judged by TLC. The reaction was then quenched with 1N NaOH and extracted three times with chloroform. The combined organics were dried over sodium sulfate, filtered, and concentrated. This material was dissolved in 1,4-dioxane, HCl (4N in dioxane) was added and the mixture was sonicated until such time that HPLC indicated no starting material remained. The mixture was concentrated under reduced pressure, purified by prep-HPLC, and conversion to the hydrochloride salt afforded the title compounds as off-white solids in Table 6(shown immediately below):

Table 6

Example	Column 2	MW	MS MH^+ m/z	HPLC t_R
17-1		538.6	539.8	4.08

17-2		588.23	589.1	4.84
17-3		604.2	605.9	4.35
17-4		604.2	605.2	4.38

EXAMPLE 18



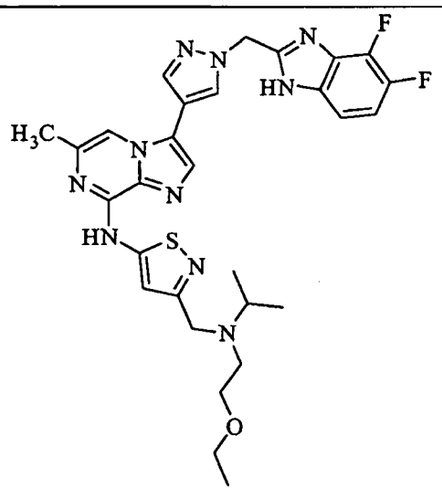
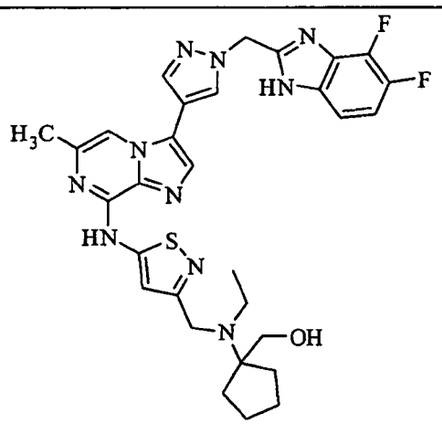
Part A: Sodium borohydride (2.0 equiv) was added to a stirring mixture of aldehyde from Example 17 part A (1.00 equiv) in acetic acid (5.7 mL) in 1,2-dichloromethane (17 mL) at room temperature. The mixture was stirred until no starting material remained as judged by TLC. The reaction was then quenched with 2N NaOH (11 mL) and a saturated solution of aqueous sodium bicarbonate (35 mL). After stirring at room temperature for 15 minutes, the phases were separated and the organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure to afford the alcohol as a brown foam 1.01 g (100%).

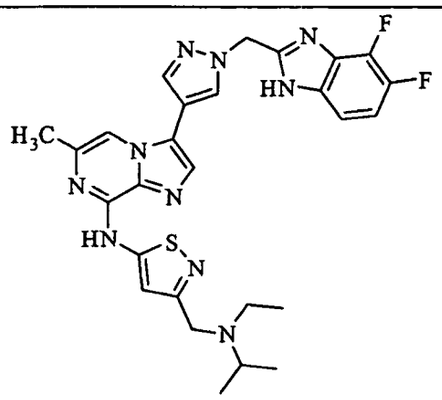
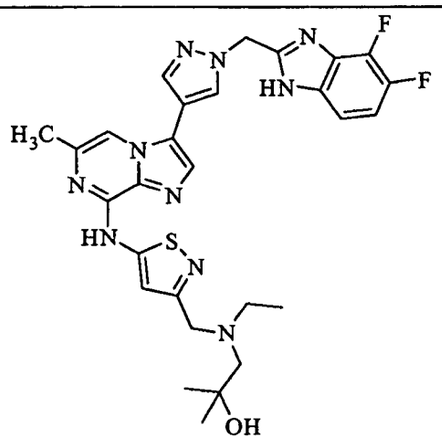
Part B: Methane sulfonyl chloride (2 equiv) was added to a stirring solution of alcohol from Example 18 part A (1 equiv) and triethylamine (4 equiv) in THF (40 mL). After stirring at room temperature for 30 minutes the reaction was quenched with a saturated aqueous solution of ammonium chloride (14 mL) and water (14 mL), extracted with dichloromethane (2×80 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure affording the mesylate as a brown foam 1.04 g (90%).

Part C: To a stirring solution of mesylate from Example 18 part B (1 equiv), amine (3 equiv), sodium iodide (0.5 equiv) in THF (1.0 mL) was added diisopropylethylamine (3 equiv) and the reaction heated at 60 °C for 18 hours. The reaction was cooled to room temperature, diluted with dichloromethane (50 mL) and the organic layer washed with water (30 mL), brine (30 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. This material was dissolved in 1,4-dioxane, HCl (4N in dioxane) was added and the mixture was

sonicated until such time that HPLC indicated no starting material remained. The mixture was concentrated under reduced pressure, purified by prep-HPLC, and conversion to the hydrochloride salt afforded the title compounds as off-white solids in Table 7 (shown immediately below):

Table 7

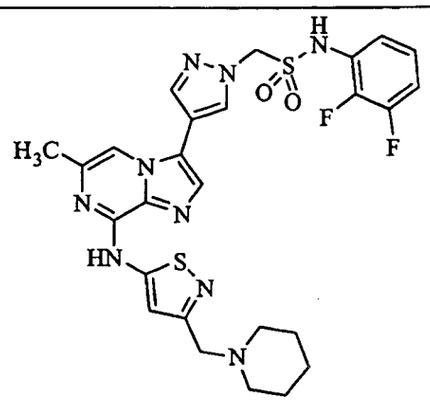
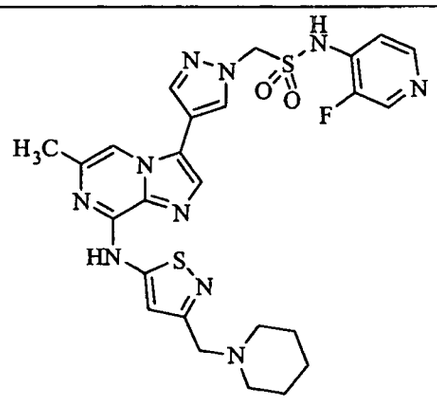
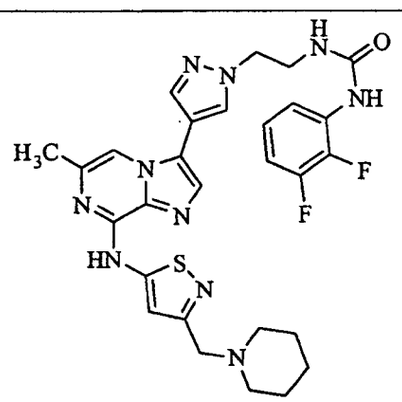
Example	Column 2	MW	MS MH^+ m/z	HPLC t_R
18-1		606.2	607.1	4.95
18-2		618.2	619.9	4.67

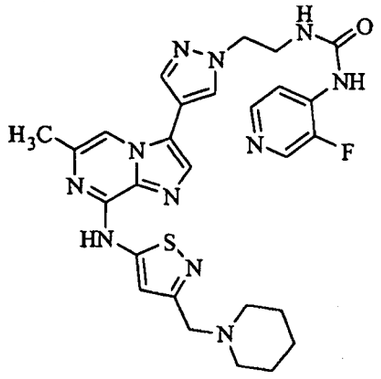
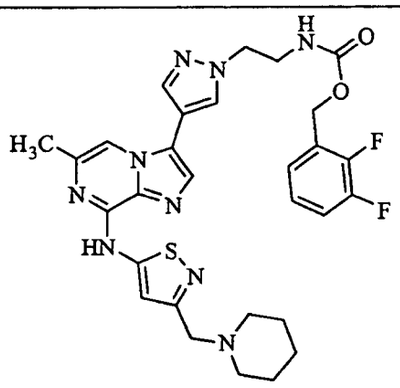
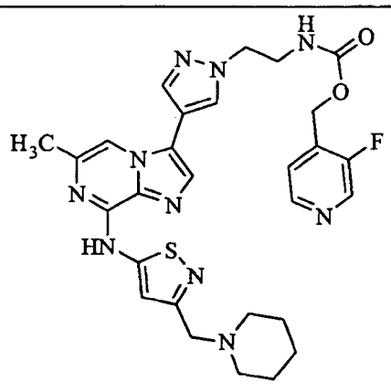
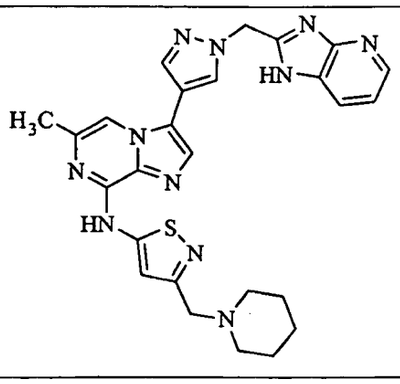
18-3		562.2	563.5	4.48
18-4		592.2	593.5	4.37

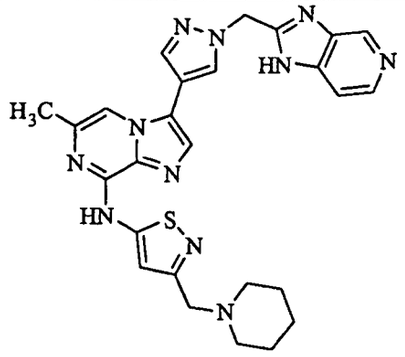
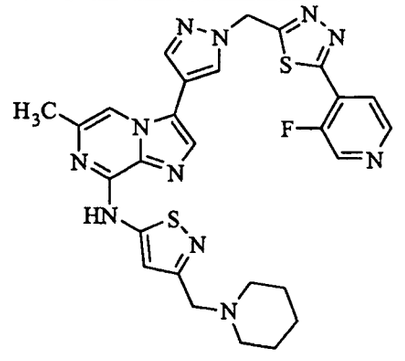
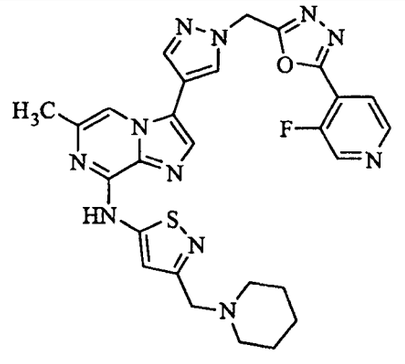
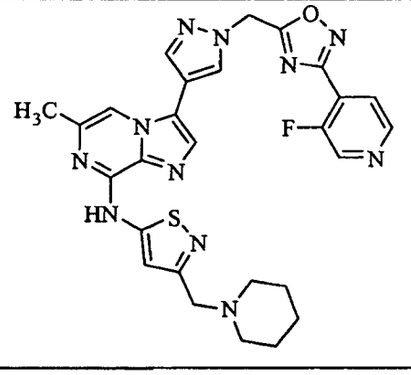
EXAMPLE 19

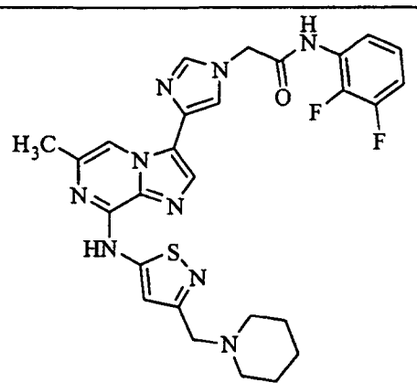
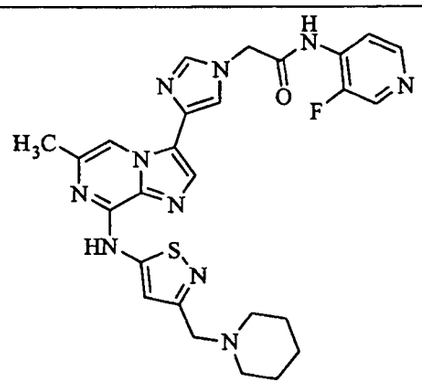
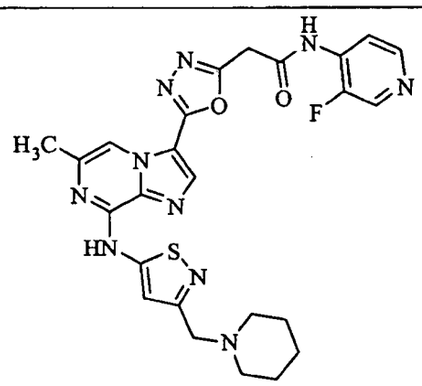
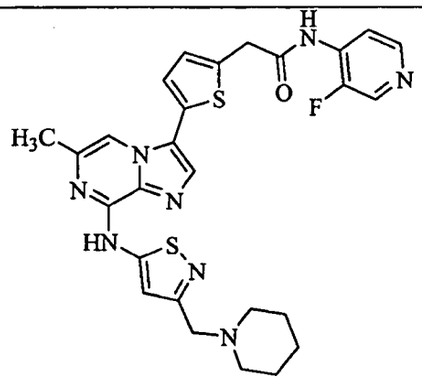
The following compounds in Table 8 (shown immediately below) were prepared by a method similar to the method described in Example 18.

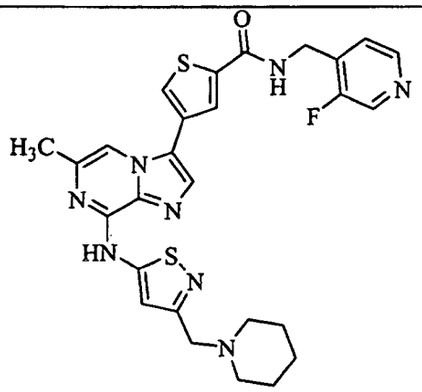
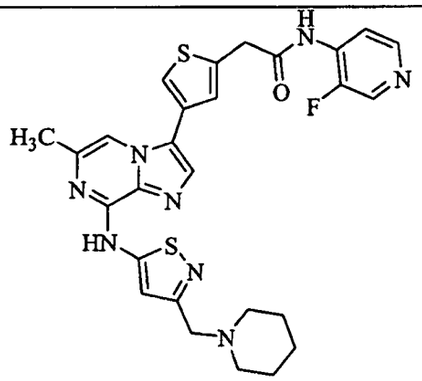
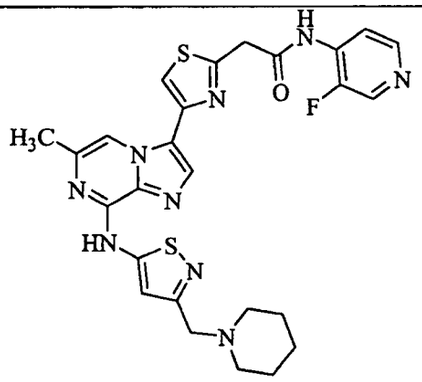
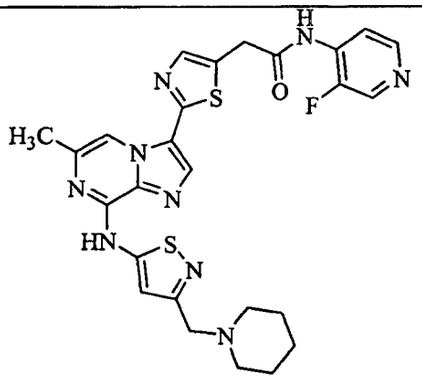
Table 8

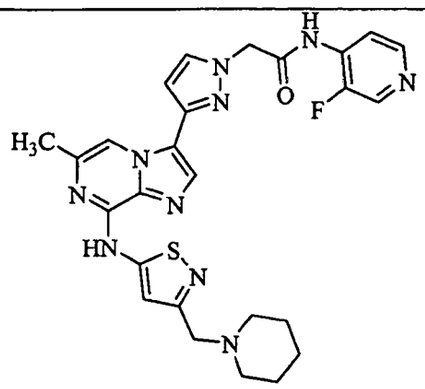
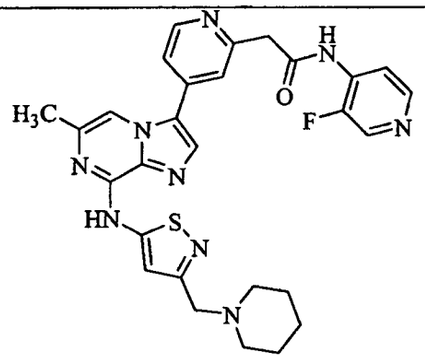
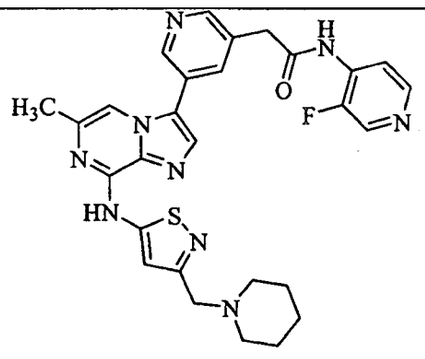
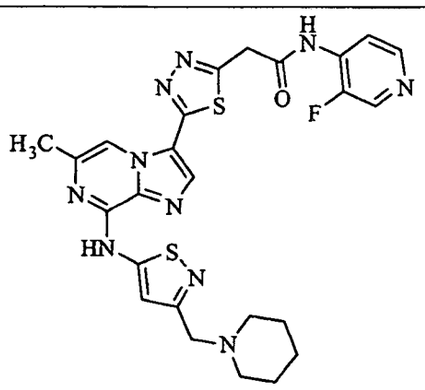
Example	Column 2	MW	MS MH^+ m/z	HPLC t_R
19-1		599.1		
19-2		582.1		
19-3		592.2		

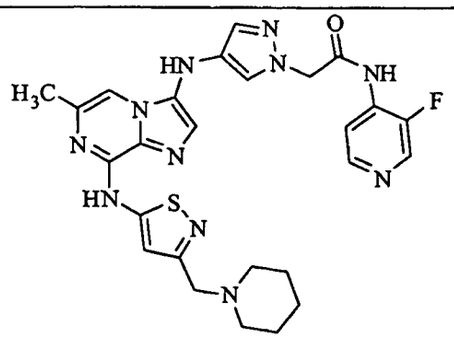
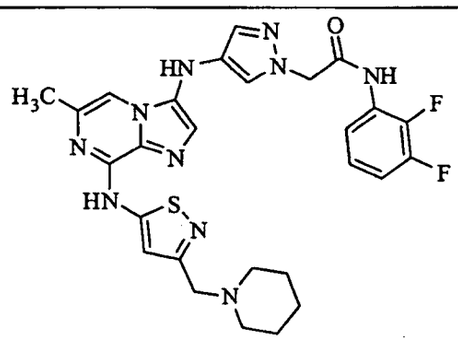
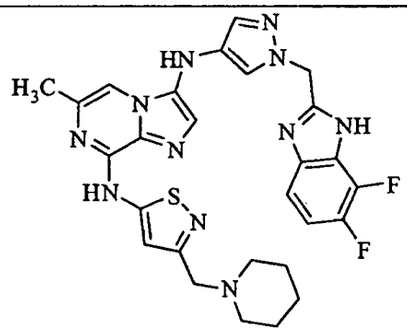
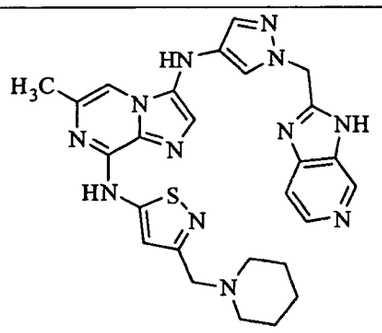
19-4		575.2		
19-5		607.2		
19-6		590.6		
19-7		525.2		

19-8		525.2		
19-9		587.1		
19-10		571.2		
19-11		571.2		

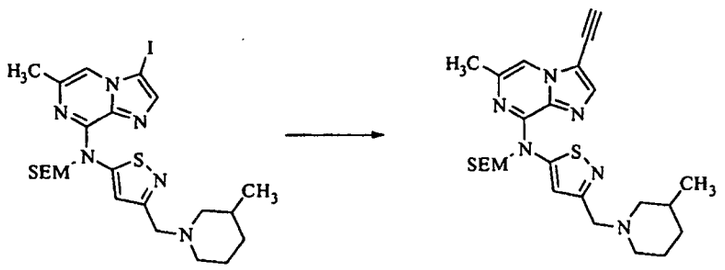
19-12		563.2		
19-13		546.2		
19-14		548.1		
19-15				

19-17				
19-16				
19-17				
19-18				

19-19				
19-20				
19-21				
19-22		564.1		

19-23		561.6		
19-24		578.6		
19-25		575.6		
19-26		540.6		

EXAMPLE 20



A solution of trimethylsilyl acetylene (46 mg, 0.46 mmol) in triethylamine (0.5 mL) was added to a nitrogen flushed mixture of iodide (136 mg, 0.23 mmol), palladium(0) triphenylphosphine (26 mg, 0.02 mmol) and copper(I) iodide (8.6 mg, 0.4 mmol). The reaction was stirred at room temperature for 12 hours then diluted with ethyl acetate (25 mL). The reaction contents were passed through Celite, concentrated, and placed onto a column (SiO_2; 12g; 10% to 50% ethyl acetate in hexanes) which afforded the desired coupled intermediate. The intermediate was dissolved in methanol (8 mL) then treated with potassium carbonate (790 mg). The reaction was stirred at room temperature for 72 hours then diluted with methylene chloride (50 mL). The organic layer was washed with saturated aqueous sodium bicarbonate (50 mL), dried (sodium sulfate), filtered and concentrated to dryness. The resultant residue was placed onto a flash column (SiO_2; 4 g; 10% to 50% ethyl acetate in hexanes) to afford the title compound as a white solid 19 mg (17%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.82 (s, 1H), 7.31 (s, 1H), 6.67 (s, 2H), 3.91 (s, 1H), 3.81 (t, J = 6.4 Hz, 2H), 3.71 (s, 2H), 3.03-2.87 (m, 2H), 2.66 (s, 3H), 2.19-1.99 (m, 2H), 1.85-1.63 (m, 5H), 1.01 (t, J = 6.4 Hz, 2H), 0.93 (d, J = 5.6 Hz, 3H), 0.00 (s, 9H).

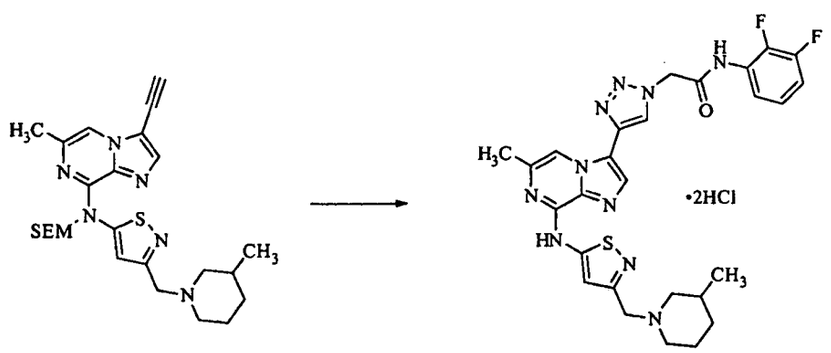
EXAMPLE 21



Sodium azide (116 mg, 1.79 mmol) was added to a solution of bromide (408 mg, 1.63 mmol) in dimethylformamide (30 mL). The reaction mixture was then heated to 60 °C and stirred for 12 hours. Upon completion, the reaction was cooled to room temperature and the solvent was removed *in vacuo*. The resultant residue was taken into ethyl acetate (75 mL) then washed with sodium bicarbonate (50 mL), water (50 mL) and brine (50 mL). The organic layer was then dried (sodium sulfate), filtered, and concentrated to dryness. The resultant solid was placed onto a flash column (SiO_2; 12 g; 10% to 50% ethyl acetate in hexanes) to give the title

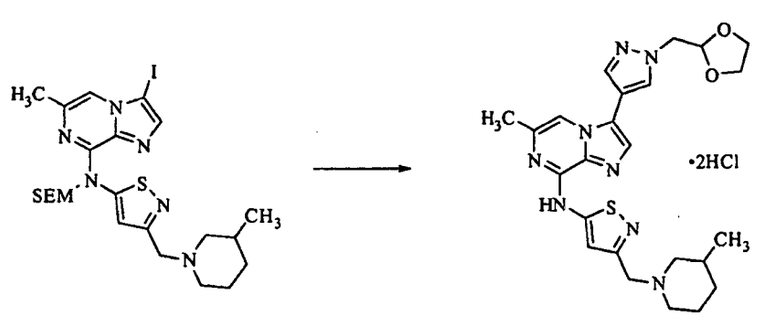
compound as a white solid 240 mg (69%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (br s, 1H), 8.12-7.96 (m, 1H), 7.16-7.02 (m, 1H), 7.01-6.87 (m, 1H), 4.20 (s, 2H).

EXAMPLE 22



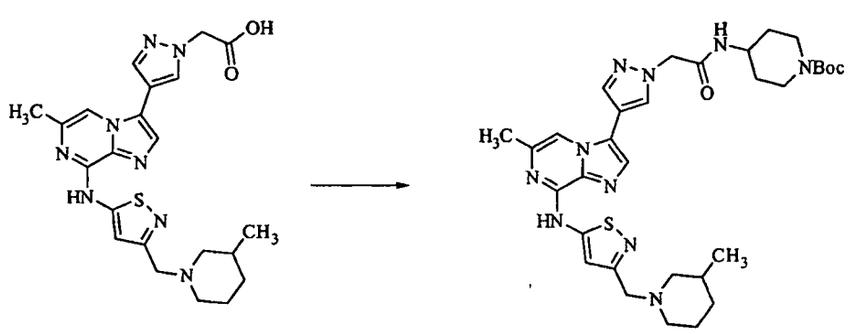
Copper powder (5 mg, 0.08 mmol) was added to a solution of alkyne (19 mg, 0.04 mmol) from Example 21 and azide (16 mg, 0.08 mmol) from Example 22 in *t*-butyl alcohol (0.3 mL) and water (0.6 mL). The reaction was stirred at room temperature for 72 hours then diluted with ethyl acetate (100 mL). The organic layer was washed with water (100 mL) and brine (100 mL) then dried (sodium sulfate), filtered and concentrated. The resultant residue was placed onto a flash column (SiO_2; 4 g; 0% to 10% methanol in methylene chloride) to afford the coupled intermediate. The desired intermediate was then dissolved in dioxane (2 mL) and treated with 4 N HCl in dioxane (2 mL). The reaction was sonicated at room temperature for 1 hour. The solvent was removed and the residue was purified by prep-HPLC (95:5 to 5:95 water/acetonitrile with 0.1% trifluoroacetic acid). The fractions were collected and dried and the residue treated with 0.2 N HCl and freeze-dried to afford the title compound as a white solid 6.9 mg (28%). ^{1}H NMR (300 MHz, CD_3OD) δ 8.65 (s, 1H), 8.58 (s, 1H), 8.13 (s, 1H), 7.77-7.70 (m, 1H), 7.21 (s, 1H), 7.17-7.04 (m, 2H), 5.59 (s, 2H), 4.38 (s, 2H), 3.71-3.46 (m, 2H), 3.13-3.09 (m, 1H), 2.79-2.63 (m, 1H), 2.58 (s, 3H), 2.06-1.74 (m, 4H), 1.32-1.11 (m, 1H), 1.00 (d, J = 6.4 Hz, 3H). HPLC t_R = 5.45 min (UV $_{254nm}$). Mass calculated for formula $C_{27}H_{28}F_2N_{10}OS$ 578.2; observed MH^+ (ESI MS) 579.8 (m/z).

EXAMPLE 23



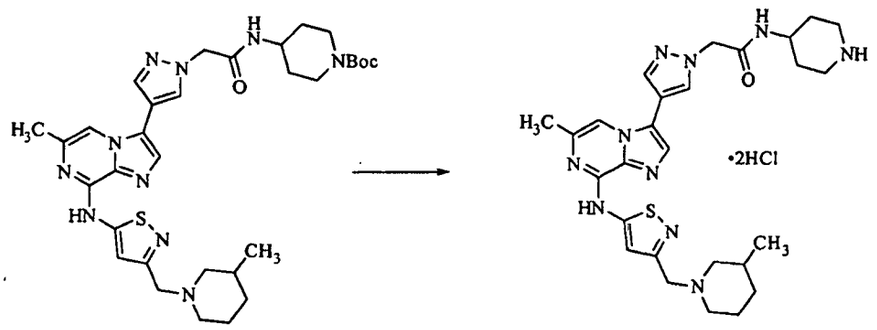
Example 24 was prepared in a similar manner to Example 15. ^{1}H NMR (300 MHz, CD_3OD) δ 8.30 (s, 1H), 8.21 (s, 1H), 8.03 (s, 1H), 8.00 (s, 1H), 7.35 (s, 1H), 5.31-5.22 (m, 1H), 4.49-4.37 (m, 4H), 3.91 (s, 4H), 3.69-3.46 (m, 2H), 3.10-2.91 (m, 1H), 2.80-2.66 (m, 1H), 2.63 (s, 3H), 2.07-1.74 (m. 4H), 1.39-1.12 (m, 1H), 1.00 (d, J = 6.5 Hz, 3H). HPLC t_R = 7.36 min (UV $_{254nm}$). Mass calculated for formula $C_{24}H_{30}N_8O_2S$ 494.2; observed MH^+ (ESI MS) 495.8 (m/z).

EXAMPLE 24



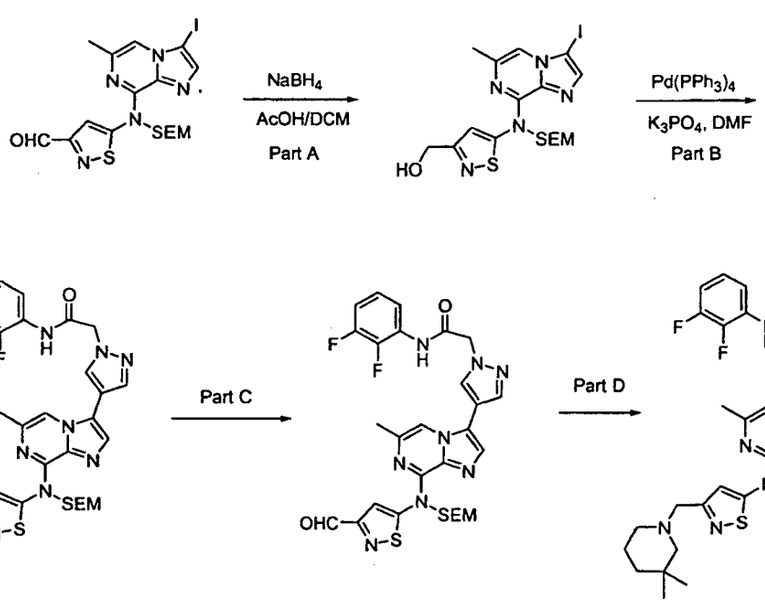
Example 25 was prepared in a similar manner to Example 6. ^{1}H NMR (300 MHz, CD_3OD) δ 8.20 (s, 1H), 7.94 (s, 1H), 7.85 (s, 1H), 7.77 (s, 1H), 7.18 (s, 1H), 4.98 (s, 2H), 4.37 (br s, 2H), 4.17-3.81 (m, 2H), 3.71-3.40 (m, 2H), 3.20-3.05 (m, 1H), 3.03-2.84 (m, 2H), 2.79-2.62 (m, 1H), 2.52 (s, 3H), 2.06-1.97 (m, 4H), 1.97-1.69 (m, 5H), 1.46 (s, 9H), 1.32-1.14 (m, 1H), 1.00 (d, J = 6.4 Hz, 3H).

EXAMPLE 25



Trifluoroacetic acid (2 mL) was added to a solution of amide (20 mg, 0.02 mmol) in methylene chloride (2 mL). The reaction was allowed to stir at room temperature for 2 hours. The solvent was removed and the resultant residue placed onto a prep-HPLC (95:5 to 40:60 water/acetonitrile with 0.1% trifluoroacetic acid). The collected fractions were concentrated then treated with 0.2 N HCl and freeze-dried to afford the title compound as a white solid 3.2 mg (23%). ^{1}H NMR (300 MHz, CD_3OD) δ 8.23 (s, 1H), 7.96 (s, 1H), 7.91 (s, 1H), 7.85 (s, 1H), 7.21 (s, 1H), 5.00 (s, 2H), 4.39 (br s, 2H), 4.09-3.93 (m, 1H), 3.68-3.39 (m, 4H), 3.20-3.04 (m, 2H), 3.04-2.89 (m, 1H), 2.79-2.63 (m, 1H), 2.51 (s, 3H), 2.24-2.09 (m, 2H), 2.05-1.67 (m, 6H), 1.32-1.12 (m, 1H), 1.01 (d, J = 6.4 Hz, 3H). HPLC t_R = 3.47 min (UV $_{254nm}$). Mass calculated for formula $C_{27}H_{36}N_{10}OS$ 548.3; observed MH^+ (ESI MS) 549.9 (m/z).

EXAMPLE 26



Part A: To a solution of iodide (390 mg, 0.757 mmol) in 10 mL of CH_2Cl_2 was added 8 mL of AcOH. $NaBH_4$ (57 mg, 1.51 mmol) was then added in one portion. The reaction was stirred at

room temperature for 15 min. It was diluted with 100 mL of CH_2Cl_2, and neutralized by 5 N NaOH (aq.). To the mixture was added 100 ml of saturated aqueous $NaHCO_3$. The resulting mixture was stirred at room temperature for 30 min. The organic layer was isolated. It was dried over anhydrous Na_2SO_4, and then concentrated. The residue was purified by flash chromatography eluting with 60% EtOAc/ CH_2Cl_2 to give 390 mg of the title compound. ^1H NMR (400 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.60 (s, 1H), 7.13 (s, 1H), 6.58 (brs, 2H), 4.78 (s, 2H), 3.72 (t, 2H), 2.60 (s, 3H), 0.95 (t, 2H), -0.10 (s, 9H).

Part B: To a mixture of alcohol from Part A (80 mg, 0.15 mmol), boronate from Example 7, Part A (84 mg, 0.23 mmol) and $Pd(PPh_3)_4$ (17.8 mg, 0.015 mmol) was added 2 mL of DMF followed by 3 M aqueous K_3PO_4 solution (0.21 mL, 0.63 mmol). The reaction mixture was heated at 65 °C for 18 h. It was diluted with 30 mL of EtOAc and washed with 1 N aqueous NH_4Cl solution (20 mL x 2). The organic layer was concentrated under vacuum. The residue was purified by flash chromatography eluting with 4% MeOH/CH_2Cl_2 to give 68 m g of **5**. ^1H NMR (400 MHz, $CDCl_3$) δ 8.90 (brs, 1H), 8.02-8.12 (m, 1H), 8.00 (s, 1H), 7.87 (s, 1H), 7.68 (s, 1H), 7.57 (s, 1H), 7.15 (s, 1H), 6.90-7.13 (m, 2H), 6.65 (brs, 2H), 5.09 (s, 2H), 4.75-4.81 (m, 2H), 3.77 (t, 2H), 2.80 (brs, 1H), 2.60 (s, 3H), 0.95 (t, 2H), -0.10 (s, 9H).

Part C: To a solution of alcohol from Part B (31 mg, 0.049 mmol) in 1.5 mL of THF, was added 3 □L of water followed by Dess-Martin periodinane (64 mg, 0.15 mmol). The reaction mixture was stirred at room temperature for 30 min. It was diluted with 5 mL of THF. The mixture was filtered. The filtrate was diluted with 20 mL of CH_2Cl_2 and washed with 10 mL of saturated aqueous $NaHCO_3$ solution. It was dried over anhydrous Na_2SO_4 and then concentrated to give 30 mg of the title compound which was used in the subsequent reactions without further purification.

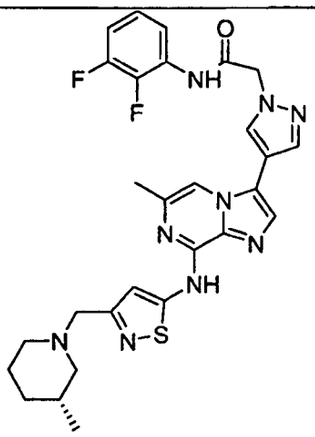
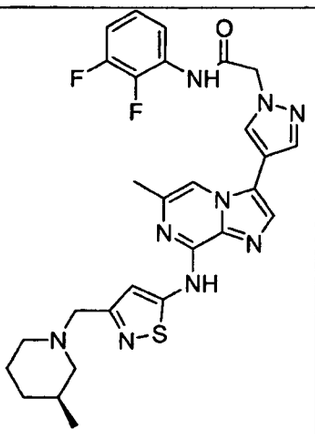
Part D: A solution of aldehyde (12 mg, 0.019 mmol), 3,3-dimethylpiperidine (22 mg, 0.19 mmol) in 1 mL of CH_2Cl_2 was stirred at room temperature for 30 min. To the solution was added $NaBH_4$ (3.6 mg, 0.096 mmol) followed by 0.3 mL of MeOH. The reaction was stirred at room temperature for 1 h. It was diluted with 10 mL of CH_2Cl_2 and 10 mL of saturated aqueous $NaHCO_3$ solution. The resulting mixture was stirred for 1 h. The organic was separated and concentrated under vacuum. The residue was purified by flash chromatography eluting with NH_4OH (aq.)/MeOH/ CH_2Cl_2 (1:10:190) to give 10 mg of the SEM-protected title compound. To a solution of SEM-protected material (10 mg, 0.014 mmol) in 2 mL of THF heated at 80 °C was added 0.2 mL of 4 N HCl in dioxane. The reaction was stirred at 80 °C for

1.5 h. It was cooled to room temperature and then added 8 mL of ether. The solid was collected by filtration and washed with ether to give 8.7 mg of the title compound. ^{1}H NMR (400 MHz, CD_3OD) δ 8.38 (s, 1H), 8.15 (s, 1H), 8.08 (s, 1H), 8.02 (s, 1H), 7.72-7.81 (m, 1H), 7.27 (s, 1H), 7.03-7.20 (m, 2H), 5.30 (s, 2H), 4.35-4.60 (m, 2H), 3.55-3.65 (d, 1H), 3.00-3.10 (m, 1H), 2.80-2.90 (d, 1H), 2.60 (s, 3H), 1.81-2.10 (m, 2H), 1.40-1.69 (m, 2H), 1.20 (s, 3H), 1.00 (s, 3H). HPLC-MS t_R = 2.96 min (UV $_{254nm}$). Mass calculated for formula $C_{29}H_{31}F_2N_9OS$ 591.2; observed MH^+ (LCMS) 592.3 (m/z).

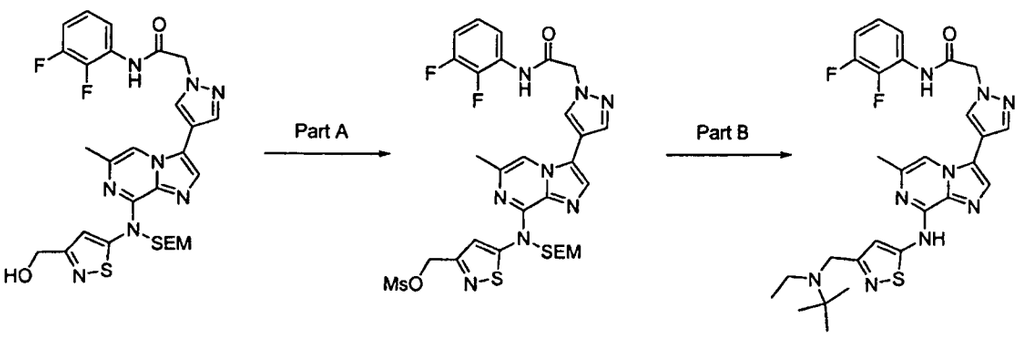
EXAMPLE 27

By essentially the same procedure set forth in Example 26, only replacing 3,3-dimethylpiperidine with other respective amines in Part A, compounds shown in column 2 of Table 9 (shown immediately below) were prepared.

TABLE 9

Example	Column 2	MW	LCMS MH^+ m/z	HPLC MS t_R
9-1		577.2	578.3	2.87
9-2		577.2	578.3	2.87

EXAMPLE 28

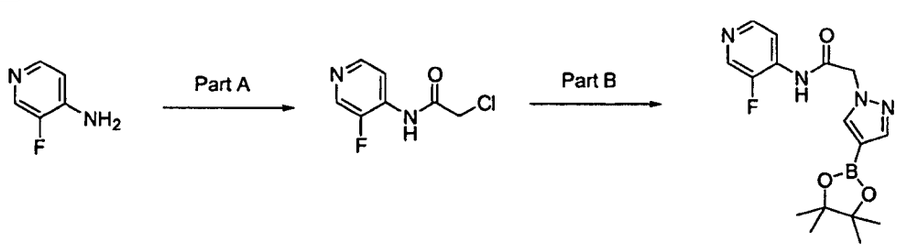


Part A: To a solution of alcohol from Example 26, Part B (30 mg, 0.047 mmol) in 1.5 mL of THF, was added triethylamine (9.5 mg, 0.094 mmol) followed by methanesulfonylchloride

(7.3 □L, 0.094 mmol). The reaction was stirred at room temperature for 20 min. It was diluted with 10 mL of CH_2Cl_2, washed with 5 mL of 1 N aqueous HCl. The organic was dried over anhydrous Na_2SO_4. The solvent was removed to give 31 mg of the title compound as a crude material which was used in the subsequent reaction without further purification.

Part B: A mixture of mesylate from Part A (9.6 mg, 0.014 mmol), N,N-diethylisopropylamine (6.0 mg, 0.068 mmol) and NaI (4.1 mg, 0.027 mmol) in 1 mL of THF was stirred at 60 °C for 3 h. It was diluted with 10 mL of CH_2Cl_2 and washed with water. The organic was concentrated under vacuum. The residue was purified by flash chromatography eluting with NH_4OH (aq.)/MeOH/CH_2Cl_2 (1:10:190) to give 8 mg of *N*-(2,3-difluoro-phenyl)-2-(4-{8-[{3-[(ethyl-isopropyl-amino)-methyl]-isothiazol-5-yl}-(2-trimethylsilanyl-ethoxymethyl)-amino]-6-methyl-imidazo[1,2-a]pyrazin-3-yl}-pyrazol-1-yl)-acetamide. To a solution of *N*-(2,3-difluoro-phenyl)-2-(4-{8-[{3-[(ethyl-isopropyl-amino)-methyl]-isothiazol-5-yl}-(2-trimethylsilanyl-ethoxymethyl)-amino]-6-methyl-imidazo[1,2-a]pyrazin-3-yl}-pyrazol-1-yl)-acetamide (8.0 mg, 0.011 mmol) in 2 mL of THF heated at 80 °C was added 0.2 mL of 4 N HCl in dioxane. The reaction was stirred at 80 °C for 1.5 h. It was cooled to room temperature and then added 8 mL of ether. The solid was collected by filtration and washed with ether to give 5.8 mg of the title compound. ^{1}H NMR (400 MHz, CD_3OD) δ 8.35 (s, 1H), 7.95-8.10 (m, 3H), 7.70-7.82 (m, 1H), 7.25 (s, 1H), 7.00-7.20 (m, 2H), 5.30 (s, 2H), 4.30-4.60 (m, 2H), 3.75-3.85 (m, 1H), 2.60 (s, 3H), 1.30-1.50 (m, 9H). HPLC-MS t_R = 2.80 min (UV $_{254nm}$). Mass calculated for formula $C_{27}H_{29}F_2N_9OS$ 565.2; observed MH^+ (LCMS) 566.3 (m/z).

EXAMPLE 29

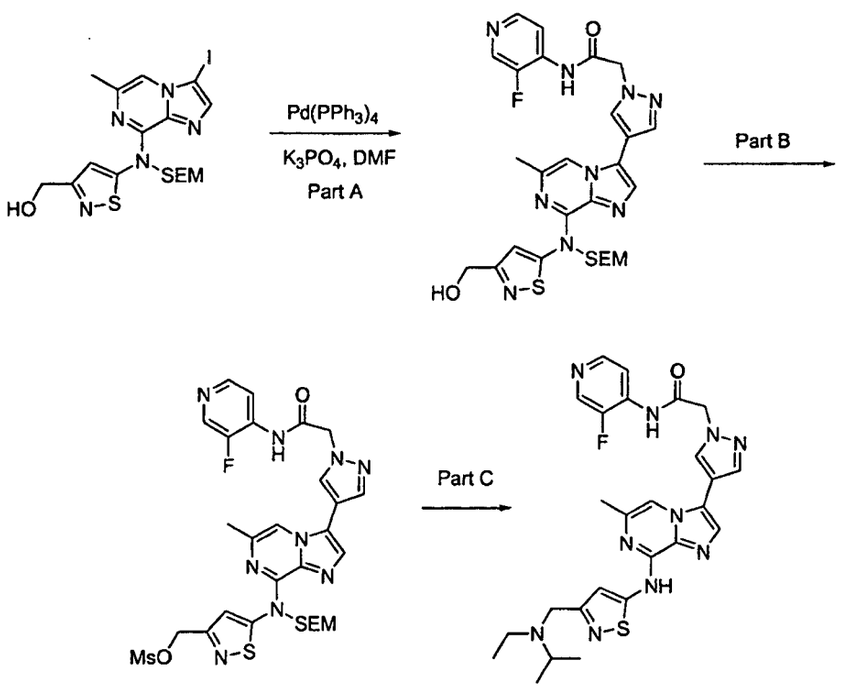


Part A: To a solution of 4-amino-3-fluoro pyridine (560 mg, 5.0 mmol) and Et_3N (760 mg, 7.5 mmol) in 20 mL of THF, was added chloroacetyl chloride (622 mg, 5.5 mmol). The reaction was stirred at room temperature and monitored by thin layer chromatography. More chloroacetyl chloride was added until 4-amino-3-fluoro pyridine was consumed. It was quenched by adding 20 mL of saturated aqueous $NaHCO_3$. The mixture was diluted with 150 mL of CH_2Cl_2. The organic layer was concentrated and purified by flash chromatography

eluting with 35% EtOAc/CH_2Cl_2 to give 850 mg of the title compound. NMR (400 MHz, $CDCl_3$) δ 8.62 (brs, 1H), 8.41 (d, 1H), 8.33 (d, 1H), 8.26 (t, 1H), 4.20 (s, 2H).

Part B: A mixture of amide from Part A (106 mg, 0.55 mmol) and Cs_2CO_3 (326 mg, 1.0 mmol) in 2 mL of DMSO was heated at 100 °C for 5 min. To the mixture was added 4-pyrazoleboronic acid pinacol ester (94 mg, 0.50 mmol). The reaction was stirred at 100 °C for 20 min. It was cooled to room temperature and diluted with 30 mL of CH_2Cl_2. The mixture was washed with water. The organic was concentrated and purified by running a quick column eluting with 2% MeOH/EtOAc to give 52 mg of the title compound. NMR (400 MHz, $CDCl_3$) δ 9.30 (brs, 1H), 8.33 (d, 1H), 8.20-8.30 (m, 2H), 7.93 (s, 1H), 7.75 (s, 1H), 4.90 (s, 2H), 1.24 (s, 12H).

EXAMPLE 30



Part A: To a mixture of iodide (43 mg, 0.083 mmol), boronate from Example 29, Part B (43 mg, 0.124 mmol) and $Pd(PPh_3)_4$ (14 mg, 0.012 mmol) in a vial, was added 1.1 mL of DMF, followed by adding 0.11 mL of 3 M aqueous K_3PO_4 solution (0.33 mmol). The vial was sealed and stirred at 65 °C overnight. It was diluted with 30 mL of EtOAc and washed with water. It was concentrated and purified by flash chromatography eluting with 7% MeOH/DCM to give 24 mg of the title compound. NMR (400 MHz, $CDCl_3$) δ 9.25 (brs, 1H), 8.25-8.43 (m, 3H),

7.95 (s, 1H), 7.80 (s, 1H), 7.61 (s, 1H), 7.50 (s, 1H), 7.09 (s, 1H), 6.60 (s, 2H), 5.05 (s, 2H), 4.72 (s, 2H), 3.70 (t, 2H), 2.75 (brs, 1H), 2.48 (s, 3H), 0.90 (t, 2H), -0.14 (s, 9H).

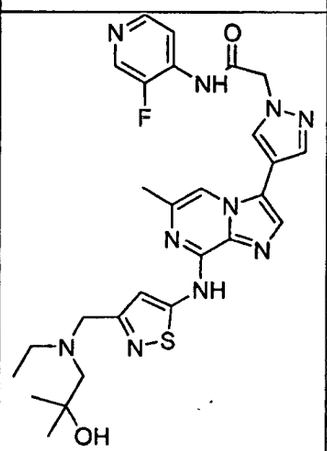
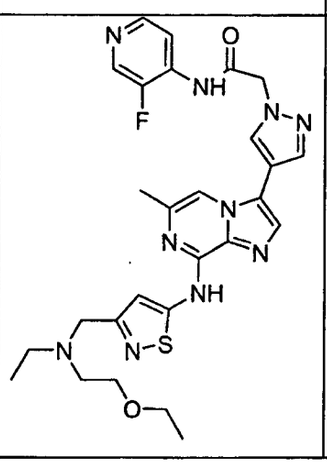
Part B: To a solution of alcohol from Part A (102 mg, 0.17 mmol) in 5 mL of THF, was added NEt_3 (0.094 mL, 0.67 mmol), followed by methanesulfonylchloride (0.029 mL, 0.37 mmol). The reaction was stirred at room temperature for 15 min. It was monitored by thin layer chromatography and found starting alcohol was not totally consumed. Additional methanesulfonylchloride (0.0035 mL, 0.039 mmol) was added. The stirring was continued for 5 min. It was quenched by adding 2 mL of saturated NH_4Cl (aq.) and 2 mL of water. The organic layer was collected. The aqueous layer was extracted with CH_2Cl_2 (10 mL X 3) until no desired product remains in aqueous layer. The combined organics were further purified by flash chromatography eluting with MeOH/CH_2Cl_2 (1:10) to give 63.3 mg of the title compound as a light yellow solid. ^1H NMR (400 MHz, DMSO-d_6) δ 10.75 (s, 1H), 8.60 (d, 1H), 8.51 (s, 1H), 8.36 (d, 1H), 8.20 (t, 1H), 8.10 (s, 2H), 7.96 (s, 1H), 7.38 (s, 1H), 6.70 (brs, 2H), 5.34 (s, 2H), 5.28 (s, 2H), 3.68 (t, 2H), 3.28 (s, 3H), 2.54 (s, 3H), 0.85 (t, 2H), -0.10 (s, 9H).

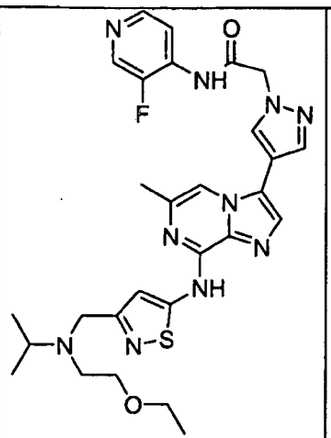
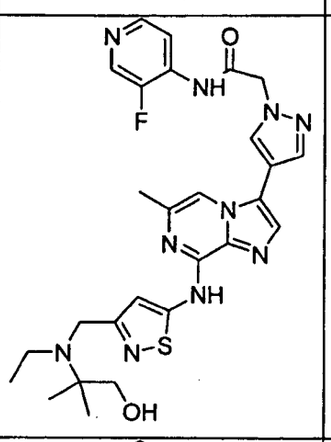
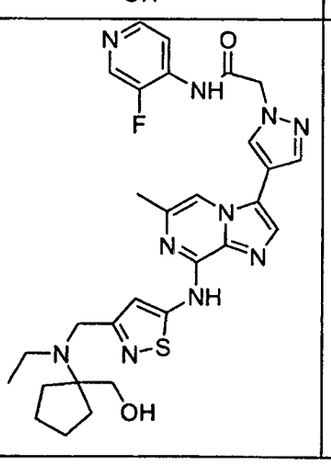
Part C: A mixture of mesylate from Part B (24.7 mg, 0.036 mmol), N,N-diethylisopropylamine (7.8 mg, 0.089 mmol) and NaI (1 mg, 0.007 mmol) in 1.5 mL of THF was stirred at 80 °C for 4 h. It was diluted with 10 mL of CH_2Cl_2 and washed with water and brine. It was dried over anhydrous Na_2SO_4. The organic was concentrated under vacuum. The residue was purified by flash chromatography eluting with 7N NH_3 in MeOH /CH_2Cl_2 (1:30) to give 11.5 mg of 2-(4-{8-[{3-[(ethyl-isopropyl-amino)-methyl]-isothiazol-5-yl}-(2-trimethylsilanyl-ethoxymethyl)-amino]-6-methyl-imidazo[1,2-a]pyrazin-3-yl}-pyrazol-1-yl)-*N*-(3-fluoro-pyridin-4-yl)-acetamide. NMR (400 MHz, $CDCl_3$) δ 9.36 (brs, 1H), 8.30-8.48 (m, 3H), 8.02 (s, 1H), 7.85 (s, 1H), 7.66 (s, 1H), 7.55 (s, 1H), 7.30 (s, 1H), 6.62 (s, 2H), 3.60-3.85 (m, 4H), 2.96-3.15 (brs, 3H), 2.40-2.68 (m, 5H), 0.90-1.20 (m, 12H), 0.00 (s, 9H). To a solution of 2-(4-{8-[{3-[(ethyl-isopropyl-amino)-methyl]-isothiazol-5-yl}-(2-trimethylsilanyl-ethoxymethyl)-amino]-6-methyl-imidazo[1,2-a]pyrazin-3-yl}-pyrazol-1-yl)-*N*-(3-fluoro-pyridin-4-yl)-acetamide (11.5 mg, 0.0169 mmol) in 0.4 mL of THF heated at 80 °C was added 0.4 mL of 4 N HCl in dioxane. The reaction was stirred at 80 °C for 1 h. It was cooled to room temperature and then added 8 mL of ether. The solid was collected by filtration and washed with ether to give 10 mg of the title compound. HPLC-MS t_R = 2.18 min (UV $_{254nm}$). Mass calculated for formula $C_{26}H_{29}FN_{10}OS$ 548.2; observed MH^+ (LCMS) 549.3 (m/z).

EXAMPLE 31

By essentially the same procedure set forth in Example 30, only replacing ethylisopropylamine with other respective amines in Part C, compounds shown in column 2 of Table 10 (shown immediately below) were prepared.

TABLE 10

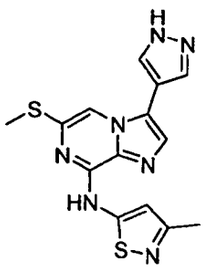
Example	Column 2	MW	LCMS MH^+ m/z	HPLC MS t_R
17-1		578.7	579.3	2.17
17-2		578.7	579.3	2.28

17-3		592.7	593.3	2.23
17-4		578.7	579.3	2.28
17-5		604.7	605.3	2.40

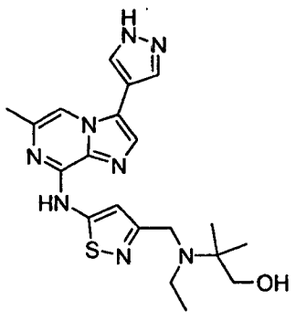
EXAMPLES

Asynchronous cells require 24 hour exposure to Aurora kinase inhibitors (such as 250 nM VX-680 or 1000 nM COMPOUND X. (Compound X is disclosed in WO 2008/057512, filed November 6, 2007, Example 4-3 and Claim 70, Example 4-3 and Claim 70 and is shown below and it is represented in Formula H and Table 2, column 2, row 17 of the present application) or 25 nM COMPOUND Z (Compound Z is disclosed in PCT US2008/007295,

filed June 11, 2008, Example 76-2 and Claim 25, row 7, column 4 and it is represented in Table 13, compound 76-2 of the present application)) to induce endoreduplication (>4N DNA content) or cell death. For example, HCT-116 colon cancer cells were treated with 1000 nM COMPOUND X or 25 nM COMPOUND Z for the indicated times at which time the drug was washed off and replaced with new media see Figure 1 and Figure 8 respectively. Cells were analyzed by FACS after a total of 72 hours. Exposures less than 24 hours were insufficient to induce endoreduplication (>4N DNA content), while drug exposure for 24, 48, or 72 hours resulted in the accumulation of cells that underwent endoreduplication. Similar findings were found in HT29 colon, MCF-7 and T47D breast, NCI-460 and A549 lung, PC3, DU145, LNCAp prostate, A2780, SKOV3, PA1, TOV112D, and ES2 ovarian cells.



Compound X

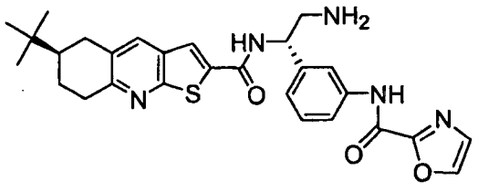


Compound Z

When asynchronous cells were analyzed by FACS at 24 hours, 24 hour exposure to an Aurora kinase inhibitor (such as 250 nM VX-680 or 1000 nM COMPOUND X) was sufficient to induce endoreduplication. However less exposure time was insufficient to induce endoreduplication. For example, HCT-116 colon cancer cells were treated with 1000 nM COMPOUND X or 25 nM COMPOUND Z for the indicated times at which time the drug was washed off and replaced with new media see Figure 2 and Figure 9 respectively. Cells were analyzed by FACS after a total of 24 hours. Exposures less than 24 hours were insufficient to induce endoreduplication (>4N DNA content), while drug exposure for the entire 24 hours resulted in the accumulation of cells that underwent endoreduplication.

Interestingly, following a 16 hour pre-treatment with taxanes (Taxol or Taxotere) or KSP inhibitors, Ispinesib SB-715992 or COMPOUND A (Compound A is a KSP inhibitor disclosed in WO 2006/098,961 filed March 7, 2006, Example 263, Claim 51 and Compound A, shown below, is represented in the present application in Formula B and Table 1, column 2, row 7). Following the pre-treatment of the HCT-116 colon cancer cells with a taxane or the

KSP inhibitor described above, the time of exposure to the Aurora kinase inhibitor, Compound X or Z required to induce endoreduplication, was reduced to less than 4-hours.



Compound A

For example, HCT-116 colon cancer cells were treated for 16 hours with DMSO (Figure 3) or 5 nM taxotere and then exposed to DMSO or 1000 nM COMPOUND X or 25 nM COMPOUND Z for 4, 8, and 24 hours. After 4 or 8 hours, COMPOUND X or COMPOUND Z was washed off and new media was added to the cells. Cells were harvested after 24 hours and analyzed by FACS (see Figure 4 and Figure 11 respectively). Following DMSO pretreatment, DMSO had no effect on cell cycle distribution. DMSO pretreatment followed by COMPOUND X or COMPOUND Z induced endoreduplication, but only when COMPOUND X or COMPOUND Z exposure was 24 hours, similar to the results in Figure 2. Taxotere pretreatment (labeled 0 hours) cells accumulated in mitosis (4N DNA). Over time, when released into DMSO the cells exited mitosis. Taxotere followed by COMPOUND X or COMPOUND Z induced endoreduplication. Endoreduplication was observed even when COMPOUND X or COMPOUND Z exposure was as little as 4 hours. A similar shortening of the time required for an Aurora kinase inhibitor to be exposed to cells in order to induce endoreduplication was observed following pretreatment with 5 nM taxol or 10-50 nM KSP inhibitors.

However, following a 16 hour pre-treatment with nocodazole for incrusting, the time required for an Aurora inhibitor (such as 250 nM VX-680 or 1000 nM COMPOUND X or COMPOUND Z) to induce endoreduplication was not reduced. For example, HCT-116 colon cancer cells were treated for 16 hours with 0.4 μg/ml nocodazole see Figure 5, and then exposed to DMSO or 1000 nM COMPOUND X or COMPOUND Z for 4, 8 or 24 hours. After 4 or 8 hours, COMPOUND X or COMPOUND Z was washed off and new media was added to the cells. Cells were harvested after 24 hours and analyzed by FACS. Following nocodazole pretreatment (labeled 0 hour) cells accumulated in mitosis (4N DNA). Over time, when released into DMSO the cells exited mitosis. Nocodazole followed by 24 hour exposure to COMPOUND X or COMPOUND Z induced endoreduplication, however a 4- or 8- hour exposure to COMPOUND X or COMPOUND Z was insufficient to induce endoreduplication.

To further explore the combination with taxotere we analyzed simultaneous treatment with an Aurora kinase inhibitor, Compound X or COMPOUND Z. If the Aurora kinase inhibitor is given at the same time as taxotere, 4 hour exposure is not sufficient and 24 hour exposure is needed to induce endoreduplication. For example, HCT-116 colon cancer cells that were not pretreated, were treated with 5 nM taxotere plus DMSO or 1000 nM COMPOUND X or COMPOUND Z concurrently for 4, 8, or 24 hours. At the indicated time the media was removed and replaced with new media and taxotere was added back into these cells. Cells were harvested after 24 hours and analyzed by FACS see Figure 6 or Figure 12 respectively. This data suggest that concurrent treatment was not sufficient to reduce the exposure time required for an Aurora kinase inhibitor to induce endoreduplication.

Single agent Aurora kinase inhibitors require a drug exposure time of 24 hours to induce endoreduplication in asynchronous cells. A 16 hour pre-treatment with a taxane or KSP inhibitor was sufficient to reduce the time required for an Aurora kinase inhibitor to induce endoreduplication but pre-treatment with other anti-mitotic agents tested (nocodazole and vincristine) did not result in the same reduction in required exposure time. Aurora kinase inhibitors (such as VX-680 and COMPOUND X and COMPOUND Z) are capable of inhibiting phosphorylation of Histone H3 (at serine-10) stimulated by taxanes, KSP inhibitor, and nocodazole. Therefore, this does not explain the difference. We found that Aurora kinase inhibitors accelerated the exit from mitosis, as measured by phos-MPM2 marker, in response to taxane and KSP induced arrest, but not that of a nocodazole arrest. This effect was seen with dual Aurora A/B inhibitors such as VX-680, COMPOUND X, COMPOUND Z and AT9283, as well as with the Aurora B selective inhibitor AZD1152.

Acceleration from taxane, but not nocodazole, confirms published reports of similar findings. Morrow et al. (*Journal of Cell Science* 2005; 118: 3639) and Ditchfield et. al. (*Journal of Cell Biology* 2003; 161: 267) showed the Aurora kinase inhibitor ZM4477439 abrogated mitotic arrest induced by taxol but not by nocodazole. The former group suggested this was caused by accelerated exit from taxol induced arrest. Hauf et al (*Journal of Cell Biology* 2003; 161: 281) demonstrated that Hesperadin, a non-selective Aurora kinase inhibitor, caused cells arrested with taxol or monastrol (an inhibitor of KSP) to enter anaphase in less than 1 hour, whereas cells in nocodazole stay arrested for 3-5 hours. Similarly, Carvalho et al (*Journal of Cell Science* 2003; 116: 2987) showed cells depleted of Surviving (a

regulator of Aurora B) by siRNA arrested in mitosis in the presence of nocodazole but not Taxol.

Our data suggests clinically, shorter exposures of cancer cells to Aurora kinase inhibitors may be needed if it follows taxane treatment. Ideal treatment of cancer cells with an Aurora kinase inhibitor would follow treatment of the cancer cells with anti-mitotic agents such as taxanes.

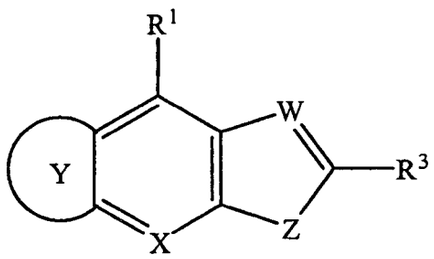
The above description is not intended to detail all modifications and variations of the invention. It will be appreciated by those skilled in the art that changes can be made to the embodiments described above without departing from the inventive concept. It is understood, therefore, that the invention is not limited to the particular embodiments described above, but is intended to cover modifications that are within the spirit and scope of the invention, as defined by the language of the following claims.

CLAIMS

What is claimed is:

1. A pharmaceutical composition for treating or ameliorating cancer comprising in combination (a) at least one anti-mitotic agent selected from the group consisting of a taxane, paclitaxel, docetaxel, a Cenp-E Inhibitor, Abraxane, Epothilone, Monastrol, a KSP inhibitor, Ispinesib, and a compound of Formulas A-D Formulas A-D shown in paragraphs a-d below:

a. A compound represented by the structural Formula A:



Formula A

or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:

ring Y is a 5- to 6-membered aryl or a 5- or 6-membered heteroaryl fused as shown in Formula A, wherein in said aryl and heteroaryl each substitutable ring carbon is independently substituted with R^2 and each substitutable ring nitrogen is independently substituted with R^6;

W is N or $C(R^{12})$;

X is N or N-oxide;

Z is S, S(=O) or $S(=O)_2$;

R^1 is H, alkyl, alkoxy, hydroxy, halo, -CN, $-S(O)_m$-alkyl, $-C(O)NR^9R^{10}$, $-(CR^9R^{10})_{1-6}OH$, or $-NR^4(CR^9R^{10})_{1-2}OR^9$;

each R^2 is independently selected from the group consisting of H, halo, alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, $-(CR^{10}R^{11})_{0-6}-OR^7$, $-C(O)R^4$, $-C(S)R^4$, $-C(O)OR^7$, $-C(S)OR^7$, $-OC(O)R^7$, $-OC(S)R^7$, $-C(O)NR^4R^5$, $-C(S)NR^4R^5$, $-C(O)NR^4OR^7$, $-C(S)NR^4OR^7$, $-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, -CN, $-OCF_3$, $-SCF_3$, $-C(=NR^7)NR^4$, $-C(O)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}OR^7$, $-C(S)NR^7(CH_2)_{1-10}NR^4R^5$,

-C(S)NR^7(CH$_2$)$_{1-10}$OR^7, haloalkyl and alkylsilyl, wherein each of said alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl or heteroaralkyl is independently optionally substituted with 1-5 R^9 moieties;

each R^3 is independently selected from the group consisting of H, halo, alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, -(CR^{10}R^{11})$_{0-6}$-OR^7, -C(O)R^4, -C(S)R^4, -C(O)OR^7, -C(S)OR^7, -OC(O)R^7, -OC(S)R^7, -C(O)NR^{4}R^5, -C(S)NR^{4}R^5, -C(O)NR^{4}OR^7, -C(S)NR^{4}OR^7, -C(O)NR^{7}NR^{4}R^5, -C(S)NR^{7}NR^{4}R^5, -C(S)NR^{4}OR^7, -C(O)SR^7, -NR^{4}R^5, -NR^{4}C(O)R^5, -NR^{4}C(S)R^5, -NR^{4}C(O)OR^7, -NR^{4}C(S)OR^7, -OC(O)NR^{4}R^5, -OC(S)NR^{4}R^5, -NR^{4}C(O)NR^{4}R^5, -NR^{4}C(S)NR^{4}R^5, -NR^{4}C(O)NR^{4}OR^7, -NR^{4}C(S)NR^{4}OR^7, -(CR^{10}R^{11})$_{0-6}$SR^7, SO$_2$R^7, -S(O)$_{1-2}$NR^{4}R^5, -N(R^7)SO$_2$R^7, -S(O)$_{1-2}$NR^{5}OR^7, -CN, -OCF$_3$, -SCF$_3$, -C(=NR^7)NR^{4}R^5, -C(O)NR^7(CH$_2$)$_{1-10}$NR^{4}R^5, -C(O)NR^7(CH$_2$)$_{1-10}$OR^7, -C(S)NR^7(CH$_2$)$_{1-10}$NR^{4}R^5, -C(S)NR^7(CH$_2$)$_{1-10}$OR^7, haloalkyl and alkylsilyl, wherein each of said alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl or heteroaralkyl is independently optionally substituted with 1-5 R^9 moieties;

each R^4 and R^5 is independently selected from the group consisting of H, alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, -OR^7, -C(O)R^7, and -C(O)OR^7, wherein each of said alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl is optionally substituted with 1-4 R^8 moieties;

or R^4 and R^5, when attached to the same nitrogen atom, are optionally taken together with the nitrogen atom to which they are attached to form a 3-6 membered heterocyclic ring having 0-2 additional heteroatoms selected from N, O or S;

each R^6 is independently selected from the group consisting of H, alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroaralkyl, -(CH$_2$)$_{1-6}$CF$_3$, -C(O)R^7, –C(O)OR^7 and –SO$_2$R^7;

each R^7 is independently selected from the group consisting of H, alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, and heteroaralkyl, wherein each member of R^7 except H is optionally substituted with 1-4 R^8 moieties;

each R^8 is independently selected from the group consisting of halo, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, -NO$_2$, -OR^{10}, -(C$_1$-C$_6$ alkyl)-OR^{10}, –CN, –

$NR^{10}R^{11}$, $-C(O)R^{10}$, $-C(O)OR^{10}$, $-C(O)NR^{10}R^{11}$, $-CF_3$, $-OCF_3$, $-CF_2CF_3$, $-C(=NOH)R^{10}$, $-N(R^{10})C(O)R^{11}$, $-C(=NR^{10})NR^{10}R^{11}$, and $-NR^{10}C(O)OR^{11}$, wherein each of said alkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally independently substituted with 1-3 moieties selected from the group consisting of halo, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-NO_2$, $-OR^{10}$, $-(C_1-C_6$ alkyl$)-OR^{10}$, -CN, $-NR^{10}R^{11}$, $-C(O)OR^{10}$, $-C(O)NR^{10}R^{11}$, $-CF^3$, $-OCF_3$, $-NR^{10}C(O)OR^{11}$, and $-NR^{10}C(O)R^{40}$;

or two R^8 groups, when attached to the same carbon atom, are optionally taken together with the carbon atom to which they are attached to form a C=O or a C=S group;

each R^9 is independently selected from the group consisting of H, alkyl, alkoxy, OH, CN, halo, $-(CR^{10}R^{11})_{0-4}NR^4R^5$, haloalkyl, hydroxyalkyl, alkoxyalkyl, $-C(O)NR^4R^5$, $-C(O)OR^7$, $-OC(O)NR^4R^5$, $-NR^4C(O)R^5$, and $-NR^4C(O)NR^4R^5$;

each R^{10} is independently H or alkyl; or R^9 and R^{10}, when attached to the same nitrogen atom, are optionally taken together with the nitrogen atom to which they are attached to form a 3-6 membered heterocyclic ring having 0-2 additional heteroatoms selected from N, O or S;

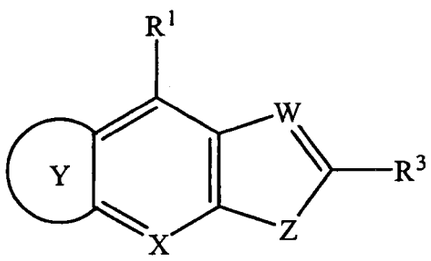
each R^{11} is independently H or alkyl; or R^{10} and R^{11}, when attached to the same nitrogen atom, are optionally taken together with the nitrogen atom to which they are attached to form a 3-6 membered heterocyclic ring having 0-2 additional heteroatoms selected from N, O or S;

each R^{12} is independently selected from the group consisting of H, halo, alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, $-(CR^{10}R^{11})_{0-6}-OR^7$, $-C(O)R^4$, $-C(S)R^4$, $-C(O)OR^7$, $-C(S)OR^7$, $-OC(O)R^7$, $-OC(S)R^7$, $-C(O)NR^4R^5$, $-C(S)NR^4R^5$, $-C(O)NR^4OR^7$, $-C(S)NR^4OR^7$, $-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, -CN, $-OCF_3$, $-SCF_3$, $-C(=NR^7)NR^4$, $-C(O)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}OR^7$, $-C(S)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(S)NR^7(CH_2)_{1-10}OR^7$, haloalkyl and alkylsilyl, wherein each of said alkyl, cycloalkyl,

cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl or heteroaralkyl is independently optionally substituted with 1-5 R^9 moieties; and

R^{40} is selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl, wherein each of said cycloalkyl, heterocyclyl, aryl and heteroaryl are optionally independently substituted with 1-3 moieties independently selected from the group consisting of -CN, -OH, halo, alkyl, haloalkyl, alkoxy, and $-NR^{10}R^{11}$;

b. A compound represented by the structural Formula B:



Formula B

or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:

ring Y is a 5- to 7-membered ring selected from the group consisting of cycloalkyl, cycloalkenyl, heterocyclyl or heterocyclenyl fused as shown in Formula B, wherein in each of said 5- to 7-membered ring, each substitutable ring carbon is independently substituted with 1-2 R^2 moieties and each substitutable ring heteroatom is independently substituted with R^6;

W is N or $C(R^{12})$;

X is N or N-oxide;

Z is S, S(=O) or $S(=O)_2$;

R^1 is H, alkyl, alkoxy, hydroxy, halo, -CN, $-S(O)_m$-alkyl, $-C(O)NR^9R^{10}$, $-(CR^9R^{10})_{1-6}OH$, or $-NR^4(CR^9R^{10})_{1-2}OR^9$; wherein m is 0 to 2;

each R^2 is independently selected from the group consisting of H, halo, alkyl, cycloalkyl, alkylsilyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, heteroaryl, $-(CR^{10}R^{11})_{0-6}-OR^7$, $-C(O)R^4$, $-C(S)R^4$, $-C(O)OR^7$, $-C(S)OR^7$, $-OC(O)R^7$, $-OC(S)R^7$, $-C(O)NR^4R^5$, $-C(S)NR^4R^5$, $-C(O)NR^4OR^7$, $-C(S)NR^4OR^7$, $-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, -CN, $-OCF_3$, $-SCF_3$, $-C(=NR^7)NR^4$, $-C(O)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}OR^7$,

$-C(S)NR^7(CH_2)_{1-10}NR^4R^5$, and $-C(S)NR^7(CH_2)_{1-10}OR^7$, wherein each of said alkyl, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, and heteroaryl is independently optionally substituted with 1-5 R^9 moieties;

or two R^2s on the same carbon atom are optionally taken together with the carbon atom to which they are attached to form a C=O, a C=S or an ethylenedioxy group;

R^3 is independently selected from the group consisting of H, halo, alkyl, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, heteroaryl, $-(CR^{10}R^{11})_{0-6}-OR^7$, $-C(O)R^4$, $-C(S)R^4$, $-C(O)OR^7$, $-C(S)OR^7$, $-OC(O)R^7$, $-OC(S)R^7$, $-C(O)NR^4R^5$, $-C(S)NR^4R^5$, $-C(O)NR^4OR^7$, $-C(S)NR^4OR^7$, $-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, $-CN$, $-C(=NR^7)NR^4R^5$, $-C(O)N(R^7)-(CR^{40}R^{41})_{1-5}-C(=NR^7)NR^4R^5$, $-C(O)N(R^7)(CR^{40}R^{41})_{1-5}-NR^4R^5$, $-C(O)N(R^7)(CR^{40}R^{41})_{1-5}-C(O)-NR^4R^5$, $-C(O)N(R^7)(CR^{40}R^{41})_{1-5}-OR^7$, $-C(S)NR^7(CH_2)_{1-5}NR^4R^5$, and $-C(S)NR^7(CH_2)_{1-5}OR^7$, wherein each of said alkyl, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, and heteroaryl is independently optionally substituted with 1-5 R^9 moieties;

each of R^4 and R^5 is independently selected from the group consisting of H, alkyl, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, heteroaryl, $-OR^7$, $-C(O)R^7$, and $-C(O)OR^7$, wherein each of said alkyl, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, and heteroaryl, is optionally substituted with 1-4 R^8 moieties;

or R^4 and R^5, when attached to the same nitrogen atom, are optionally taken together with the nitrogen atom to which they are attached to form a 3-6 membered heterocyclic ring having 0-2 additional heteroatoms selected from N, O or S;

each R^6 is independently selected from the group consisting of H, alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroaralkyl, $-(CH_2)_{1-6}CF_3$, $-C(O)R^7$, $-C(O)OR^7$ and $-SO_2R^7$;

each R^7 is independently selected from the group consisting of H, alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, and heteroaralkyl, wherein each member of R^7 except H is optionally substituted with 1-4 R^8 moieties;

each R^8 is independently selected from the group consisting of halo, alkyl, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, heteroaryl, $-NO_2$, $-OR^{10}$, $-(C_1-C_6$ alkyl$)-OR^{10}$, $-CN$, $-NR^{10}R^{11}$, $-C(O)R^{10}$, $-C(O)OR^{10}$, $-C(O)NR^{10}R^{11}$, $-CF_3$, $-OCF_3$, $-CF_2CF_3$, $-C(=NOH)R^{10}$, $-N(R^{10})C(O)R^{11}$, $-C(=NR^{10})NR^{10}R^{11}$, and $-NR^{10}C(O)OR^{11}$; wherein said each of said alkyl, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, and heteroaryl is independently optionally substituted with 1-4 R^{42} moieties; wherein when each of said cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, and heteroaryl contains two radicals on adjacent carbon atoms anywhere within said cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, and heteroaryl, such radicals may optionally and independently in each occurrence, be taken together with the carbon atoms to which they are attached, to form a five- or six-membered carbocyclic or heterocyclic ring;

or two R^8 groups, when attached to the same carbon, are optionally taken together with the carbon atom to which they are attached to form a C=O or a C=S group;

each R^9 is independently selected from the group consisting of H, alkyl, alkoxy, OH, CN, halo, $-(CR^{10}R^{11})_{0-4}NR^4R^5$, haloalkyl, hydroxyalkyl, alkoxyalkyl, $-C(O)NR^4R^5$, $-C(O)OR^7$, $-OC(O)NR^4R^5$, $-NR^4C(O)R^5$, and $-NR^4C(O)NR^4R^5$;

each R^{10} is independently H or alkyl; or R^9 and R^{10}, when attached to the same nitrogen atom, are optionally taken together with the nitrogen atom to which they are attached to form a 3-6 membered heterocyclic ring having 0-2 additional heteroatoms selected from N, O or S;

each R^{11} is independently H, alkyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heterocyclenyl, or heteroaryl; or R^{10} and R^{11}, when attached to the same nitrogen atom, are optionally taken together with the nitrogen atom to which they are attached to form a 3-6 membered heterocyclic ring having 0-2 additional heteroatoms selected from N, O or S; wherein each of said R^{11} alkyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heterocyclenyl, and heteroaryl is independently optionally substituted with 1-3 moieties selected from the group consisting of –CN, -OH, $-NH_2$, -N(H)alkyl, $-N(alkyl)_2$, halo, haloalkyl, CF_3, alkyl, hydroxyalkyl, alkoxy, aryl, aryloxy, and heteroaryl;

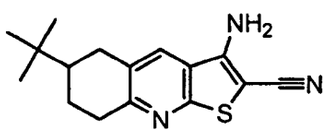
each R^{12} is independently selected from the group consisting of H, halo, alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, $-(CR^{10}R^{11})_{0-6}-OR^7$, $-C(O)R^4$, $-C(S)R^4$, $-C(O)OR^7$, $-C(S)OR^7$, $-OC(O)R^7$, $-OC(S)R^7$, $-C(O)NR^4R^5$, $-C(S)NR^4R^5$, $-C(O)NR^4OR^7$, $-C(S)NR^4OR^7$, $-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, -

$NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, -CN, $-OCF_3$, $-SCF_3$, $-C(=NR^7)NR^4$, $-C(O)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}OR^7$, $-C(S)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(S)NR^7(CH_2)_{1-10}OR^7$, haloalkyl and alkylsilyl, wherein each of said alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl or heteroaralkyl is independently optionally substituted with 1-5 R^9 moieties;

R^{40} and R^{41} can be the same or different, each being independently selected from the group consisting of H, alkyl, aryl, heteroaryl, heterocyclyl, heterocyclenyl, cycloalkyl and cycloalkenyl;

each R^{42} is independently selected from the group consisting of halo, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-NO_2$, $-OR^{10}$, $-(C_1-C_6$ alkyl$)-OR^{10}$, -CN, $-NR^{10}R^{11}$, $-C(O)R^{10}$, $-C(O)OR^{10}$, $-C(O)NR^{10}R^{11}$, $-CF_3$, $-OCF_3$, $-N(R^{10})C(O)R^{11}$, and $-NR^{10}C(O)OR^{11}$;

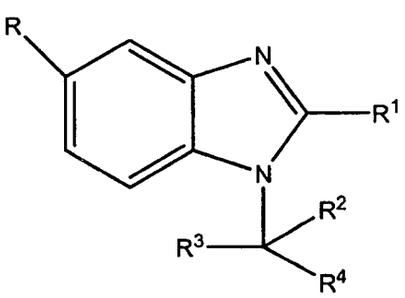
with the proviso that when W is $C(R^{12})$, R^{12} and R^3 are optionally taken together, with the two ring carbon atoms to which they are attached to form a 6-membered ring selected from the group consisting of cycloalkenyl, aryl, heteroaryl, heterocyclyl and heterocyclenyl, wherein said 6-membered ring is optionally substituted with 1-3 moieties independently selected from oxo, thioxo, $-OR^{11}$, $-NR^{10}R^{11}$, $-C(O)R^{11}$, $-C(O)OR^{11}$, $-C(O)N(R^{10})(R^{11})$, or $-N(R^{10})C(O)R^{11}$;

c. 

Formula C

or a pharmaceutically acceptable salt, solvate, or ester thereof; and

d. A compound of Formula D



Formula D

or a pharmaceutically acceptable salt, solvate, or ester thereof, wherein:

R is selected from the group consisting of H, alkyl, cyano, haloalkyl, halo, —SH, -S-alkyl, -S-haloalkyl, $-S(=O)_2$alkyl, $-S(=O)_2OH$, $-S(=O)_2NH_2$, $-S(=O)_2NH$(alkyl), $S(=O)_2NH$(cycloalkyl), $-S(=O)_2N(alkyl)_2$, $-S(=O)_2$heterocyclyl, $-S(=O)_2$heteroaryl, cycloalkyl, aryl, heterocyclyl, heteroaryl, -NHC(=O)alkyl, –$C(=O)NH_2$, –C(=O)NH(alkyl), -C(=O)NH(cycloalkyl), $-C(=O)N(alkyl)_2$, –C(=O)OH, –C(=O)Oalkyl, -C(=O)heterocyclyl, -C(=O)NH(aryl), wherein when each of said cycloalkyl, aryl, heterocyclyl, heteroaryl, and the "heterocyclyl" and "aryl" portions of said R groups has two substituents on adjacent carbon atoms, said substituents, may optionally be taken together with the carbon atoms to which they are attached to form a five- to six-membered cycloalkyl, aryl, heterocyclyl, heterocyclenyl, or heteroaryl ring; wherein each of the aforementioned R alkyl, aryl, cycloalkyl, heterocyclyl, and heteroaryl, and the "alkyl", "cycloalkyl", "heterocyclyl", and "aryl" portions of said R groups, optionally with said five- to six-membered aryl, heterocyclyl, heterocyclenyl, or heteroaryl ring, is optionally substituted with 1-3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, hydroxyl, cyano, halo, haloalkyl, haloalkoxy, -C(O)OH, -C(=O)Oalkyl, and $-C(O)NH_2$;

R^1 is selected from the group consisting of alkyl, heterocyclyl, -C(=O)aryl, $-NH_2$, -NH(alkyl), -NH(cycloalkyl), -N(alkyl)(cycloalkyl), -NH(heterocyclyl), -N(alkyl)(heterocyclyl), $N(alkyl)_2$, -NH(aryl), -N(alkyl)(aryl), $-N(aryl)_2$, -NH(heteroaryl), -N(alkyl)(heteroaryl), -NHC(=O)-alkyl, -N(alkyl)C(=O)-alkyl, -NHC(=O)Oalkyl, -N(alkyl)C(=O)O-alkyl, wherein each of the aforesaid alkyl, heterocyclyl, and the "alkyl", "cycloalkyl", "aryl", and "heteroaryl" portions of said R^1 groups is optionally substituted with 1-3 substituents independently selected from the group consisting of halo, heterocyclyl, aryl, heteroaryl, haloalkyl, haloalkoxy, aryloxy, cyano, –SH, -S-alkyl, -S-haloalkyl, $-S(=O)_2$alkyl, $-S(=O)_2OH$, $-S(=O)_2NH_2$, $-S(=O)_2NH$(alkyl), $S(=O)_2NH$(cycloalkyl), $-S(=O)_2N(alkyl)_2$, $-S(=O)_2$heterocyclyl, $-S(=O)_2$heteroaryl, hydroxy, alkyl, alkenyl, alkynyl, $-NH_2$, -NH(alkyl), $-N(alkyl)_2$, alkoxy, -NHC(=O)alkyl, -C(=O)H, -C(=O)alkyl, -C(=O)aryl, , -C(=O)heteroaryl, -C(=O)Oalkyl, $-C(=O)NH_2$, -C(O)NHalkyl, $-C(=O)N(alkyl)_2$; wherein when each of said heterocyclyl, aryl and heteroaryl has two substituents on adjacent carbon atoms,

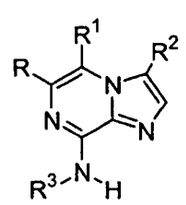
said substituents, may optionally be taken together with the carbon atoms to which they are attached to form a five to six-membered aryl, heterocyclyl, heterocyclenyl, or heteroaryl ring;

R^2 and R^3 independently are H or alkyl, or $-C(R^2)(R^3)-$ is absent;

R^4 is selected from the group consisting of alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl, wherein when each of said cycloalkyl, heterocyclyl, aryl, and heteroaryl has two substituents on adjacent carbon atoms, said substituents, may optionally be taken together with the carbon atoms to which they are attached to form a five to six-membered aryl, heterocyclyl, heterocyclenyl, or heteroaryl ring; wherein each of the aforementioned R^4 alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl, optionally with said five to six-membered aryl, heterocyclyl, heterocyclenyl, or heteroaryl ring is optionally substituted with 1-3 substituents independently selected from the group consisting of cyano, halo, haloalkyl, alkyl, alkoxy, hydroxyl, haloalkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-S(=O)_2$alkyl, $-S(=O)_2NH_2$, $-S(=O)_2NH$(alkyl), $-S(=O)_2N$(alkyl)$_2$, -S-alkyl, -S-haloalkyl, $-C(=O)OH$, $-NH_2$, -NH(alkyl), $-N$(alkyl)$_2$, and $-C(=O)O$alkyl;

and (b) one or more of a second compound, wherein said second compound is an aurora kinase inhibitor selected from the group consisting of compounds represented by Formulas E-K shown below in paragraphs e-k:

e. A compound represented by the structural Formula E:



Formula E

or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, wherein:

R is H, CN, $-NR^5R^6$, cycloalkyl, cycloalkenyl, heterocyclenyl, heteroaryl, $-C(O)NR^5R^6$, $-N(R^5)C(O)R^6$, heterocyclyl, heteroaryl substituted with $(CH_2)_{1-3}$ NR^5R^6, unsubstituted alkyl, or alkyl substituted with one or more moieties which can be the same or different each moiety being independently selected from the group consisting of $-OR^5$, heterocyclyl,

$-N(R^5)C(O)N(R^5R^6)$, $-N(R^5)-C(O)OR^6$, $-(CH_2)_{1-3}-N(R^5R^6)$ and $-NR^5R^6$;

R^1 is H, halo, aryl or heteroaryl, wherein each of said aryl and heteroaryl can be unsubstituted or substituted with one or more moieties which can be the same or different each moiety being independently selected from the group consisting of halo, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, $-CH_2OR^5$, $-C(O)NR^5R^6$, -C(O)OH, $-C(O)NH_2$,
$-NR^5R^6$ (wherein the R^5 and R^6, together with the N of said $-NR^5R^6$, form a heterocyclyl ring), $-S(O)R^5$, $-S(O_2)R^5$, -CN, -CHO, $-SR^5$, $-C(O)OR^5$, $-C(O)R^5$ and $-OR^5$;

R^2 is H, halo, aryl, arylalkyl or heteroaryl, wherein each of said aryl, arylalkyl and heteroaryl can be unsubstituted or optionally independently be substituted with one or more moieties which can be the same or different each moiety being independently selected from the group consisting of halo, amide, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, -C(O)OH, $-C(O)NH_2$, $-NR^5R^6$ (wherein the R^5 and R^6, together with the N of said $-NR^5R^6$, form a heterocyclyl ring), -CN, arylalkyl, $-CH_2OR^5$, $-S(O)R^5$, $-S(O_2)R^5$, -CN, -CHO, $-SR^5$, $-C(O)OR^5$, $-C(O)R^5$, heteroaryl and heterocyclyl;

R^3 is H, alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl, wherein:

- said alkyl shown above for R^3 can be unsubstituted or substituted with one or more moieties which can be the same or different each moiety being independently selected from the group consisting of $-OR^5$, alkoxy, heteroaryl, and $-NR^5R^6$;
- said aryl shown above for R^3 is unsubstituted, or optionally substituted, or optionally fused, with halo, heteroaryl, heterocyclyl, cycloalkyl or heteroarylalkyl, wherein each of said heteroaryl, heterocyclyl, cycloalkyl and heteroarylalkyl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different each moiety being independently selected from alkyl, $-OR^5$, $-N(R^5R^6)$ and $-S(O_2)R^5$; and
- said heteroaryl shown above for R^3 can be unsubstituted or optionally substituted, or optionally fused, with one or more moieties which can be the same or different with each moiety being independently selected from the group consisting of halo, amino, alkoxycarbonyl, $-OR^5$, alkyl, -CHO, $-NR^5R^6$, $-S(O_2)N(R^5R^6)$,

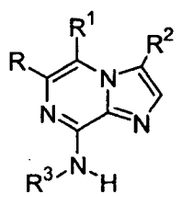
-C(O)N(R^5R^6), -SR^5, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclenyl, and heterocyclyl;

R^5 is H, alkyl, aminoalkyl, aryl, heteroaryl, heterocyclyl or cycloalkyl; and

R^6 is H, alkyl, aryl, arylalkyl, heteroaryl, heterocyclyl or cycloalkyl;

further wherein in any -NR^5R^6 in Formula I, said R^5 and R^6 can optionally be joined together with the N of said -NR^5R^6 to form a cyclic ring;

f. A compound represented by the structural formula:

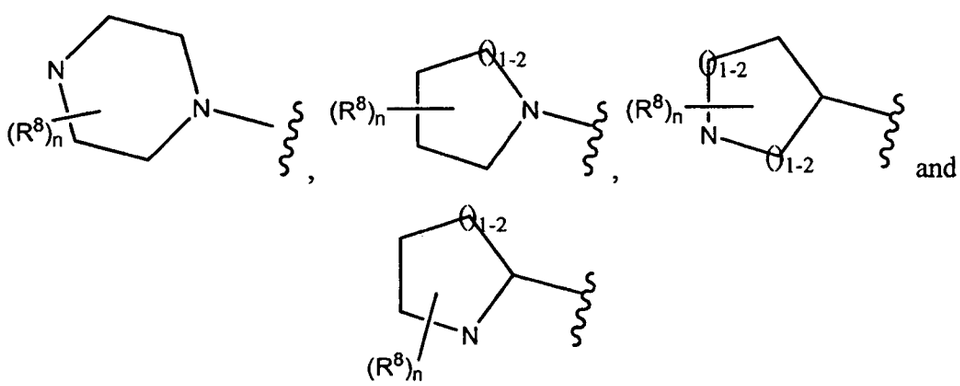


Formula F

or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, wherein:

R is selected from the group consisting of H, halogen, aryl, heteroaryl, cycloalkyl, arylalkyl, heterocyclyl, heterocyclylalkyl, alkenyl, alkynyl,

-C(O)R^7,



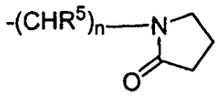
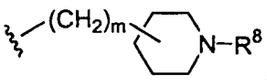
and

wherein each of said aryl, heteroaryl, cycloalkyl, arylalkyl, alkenyl, heterocyclyl and the heterocyclyl moieties whose structures are shown immediately above for R can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, cycloalkyl, CF_3, CN, -OCF_3,

-OR^6, -C(O)R^7, -NR^5R^6, -$C(O_2)R^6$, -C(O)NR^5R^6, -$(CHR^5)_nOR^6$, -SR^6, -$S(O_2)R^7$, -$S(O_2)NR^5R^6$, -$N(R^5)S(O_2)R^7$, -$N(R^5)C(O)R^7$ and -$N(R^5)C(O)NR^5R^6$;

R^1 is H, halogen or alkyl;

R^2 is alkyl;

R^3 is selected from the group consisting of H, aryl, heteroaryl, heterocyclyl, -$(CHR^5)_n$-aryl, - $(CHR^5)_n$-heteroaryl, -$(CHR^5)_n$-OR^6, -$S(O_2)R^6$, -$C(O)R^6$, -$S(O_2)NR^5R^6$, -$C(O)OR^6$, -$C(O)NR^5R^6$, cycloalkyl, -$CH(aryl)_2$, –$(CH_2)_m$-NR^8, -$(CHR^5)_n$-$CH(aryl)_2$, 
and  , wherein each of said aryl, heteroaryl and heterocyclyl can be substituted or optionally substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl, cycloalkyl, CF_3, CN, -OCF_3, -OR^5, -NR^5R^6, -$C(O_2)R^5$, -$C(O)NR^5R^6$, -SR^6, -$S(O_2)R^6$, -$S(O_2)NR^5R^6$, -$N(R^5)S(O_2)R^7$, -$N(R^5)C(O)R^7$ and -$N(R^5)C(O)NR^5R^6$;

R^5 is H or alkyl;

R^6 is selected from the group consisting of H, alkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, wherein each of said alkyl, heteroarylalkyl, aryl, heteroaryl and arylalkyl can be unsubstituted or optionally substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl, cycloalkyl, CF_3, OCF_3, CN, -OR^5, -NR^5R^6, -CH_2OR^5, -$C(O_2)R^5$, -$C(O)NR^5R^6$, -SR^6, -$S(O_2)R^7$, -$S(O_2)NR^5R^6$, -$N(R^5)S(O_2)R^7$, -$N(R^5)C(O)R^7$ and -$N(R^5)C(O)NR^5R^6$;

R^7 is selected from the group consisting of alkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, wherein each of said alkyl, heteroarylalkyl, aryl, heteroaryl and arylalkyl can be unsubstituted or optionally substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl, cycloalkyl, CF_3, OCF_3, CN, -OR^5, -NR^5R^6, -CH_2OR^5, -$C(O_2)R^5$, -$C(O)NR^5R^6$, -SR^6, -$S(O_2)R^7$, -$S(O_2)NR^5R^6$, -$N(R^5)S(O_2)R^7$, -$N(R^5)C(O)R^7$ and -$N(R^5)C(O)NR^5R^6$;

R^8 is selected from the group consisting of R^6, -$C(O)NR^5R^6$, -$S(O_2)NR^5R^6$, -$C(O)R^7$, -$C(O_2)R^6$, –$S(O_2)R^7$ and –(CH_2)-aryl;

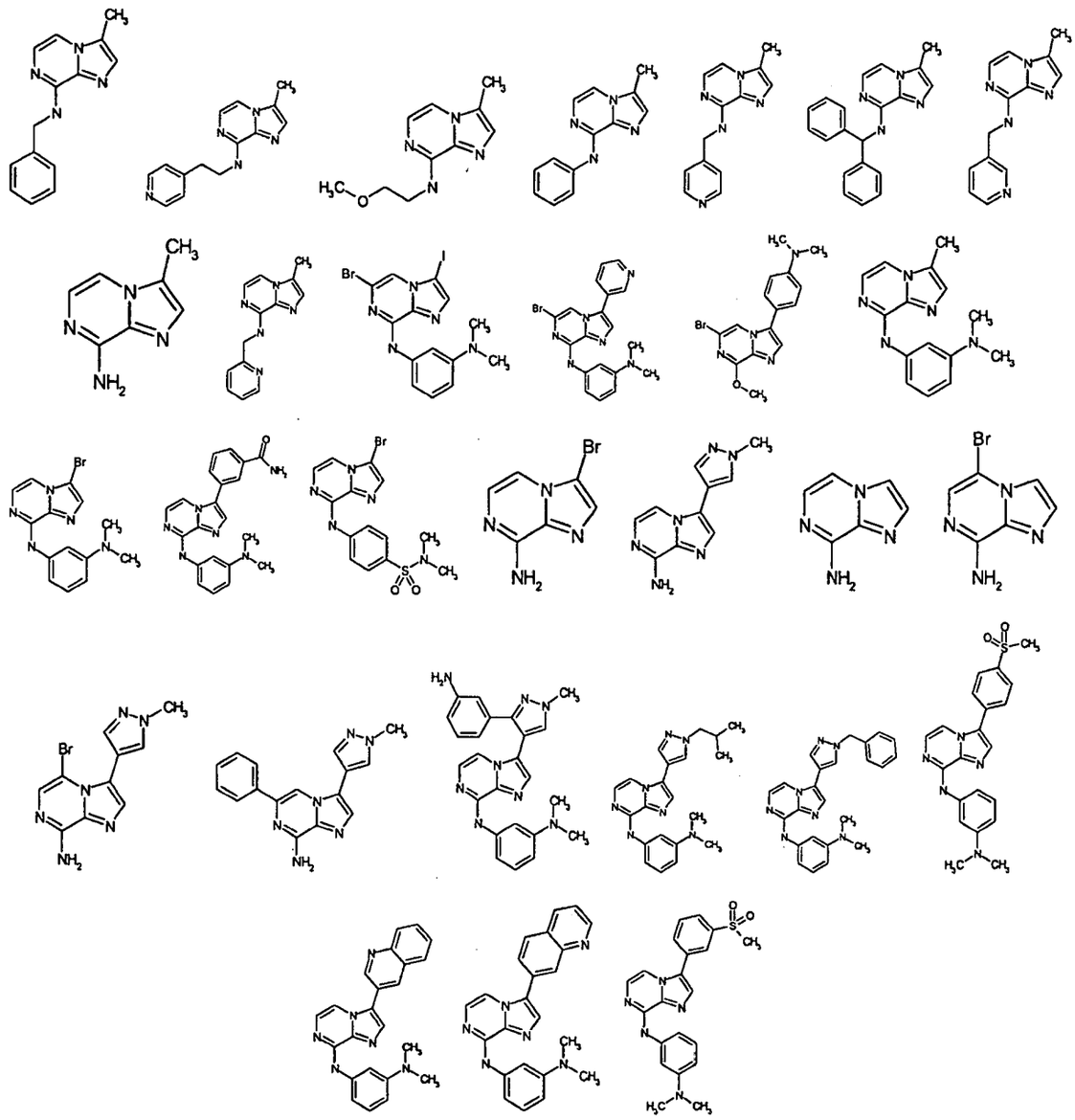
R^9 is selected from the group consisting of halogen, CN, NR^5R^6, -$C(O_2)R^6$, -$C(O)NR^5R^6$, -OR^6, -$C(O)R^7$, -SR^6, -$S(O_2)R^7$, -$S(O_2)NR^5R^6$, -$N(R^5)S(O_2)R^7$, -$N(R^5)C(O)R^7$and –$N(R^5)C(O)NR^5R^6$;

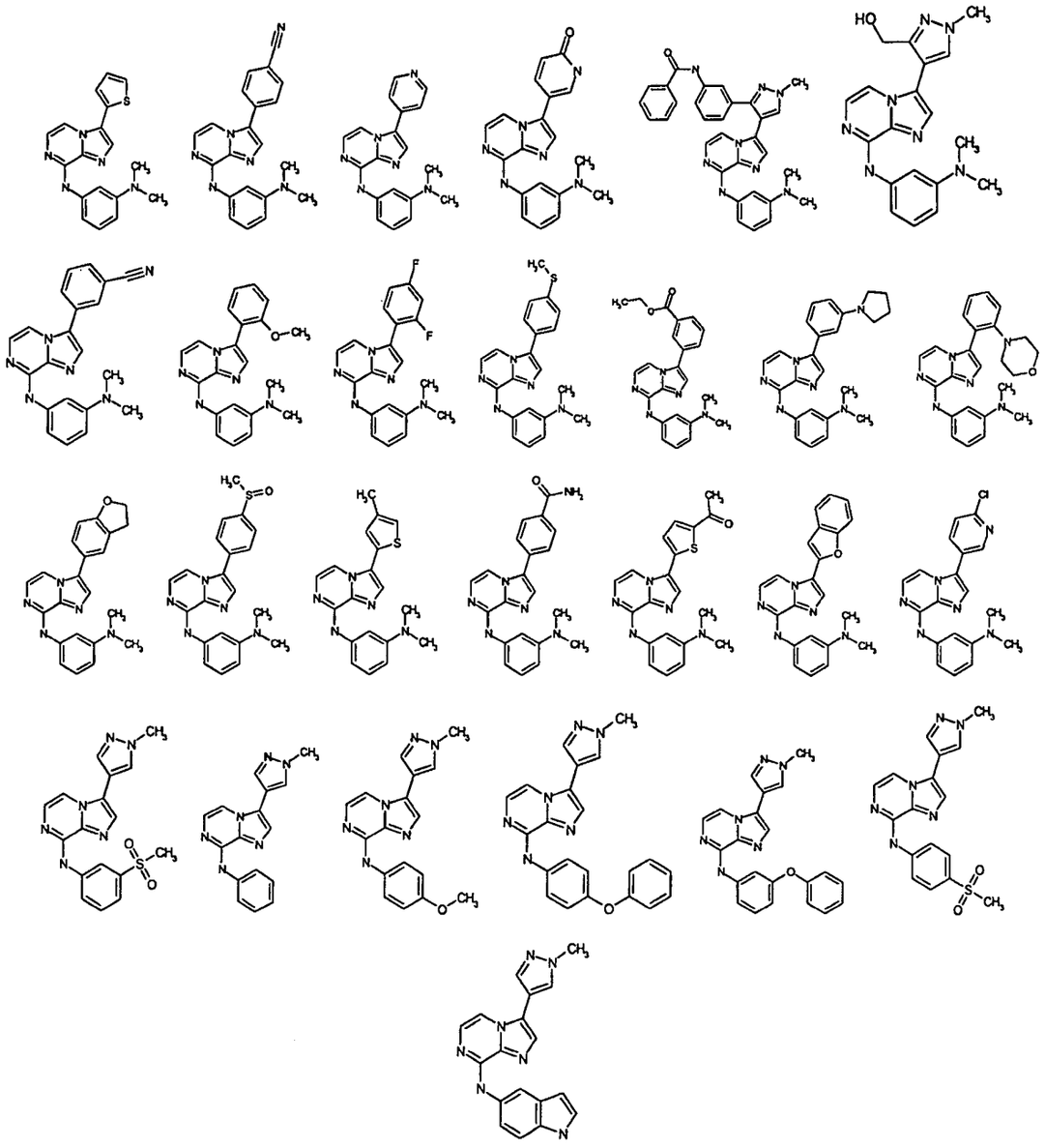
m is 0 to 4;

n is 1-4; and

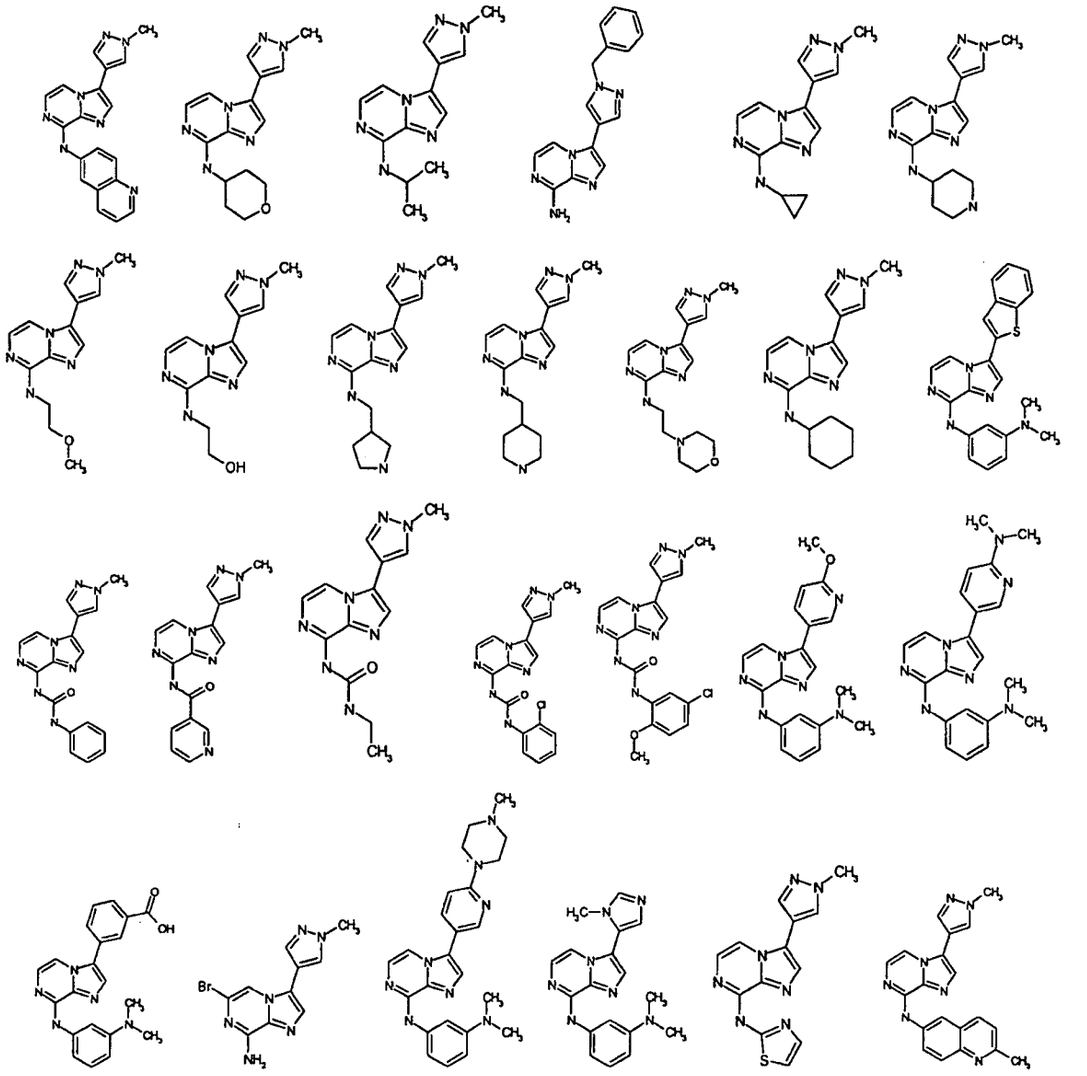
p is 0-3;

g. A compound selected from the compounds of the formulas:

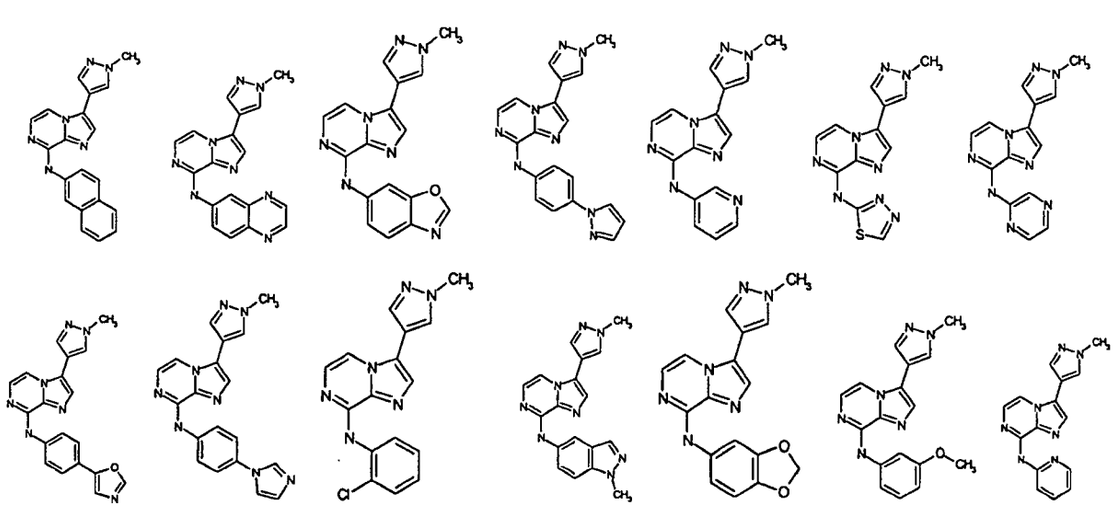


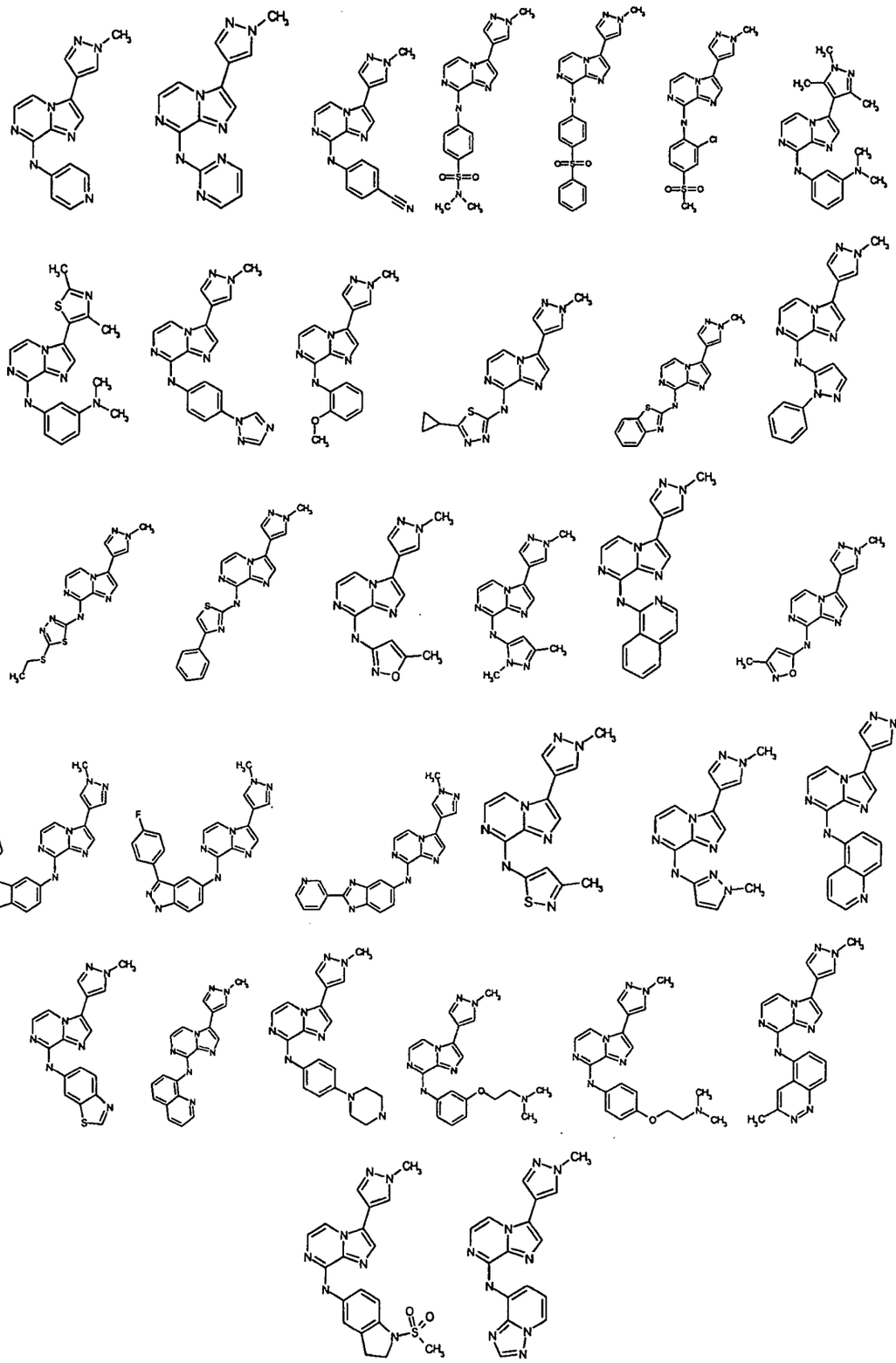


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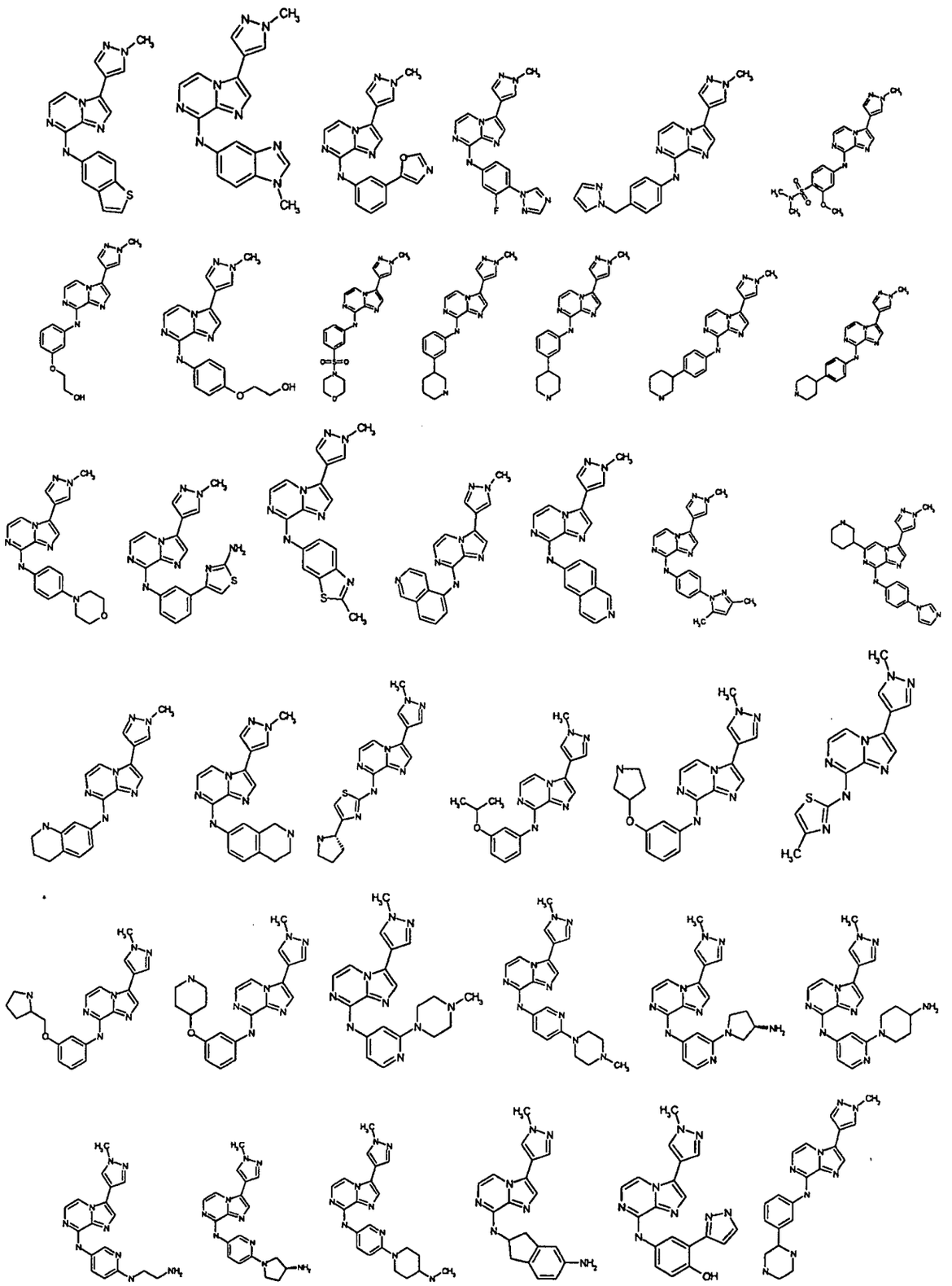


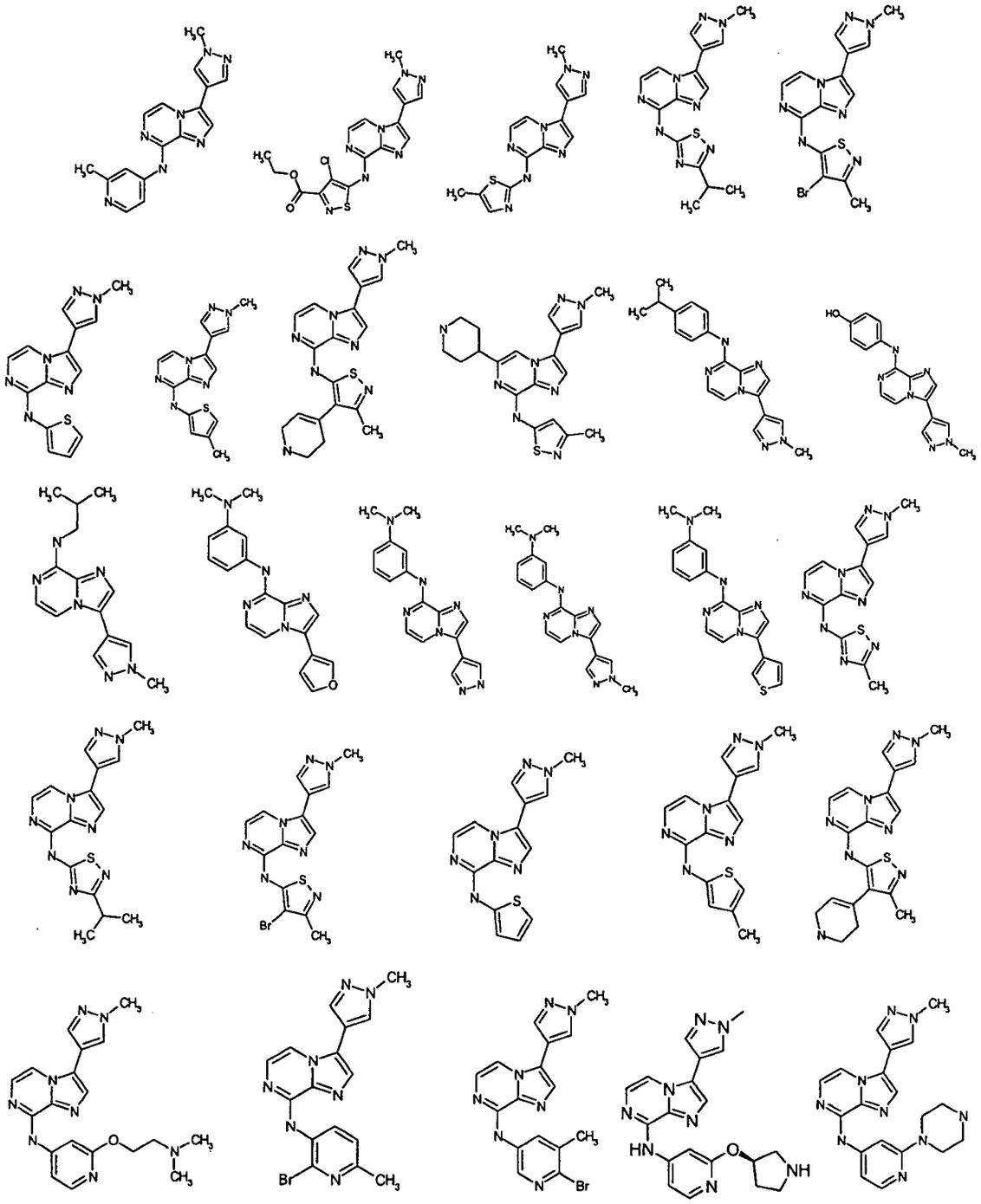
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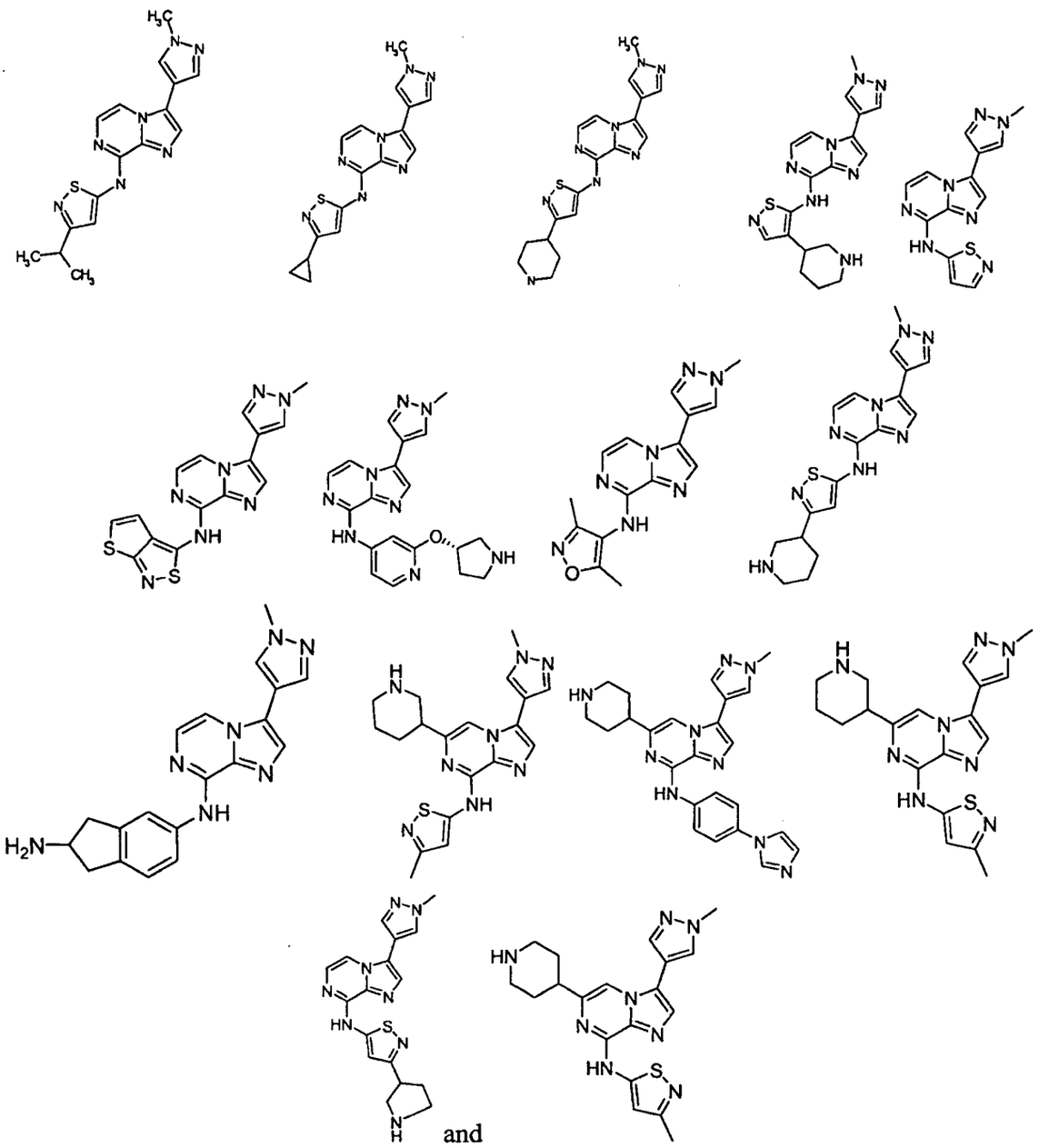


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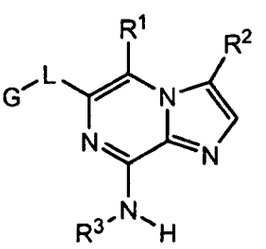
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and

or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof;

h. A compound of the formula:



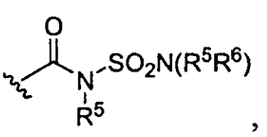
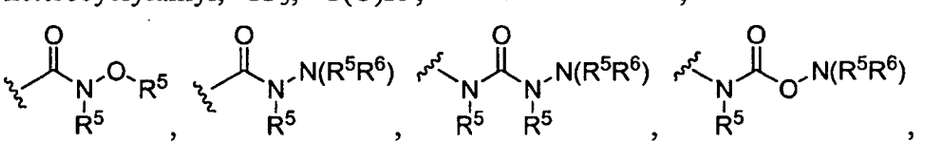
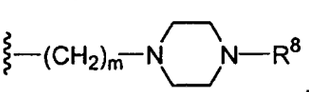
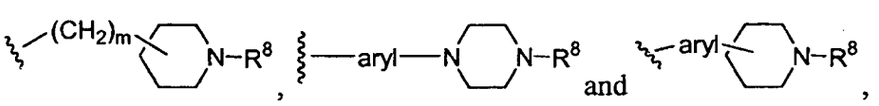
Formula H

or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, wherein:

L is selected from the group consisting of S, S(O) and $S(O_2)$;

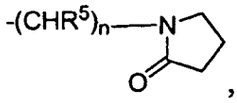
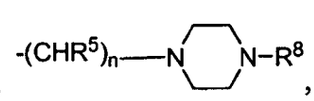
G is alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclenyl or heterocyclyl, wherein each of said alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclenyl or heterocyclyl can be unsubstituted or optionally independently substituted with one or more moieties which are independently selected from the group consisting of $-OR^5$, halo, -CN, $-C(O)NR^5R^6$, $-N(H)-C(O)R^5$, $-N(H)-C(O)-NR^5R^6$, $-S(O_2)NR^5R^6$, $-NR^5R^6$, $-C(O)R^5$, $-C(O_2)R^5$, $-SR^5$, $-S(O)R^5$, $-S(O_2)R^5$;

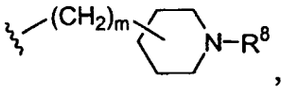
R^1 is H, halo, alkyl, aryl or heteroaryl, wherein each of said alkyl, aryl and heteroaryl can be unsubstituted or substituted with one or more moieties which can be the same or different each moiety being independently selected from the group consisting of halo, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C(O)NR^5R^6$ and $-OR^5$;

R^2 is selected from the group consisting of H, R^9, alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclylalkyl, $-CF_3$, $-C(O)R^7$,  ,  , alkyl substituted with 1-6 R^9 groups which groups can be the same or different with each R^9 being independently selected,  ,  , wherein each of the above-said aryl, heteroaryl, cycloalkyl, arylalkyl and heterocyclyl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halo, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, CF_3, CN, $-OCF_3$, $-OR^6$, $-C(O)R^7$, $-NR^5R^6$, $-C(O_2)R^6$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$,

$-N(R^5)C(O)R^7$ and $-N(R^5)C(O)NR^5R^6$;

R^3 is selected from the group consisting of H, alkyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroarylalkyl, cycloalkylalkyl, heterocyclylalkyl,



$-(CHR^5)_n-OR^6$, $-S(O_2)R^6$, $-C(O)R^6$, $-S(O_2)NR^5R^6$, $-C(O)OR^6$, $-C(O)NR^5R^6$, cycloalkyl, $-CH(aryl)_2$, $-CH(heteroaryl)_2$, $-(CH_2)_m-NR^8$, and


, wherein each of said alkyl, aryl, heteroaryl and heterocyclyl can be substituted or optionally substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halo, alkyl, aryl, cycloalkyl, CF_3, CN, $-OCF_3$, $-OR^5$, $-NR^5R^6$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^6$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ and $-N(R^5)C(O)NR^5R^6$;

R^5 is H, alkyl, aryl, heteroaryl, heterocyclyl or cycloalkyl; and

R^6 is selected from the group consisting of H, alkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, wherein each of said alkyl, heteroarylalkyl, aryl, heteroaryl and arylalkyl can be unsubstituted or optionally substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl, cycloalkyl, CF_3, OCF_3, CN, $-OR^5$, $-NR^5R^6$, $-CH_2OR^5$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ and $-N(R^5)C(O)NR^5R^6$;

R^7 is selected from the group consisting of alkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, wherein each of said alkyl, heteroarylalkyl, aryl, heteroaryl and arylalkyl can be unsubstituted or optionally substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl, cycloalkyl, CF_3, OCF_3, CN, $-OR^5$, $-NR^5R^6$, $-CH_2OR^5$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ and $-N(R^5)C(O)NR^5R^6$;

R^8 is selected from the group consisting of R^6, $-C(O)NR^5R^6$, $-S(O_2)NR^5R^6$, $-C(O)R^7$, $-C(O_2)R^6$, $-S(O_2)R^7$ and $-(CH_2)$-aryl;

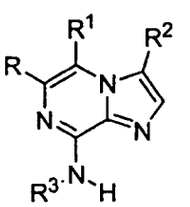
R^9 is selected from the group consisting of halogen, CN, NR^5R^6, $-C(O_2)R^6$, $-C(O)NR^5R^6$, $-OR^6$, $-C(O)R^7$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$,

$-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$and $-N(R^5)C(O)NR^5R^6$;

m is 0 to 4; and

p is 0-3;

i. A compound of Formula I:



Formula I

or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, wherein:

R is H, CN, $-NR^5R^6$, cycloalkyl, cycloalkenyl, heterocyclenyl, heteroaryl, $-C(O)NR^5R^6$, $-N(R^5)C(O)R^6$, heterocyclyl, heteroaryl substituted with $(CH_2)_{1-3}$ NR^5R^6, unsubstituted alkyl, or alkyl substituted with one or more moieties which can be the same or different each moiety being independently selected from the group consisting of $-OR^5$, heterocyclyl, $-N(R^5)C(O)N(R^5R^6)$, $-N(R^5)$-$C(O)OR^6$, $-(CH_2)_{1-3}$-$N(R^5R^6)$ and $-NR^5R^6$;

R^1 is H, halo, aryl or heteroaryl, wherein each of said aryl and heteroaryl can be unsubstituted or substituted with one or more moieties which can be the same or different each moiety being independently selected from the group consisting of halo, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, $-CH_2OR^5$, $-C(O)NR^5R^6$, -C(O)OH, $-C(O)NH_2$, $-NR^5R^6$ (wherein the R^5 and R^6, together with the N of said $-NR^5R^6$, form a heterocyclyl ring), $-S(O)R^5$, $-S(O_2)R^5$, -CN, -CHO, $-SR^5$, $-C(O)OR^5$, $-C(O)R^5$ and $-OR^5$;

R^2 is H, halo, aryl, arylalkyl or heteroaryl, wherein each of said aryl, arylalkyl and heteroaryl can be unsubstituted or optionally independently be substituted with one or more moieties which can be the same or different each moiety being independently selected from the group consisting of halo, amide, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, -C(O)OH, $-C(O)NH_2$, $-NR^5R^6$ (wherein the R^5 and R^6, together with the N of said $-NR^5R^6$, form a heterocyclyl ring), -CN, arylalkyl, $-CH_2OR^5$, $-S(O)R^5$, $-S(O_2)R^5$, -CN, -CHO, $-SR^5$, $-C(O)OR^5$, $-C(O)R^5$, heteroaryl and

heterocyclyl;

R^3 is heterocyclyl–$(CR^7R^8)_n$-X, heterocyclenyl–$(CR^7R^8)_n$-X, heteroaryl–$(CR^7R^8)_n$-X or aryl–$(CR^7R^8)_n$-X wherein each of the heterocyclyl-, heterocyclenyl-, heteroaryl- or aryl-moieties of said R^3 can be unsubstituted or substituted with one or more moieties, independently selected from the group consisting of $–CONR^5R^6$, $–OR^5$ and alkyl,

n is 1-6,

X is selected from the group consisting of $-NR^5R^6$, $-OR^5$, –SO-R^5, $-SR^5$, SO_2R^5, heteroaryl, heterocyclyl and aryl, wherein said heteroaryl or aryl can be unsubstituted or substituted with one or more moieties, independently selected from the group consisting of –O-alkyl, alkyl, halo, or NR^5R^6;

R^7 and R^8 are each independently hydrogen, alkyl, heterocyclyl, aryl, heteroaryl or cycloalkyl;

R^5 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkoxyalkyl, -alkyl-S-alkyl, aminoalkyl, aryl, heteroaryl, heterocyclenyl, heterocycloalkyl, cycloalkyl, cyclenyl, heterocyclylalkoxyl, -S-alkylheterocyclyl, heterocyclyl, heterocyclenyl, alkylN(alkyl)$_2$, alkylNH(alkyl), alkylN(alkenyl)2, -alkylN(alkoxyl)2, -alkyl-SH, hydroxyalkyl, trihaloalkyl, dihaloalkyl, monohaloalkyl, wherein each of said alkyl, alkenyl, alkoxyalkyl, -alkyl-S-alkyl, aminoalkyl, aryl, heteroaryl, heterocyclenyl, heterocycloalkyl, cycloalkyl, cyclenyl, heterocyclylalkoxyl, -S-alkylheterocyclyl, heterocyclyl, heterocyclenyl, alkylN(alkyl)$_2$, alkylNH(alkyl), alkylN(alkenyl)2, -alkylN(alkoxyl)2, -alkyl-SH, hydroxyalkyl, trihaloalkyl, dihaloalkyl, monohaloalkyl can be unsubstituted or substituted with one or more moieties independently selected from the group consisting of alkyl, alkenyl, aryl, cyclenyl, cycloalkyl, arylalkyl, cyclenylalkyl, cycloalkylalkyl, heteroaryl, heterocyclenyl, heterocyclyl, heteroarylalkyl, heterocyclenylalkyl, heterocycloalkylalkyl, alkoxyalkyl, -alkyl-S-alkyl, -alkylSH, alkoxyl, -S-alkyl, hydroxyalkyl, and aminoalkyl;

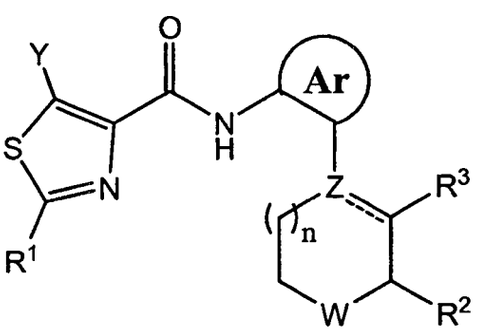
R^6 is selected from the group consisting of hydrogen, alkyl, alkenyl, aryl, cyclenyl, cycloalkyl, arylalkyl, cyclenylalkyl, cycloalkylalkyl, heteroaryl, heterocyclenyl, heterocyclyl, heteroarylalkyl, heterocyclenylalkyl, heterocycloalkylalkyl, alkoxyalkyl, -alkyl-S-alkyl, -alkylSH, alkoxyl, -S-alkyl, hydroxyalkyl,

aminoalkyl, -alkyl-OC(O)alkyl, -alkylOC(O)cycloalkyl, -alkylOC(O)aryl, -alkylOC(O)aralkyl, -alkylOC(O)NR^{5}aryl, -alkylOC(O)NR^{5}alkyl, -alkylOC(O)NR^{5}heterocyclyl, -alkylOC(O)NR^{5}heteroaryl -alkylOC(O)NR^{5}cycloalkyl, -alkylOC(O)heterocyclyl, alkylC(O)OH, alkylC(O)Oalkyl, -alkylC(O)Ocycloalkyl, -alkylC(O)Oaryl, -alkylC(O)Oaralkyl, -alkylC(O)ONR^{5}aryl, -alkylC(O)ONR^{5}alkyl, -alkylC(O)ONR^{5}heterocyclyl, -alkylC(O)ONR^{5}heteroaryl -alkylC(O)ONR^{5}cycloalkyl, -alkylC(O)Oheterocyclyl, alkylC(O)OH, and alkylC(O)Oalkyl wherein each of said aryl, cyclenyl, cycloalkyl, arylalkyl, cyclenylalkyl, cycloalkylalkyl, heteroaryl, heterocyclenyl, heterocyclyl, heteroarylalkyl, heterocyclenylalkyl, heterocycloalkylalkyl, -alkyl-OC(O)alkyl, -alkylOC(O)cycloalkyl, -alkylOC(O)aryl, -alkylOC(O)aralkyl, -alkylOC(O)NR^{5}aryl, -alkylOC(O)NR^{5}alkyl, -alkylOC(O)NR^{5}heterocyclyl, -alkylOC(O)NR^{5}heteroaryl -alkylOC(O)NR^{5}cycloalkyl, -alkylOC(O)heterocyclyl, alkylC(O)OH, alkylC(O)Oalkyl, -alkylC(O)Ocycloalkyl, -alkylC(O)Oaryl, -alkylC(O)Oaralkyl, -alkylC(O)ONR^{5}aryl, -alkylC(O)ONR^{5}alkyl, -alkylC(O)ONR^{5}heterocyclyl, -alkylC(O)ONR^{5}heteroaryl -alkylC(O)ONR^{5}cycloalkyl, -alkylC(O)Oheterocyclyl, alkylC(O)OH, and alkylC(O)Oalkyl,can be unsubstituted or substituted with one or more moieties independently selected from the group consisting of alkyl, alkenyl, aryl, cyclenyl, cycloalkyl, arylalkyl, cyclenylalkyl, cycloalkylalkyl, heteroaryl, heterocyclenyl, heterocyclyl, heteroarylalkyl, heterocyclenylalkyl, heterocycloalkylalkyl, alkoxyalkyl, -alkyl-S-alkyl, -alkylSH, alkoxyl, -S-alkyl, hydroxyalkyl, aminoalkyl, amino, aminodialkyl, aminocycloalkyl, halo, trihaloalkyl, dihaloalkyl, and monohaloalkyl;

further wherein in any -NR^{5}R^6 in Formula I, said R^5 and R^6 can optionally be joined together with the N of said -NR^{5}R^6 to form a cyclic ring or bridged cyclic ring, wherein each of said cyclic ring or bridged cyclic ring, can be unsubstituted or substituted with one or more moieties, which can be the same or different, independently selected from the group consisting of hydroxyl, -SH, alkyl, alkenyl, hydroxyalkyl, -alkyl-SH, alkoxyl, -S-alkyl, -CO_2-alkyl, -CO_2-alkenyl,

arylalkyl, cyclenylalkyl, cycloalkylalkyl, heteroarylalkyl, heterocyclenylalkyl, heterocycloalkylalkyl, heteroaryl, aryl, cyclenyl, cycloalkyl, spiroheterocyclyl, spiroheterocyclenyl, spiroheteroaryl, spirocyclyl, spirocyclenyl, spiroaryl, alkoxyalkyl, -alkyl-S-alkyl, heterocyclyl, heterocyclenyl, halo, trihaloalkyl, dihaloalkyl, CN and monohaloalkyl.

j. A compound having the formula:



(J)

or a pharmaceutically acceptable salt, solvate, ester, prodrug or stereoisomer thereof, wherein the dashed lines indicate an optional and additional bond, and wherein:

R^1 is nitrogen-containing heteroaryl, nitrogen-containing heterocyclyl, nitrogen-containing benzofused heteroaryl or nitrogen-containing benzofused heterocyclyl, wherein R^1 is joined to the rest of the compound of formula (I) via a ring nitrogen atom, and wherein one or more ring carbon atoms of a nitrogen-containing heteroaryl, nitrogen-containing heterocyclyl, nitrogen-containing benzofused heteroaryl or nitrogen-containing benzofused heterocyclyl group can be substituted with up to 5 substituents, which may be the same or different, and are independently selected from alkyl, aryl, halo, -OH, -O-alkyl, -O-aryl, -$N(R^8)_2$, $-CF_3$, $-NO_2$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)N(R^8)_2$, $-OC(O)R^8$ or $-NHC(O)R^8$;

R^2 is –H, -alkyl, $–NH_2$ or $–CH_2NH_2$;

R^3 is –H, -alkyl, $–NH_2$ or $–CH_2NH_2$;

each occurrence of R^4 is independently –H, -alkyl, $–NH_2$, -OH, -alkylene-OH, $–CH_2NH_2$, $-C(O)R^5$, $-C(O)NH_2$, -C(O)NH-alkyl, $-C(O)N(alkyl)_2$, $-NHC(O)R^6$ or $–NHS(O)_2R^6$;

R^5 is –H, -alkyl, -aryl, -heteroaryl, -NHOH;

R^6 is –H, -alkyl or $–CF_3$;

R^7 is –H, -OH, $-C_1$-C_6 alkyl, $-O-(C_1$-C_6 alkyl), or $–CF_3$;

R^8 is –H, alkyl, aryl, heterocyclyl, heteroaryl or cycloalkyl;

Ar is -arylene- or -heteroarylene-, wherein the arylene or heteroarylene is joined via 2 of its adjacent ring carbon atoms, and wherein the -arylene- or -heteroarylene- can be substituted with up to 4 substituents, which may be the same or different, and are independently selected from –halo, alkyl, alkoxy, aryloxy, $-SR^8$, $-S(O)R^8$, $-S(O)_2R^8$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)N(R^8)_2$, $-NHC(O)R^8$, $-CF_3$, -CN or NO_2, and such that when Ar is tetrahydronaphthylene, R^1 and R^2 cannot both be hydrogen

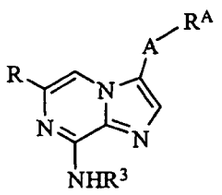
W is –NH- or $–C(R^4)_2$-, wherein both R^4 groups and the carbon atom to which they are attached can combine to form a five to seven membered heterocyclyl or heteroaryl group;

Y is –H, -halo, -alkyl or –CN;

Z is $–CR^7$- or –N-, when the optional additional bond is absent, and –C- when the optional additional bond is present;

n is an integer ranging from 0 to 2; and

(k) A compound of Formula K:



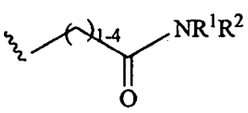
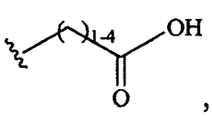
Formula K

or a pharmaceutically acceptable salt, solvate, ester, prodrug or stereoisomer thereof, wherein:

R is H, halo or alkyl;

R^3 is heteroaryl-X, wherein X is heterocyclylalkyl- wherein said heterocyclyl can be unsubstituted or optionally substituted with 1-4 alkyl moieties;

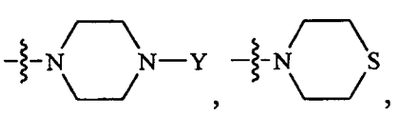
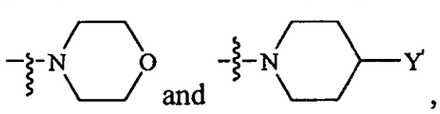
A is -aryl- , -heteroaryl-, $-N(R^1)$-aryl- or $-N(R^1)$-heteroaryl- , wherein each of said aryl and heteroaryl can be independently unsubstituted or optionally substituted with one or more substituents, which substituents can be the same or different, each substituent being independently selected from the group consisting of alkyl, $–NO_2$, halo, hydroxy, trihaloalkyl, alkoxy, and dialkylamino;

R^A is $-(CH_2)_{1-4}$-heteroaryl,  or  , wherein said heteroaryl can optionally be fused with an aryl, wherein each of said aryl and heteroaryl can

independently be optionally substituted with one or more moieties each moiety being independently selected from the group consisting of trihaloalkyl, $-NO_2$, halo, hydroxyalkyl, alkoxyalkyl and dialkylamino;

R^1 is H or alkyl;

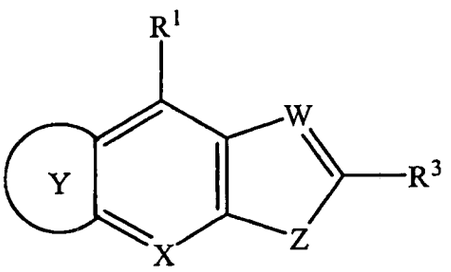
R^2 is H, hydroxyalkyl-, arylalkyl-, heteroaryl, aryl, heteroarylalkyl-, alkyl, dialkylaminoalkyl-, alkylaminoalkyl-, cycloalkylalkyl-, cycloalkyl, heterocyclylalkyl- or heterocyclyl, wherein said aryl and aryl of arylalkyl can be unsubstituted or substituted with one or more moieties independently selected from the group consisting of trihaloalkyl, $-NO_2$, halo, hydroxyalkyl, alkoxyalkyl, dialkylamino and heterocyclylalkyl-, wherein said heterocyclylalkyl can be unsubstituted or substituted with alkyl or $-SO_2NH_2$; said heteroaryl and heteroaryl of heteroarylalkyl can be unsubstituted or substituted with one or more moieties, each moiety being independently selected from the group consisting of hydroxyalkyl, alkoxy, alkyl, halo, hydroxyl, and $-NO_2$; and said cycloalkyl is unsubstituted or substituted with hydroxyl; or

R^1 and R^2 together with the N to which each is attached, form a heterocyclic group selected from the group consisting of  ,  and , wherein

Y is alkoxyalkyl, hydroxyalkyl, dialkylaminoalkyl or alkyl, further wherein Y' is hydroxyl.

2. A method of treating or ameliorating cancer comprising administering sequentially to a mammal in need of such treatment an amount of at least one first compound, wherein said first compound is an anti-mitotic agent selected from the group consisting of a taxane, paclitaxel, docetaxel, a Cenp-E Inhibitor, Abraxane, Epothilone, Monastrol, a KSP inhibitor, Ispinesib, and a compound of Formulas A-D shown in paragraphs a-d below:

a. A compound represented by the structural Formula A:



Formula A

or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:

ring Y is a 5- to 6-membered aryl or a 5- or 6-membered heteroaryl fused as shown in Formula A, wherein in said aryl and heteroaryl each substitutable ring carbon is independently substituted with R^2 and each substitutable ring nitrogen is independently substituted with R^6;

W is N or $C(R^{12})$;

X is N or N-oxide;

Z is S, S(=O) or $S(=O)_2$;

R^1 is H, alkyl, alkoxy, hydroxy, halo, -CN, $-S(O)_m$-alkyl, $-C(O)NR^9R^{10}$, $-(CR^9R^{10})_{1-6}OH$, or $-NR^4(CR^9R^{10})_{1-2}OR^9$;

each R^2 is independently selected from the group consisting of H, halo, alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, $-(CR^{10}R^{11})_{0-6}-OR^7$, $-C(O)R^4$, $-C(S)R^4$, $-C(O)OR^7$, $-C(S)OR^7$, $-OC(O)R^7$, $-OC(S)R^7$, $-C(O)NR^4R^5$, $-C(S)NR^4R^5$, $-C(O)NR^4OR^7$, $-C(S)NR^4OR^7$, $-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, -CN, $-OCF_3$, $-SCF_3$, $-C(=NR^7)NR^4$, $-C(O)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}OR^7$, $-C(S)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(S)NR^7(CH_2)_{1-10}OR^7$, haloalkyl and alkylsilyl, wherein each of said alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl or heteroaralkyl is independently optionally substituted with 1-5 R^9 moieties;

each R^3 is independently selected from the group consisting of H, halo, alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, $-(CR^{10}R^{11})_{0-6}-OR^7$, $-C(O)R^4$, $-C(S)R^4$, $-C(O)OR^7$, $-C(S)OR^7$, $-OC(O)R^7$, $-OC(S)R^7$, $-C(O)NR^4R^5$, $-C(S)NR^4R^5$, $-C(O)NR^4OR^7$, $-C(S)NR^4OR^7$, $-C(O)NR^7NR^4R^5$,

$-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, $-CN$, $-OCF_3$, $-SCF_3$, $-C(=NR^7)NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}OR^7$, $-C(S)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(S)NR^7(CH_2)_{1-10}OR^7$, haloalkyl and alkylsilyl, wherein each of said alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl or heteroaralkyl is independently optionally substituted with 1-5 R^9 moieties;

each R^4 and R^5 is independently selected from the group consisting of H, alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, $-OR^7$, $-C(O)R^7$, and $-C(O)OR^7$, wherein each of said alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl is optionally substituted with 1-4 R^8 moieties;

or R^4 and R^5, when attached to the same nitrogen atom, are optionally taken together with the nitrogen atom to which they are attached to form a 3-6 membered heterocyclic ring having 0-2 additional heteroatoms selected from N, O or S;

each R^6 is independently selected from the group consisting of H, alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroaralkyl, $-(CH_2)_{1-6}CF_3$, $-C(O)R^7$, $-C(O)OR^7$ and $-SO_2R^7$;

each R^7 is independently selected from the group consisting of H, alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, and heteroaralkyl, wherein each member of R^7 except H is optionally substituted with 1-4 R^8 moieties;

each R^8 is independently selected from the group consisting of halo, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-NO_2$, $-OR^{10}$, $-(C_1\text{-}C_6$ alkyl$)\text{-}OR^{10}$, $-CN$, $-NR^{10}R^{11}$, $-C(O)R^{10}$, $-C(O)OR^{10}$, $-C(O)NR^{10}R^{11}$, $-CF_3$, $-OCF_3$, $-CF_2CF_3$, $-C(=NOH)R^{10}$, $-N(R^{10})C(O)R^{11}$, $-C(=NR^{10})NR^{10}R^{11}$, and $-NR^{10}C(O)OR^{11}$, wherein each of said alkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally independently substituted with 1-3 moieties selected from the group consisting of halo, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-NO_2$, $-OR^{10}$, $-(C_1\text{-}C_6$ alkyl$)\text{-}OR^{10}$, $-CN$, $-NR^{10}R^{11}$, $-C(O)OR^{10}$, $-C(O)NR^{10}R^{11}$, $-CF^3$, $-OCF_3$, $-NR^{10}C(O)OR^{11}$, and $-NR^{10}C(O)R^{40}$;

or two R^8 groups, when attached to the same carbon atom, are optionally taken together with the carbon atom to which they are attached to form a C=O or a C=S group;

each R^9 is independently selected from the group consisting of H, alkyl, alkoxy, OH, CN, halo, $-(CR^{10}R^{11})_{0-4}NR^4R^5$, haloalkyl, hydroxyalkyl, alkoxyalkyl, $-C(O)NR^4R^5$, $-C(O)OR^7$, $-OC(O)NR^4R^5$, $-NR^4C(O)R^5$, and $-NR^4C(O)NR^4R^5$;

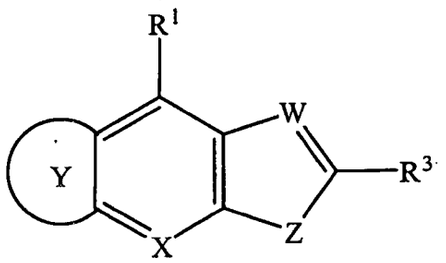
each R^{10} is independently H or alkyl; or R^9 and R^{10}, when attached to the same nitrogen atom, are optionally taken together with the nitrogen atom to which they are attached to form a 3-6 membered heterocyclic ring having 0-2 additional heteroatoms selected from N, O or S;

each R^{11} is independently H or alkyl; or R^{10} and R^{11}, when attached to the same nitrogen atom, are optionally taken together with the nitrogen atom to which they are attached to form a 3-6 membered heterocyclic ring having 0-2 additional heteroatoms selected from N, O or S;

each R^{12} is independently selected from the group consisting of H, halo, alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, $-(CR^{10}R^{11})_{0-6}-OR^7$, $-C(O)R^4$, $-C(S)R^4$, $-C(O)OR^7$, $-C(S)OR^7$, $-OC(O)R^7$, $-OC(S)R^7$, $-C(O)NR^4R^5$, $-C(S)NR^4R^5$, $-C(O)NR^4OR^7$, $-C(S)NR^4OR^7$, $-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, -CN, $-OCF_3$, $-SCF_3$, $-C(=NR^7)NR^4$, $-C(O)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}OR^7$, $-C(S)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(S)NR^7(CH_2)_{1-10}OR^7$, haloalkyl and alkylsilyl, wherein each of said alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl or heteroaralkyl is independently optionally substituted with 1-5 R^9 moieties; and

R^{40} is selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl, wherein each of said cycloalkyl, heterocyclyl, aryl and heteroaryl are optionally independently substituted with 1-3 moieties independently selected from the group consisting of -CN, -OH, halo, alkyl, haloalkyl, alkoxy, and $-NR^{10}R^{11}$;

b. A compound represented by the structural Formula B:



Formula B

or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:

ring Y is a 5- to 7-membered ring selected from the group consisting of cycloalkyl, cycloalkenyl, heterocyclyl or heterocyclenyl fused as shown in Formula B, wherein in each of said 5- to 7-membered ring, each substitutable ring carbon is independently substituted with 1-2 R^2 moieties and each substitutable ring heteroatom is independently substituted with R^6;

W is N or $C(R^{12})$;

X is N or N-oxide;

Z is S, S(=O) or $S(=O)_2$;

R^1 is H, alkyl, alkoxy, hydroxy, halo, -CN, $-S(O)_m$-alkyl, $-C(O)NR^9R^{10}$, $-(CR^9R^{10})_{1-6}OH$, or $-NR^4(CR^9R^{10})_{1-2}OR^9$; wherein m is 0 to 2;

each R^2 is independently selected from the group consisting of H, halo, alkyl, cycloalkyl, alkylsilyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, heteroaryl, $-(CR^{10}R^{11})_{0-6}-OR^7$, $-C(O)R^4$, $-C(S)R^4$, $-C(O)OR^7$, $-C(S)OR^7$, $-OC(O)R^7$, $-OC(S)R^7$, $-C(O)NR^4R^5$, $-C(S)NR^4R^5$, $-C(O)NR^4OR^7$, $-C(S)NR^4OR^7$, $-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, -CN, $-OCF_3$, $-SCF_3$, $-C(=NR^7)NR^4$, $-C(O)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}OR^7$, $-C(S)NR^7(CH_2)_{1-10}NR^4R^5$, and $-C(S)NR^7(CH_2)_{1-10}OR^7$, wherein each of said alkyl, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, and heteroaryl is independently optionally substituted with 1-5 R^9 moieties;

or two R^2s on the same carbon atom are optionally taken together with the carbon atom to which they are attached to form a C=O, a C=S or an ethylenedioxy group;

R^3 is independently selected from the group consisting of H, halo, alkyl, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, heteroaryl, $-(CR^{10}R^{11})_{0-6}-OR^7$, $-C(O)R^4$, $-C(S)R^4$, $-C(O)OR^7$, $-C(S)OR^7$, $-OC(O)R^7$, $-OC(S)R^7$, $-C(O)NR^4R^5$, $-C(S)NR^4R^5$, -

$C(O)NR^4OR^7$, $-C(S)NR^4OR^7$, $-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, -CN, $-C(=NR^7)NR^4R^5$, $-C(O)N(R^7)-(CR^{40}R^{41})_{1-5}-C(=NR^7)NR^4R^5$, $-C(O)N(R^7)(CR^{40}R^{41})_{1-5}-NR^4R^5$, $-C(O)N(R^7)(CR^{40}R^{41})_{1-5}-C(O)-NR^4R^5$, $-C(O)N(R^7)(CR^{40}R^{41})_{1-5}-OR^7$, $-C(S)NR^7(CH_2)_{1-5}NR^4R^5$, and $-C(S)NR^7(CH_2)_{1-5}OR^7$, wherein each of said alkyl, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, and heteroaryl is independently optionally substituted with 1-5 R^9 moieties;

each of R^4 and R^5 is independently selected from the group consisting of H, alkyl, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, heteroaryl, $-OR^7$, $-C(O)R^7$, and $-C(O)OR^7$, wherein each of said alkyl, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, and heteroaryl, is optionally substituted with 1-4 R^8 moieties;

or R^4 and R^5, when attached to the same nitrogen atom, are optionally taken together with the nitrogen atom to which they are attached to form a 3-6 membered heterocyclic ring having 0-2 additional heteroatoms selected from N, O or S;

each R^6 is independently selected from the group consisting of H, alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroaralkyl, $-(CH_2)_{1-6}CF_3$, $-C(O)R^7$, $-C(O)OR^7$ and $-SO_2R^7$;

each R^7 is independently selected from the group consisting of H, alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, and heteroaralkyl, wherein each member of R^7 except H is optionally substituted with 1-4 R^8 moieties;

each R^8 is independently selected from the group consisting of halo, alkyl, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, heteroaryl, $-NO_2$, $-OR^{10}$, $-(C_1-C_6$ alkyl$)-OR^{10}$, $-CN$, $-NR^{10}R^{11}$, $-C(O)R^{10}$, $-C(O)OR^{10}$, $-C(O)NR^{10}R^{11}$, $-CF_3$, $-OCF_3$, $-CF_2CF_3$, $-C(=NOH)R^{10}$, $-N(R^{10})C(O)R^{11}$, $-C(=NR^{10})NR^{10}R^{11}$, and $-NR^{10}C(O)OR^{11}$; wherein said each of said alkyl, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, and heteroaryl is independently optionally substituted with 1-4 R^{42} moieties; wherein when each of said cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, and heteroaryl contains two radicals on adjacent carbon atoms anywhere within said cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, and heteroaryl, such radicals may optionally and independently in each

occurrence, be taken together with the carbon atoms to which they are attached, to form a five- or six-membered carbocyclic or heterocyclic ring;

or two R^8 groups, when attached to the same carbon, are optionally taken together with the carbon atom to which they are attached to form a C=O or a C=S group;

each R^9 is independently selected from the group consisting of H, alkyl, alkoxy, OH, CN, halo, $-(CR^{10}R^{11})_{0-4}NR^4R^5$, haloalkyl, hydroxyalkyl, alkoxyalkyl, $-C(O)NR^4R^5$, $-C(O)OR^7$, $-OC(O)NR^4R^5$, $-NR^4C(O)R^5$, and $-NR^4C(O)NR^4R^5$;

each R^{10} is independently H or alkyl; or R^9 and R^{10}, when attached to the same nitrogen atom, are optionally taken together with the nitrogen atom to which they are attached to form a 3-6 membered heterocyclic ring having 0-2 additional heteroatoms selected from N, O or S;

each R^{11} is independently H, alkyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heterocyclenyl, or heteroaryl; or R^{10} and R^{11}, when attached to the same nitrogen atom, are optionally taken together with the nitrogen atom to which they are attached to form a 3-6 membered heterocyclic ring having 0-2 additional heteroatoms selected from N, O or S;

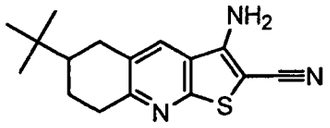
wherein each of said R^{11} alkyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heterocyclenyl, and heteroaryl is independently optionally substituted with 1-3 moieties selected from the group consisting of –CN, -OH, $-NH_2$, -N(H)alkyl, $-N(alkyl)_2$, halo, haloalkyl, CF_3, alkyl, hydroxyalkyl, alkoxy, aryl, aryloxy, and heteroaryl;

each R^{12} is independently selected from the group consisting of H, halo, alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, $-(CR^{10}R^{11})_{0-6}-OR^7$, $-C(O)R^4$, $-C(S)R^4$, $-C(O)OR^7$, $-C(S)OR^7$, $-OC(O)R^7$, $-OC(S)R^7$, $-C(O)NR^4R^5$, $-C(S)NR^4R^5$, $-C(O)NR^4OR^7$, $-C(S)NR^4OR^7$, $-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, -CN, $-OCF_3$, $-SCF_3$, $-C(=NR^7)NR^4$, $-C(O)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}OR^7$, $-C(S)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(S)NR^7(CH_2)_{1-10}OR^7$, haloalkyl and alkylsilyl, wherein each of said alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl or heteroaralkyl is independently optionally substituted with 1-5 R^9 moieties;

R^{40} and R^{41} can be the same or different, each being independently selected from the group consisting of H, alkyl, aryl, heteroaryl, heterocyclyl, heterocyclenyl, cycloalkyl and cycloalkenyl;

each R^{42} is independently selected from the group consisting of halo, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-NO_2$, $-OR^{10}$, $-(C_1-C_6\ alkyl)-OR^{10}$, $-CN$, $-NR^{10}R^{11}$, $-C(O)R^{10}$, $-C(O)OR^{10}$, $-C(O)NR^{10}R^{11}$, $-CF_3$, $-OCF_3$, $-N(R^{10})C(O)R^{11}$, and $-NR^{10}C(O)OR^{11}$;

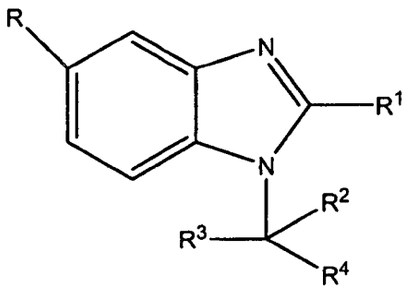
with the proviso that when W is $C(R^{12})$, R^{12} and R^3 are optionally taken together, with the two ring carbon atoms to which they are attached to form a 6-membered ring selected from the group consisting of cycloalkenyl, aryl, heteroaryl, heterocyclyl and heterocyclenyl, wherein said 6-membered ring is optionally substituted with 1-3 moieties independently selected from oxo, thioxo, $-OR^{11}$, $-NR^{10}R^{11}$, $-C(O)R^{11}$, $-C(O)OR^{11}$, $-C(O)N(R^{10})(R^{11})$, or $-N(R^{10})C(O)R^{11}$;

c. 

Formula C

or a pharmaceutically acceptable salt, solvate, or ester thereof; and

d. A compound of Formula D



Formula D

or a pharmaceutically acceptable salt, solvate, or ester thereof, wherein:

R is selected from the group consisting of H, alkyl, cyano, haloalkyl, halo, —SH, -S-alkyl, -S-haloalkyl, $-S(=O)_2$alkyl, $-S(=O)_2OH$, $-S(=O)_2NH_2$, $-S(=O)_2NH$(alkyl), $S(=O)_2NH$(cycloalkyl), $-S(=O)_2N(alkyl)_2$, $-S(=O)_2$heterocyclyl, $-S(=O)_2$heteroaryl, cycloalkyl, aryl, heterocyclyl, heteroaryl, -NHC(=O)alkyl, $-C(=O)NH_2$, $-C(=O)NH$(alkyl), $-C(=O)NH$(cycloalkyl), $-C(=O)N(alkyl)_2$, $-C(=O)OH$, –

C(=O)Oalkyl, -C(=O)heterocyclyl, -C(=O)NH(aryl), wherein when each of said cycloalkyl, aryl, heterocyclyl, heteroaryl, and the "heterocyclyl" and "aryl" portions of said R groups has two substituents on adjacent carbon atoms, said substituents, may optionally be taken together with the carbon atoms to which they are attached to form a five- to six-membered cycloalkyl, aryl, heterocyclyl, heterocyclenyl, or heteroaryl ring; wherein each of the aforementioned R alkyl, aryl, cycloalkyl, heterocyclyl, and heteroaryl, and the "alkyl", "cycloalkyl", "heterocyclyl", and "aryl" portions of said R groups, optionally with said five- to six-membered aryl, heterocyclyl, heterocyclenyl, or heteroaryl ring, is optionally substituted with 1-3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, hydroxyl, cyano, halo, haloalkyl, haloalkoxy, -C(O)OH, -C(=O)Oalkyl, and -C(O)NH_2;

R^1 is selected from the group consisting of alkyl, heterocyclyl, -C(=O)aryl, -NH_2, -NH(alkyl), -NH(cycloalkyl), -N(alkyl)(cycloalkyl), -NH(heterocyclyl), -N(alkyl)(heterocyclyl), $N(alkyl)_2$, -NH(aryl), -N(alkyl)(aryl), $-N(aryl)_2$, -NH(heteroaryl), -N(alkyl)(heteroaryl), -NHC(=O)-alkyl, -N(alkyl)C(=O)-alkyl, -NHC(=O)Oalkyl, -N(alkyl)C(=O)O-alkyl, wherein each of the aforesaid alkyl, heterocyclyl, and the "alkyl", "cycloalkyl", "aryl", and "heteroaryl" portions of said R^1 groups is optionally substituted with 1-3 substituents independently selected from the group consisting of halo, heterocyclyl, aryl, heteroaryl, haloalkyl, haloalkoxy, aryloxy, cyano, –SH, -S-alkyl, -S-haloalkyl, $-S(=O)_2$alkyl, $-S(=O)_2OH$, $-S(=O)_2NH_2$, $-S(=O)_2NH$(alkyl), $S(=O)_2NH$(cycloalkyl), $-S(=O)_2N(alkyl)_2$, $-S(=O)_2$heterocyclyl, $-S(=O)_2$heteroaryl, hydroxy, alkyl, alkenyl, alkynyl, $-NH_2$, -NH(alkyl), $-N(alkyl)_2$, alkoxy, -NHC(=O)alkyl, -C(=O)H, -C(=O)alkyl, -C(=O)aryl, , -C(=O)heteroaryl, -C(=O)Oalkyl, $-C(=O)NH_2$, -C(O)NHalkyl, $-C(=O)N(alkyl)_2$; wherein when each of said heterocyclyl, aryl and heteroaryl has two substituents on adjacent carbon atoms, said substituents, may optionally be taken together with the carbon atoms to which they are attached to form a five to six-membered aryl, heterocyclyl, heterocyclenyl, or heteroaryl ring;

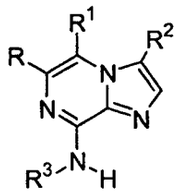
R^2 and R^3 independently are H or alkyl, or $-C(R^2)(R^3)-$ is absent;

R^4 is selected from the group consisting of alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl, wherein when each of said cycloalkyl, heterocyclyl, aryl, and heteroaryl has two substituents on adjacent carbon atoms, said substituents, may optionally be

taken together with the carbon atoms to which they are attached to form a five to six-membered aryl, heterocyclyl, heterocyclenyl, or heteroaryl ring; wherein each of the aforementioned R^4 alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl, optionally with said five to six-membered aryl, heterocyclyl, heterocyclenyl, or heteroaryl ring is optionally substituted with 1-3 substituents independently selected from the group consisting of cyano, halo, haloalkyl, alkyl, alkoxy, hydroxyl, haloalkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-S(=O)_2$alkyl, $-S(=O)_2NH_2$, $-S(=O)_2NH$(alkyl), $-S(=O)_2N$(alkyl)$_2$, -S-alkyl, -S-haloalkyl, $-C(=O)OH$, $-NH_2$, -NH(alkyl), $-N(alkyl)_2$, and $-C(=O)O$alkyl;

followed by administering one or more of a second compound, wherein said second compound is an aurora kinase inhibitor selected from the group consisting of compounds represented by Formulas E-K shown below in paragraphs e-k:

e. A compound represented by the structural Formula E:



Formula E

or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, wherein:

R is H, CN, $-NR^5R^6$, cycloalkyl, cycloalkenyl, heterocyclenyl, heteroaryl, $-C(O)NR^5R^6$, $-N(R^5)C(O)R^6$, heterocyclyl, heteroaryl substituted with $(CH_2)_{1-3}$ NR^5R^6, unsubstituted alkyl, or alkyl substituted with one or more moieties which can be the same or different each moiety being independently selected from the group consisting of $-OR^5$, heterocyclyl, $-N(R^5)C(O)N(R^5R^6)$, $-N(R^5)-C(O)OR^6$, $-(CH_2)_{1-3}-N(R^5R^6)$ and $-NR^5R^6$;

R^1 is H, halo, aryl or heteroaryl, wherein each of said aryl and heteroaryl can be unsubstituted or substituted with one or more moieties which can be the same or different each moiety being independently selected from the group consisting of halo, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, $-CH_2OR^5$, $-C(O)NR^5R^6$, -C(O)OH, $-C(O)NH_2$, $-NR^5R^6$ (wherein the R^5 and R^6, together with the N of said $-NR^5R^6$, form a heterocyclyl ring), $-S(O)R^5$, $-S(O_2)R^5$, -CN, -CHO, $-SR^5$, $-C(O)OR^5$, $-C(O)R^5$ and $-OR^5$;

R^2 is H, halo, aryl, arylalkyl or heteroaryl, wherein each of said aryl, arylalkyl and heteroaryl can be unsubstituted or optionally independently be substituted with one or more moieties which can be the same or different each moiety being independently selected from the group consisting of halo, amide, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, -C(O)OH, $-C(O)NH_2$, $-NR^5R^6$ (wherein the R^5 and R^6, together with the N of said $-NR^5R^6$, form a heterocyclyl ring), -CN, arylalkyl, $-CH_2OR^5$, $-S(O)R^5$, $-S(O_2)R^5$, -CN, -CHO, $-SR^5$, $-C(O)OR^5$, $-C(O)R^5$, heteroaryl and heterocyclyl;

R^3 is H, alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl, wherein:

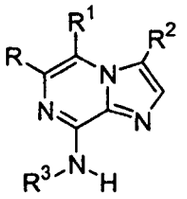
- said alkyl shown above for R^3 can be unsubstituted or substituted with one or more moieties which can be the same or different each moiety being independently selected from the group consisting of $-OR^5$, alkoxy, heteroaryl, and $-NR^5R^6$;
- said aryl shown above for R^3 is unsubstituted, or optionally substituted, or optionally fused, with halo, heteroaryl, heterocyclyl, cycloalkyl or heteroarylalkyl, wherein each of said heteroaryl, heterocyclyl, cycloalkyl and heteroarylalkyl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different each moiety being independently selected from alkyl, $-OR^5$, $-N(R^5R^6)$ and $-S(O_2)R^5$; and
- said heteroaryl shown above for R^3 can be unsubstituted or optionally substituted, or optionally fused, with one or more moieties which can be the same or different with each moiety being independently selected from the group consisting of halo, amino, alkoxycarbonyl, $-OR^5$, alkyl, -CHO, $-NR^5R^6$, $-S(O_2)N(R^5R^6)$, $-C(O)N(R^5R^6)$, $-SR^5$, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclenyl, and heterocyclyl;

R^5 is H, alkyl, aminoalkyl, aryl, heteroaryl, heterocyclyl or cycloalkyl; and

R^6 is H, alkyl, aryl, arylalkyl, heteroaryl, heterocyclyl or cycloalkyl;

further wherein in any $-NR^5R^6$ in Formula I, said R^5 and R^6 can optionally be joined together with the N of said $-NR^5R^6$ to form a cyclic ring;

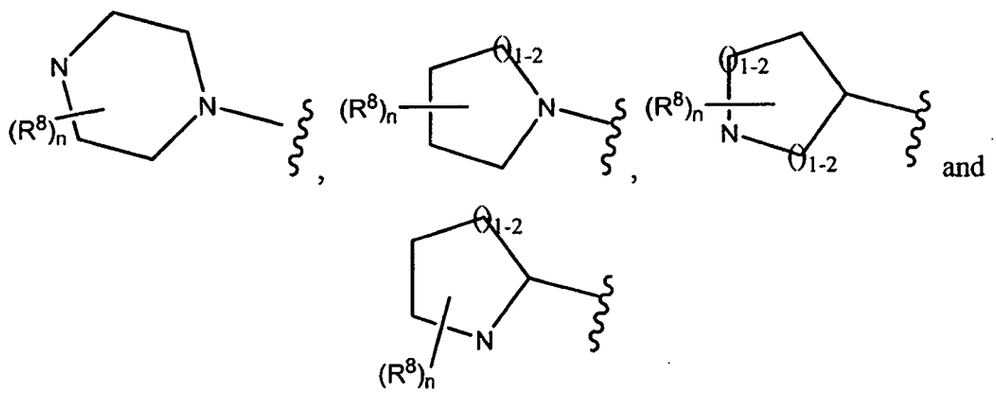
f. A compound represented by the structural formula:



Formula F

or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, wherein:

R is selected from the group consisting of H, halogen, aryl, heteroaryl, cycloalkyl, arylalkyl, heterocyclyl, heterocyclylalkyl, alkenyl, alkynyl, $-C(O)R^7$,

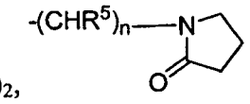


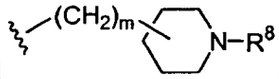
wherein each of said aryl, heteroaryl, cycloalkyl, arylalkyl, alkenyl, heterocyclyl and the heterocyclyl moieties whose structures are shown immediately above for R can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, cycloalkyl, CF_3, CN, $-OCF_3$, $-OR^6$, $-C(O)R^7$, $-NR^5R^6$, $-C(O_2)R^6$, $-C(O)NR^5R^6$, $-(CHR^5)_nOR^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ and $-N(R^5)C(O)NR^5R^6$;

R^1 is H, halogen or alkyl;

R^2 is alkyl;

R^3 is selected from the group consisting of H, aryl, heteroaryl, heterocyclyl, $-(CHR^5)_n$-aryl, $-(CHR^5)_n$-heteroaryl, $-(CHR^5)_n-OR^6$, $-S(O_2)R^6$, $-C(O)R^6$, $-S(O_2)NR^5R^6$, $-C(O)OR^6$, $-C(O)NR^5R^6$, cycloalkyl, $-CH(aryl)_2$, $-(CH_2)_m-NR^8$, $-(CHR^5)_n-CH(aryl)_2$,



and  , wherein each of said aryl, heteroaryl and heterocyclyl can be

substituted or optionally substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl, cycloalkyl, CF_3, CN, $-OCF_3$, $-OR^5$, $-NR^5R^6$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^6$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ and $-N(R^5)C(O)NR^5R^6$;

R^5 is H or alkyl;

R^6 is selected from the group consisting of H, alkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, wherein each of said alkyl, heteroarylalkyl, aryl, heteroaryl and arylalkyl can be unsubstituted or optionally substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl, cycloalkyl, CF_3, OCF_3, CN, $-OR^5$, $-NR^5R^6$, $-CH_2OR^5$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ and $-N(R^5)C(O)NR^5R^6$;

R^7 is selected from the group consisting of alkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, wherein each of said alkyl, heteroarylalkyl, aryl, heteroaryl and arylalkyl can be unsubstituted or optionally substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl, cycloalkyl, CF_3, OCF_3, CN, $-OR^5$, $-NR^5R^6$, $-CH_2OR^5$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ and $-N(R^5)C(O)NR^5R^6$;

R^8 is selected from the group consisting of R^6, $-C(O)NR^5R^6$, $-S(O_2)NR^5R^6$, $-C(O)R^7$, $-C(O_2)R^6$, $-S(O_2)R^7$ and $-(CH_2)$-aryl;

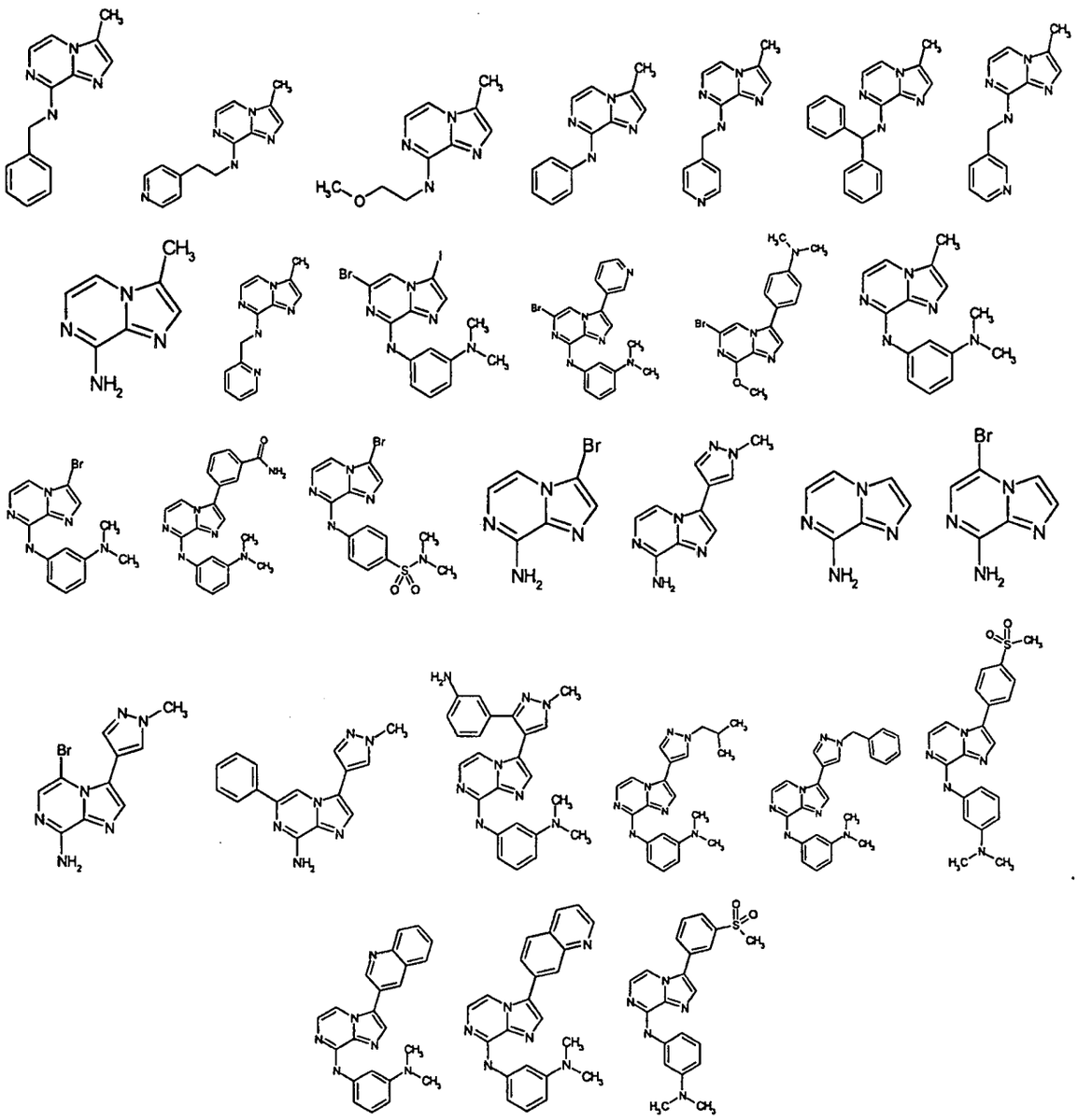
R^9 is selected from the group consisting of halogen, CN, NR^5R^6, $-C(O_2)R^6$, $-C(O)NR^5R^6$, $-OR^6$, $-C(O)R^7$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$and $-N(R^5)C(O)NR^5R^6$;

m is 0 to 4;

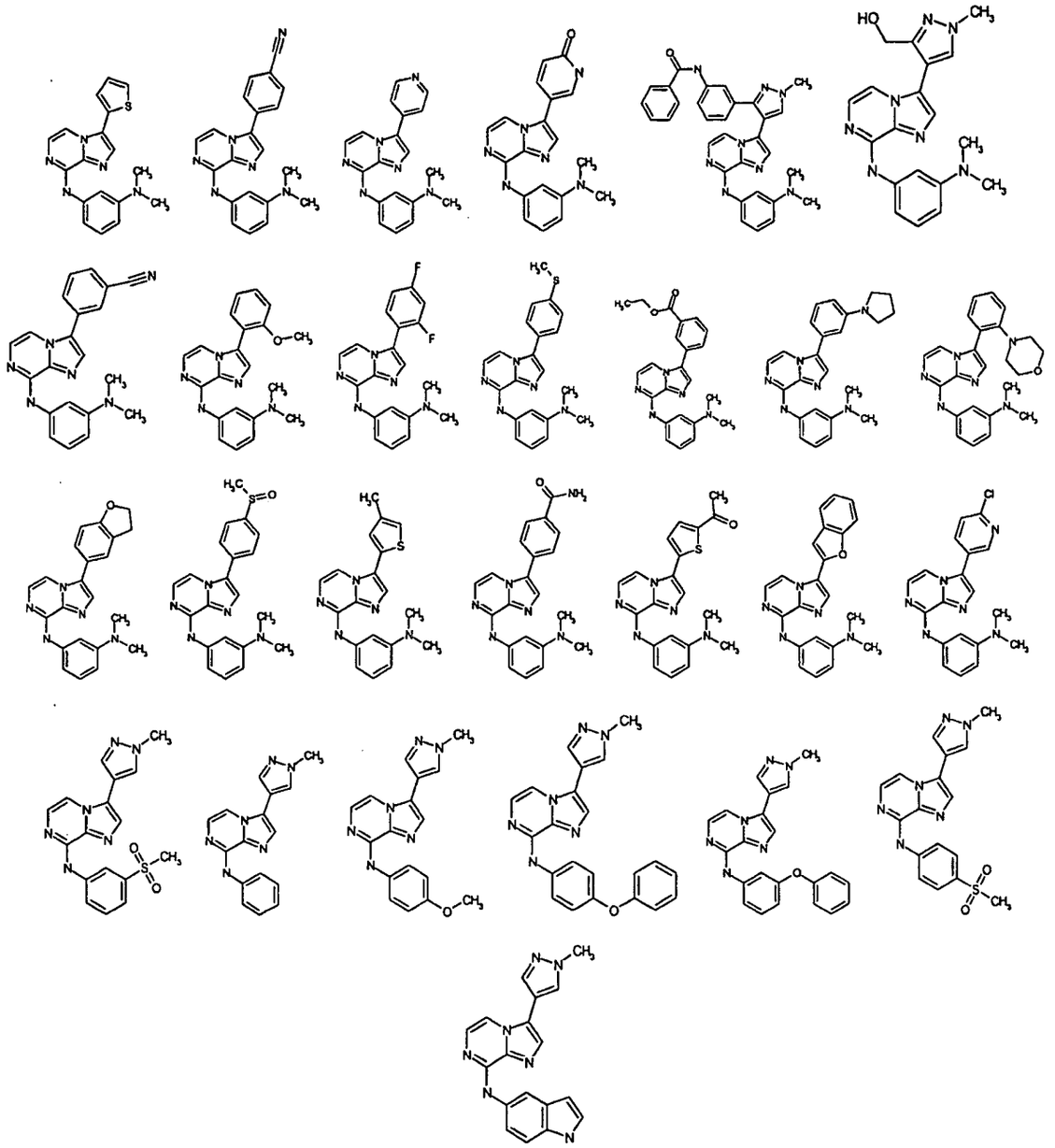
n is 1-4; and

p is 0-3;

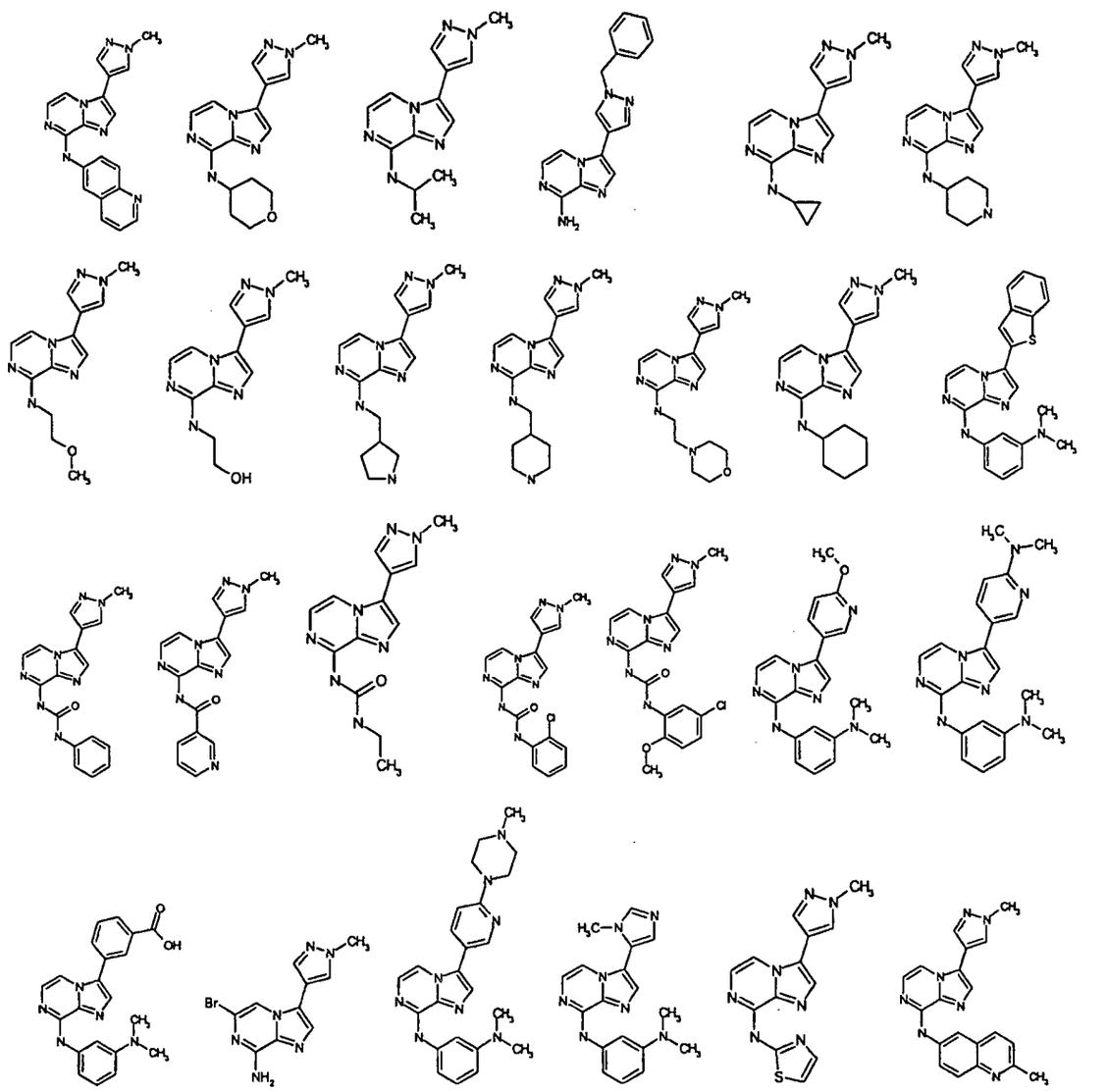
g. A compound selected from the compounds of the formulas:



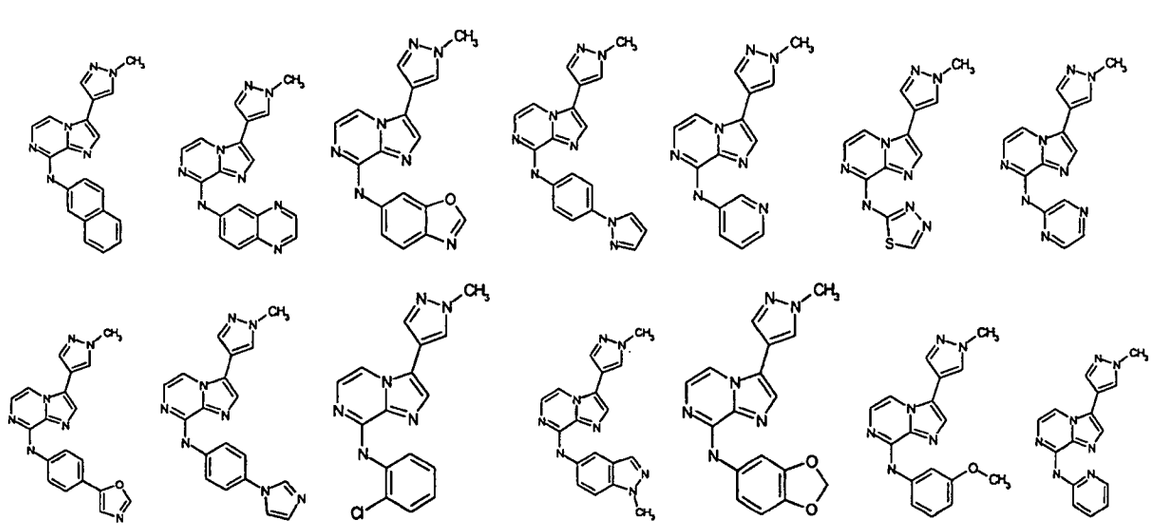
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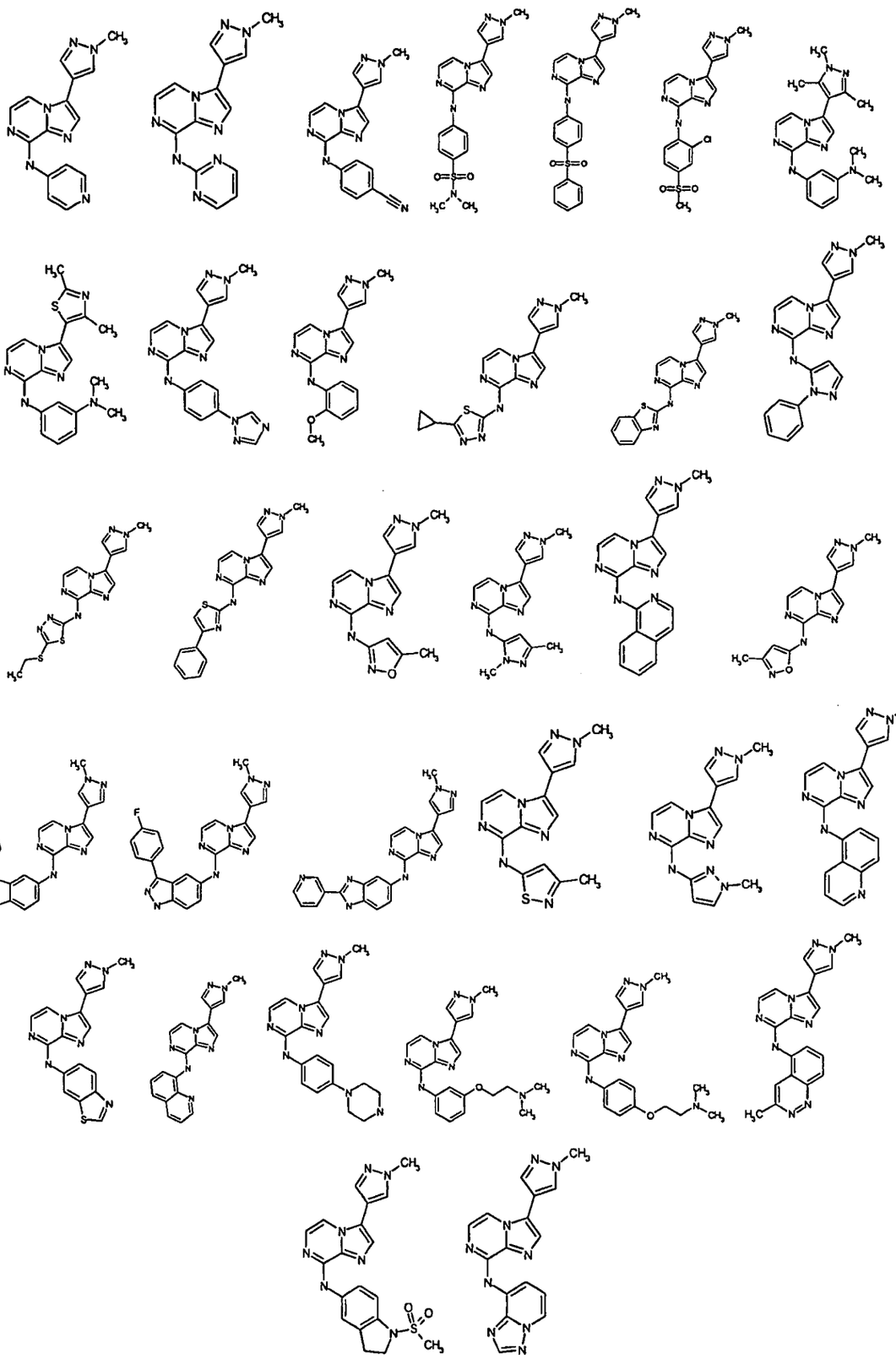


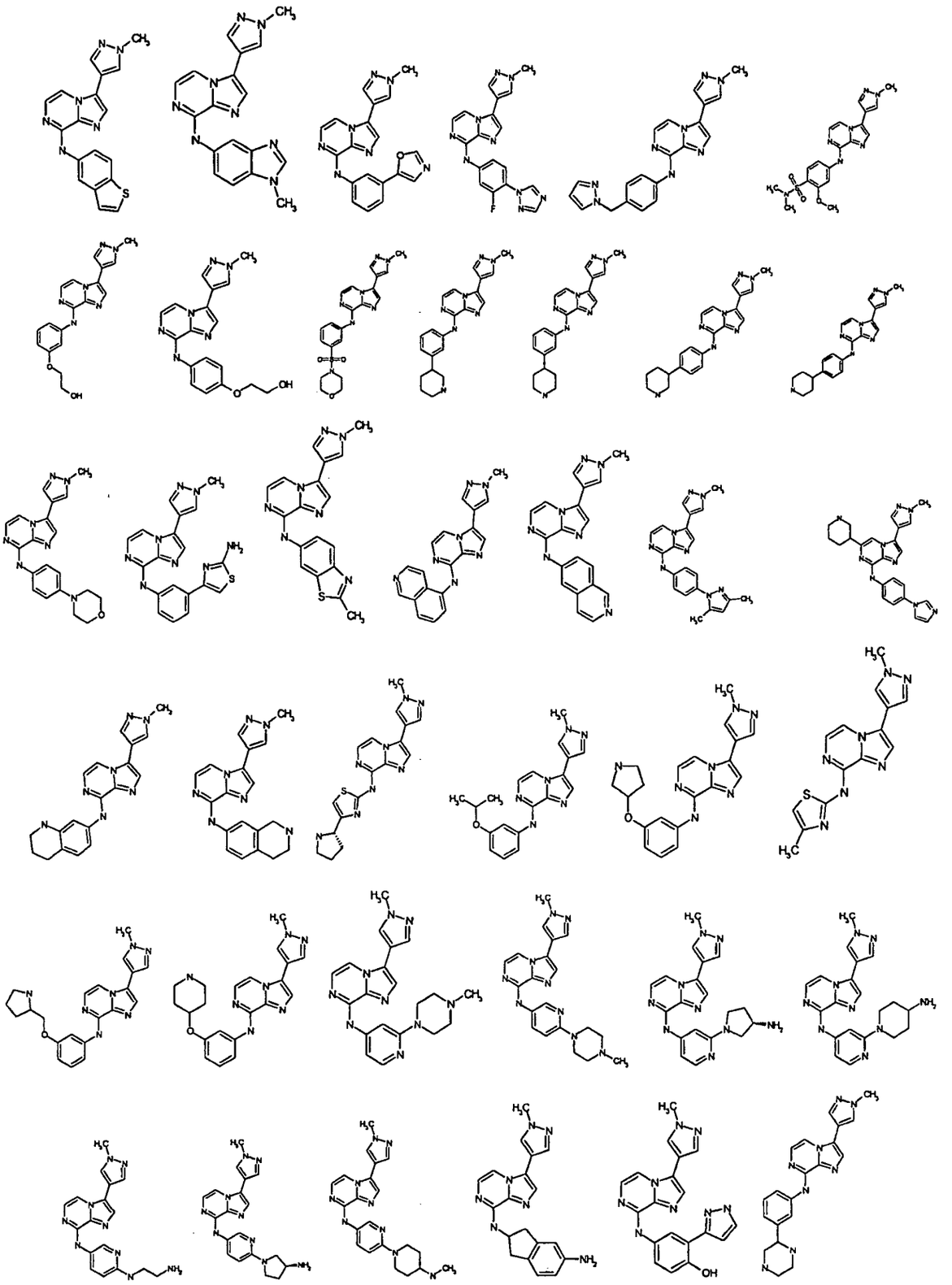
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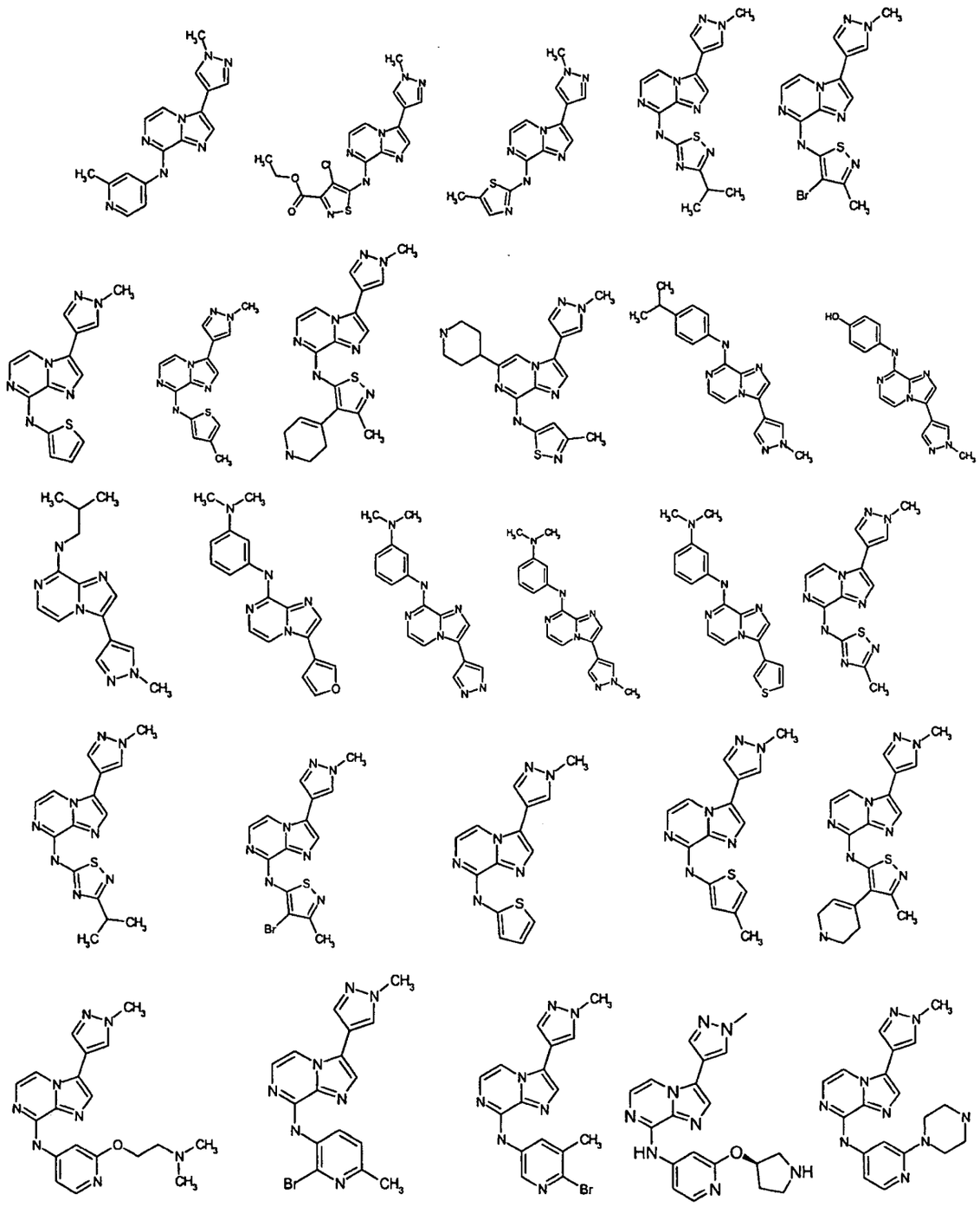


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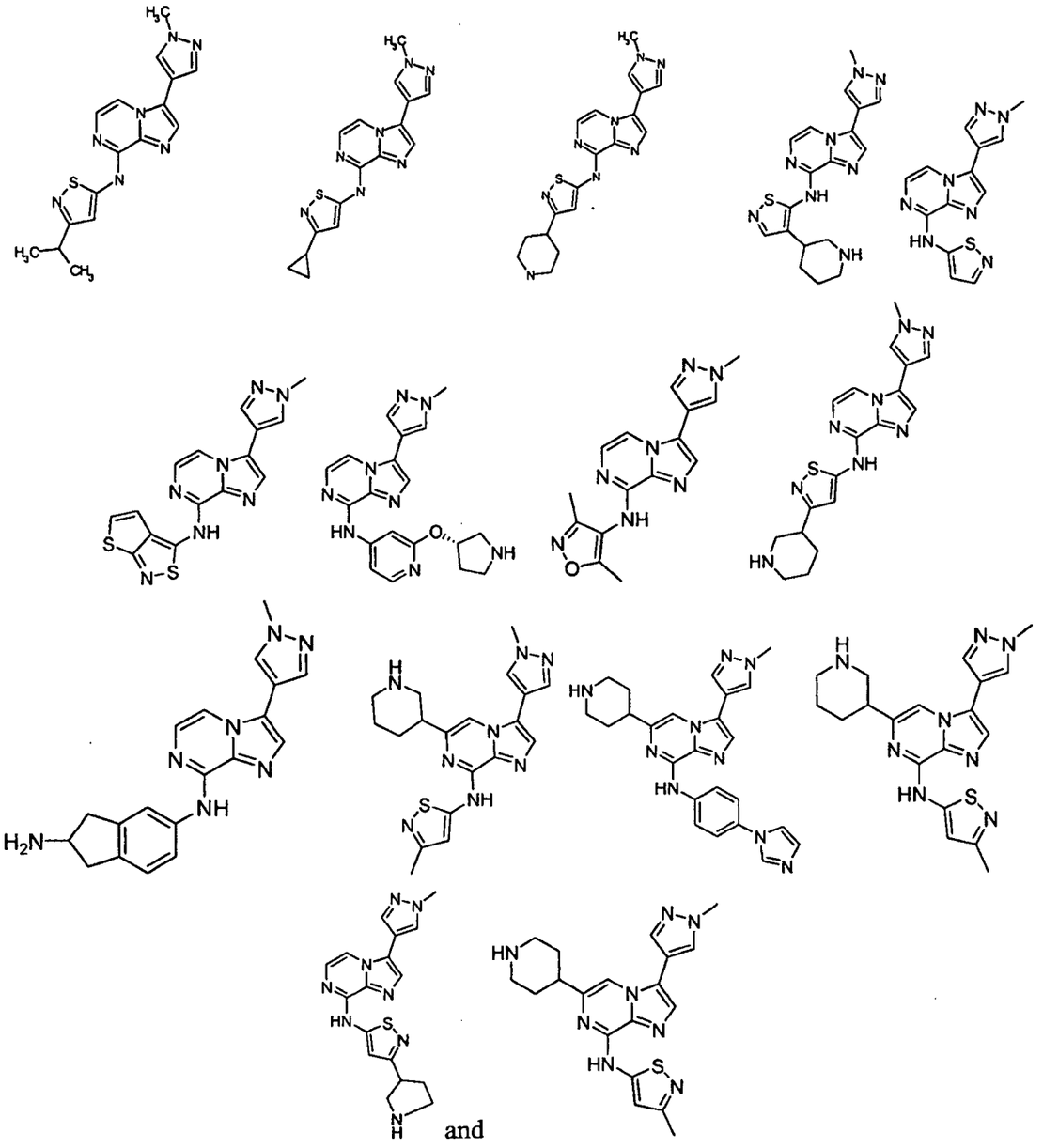








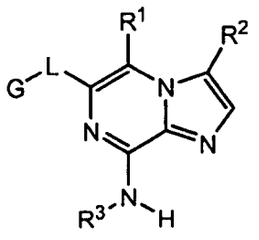
5



and

or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof;

h. A compound of the formula:



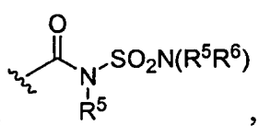
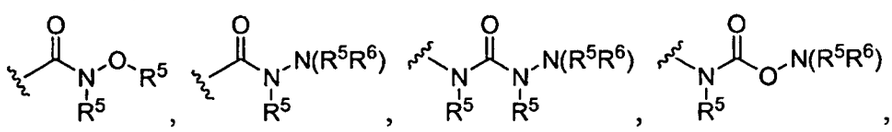
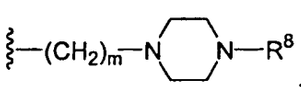
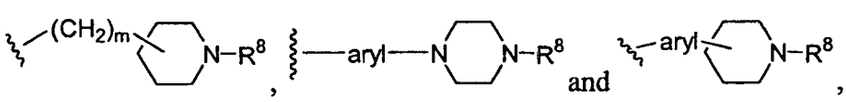
Formula H

or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, wherein:

L is selected from the group consisting of S, S(O) and $S(O_2)$;

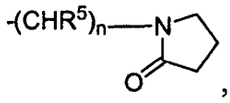
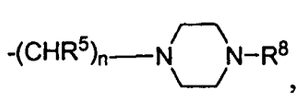
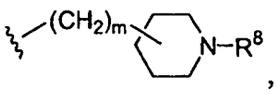
G is alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclenyl or heterocyclyl, wherein each of said alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclenyl or heterocyclyl can be unsubstituted or optionally independently substituted with one or more moieties which are independently selected from the group consisting of $-OR^5$, halo, -CN, $-C(O)NR^5R^6$, $-N(H)-C(O)R^5$,$-N(H)-C(O)-NR^5R^6$, $-S(O_2)NR^5R^6$, $-NR^5R^6$, $-C(O)R^5$, $-C(O_2)R^5$, $-SR^5$, $-S(O)R^5$, $-S(O_2)R^5$;

R^1 is H, halo, alkyl, aryl or heteroaryl, wherein each of said alkyl, aryl and heteroaryl can be unsubstituted or substituted with one or more moieties which can be the same or different each moiety being independently selected from the group consisting of halo, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C(O)NR^5R^6$ and $-OR^5$;

R^2 is selected from the group consisting of H, R^9, alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclylalkyl, $-CF_3$, $-C(O)R^7$,  ,  , alkyl substituted with 1-6 R^9 groups which groups can be the same or different with each R^9 being independently selected,  ,  , and , wherein each of the above-said aryl, heteroaryl, cycloalkyl, arylalkyl and heterocyclyl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halo, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, CF_3, CN, $-OCF_3$, $-OR^6$, $-C(O)R^7$, $-NR^5R^6$, $-C(O_2)R^6$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$,

$-N(R^5)C(O)R^7$ and $-N(R^5)C(O)NR^5R^6$;

R^3 is selected from the group consisting of H, alkyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroarylalkyl, cycloalkylalkyl, heterocyclylalkyl,


, 
, $-(CHR^5)_n-OR^6$, $-S(O_2)R^6$, $-C(O)R^6$, $-S(O_2)NR^5R^6$, $-C(O)OR^6$, $-C(O)NR^5R^6$, cycloalkyl, $-CH(aryl)_2$, $-CH(heteroaryl)_2$, $-(CH_2)_m-NR^8$, and 
, wherein each of said alkyl, aryl, heteroaryl and heterocyclyl can be substituted or optionally substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halo, alkyl, aryl, cycloalkyl, CF_3, CN, $-OCF_3$, $-OR^5$, $-NR^5R^6$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^6$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ and $-N(R^5)C(O)NR^5R^6$;

R^5 is H, alkyl, aryl, heteroaryl, heterocyclyl or cycloalkyl; and

R^6 is selected from the group consisting of H, alkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, wherein each of said alkyl, heteroarylalkyl, aryl, heteroaryl and arylalkyl can be unsubstituted or optionally substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl, cycloalkyl, CF_3, OCF_3, CN, $-OR^5$, $-NR^5R^6$, $-CH_2OR^5$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ and $-N(R^5)C(O)NR^5R^6$;

R^7 is selected from the group consisting of alkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, wherein each of said alkyl, heteroarylalkyl, aryl, heteroaryl and arylalkyl can be unsubstituted or optionally substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl, cycloalkyl, CF_3, OCF_3, CN, $-OR^5$, $-NR^5R^6$, $-CH_2OR^5$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ and $-N(R^5)C(O)NR^5R^6$;

R^8 is selected from the group consisting of R^6, $-C(O)NR^5R^6$, $-S(O_2)NR^5R^6$, $-C(O)R^7$, $-C(O_2)R^6$, $-S(O_2)R^7$ and $-(CH_2)$-aryl;

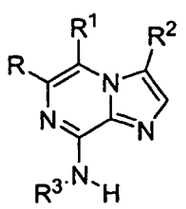
R^9 is selected from the group consisting of halogen, CN, NR^5R^6, $-C(O_2)R^6$, $-C(O)NR^5R^6$, $-OR^6$, $-C(O)R^7$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$,

$-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$and $-N(R^5)C(O)NR^5R^6$;

m is 0 to 4; and

p is 0-3;

i. A compound of Formula I:



Formula I

or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, wherein:

R is H, CN, $-NR^5R^6$, cycloalkyl, cycloalkenyl, heterocyclenyl, heteroaryl, $-C(O)NR^5R^6$, $-N(R^5)C(O)R^6$, heterocyclyl, heteroaryl substituted with $(CH_2)_{1-3}$ NR^5R^6, unsubstituted alkyl, or alkyl substituted with one or more moieties which can be the same or different each moiety being independently selected from the group consisting of $-OR^5$, heterocyclyl, $-N(R^5)C(O)N(R^5R^6)$, $-N(R^5)-C(O)OR^6$, $-(CH_2)_{1-3}-N(R^5R^6)$ and $-NR^5R^6$;

R^1 is H, halo, aryl or heteroaryl, wherein each of said aryl and heteroaryl can be unsubstituted or substituted with one or more moieties which can be the same or different each moiety being independently selected from the group consisting of halo, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, $-CH_2OR^5$, $-C(O)NR^5R^6$, -C(O)OH, $-C(O)NH_2$, $-NR^5R^6$ (wherein the R^5 and R^6, together with the N of said $-NR^5R^6$, form a heterocyclyl ring), $-S(O)R^5$, $-S(O_2)R^5$, -CN, -CHO, $-SR^5$, $-C(O)OR^5$, $-C(O)R^5$ and $-OR^5$;

R^2 is H, halo, aryl, arylalkyl or heteroaryl, wherein each of said aryl, arylalkyl and heteroaryl can be unsubstituted or optionally independently be substituted with one or more moieties which can be the same or different each moiety being independently selected from the group consisting of halo, amide, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, -C(O)OH, $-C(O)NH_2$, $-NR^5R^6$ (wherein the R^5 and R^6, together with the N of said $-NR^5R^6$, form a heterocyclyl ring), -CN, arylalkyl, $-CH_2OR^5$, $-S(O)R^5$, $-S(O_2)R^5$, -CN, -CHO, $-SR^5$, $-C(O)OR^5$, $-C(O)R^5$, heteroaryl and heterocyclyl;

R^3 is heterocyclyl–$(CR^7R^8)_n$-X, heterocyclenyl–$(CR^7R^8)_n$-X, heteroaryl–$(CR^7R^8)_n$-X or aryl–

$(CR^7R^8)_n$-X wherein each of the heterocyclyl-, heterocyclenyl-, heteroaryl- or aryl-moieties of said R^3 can be unsubstituted or substituted with one or more moieties, independently selected from the group consisting of $-CONR^5R^6$, $-OR^5$ and alkyl,

n is 1-6,

X is selected from the group consisting of, $-NR^5R^6$, $-OR^5$, $-SO-R^5$ and $-SR^5$,

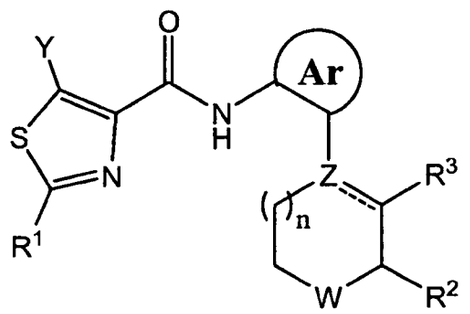
R^7 and R^8 are each independently hydrogen or alkyl;

R^5 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkoxyalkyl, -alkyl-S-alkyl, aminoalkyl, aryl, heteroaryl, heterocyclenyl, heterocycloalkyl, cycloalkyl, cycloalkenyl, heterocyclylalkoxyl, -S-alkylheterocyclyl, heterocyclyl, heterocyclenyl, alkylN(alkyl)$_2$, alkylNH(alkyl), alkylN(alkenyl)2, -alkylN(alkoxyl)2, -alkyl-SH and hydroxyalkyl, wherein each of said aryl, heteroaryl, heterocyclenyl, heterocycloalkyl, cycloalkyl, cycloalkenyl, heterocyclylalkoxyl, -S-alkylheterocyclyl, heterocyclyl, heterocyclenyl can be unsubstituted or substituted with one or more moieties independently selected from the group consisting of alkyl, alkyl, alkenyl, aryl, cycloalkenyl, cycloalkyl, arylalkyl, cycloalkenylalkyl, cycloalkylalkyl, heteroaryl, heterocyclenyl, heterocyclyl, heteroarylalkyl, heterocyclenylalkyl, heterocycloalkylalkyl, alkoxyalkyl, -alkyl-S-alkyl, -alkylSH, alkoxyl, -S-alkyl, hydroxyalkyl, and aminoalkyl;

R^6 is selected from the group consisting of hydrogen, alkyl, alkenyl, aryl, cycloalkenyl, cycloalkyl, arylalkyl, cycloalkenylalkyl, cycloalkylalkyl, heteroaryl, heterocyclenyl, heterocyclyl, heteroarylalkyl, heterocyclenylalkyl, heterocycloalkylalkyl, alkoxyalkyl, -alkyl-S-alkyl, -alkylSH, alkoxyl, -S-alkyl, hydroxyalkyl, and aminoalkyl, wherein each of said aryl, cycloalkenyl, cycloalkyl, arylalkyl, cycloalkenylalkyl, cycloalkylalkyl, heteroaryl, heterocyclenyl, heterocyclyl, heteroarylalkyl, heterocyclenylalkyl, heterocycloalkylalkyl can be unsubstituted or substituted with one or more moieties independently selected from the group consisting of alkyl, alkyl, alkenyl, aryl, cycloalkenyl, cycloalkyl, arylalkyl, cycloalkenylalkyl, cycloalkylalkyl, heteroaryl, heterocyclenyl, heterocyclyl, heteroarylalkyl, heterocyclenylalkyl, heterocycloalkylalkyl, alkoxyalkyl, -alkyl-S-alkyl, -alkylSH, alkoxyl, -S-alkyl, hydroxyalkyl, and aminoalkyl;

further wherein in any -NR^5R^6 in Formula I, said R^5 and R^6 can optionally be joined together with the N of said -NR^5R^6 to form a cyclic ring or bridged cyclic ring, wherein each of said cyclic ring or bridged cyclic ring, can be unsubstituted or substituted with one or more moieties, which can be the same or different, independently selected from the group consisting of hydroxyl, -SH, alkyl, alkenyl, hydroxyalkyl, -alkyl-SH, alkoxyl, -S-alkyl, -CO_2-alkyl, -CO_2-alkenyl, arylalkyl, cycloalkenylalkyl, cycloalkylalkyl, heteroarylalkyl, heterocyclenylalkyl, heterocycloalkylalkyl, heteroaryl, aryl, cycloalkenyl, cycloalkyl, spiroheterocyclyl, spiroheterocyclenyl, spiroheteroaryl, spirocyclyl, spirocyclenyl, spiroaryl, alkoxyalkyl, -alkyl-S-alkyl, heterocyclyl, and heterocyclenyl;

j. A compound having the formula:



(J)

or a pharmaceutically acceptable salt, solvate, ester, prodrug or stereoisomer thereof, wherein the dashed lines indicate an optional and additional bond, and wherein:

R^1 is nitrogen-containing heteroaryl, nitrogen-containing heterocyclyl, nitrogen-containing benzofused heteroaryl or nitrogen-containing benzofused heterocyclyl, wherein R^1 is joined to the rest of the compound of formula (I) via a ring nitrogen atom, and wherein one or more ring carbon atoms of a nitrogen-containing heteroaryl, nitrogen-containing heterocyclyl, nitrogen-containing benzofused heteroaryl or nitrogen-containing benzofused heterocyclyl group can be substituted with up to 5 substituents, which may be the same or different, and are independently selected from alkyl, aryl, halo, -OH, -O-alkyl, -O-aryl, -$N(R^8)_2$, -CF_3, -NO_2, -$C(O)R^8$, -$C(O)OR^8$, -$C(O)N(R^8)_2$, -$OC(O)R^8$ or -$NHC(O)R^8$;

R^2 is –H, -alkyl, –NH_2 or –CH_2NH_2;

R^3 is –H, -alkyl, $–NH_2$ or $–CH_2NH_2$;

each occurrence of R^4 is independently –H, -alkyl, $–NH_2$, -OH, -alkylene-OH, $–CH_2NH_2$, $-C(O)R^5$, $-C(O)NH_2$, -C(O)NH-alkyl, $-C(O)N(alkyl)_2$, $-NHC(O)R^6$ or $–NHS(O)_2R^6$;

R^5 is –H, -alkyl, -aryl, -heteroaryl, -NHOH;

R^6 is –H, -alkyl or $–CF_3$;

R^7 is –H, -OH, $-C_1$-C_6 alkyl, $-O-(C_1$-C_6 alkyl), or $–CF_3$;

R^8 is –H, alkyl, aryl, heterocyclyl, heteroaryl or cycloalkyl;

Ar is -arylene- or -heteroarylene-, wherein the arylene or heteroarylene is joined via 2 of its adjacent ring carbon atoms, and wherein the -arylene- or -heteroarylene- can be substituted with up to 4 substituents, which may be the same or different, and are independently selected from –halo, alkyl, alkoxy, aryloxy, $-SR^8$, $-S(O)R^8$, $-S(O)_2R^8$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)N(R^8)_2$, $-NHC(O)R^8$, $-CF_3$, -CN or NO_2, and such that when Ar is tetrahydronaphthylene, R^1 and R^2 cannot both be hydrogen

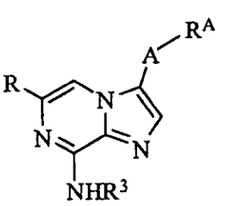
W is –NH- or $–C(R^4)_2$-, wherein both R^4 groups and the carbon atom to which they are attached can combine to form a five to seven membered heterocyclyl or heteroaryl group;

Y is –H, -halo, -alkyl or –CN;

Z is $–CR^7$- or –N-, when the optional additional bond is absent, and –C- when the optional additional bond is present;

n is an integer ranging from 0 to 2; and

(k) A compound of Formula K:



Formula K

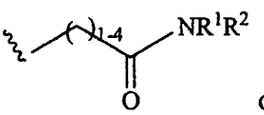
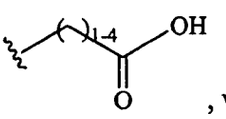
or a pharmaceutically acceptable salt, solvate, ester, prodrug or stereoisomer thereof, wherein:

R is H, halo or alkyl;

R^3 is heteroaryl-X, wherein X is heterocyclylalkyl- wherein said heterocyclyl can be unsubstituted or optionally substituted with 1-4 alkyl moieties;

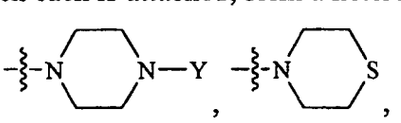
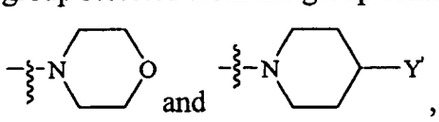
A is -aryl- , -heteroaryl-, $-N(R^1)$-aryl- or $-N(R^1)$-heteroaryl- , wherein each of said aryl and heteroaryl can be independently unsubstituted or optionally substituted with one or more

substituents, which substituents can be the same or different, each substituent being independently selected from the group consisting of alkyl, $-NO_2$, halo, hydroxy, trihaloalkyl, alkoxy, and dialkylamino;

R^A is $-(CH_2)_{1-4}$-heteroaryl,  or  , wherein said heteroaryl can optionally be fused with an aryl, wherein each of said aryl and heteroaryl can independently be optionally substituted with one or more moieties each moiety being independently selected from the group consisting of trihaloalkyl, $-NO_2$, halo, hydroxyalkyl, alkoxyalkyl and dialkylamino;

R^1 is H or alkyl;

R^2 is H, hydroxyalkyl-, arylalkyl-, heteroaryl, aryl, heteroarylalkyl-, alkyl, dialkylaminoalkyl-, alkylaminoalkyl-, cycloalkylalkyl-, cycloalkyl, heterocyclylalkyl- or heterocyclyl, wherein said aryl and aryl of arylalkyl can be unsubstituted or substituted with one or more moieties independently selected from the group consisting of trihaloalkyl, $-NO_2$, halo, hydroxyalkyl, alkoxyalkyl, dialkylamino and heterocyclylalkyl-, wherein said heterocyclylalkyl can be unsubstituted or substituted with alkyl or $-SO_2NH_2$; said heteroaryl and heteroaryl of heteroarylalkyl can be unsubstituted or substituted with one or more moieties, each moiety being independently selected from the group consisting of hydroxyalkyl, alkoxy, alkyl, halo, hydroxyl, and $-NO_2$; and said cycloalkyl is unsubstituted or substituted with hydroxyl; or

R^1 and R^2 together with the N to which each is attached, form a heterocyclic group selected from the group consisting of  ,  and , wherein

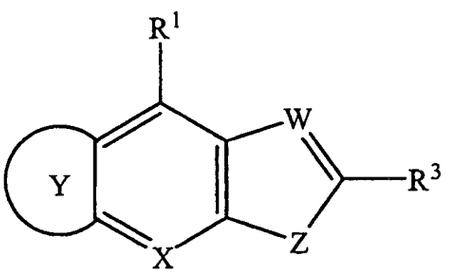
Y is alkoxyalkyl, hydroxyalkyl, dialkylaminoalkyl or alkyl, further wherein Y' is hydroxyl;

wherein the amounts of the first compound and the second compound result in a therapeutic effect.

3. A method of inducing endoreduplication in cancer cells comprising pretreatment of cancer cells with at least one anti-mitotic agent, wherein said anti-mitotic agent is selected

from the group consisting of a Taxane, paclitaxel, docetaxel, a Cenp-E Inhibitor, Abraxane, Epothilone, Monastrol, and a KSP inhibitor, Ispinesib and compounds of Formulas A-D shown in paragraphs a-d below:

a. A compound represented by the structural Formula A:



Formula A

or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:

ring Y is a 5- to 6-membered aryl or a 5- or 6-membered heteroaryl fused as shown in Formula A, wherein in said aryl and heteroaryl each substitutable ring carbon is independently substituted with R^2 and each substitutable ring nitrogen is independently substituted with R^6;

W is N or $C(R^{12})$;

X is N or N-oxide;

Z is S, S(=O) or $S(=O)_2$;

R^1 is H, alkyl, alkoxy, hydroxy, halo, -CN, $-S(O)_m$-alkyl, $-C(O)NR^9R^{10}$, $-(CR^9R^{10})_{1-6}OH$, or $-NR^4(CR^9R^{10})_{1-2}OR^9$;

each R^2 is independently selected from the group consisting of H, halo, alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, $-(CR^{10}R^{11})_{0-6}-OR^7$, $-C(O)R^4$, $-C(S)R^4$, $-C(O)OR^7$, $-C(S)OR^7$, $-OC(O)R^7$, $-OC(S)R^7$, $-C(O)NR^4R^5$, $-C(S)NR^4R^5$, $-C(O)NR^4OR^7$, $-C(S)NR^4OR^7$, $-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, -CN, $-OCF_3$, $-SCF_3$, $-C(=NR^7)NR^4$, $-C(O)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}OR^7$, $-C(S)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(S)NR^7(CH_2)_{1-10}OR^7$, haloalkyl and alkylsilyl, wherein each of said alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl or heteroaralkyl is independently optionally substituted with 1-5 R^9 moieties;

each R^3 is independently selected from the group consisting of H, halo, alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, $-(CR^{10}R^{11})_{0-6}-OR^7$, $-C(O)R^4$, $-C(S)R^4$, $-C(O)OR^7$, $-C(S)OR^7$, $-OC(O)R^7$, $-OC(S)R^7$, $-C(O)NR^4R^5$, $-C(S)NR^4R^5$, $-C(O)NR^4OR^7$, $-C(S)NR^4OR^7$, $-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, $-CN$, $-OCF_3$, $-SCF_3$, $-C(=NR^7)NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}OR^7$, $-C(S)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(S)NR^7(CH_2)_{1-10}OR^7$, haloalkyl and alkylsilyl, wherein each of said alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl or heteroaralkyl is independently optionally substituted with 1-5 R^9 moieties;

each R^4 and R^5 is independently selected from the group consisting of H, alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, $-OR^7$, $-C(O)R^7$, and $-C(O)OR^7$, wherein each of said alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl is optionally substituted with 1-4 R^8 moieties;

or R^4 and R^5, when attached to the same nitrogen atom, are optionally taken together with the nitrogen atom to which they are attached to form a 3-6 membered heterocyclic ring having 0-2 additional heteroatoms selected from N, O or S;

each R^6 is independently selected from the group consisting of H, alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroaralkyl, $-(CH_2)_{1-6}CF_3$, $-C(O)R^7$, $-C(O)OR^7$ and $-SO_2R^7$;

each R^7 is independently selected from the group consisting of H, alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, and heteroaralkyl, wherein each member of R^7 except H is optionally substituted with 1-4 R^8 moieties;

each R^8 is independently selected from the group consisting of halo, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-NO_2$, $-OR^{10}$, $-(C_1-C_6$ alkyl$)-OR^{10}$, $-CN$, $-NR^{10}R^{11}$, $-C(O)R^{10}$, $-C(O)OR^{10}$, $-C(O)NR^{10}R^{11}$, $-CF_3$, $-OCF_3$, $-CF_2CF_3$, $-C(=NOH)R^{10}$, $-N(R^{10})C(O)R^{11}$, $-C(=NR^{10})NR^{10}R^{11}$, and $-NR^{10}C(O)OR^{11}$, wherein each of said alkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally independently

substituted with 1-3 moieties selected from the group consisting of halo, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-NO_2$, $-OR^{10}$, $-(C_1-C_6\ alkyl)-OR^{10}$, -CN, $-NR^{10}R^{11}$, $-C(O)OR^{10}$, $-C(O)NR^{10}R^{11}$, $-CF^3$, $-OCF_3$, $-NR^{10}C(O)OR^{11}$, and $-NR^{10}C(O)R^{40}$;

or two R^8 groups, when attached to the same carbon atom, are optionally taken together with the carbon atom to which they are attached to form a C=O or a C=S group;

each R^9 is independently selected from the group consisting of H, alkyl, alkoxy, OH, CN, halo, $-(CR^{10}R^{11})_{0-4}NR^4R^5$, haloalkyl, hydroxyalkyl, alkoxyalkyl, $-C(O)NR^4R^5$, $-C(O)OR^7$, $-OC(O)NR^4R^5$, $-NR^4C(O)R^5$, and $-NR^4C(O)NR^4R^5$;

each R^{10} is independently H or alkyl; or R^9 and R^{10}, when attached to the same nitrogen atom, are optionally taken together with the nitrogen atom to which they are attached to form a 3-6 membered heterocyclic ring having 0-2 additional heteroatoms selected from N, O or S;

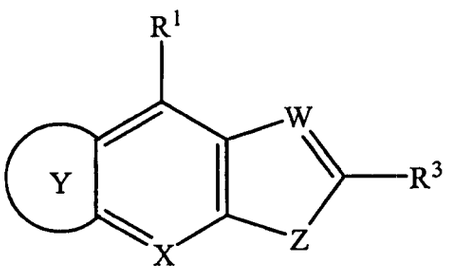
each R^{11} is independently H or alkyl; or R^{10} and R^{11}, when attached to the same nitrogen atom, are optionally taken together with the nitrogen atom to which they are attached to form a 3-6 membered heterocyclic ring having 0-2 additional heteroatoms selected from N, O or S;

each R^{12} is independently selected from the group consisting of H, halo, alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, $-(CR^{10}R^{11})_{0-6}-OR^7$, $-C(O)R^4$, $-C(S)R^4$, $-C(O)OR^7$, $-C(S)OR^7$, $-OC(O)R^7$, $-OC(S)R^7$, $-C(O)NR^4R^5$, $-C(S)NR^4R^5$, $-C(O)NR^4OR^7$, $-C(S)NR^4OR^7$, $-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, -CN, $-OCF_3$, $-SCF_3$, $-C(=NR^7)NR^4$, $-C(O)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}OR^7$, $-C(S)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(S)NR^7(CH_2)_{1-10}OR^7$, haloalkyl and alkylsilyl, wherein each of said alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl or heteroaralkyl is independently optionally substituted with 1-5 R^9 moieties; and

R^{40} is selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl, wherein each of said cycloalkyl, heterocyclyl, aryl and heteroaryl are

optionally independently substituted with 1-3 moieties independently selected from the group consisting of -CN, -OH, halo, alkyl, haloalkyl, alkoxy, and $-NR^{10}R^{11}$;

b. A compound represented by the structural Formula B:



Formula B

or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:

ring Y is a 5- to 7-membered ring selected from the group consisting of cycloalkyl, cycloalkenyl, heterocyclyl or heterocyclenyl fused as shown in Formula B, wherein in each of said 5- to 7-membered ring, each substitutable ring carbon is independently substituted with 1-2 R^2 moieties and each substitutable ring heteroatom is independently substituted with R^6;

W is N or $C(R^{12})$;

X is N or N-oxide;

Z is S, S(=O) or $S(=O)_2$;

R^1 is H, alkyl, alkoxy, hydroxy, halo, -CN, $-S(O)_m$-alkyl, $-C(O)NR^9R^{10}$, $-(CR^9R^{10})_{1-6}OH$, or $-NR^4(CR^9R^{10})_{1-2}OR^9$; wherein m is 0 to 2;

each R^2 is independently selected from the group consisting of H, halo, alkyl, cycloalkyl, alkylsilyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, heteroaryl, $-(CR^{10}R^{11})_{0-6}-OR^7$, $-C(O)R^4$, $-C(S)R^4$, $-C(O)OR^7$, $-C(S)OR^7$, $-OC(O)R^7$, $-OC(S)R^7$, $-C(O)NR^4R^5$, $-C(S)NR^4R^5$, $-C(O)NR^4OR^7$, $-C(S)NR^4OR^7$, $-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, -CN, $-OCF_3$, $-SCF_3$, $-C(=NR^7)NR^4$, $-C(O)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}OR^7$, $-C(S)NR^7(CH_2)_{1-10}NR^4R^5$, and $-C(S)NR^7(CH_2)_{1-10}OR^7$, wherein each of said alkyl, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, and heteroaryl is independently optionally substituted with 1-5 R^9 moieties;

or two R^2s on the same carbon atom are optionally taken together with the carbon atom to which they are attached to form a C=O, a C=S or an ethylenedioxy group;

R^3 is independently selected from the group consisting of H, halo, alkyl, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, heteroaryl, $-(CR^{10}R^{11})_{0-6}-OR^7$, $-C(O)R^4$, $-C(S)R^4$, $-C(O)OR^7$, $-C(S)OR^7$, $-OC(O)R^7$, $-OC(S)R^7$, $-C(O)NR^4R^5$, $-C(S)NR^4R^5$, $-C(O)NR^4OR^7$, $-C(S)NR^4OR^7$, $-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, $-CN$, $-C(=NR^7)NR^4R^5$, $-C(O)N(R^7)-(CR^{40}R^{41})_{1-5}-C(=NR^7)NR^4R^5$, $-C(O)N(R^7)(CR^{40}R^{41})_{1-5}-NR^4R^5$, $-C(O)N(R^7)(CR^{40}R^{41})_{1-5}-C(O)-NR^4R^5$, $-C(O)N(R^7)(CR^{40}R^{41})_{1-5}-OR^7$, $-C(S)NR^7(CH_2)_{1-5}NR^4R^5$, and $-C(S)NR^7(CH_2)_{1-5}OR^7$, wherein each of said alkyl, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, and heteroaryl is independently optionally substituted with 1-5 R^9 moieties;

each of R^4 and R^5 is independently selected from the group consisting of H, alkyl, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, heteroaryl, $-OR^7$, $-C(O)R^7$, and $-C(O)OR^7$, wherein each of said alkyl, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, and heteroaryl, is optionally substituted with 1-4 R^8 moieties;

or R^4 and R^5, when attached to the same nitrogen atom, are optionally taken together with the nitrogen atom to which they are attached to form a 3-6 membered heterocyclic ring having 0-2 additional heteroatoms selected from N, O or S;

each R^6 is independently selected from the group consisting of H, alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroaralkyl, $-(CH_2)_{1-6}CF_3$, $-C(O)R^7$, $-C(O)OR^7$ and $-SO_2R^7$;

each R^7 is independently selected from the group consisting of H, alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, and heteroaralkyl, wherein each member of R^7 except H is optionally substituted with 1-4 R^8 moieties;

each R^8 is independently selected from the group consisting of halo, alkyl, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, heteroaryl, $-NO_2$, $-OR^{10}$, $-(C_1-C_6$ alkyl$)-OR^{10}$, $-CN$, $-NR^{10}R^{11}$, $-C(O)R^{10}$, $-C(O)OR^{10}$, $-C(O)NR^{10}R^{11}$, $-CF_3$, $-OCF_3$, $-CF_2CF_3$, $-$

$C(=NOH)R^{10}$, $-N(R^{10})C(O)R^{11}$, $-C(=NR^{10})NR^{10}R^{11}$, and $-NR^{10}C(O)OR^{11}$; wherein said each of said alkyl, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, and heteroaryl is independently optionally substituted with 1-4 R^{42} moieties; wherein when each of said cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, and heteroaryl contains two radicals on adjacent carbon atoms anywhere within said cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, and heteroaryl, such radicals may optionally and independently in each occurrence, be taken together with the carbon atoms to which they are attached, to form a five- or six-membered carbocyclic or heterocyclic ring;

or two R^8 groups, when attached to the same carbon, are optionally taken together with the carbon atom to which they are attached to form a C=O or a C=S group;

each R^9 is independently selected from the group consisting of H, alkyl, alkoxy, OH, CN, halo, $-(CR^{10}R^{11})_{0-4}NR^4R^5$, haloalkyl, hydroxyalkyl, alkoxyalkyl, $-C(O)NR^4R^5$, $-C(O)OR^7$, $-OC(O)NR^4R^5$, $-NR^4C(O)R^5$, and $-NR^4C(O)NR^4R^5$;

each R^{10} is independently H or alkyl; or R^9 and R^{10}, when attached to the same nitrogen atom, are optionally taken together with the nitrogen atom to which they are attached to form a 3-6 membered heterocyclic ring having 0-2 additional heteroatoms selected from N, O or S;

each R^{11} is independently H, alkyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heterocyclenyl, or heteroaryl; or R^{10} and R^{11}, when attached to the same nitrogen atom, are optionally taken together with the nitrogen atom to which they are attached to form a 3-6 membered heterocyclic ring having 0-2 additional heteroatoms selected from N, O or S; wherein each of said R^{11} alkyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heterocyclenyl, and heteroaryl is independently optionally substituted with 1-3 moieties selected from the group consisting of –CN, -OH, $-NH_2$, -N(H)alkyl, $-N(alkyl)_2$, halo, haloalkyl, CF_3, alkyl, hydroxyalkyl, alkoxy, aryl, aryloxy, and heteroaryl;

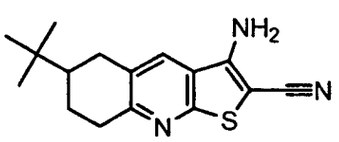
each R^{12} is independently selected from the group consisting of H, halo, alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, $-(CR^{10}R^{11})_{0-6}-OR^7$, $-C(O)R^4$, $-C(S)R^4$, $-C(O)OR^7$, $-C(S)OR^7$, $-OC(O)R^7$, $-OC(S)R^7$, $-C(O)NR^4R^5$, $-C(S)NR^4R^5$, $-C(O)NR^4OR^7$, $-C(S)NR^4OR^7$, $-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, -CN, $-OCF_3$, $-SCF_3$, $-C(=NR^7)NR^4$, $-C(O)NR^7(CH_2)_{1-}$

$_{10}NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}OR^7$, $-C(S)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(S)NR^7(CH_2)_{1-10}OR^7$, haloalkyl and alkylsilyl, wherein each of said alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl or heteroaralkyl is independently optionally substituted with 1-5 R^9 moieties;

R^{40} and R^{41} can be the same or different, each being independently selected from the group consisting of H, alkyl, aryl, heteroaryl, heterocyclyl, heterocyclenyl, cycloalkyl and cycloalkenyl;

each R^{42} is independently selected from the group consisting of halo, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-NO_2$, $-OR^{10}$, $-(C_1-C_6$ alkyl$)-OR^{10}$, $-CN$, $-NR^{10}R^{11}$, $-C(O)R^{10}$, $-C(O)OR^{10}$, $-C(O)NR^{10}R^{11}$, $-CF_3$, $-OCF_3$, $-N(R^{10})C(O)R^{11}$, and $-NR^{10}C(O)OR^{11}$;

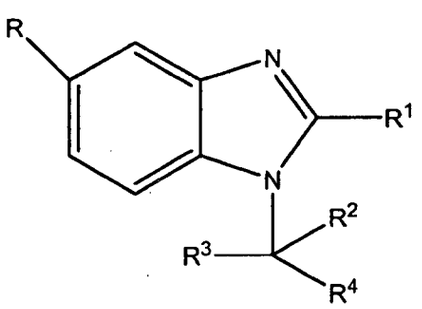
with the proviso that when W is $C(R^{12})$, R^{12} and R^3 are optionally taken together, with the two ring carbon atoms to which they are attached to form a 6-membered ring selected from the group consisting of cycloalkenyl, aryl, heteroaryl, heterocyclyl and heterocyclenyl, wherein said 6-membered ring is optionally substituted with 1-3 moieties independently selected from oxo, thioxo, $-OR^{11}$, $-NR^{10}R^{11}$, $-C(O)R^{11}$, $-C(O)OR^{11}$, $-C(O)N(R^{10})(R^{11})$, or $-N(R^{10})C(O)R^{11}$;

c. 

Formula C

or a pharmaceutically acceptable salt, solvate, or ester thereof; and

d. A compound of Formula D



Formula D

or a pharmaceutically acceptable salt, solvate, or ester thereof, wherein:

R is selected from the group consisting of H, alkyl, cyano, haloalkyl, halo, —SH, -S-alkyl, -S-haloalkyl, $-S(=O)_2$alkyl, $-S(=O)_2OH$, $-S(=O)_2NH_2$, $-S(=O)_2NH$(alkyl), $S(=O)_2NH$(cycloalkyl), $-S(=O)_2N(alkyl)_2$, $-S(=O)_2$heterocyclyl, $-S(=O)_2$heteroaryl, cycloalkyl, aryl, heterocyclyl, heteroaryl, -NHC(=O)alkyl, –$C(=O)NH_2$, –C(=O)NH(alkyl), -C(=O)NH(cycloalkyl), $-C(=O)N(alkyl)_2$, –C(=O)OH, –C(=O)Oalkyl, -C(=O)heterocyclyl, -C(=O)NH(aryl), wherein when each of said cycloalkyl, aryl, heterocyclyl, heteroaryl, and the "heterocyclyl" and "aryl" portions of said R groups has two substituents on adjacent carbon atoms, said substituents, may optionally be taken together with the carbon atoms to which they are attached to form a five- to six-membered cycloalkyl, aryl, heterocyclyl, heterocyclenyl, or heteroaryl ring; wherein each of the aforementioned R alkyl, aryl, cycloalkyl, heterocyclyl, and heteroaryl, and the "alkyl", "cycloalkyl", "heterocyclyl", and "aryl" portions of said R groups, optionally with said five- to six-membered aryl, heterocyclyl, heterocyclenyl, or heteroaryl ring, is optionally substituted with 1-3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, hydroxyl, cyano, halo, haloalkyl, haloalkoxy, -C(O)OH, -C(=O)Oalkyl, and $-C(O)NH_2$;

R^1 is selected from the group consisting of alkyl, heterocyclyl, -C(=O)aryl, $-NH_2$, -NH(alkyl), -NH(cycloalkyl), -N(alkyl)(cycloalkyl), -NH(heterocyclyl), -N(alkyl)(heterocyclyl), $N(alkyl)_2$, -NH(aryl), -N(alkyl)(aryl), $-N(aryl)_2$, -NH(heteroaryl), -N(alkyl)(heteroaryl), -NHC(=O)-alkyl, -N(alkyl)C(=O)-alkyl, -NHC(=O)Oalkyl, -N(alkyl)C(=O)O-alkyl, wherein each of the aforesaid alkyl, heterocyclyl, and the "alkyl", "cycloalkyl", "aryl", and "heteroaryl" portions of said R^1 groups is optionally substituted with 1-3 substituents independently selected from the group consisting of halo, heterocyclyl, aryl, heteroaryl, haloalkyl, haloalkoxy, aryloxy, cyano, –SH, -S-alkyl, -S-haloalkyl, $-S(=O)_2$alkyl, $-S(=O)_2OH$, $-S(=O)_2NH_2$, $-S(=O)_2NH$(alkyl), $S(=O)_2NH$(cycloalkyl), $-S(=O)_2N(alkyl)_2$, $-S(=O)_2$heterocyclyl, $-S(=O)_2$heteroaryl, hydroxy, alkyl, alkenyl, alkynyl, $-NH_2$, -NH(alkyl), $-N(alkyl)_2$, alkoxy, -NHC(=O)alkyl, -C(=O)H, -C(=O)alkyl, -C(=O)aryl, , -C(=O)heteroaryl, -C(=O)Oalkyl, $-C(=O)NH_2$, -C(O)NHalkyl, $-C(=O)N(alkyl)_2$; wherein when each of said heterocyclyl, aryl and heteroaryl has two substituents on adjacent carbon atoms, said substituents, may optionally be taken together with the carbon atoms to which they

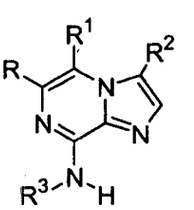
are attached to form a five to six-membered aryl, heterocyclyl, heterocyclenyl, or heteroaryl ring;

R^2 and R^3 independently are H or alkyl, or -C(R^2)(R^3)- is absent;

R^4 is selected from the group consisting of alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl, wherein when each of said cycloalkyl, heterocyclyl, aryl, and heteroaryl has two substituents on adjacent carbon atoms, said substituents, may optionally be taken together with the carbon atoms to which they are attached to form a five to six-membered aryl, heterocyclyl, heterocyclenyl, or heteroaryl ring; wherein each of the aforementioned R^4 alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl, optionally with said five to six-membered aryl, heterocyclyl, heterocyclenyl, or heteroaryl ring is optionally substituted with 1-3 substituents independently selected from the group consisting of cyano, halo, haloalkyl, alkyl, alkoxy, hydroxyl, haloalkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, -S(=O)$_2$alkyl, -S(=O)$_2$NH$_2$, -S(=O)$_2$NH(alkyl), -S(=O)$_2$N(alkyl)$_2$, -S-alkyl, -S-haloalkyl, -C(=O)OH, -NH$_2$, -NH(alkyl), -N(alkyl)$_2$, and -C(=O)Oalkyl;

followed by administering one or more of a second compound, wherein said second compound is an aurora kinase inhibitor selected from the group consisting of compounds represented by Formulas E-K shown below in paragraphs e-k:

e. A compound represented by the structural Formula E:



Formula E

or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, wherein:

R is H, CN, -NR^5R^6, cycloalkyl, cycloalkenyl, heterocyclenyl, heteroaryl, -C(O)NR^5R^6, -N(R^5)C(O)R^6, heterocyclyl, heteroaryl substituted with $(CH_2)_{1-3}$ NR^5R^6, unsubstituted alkyl, or alkyl substituted with one or more moieties which can be the same or different each moiety being independently selected from the group consisting of -OR^5, heterocyclyl, -N(R^5)C(O)N(R^5R^6), -N(R^5)-C(O)OR^6, -$(CH_2)_{1-3}$-N(R^5R^6) and -NR^5R^6;

R^1 is H, halo, aryl or heteroaryl, wherein each of said aryl and heteroaryl can be unsubstituted

or substituted with one or more moieties which can be the same or different each moiety being independently selected from the group consisting of halo, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, $-CH_2OR^5$, $-C(O)NR^5R^6$, -C(O)OH, $-C(O)NH_2$,

$-NR^5R^6$ (wherein the R^5 and R^6, together with the N of said $-NR^5R^6$, form a heterocyclyl ring), $-S(O)R^5$, $-S(O_2)R^5$, -CN, -CHO, $-SR^5$, $-C(O)OR^5$, $-C(O)R^5$ and $-OR^5$;

R^2 is H, halo, aryl, arylalkyl or heteroaryl, wherein each of said aryl, arylalkyl and heteroaryl can be unsubstituted or optionally independently be substituted with one or more moieties which can be the same or different each moiety being independently selected from the group consisting of halo, amide, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, -C(O)OH, $-C(O)NH_2$, $-NR^5R^6$ (wherein the R^5 and R^6, together with the N of said $-NR^5R^6$, form a heterocyclyl ring), -CN, arylalkyl, $-CH_2OR^5$, $-S(O)R^5$, $-S(O_2)R^5$, -CN, -CHO, $-SR^5$, $-C(O)OR^5$, $-C(O)R^5$, heteroaryl and heterocyclyl;

R^3 is H, alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl, wherein:

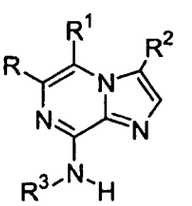
- said alkyl shown above for R^3 can be unsubstituted or substituted with one or more moieties which can be the same or different each moiety being independently selected from the group consisting of $-OR^5$, alkoxy, heteroaryl, and $-NR^5R^6$;
- said aryl shown above for R^3 is unsubstituted, or optionally substituted, or optionally fused, with halo, heteroaryl, heterocyclyl, cycloalkyl or heteroarylalkyl, wherein each of said heteroaryl, heterocyclyl, cycloalkyl and heteroarylalkyl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different each moiety being independently selected from alkyl, $-OR^5$, $-N(R^5R^6)$ and $-S(O_2)R^5$; and
- said heteroaryl shown above for R^3 can be unsubstituted or optionally substituted, or optionally fused, with one or more moieties which can be the same or different with each moiety being independently selected from the group consisting of halo, amino, alkoxycarbonyl, $-OR^5$, alkyl, -CHO, $-NR^5R^6$, $-S(O_2)N(R^5R^6)$, $-C(O)N(R^5R^6)$, $-SR^5$, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclenyl, and heterocyclyl;

R^5 is H, alkyl, aminoalkyl, aryl, heteroaryl, heterocyclyl or cycloalkyl; and

R^6 is H, alkyl, aryl, arylalkyl, heteroaryl, heterocyclyl or cycloalkyl;

further wherein in any $-NR^5R^6$ in Formula I, said R^5 and R^6 can optionally be joined together with the N of said $-NR^5R^6$ to form a cyclic ring;

f. A compound represented by the structural formula:

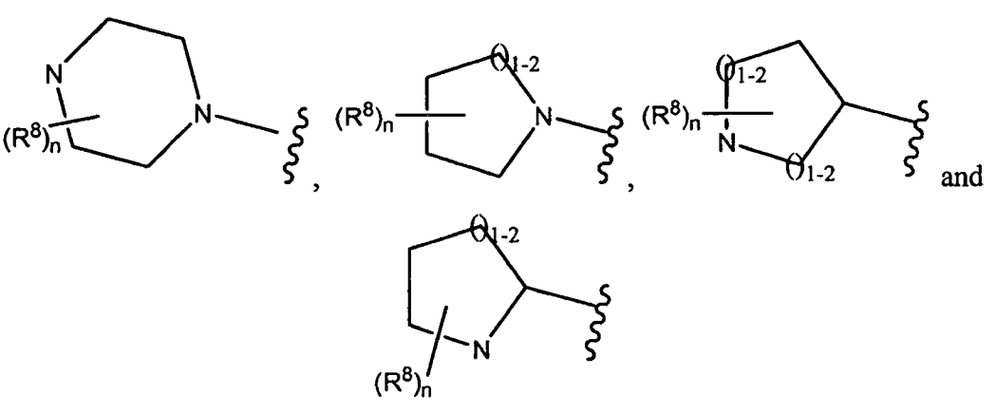


Formula F

or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, wherein:

R is selected from the group consisting of H, halogen, aryl, heteroaryl, cycloalkyl, arylalkyl, heterocyclyl, heterocyclylalkyl, alkenyl, alkynyl,

$-C(O)R^7$,



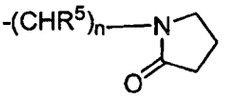
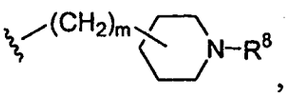
and

wherein each of said aryl, heteroaryl, cycloalkyl, arylalkyl, alkenyl, heterocyclyl and the heterocyclyl moieties whose structures are shown immediately above for R can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, cycloalkyl, CF_3, CN, $-OCF_3$,

$-OR^6$, $-C(O)R^7$, $-NR^5R^6$, $-C(O_2)R^6$, $-C(O)NR^5R^6$, $-(CHR^5)_nOR^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ and $-N(R^5)C(O)NR^5R^6$;

R^1 is H, halogen or alkyl;

R^2 is alkyl;

R^3 is selected from the group consisting of H, aryl, heteroaryl, heterocyclyl, -$(CHR^5)_n$-aryl, - $(CHR^5)_n$-heteroaryl, -$(CHR^5)_n$-OR^6, -$S(O_2)R^6$, -$C(O)R^6$, -$S(O_2)NR^5R^6$, -$C(O)OR^6$, -$C(O)NR^5R^6$, cycloalkyl, -$CH(aryl)_2$, –$(CH_2)_m$-NR^8, -$(CHR^5)_n$-$CH(aryl)_2$, 
and  , wherein each of said aryl, heteroaryl and heterocyclyl can be substituted or optionally substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl, cycloalkyl, CF_3, CN, -OCF_3, -OR^5, -NR^5R^6, -$C(O_2)R^5$, -$C(O)NR^5R^6$, -SR^6, -$S(O_2)R^6$, -$S(O_2)NR^5R^6$, -$N(R^5)S(O_2)R^7$, -$N(R^5)C(O)R^7$ and -$N(R^5)C(O)NR^5R^6$;

R^5 is H or alkyl;

R^6 is selected from the group consisting of H, alkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, wherein each of said alkyl, heteroarylalkyl, aryl, heteroaryl and arylalkyl can be unsubstituted or optionally substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl, cycloalkyl, CF_3, OCF_3, CN, -OR^5, -NR^5R^6, -CH_2OR^5, -$C(O_2)R^5$, -$C(O)NR^5R^6$, -SR^6, -$S(O_2)R^7$, -$S(O_2)NR^5R^6$, -$N(R^5)S(O_2)R^7$, -$N(R^5)C(O)R^7$ and -$N(R^5)C(O)NR^5R^6$;

R^7 is selected from the group consisting of alkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, wherein each of said alkyl, heteroarylalkyl, aryl, heteroaryl and arylalkyl can be unsubstituted or optionally substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl, cycloalkyl, CF_3, OCF_3, CN, -OR^5, -NR^5R^6, -CH_2OR^5, -$C(O_2)R^5$, -$C(O)NR^5R^6$, -SR^6, -$S(O_2)R^7$, -$S(O_2)NR^5R^6$, -$N(R^5)S(O_2)R^7$, -$N(R^5)C(O)R^7$ and -$N(R^5)C(O)NR^5R^6$;

R^8 is selected from the group consisting of R^6, -$C(O)NR^5R^6$, -$S(O_2)NR^5R^6$, -$C(O)R^7$, -$C(O_2)R^6$, –$S(O_2)R^7$ and –(CH_2)-aryl;

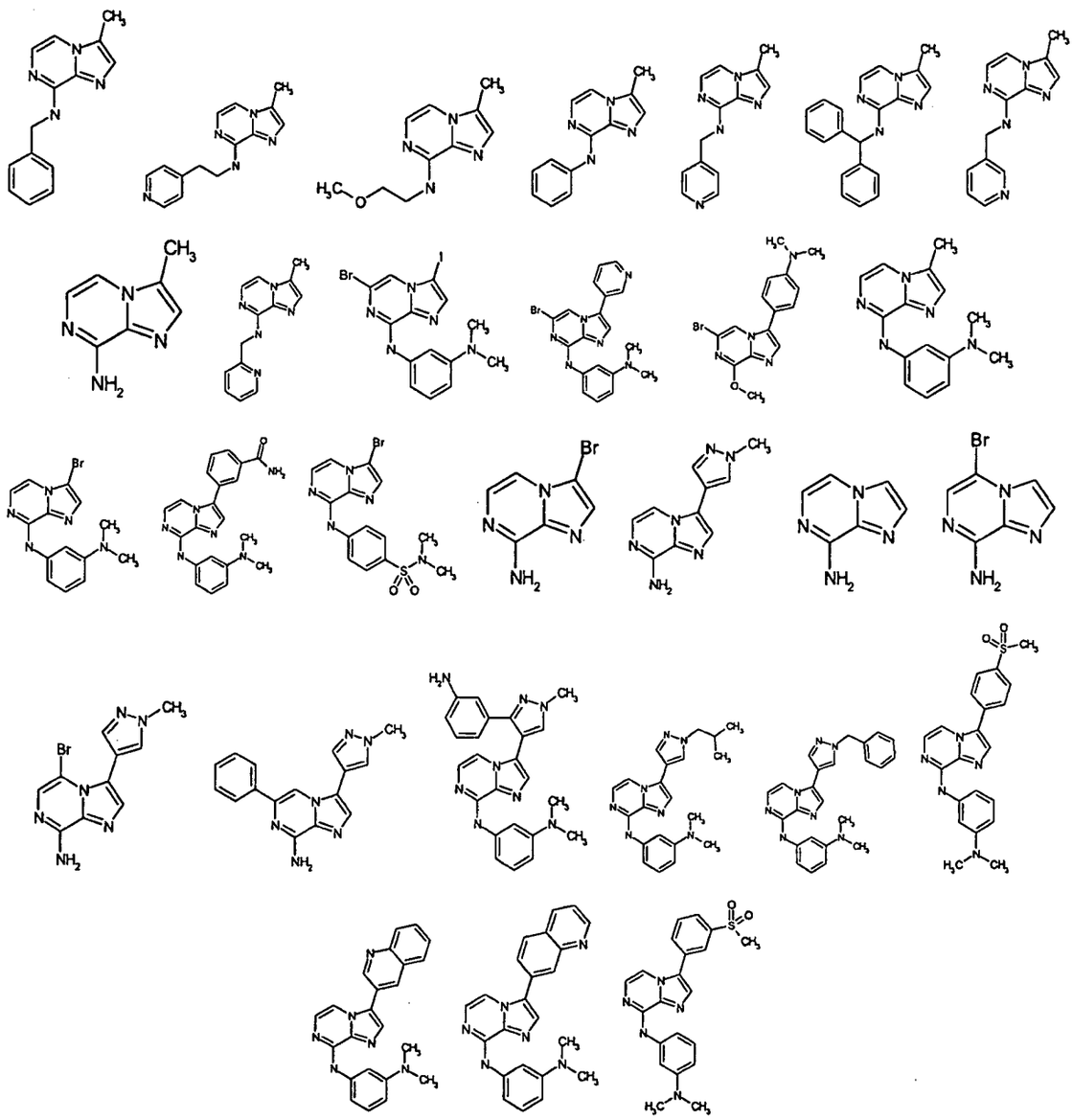
R^9 is selected from the group consisting of halogen, CN, NR^5R^6, -$C(O_2)R^6$, -$C(O)NR^5R^6$, -OR^6, -$C(O)R^7$, -SR^6, -$S(O_2)R^7$, -$S(O_2)NR^5R^6$, -$N(R^5)S(O_2)R^7$, -$N(R^5)C(O)R^7$and –$N(R^5)C(O)NR^5R^6$;

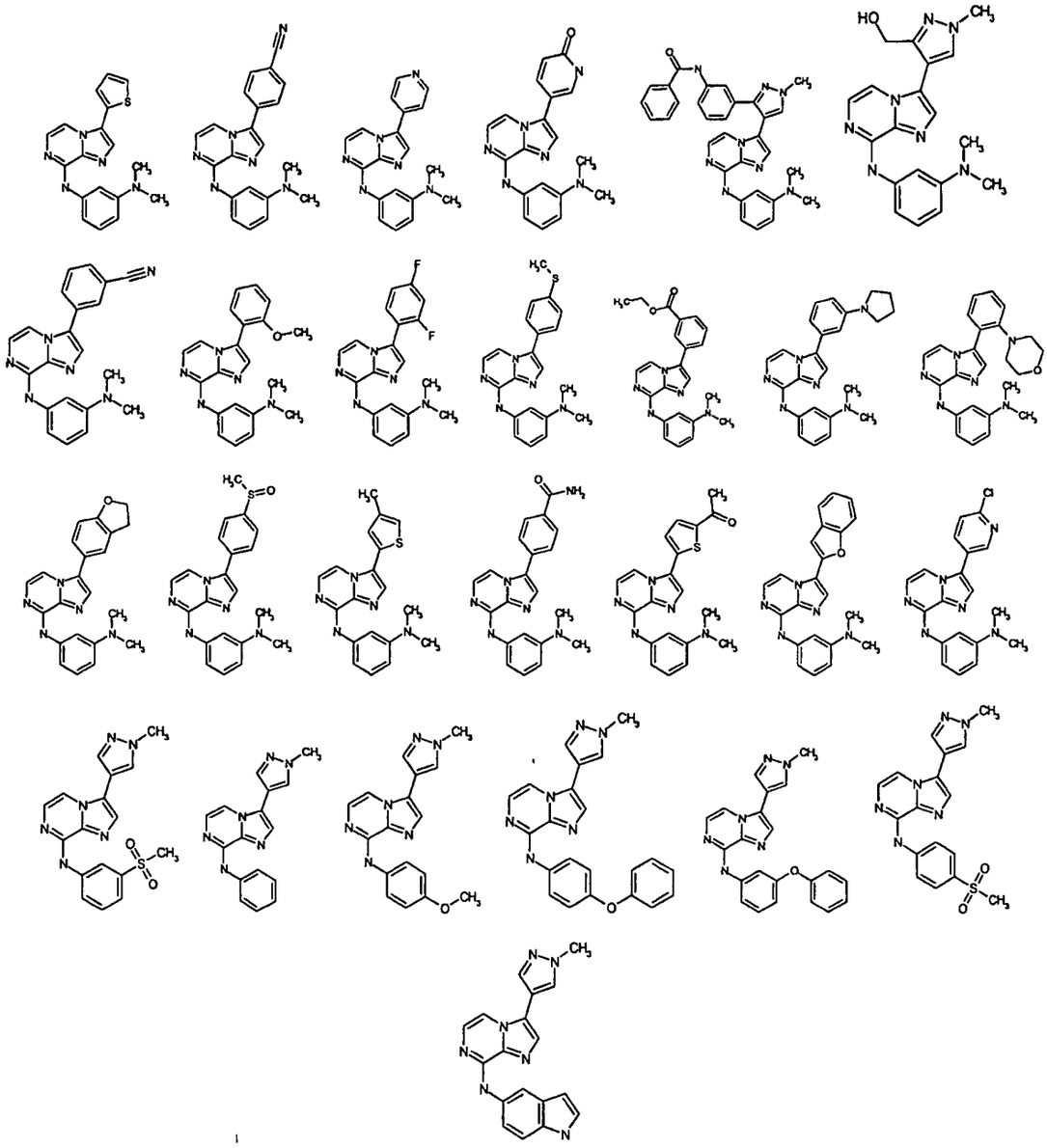
m is 0 to 4;

n is 1-4; and

p is 0-3;

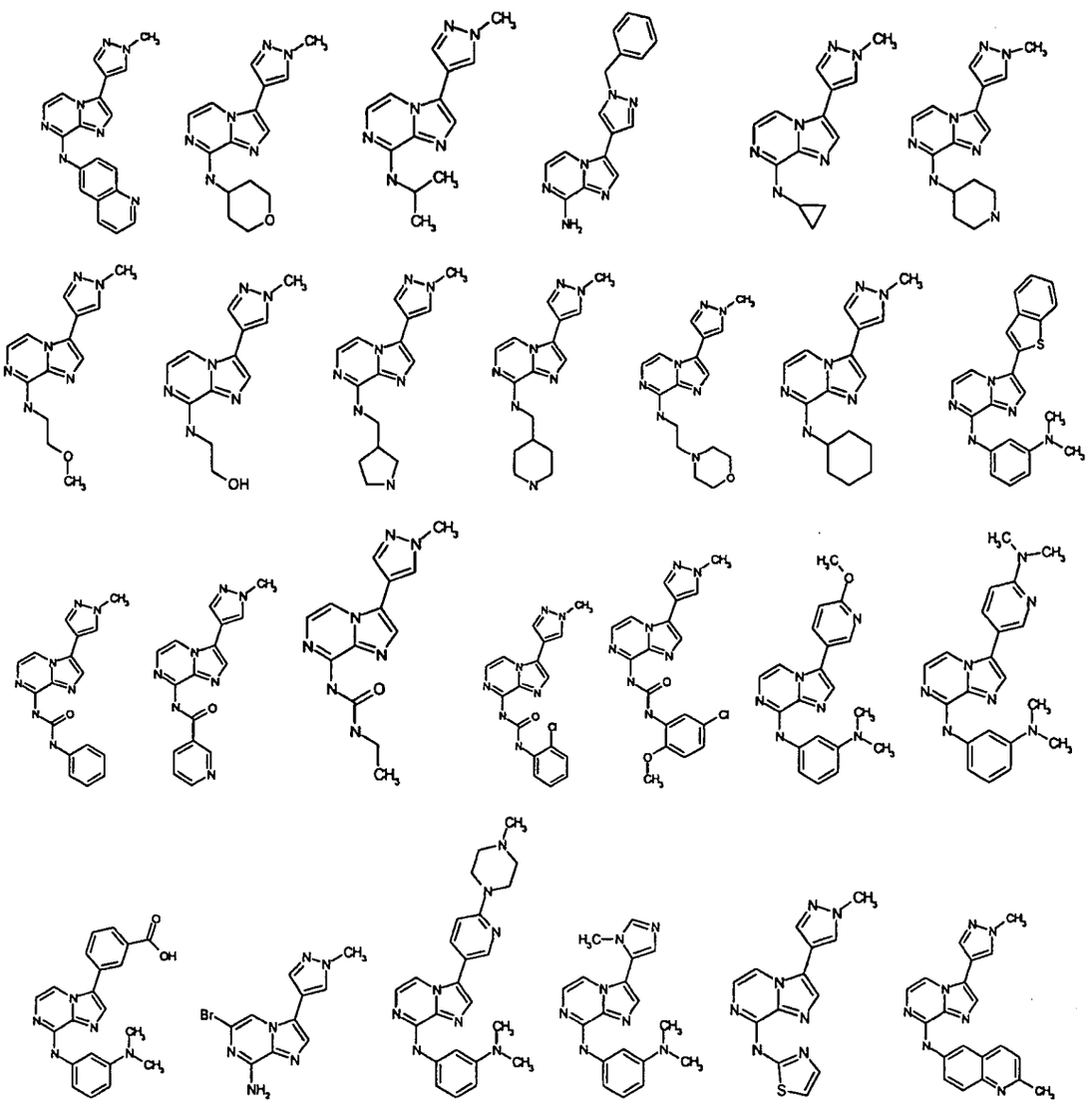
g. A compound selected from the compounds of the formulas:



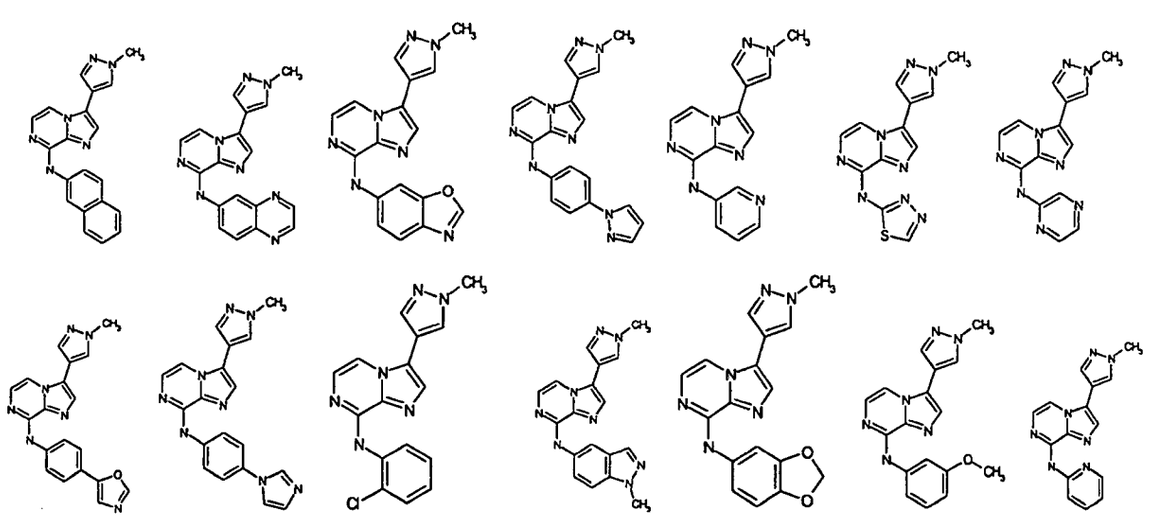


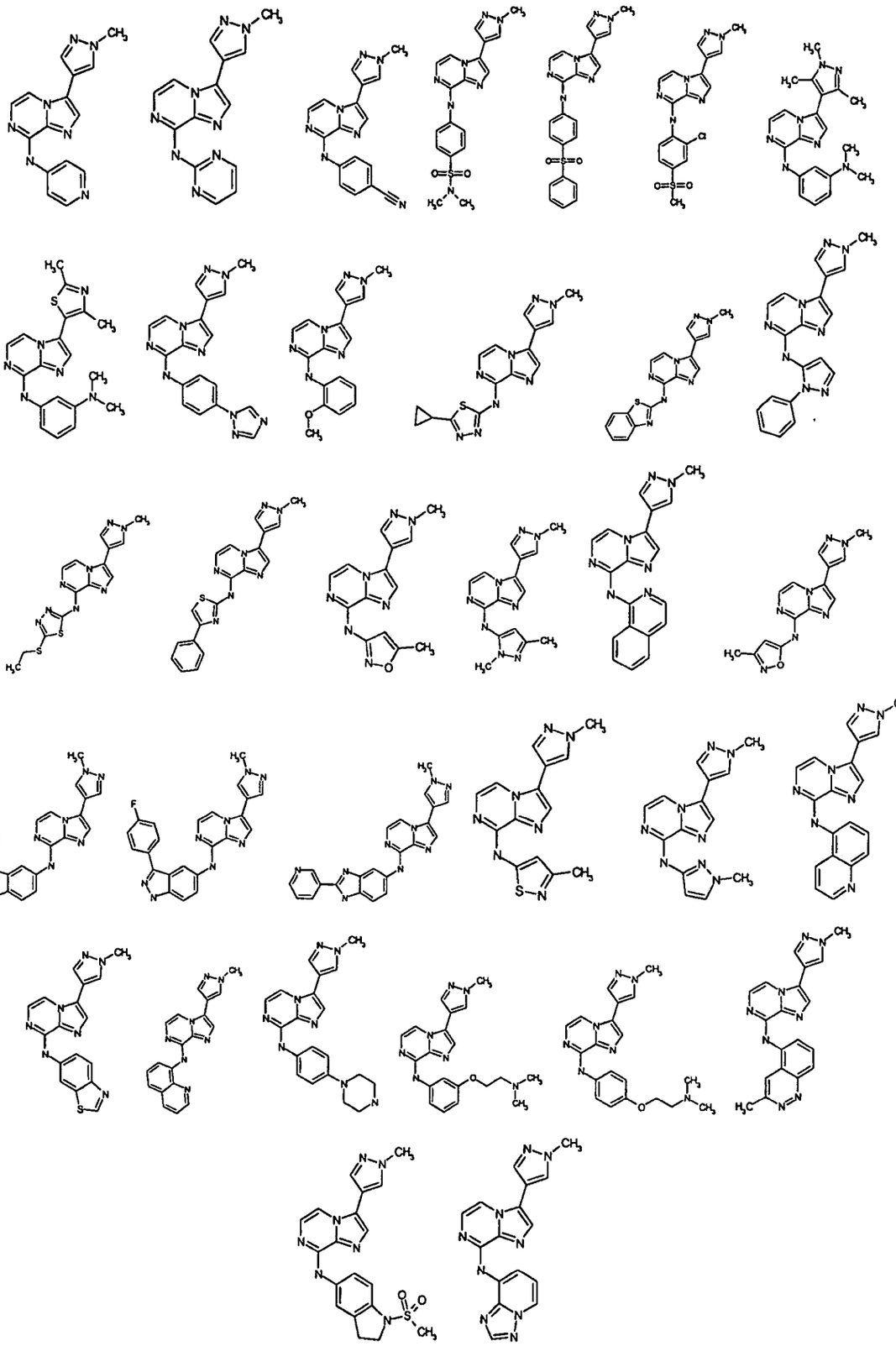
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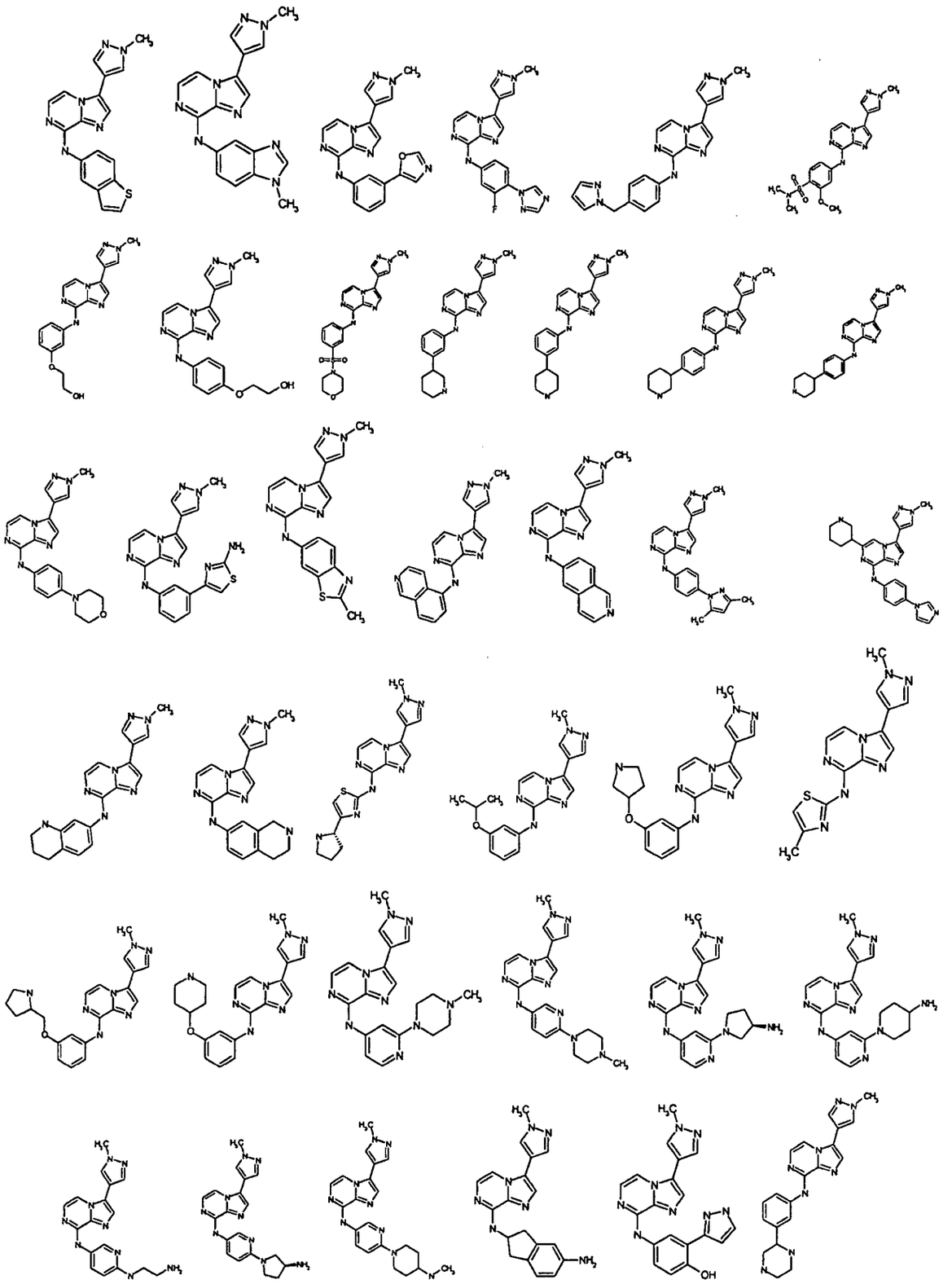


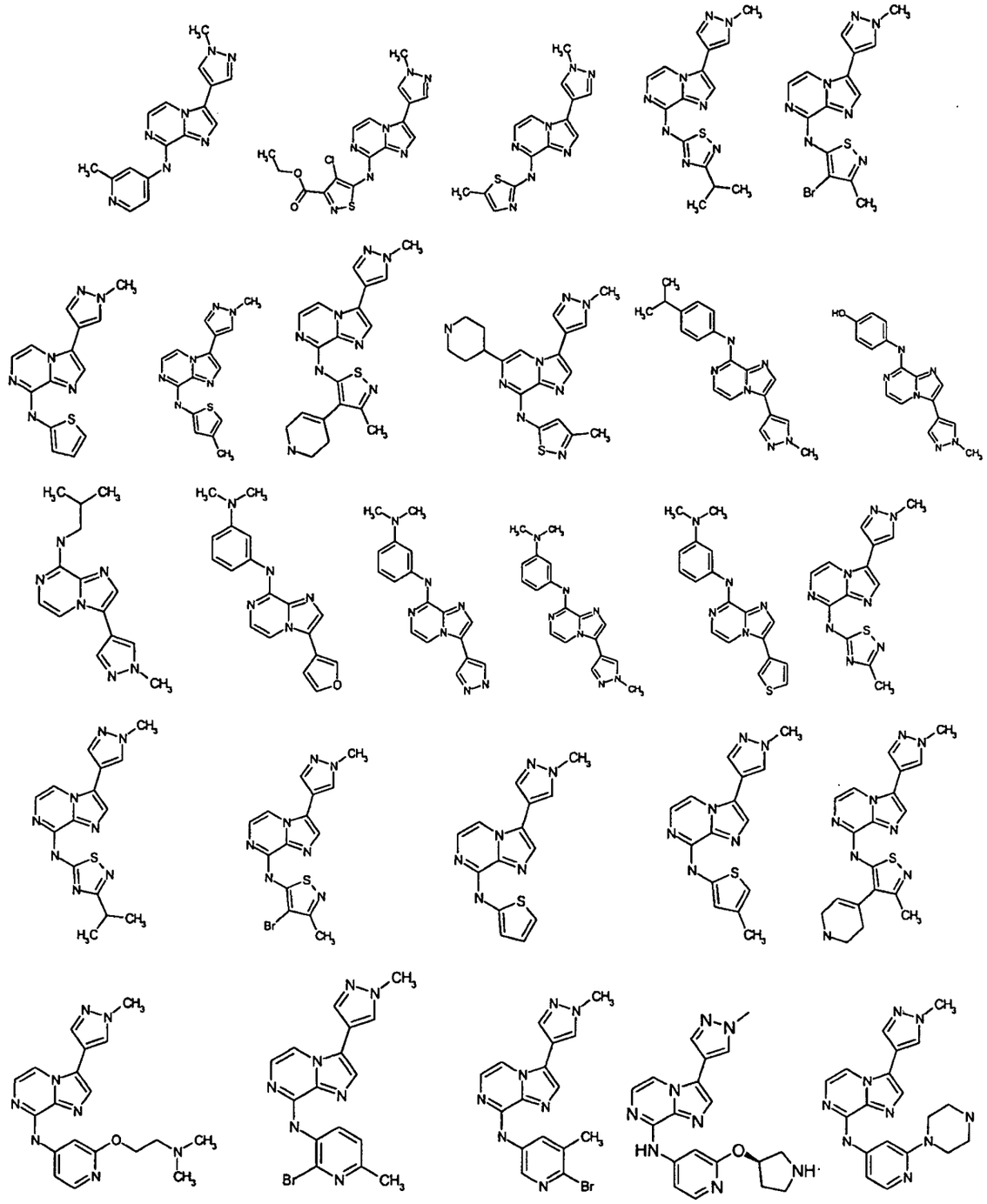
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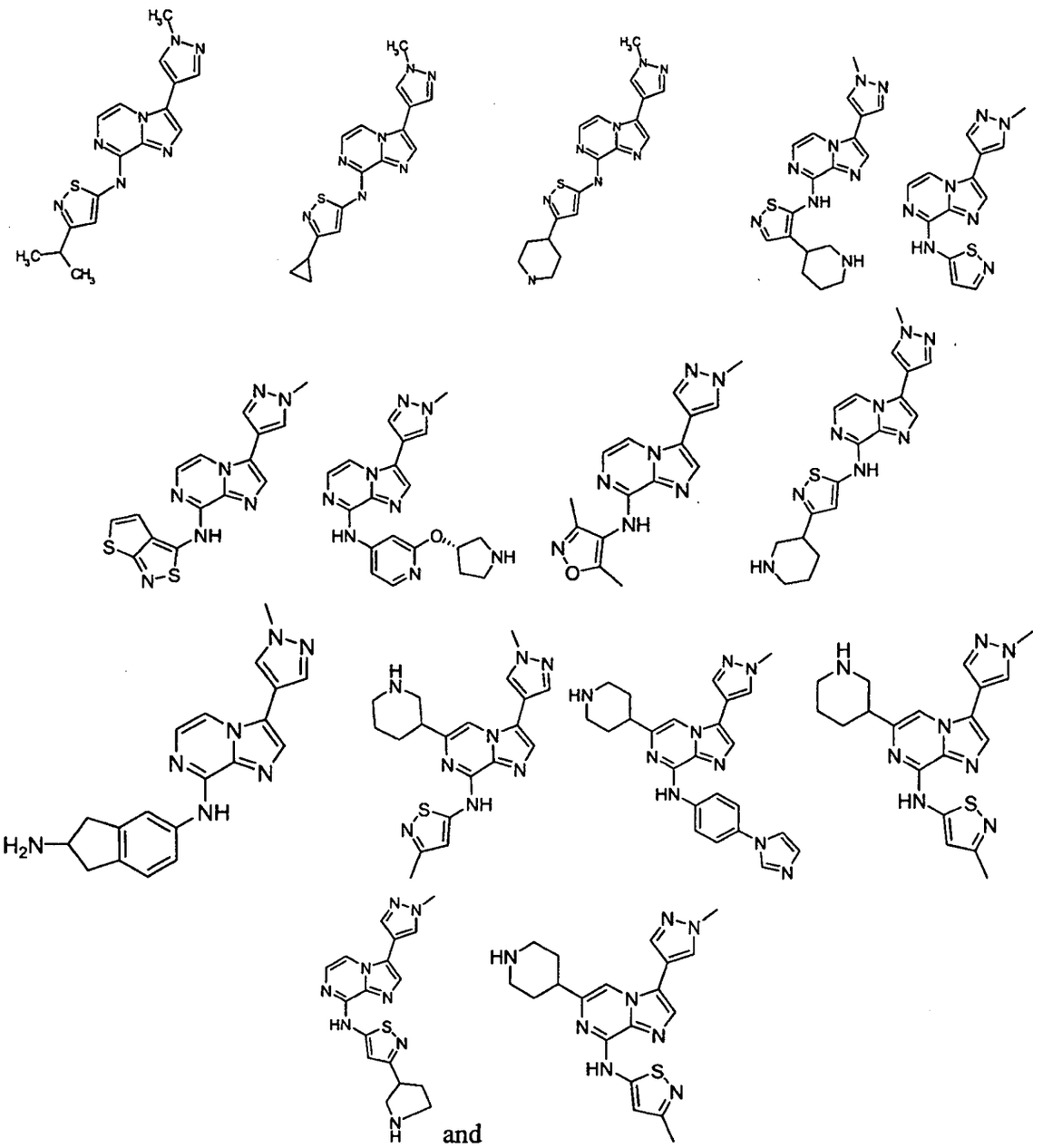


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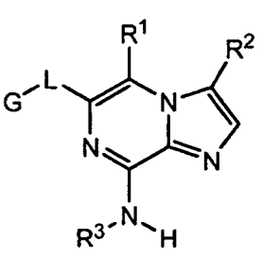
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and

or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof;

h. A compound of the formula:



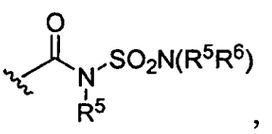
Formula H

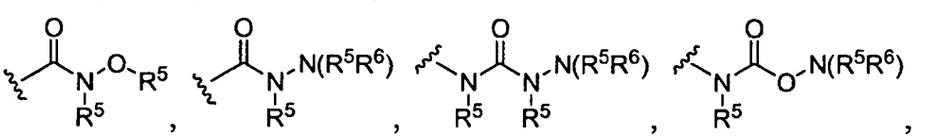
or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, wherein:

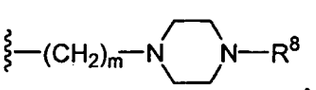
L is selected from the group consisting of S, S(O) and $S(O_2)$;

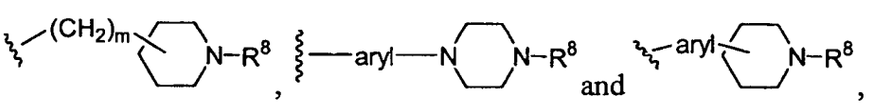
G is alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclenyl or heterocyclyl, wherein each of said alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclenyl or heterocyclyl can be unsubstituted or optionally independently substituted with one or more moieties which are independently selected from the group consisting of $-OR^5$, halo, -CN, $-C(O)NR^5R^6$, $-N(H)-C(O)R^5$,$-N(H)-C(O)-NR^5R^6$, $-S(O_2)NR^5R^6$, $-NR^5R^6$, $-C(O)R^5$, $-C(O_2)R^5$, $-SR^5$, $-S(O)R^5$, $-S(O_2)R^5$;

R^1 is H, halo, alkyl, aryl or heteroaryl, wherein each of said alkyl, aryl and heteroaryl can be unsubstituted or substituted with one or more moieties which can be the same or different each moiety being independently selected from the group consisting of halo, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C(O)NR^5R^6$ and $-OR^5$;

R^2 is selected from the group consisting of H, R^9, alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclylalkyl, $-CF_3$, $-C(O)R^7$,  ,

 ,

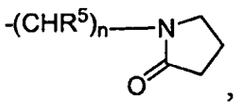
alkyl substituted with 1-6 R^9 groups which groups can be the same or different with each R^9 being independently selected,  ,

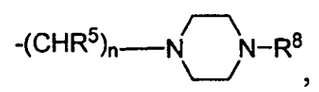
 and ,

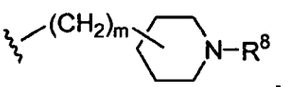
wherein each of the above-said aryl, heteroaryl, cycloalkyl, arylalkyl and heterocyclyl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halo, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, CF_3, CN, $-OCF_3$, $-OR^6$, $-C(O)R^7$, $-NR^5R^6$, $-C(O_2)R^6$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$,

$-N(R^5)C(O)R^7$ and $-N(R^5)C(O)NR^5R^6$;

R^3 is selected from the group consisting of H, alkyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroarylalkyl, cycloalkylalkyl, heterocyclylalkyl,



,


, $-(CHR^5)_n-OR^6$, $-S(O_2)R^6$, $-C(O)R^6$, $-S(O_2)NR^5R^6$, $-C(O)OR^6$, $-C(O)NR^5R^6$, cycloalkyl, $-CH(aryl)_2$, $-CH(heteroaryl)_2$, $-(CH_2)_m-NR^8$, and


, wherein each of said alkyl, aryl, heteroaryl and heterocyclyl can be substituted or optionally substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halo, alkyl, aryl, cycloalkyl, CF_3, CN, $-OCF_3$, $-OR^5$, $-NR^5R^6$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^6$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ and $-N(R^5)C(O)NR^5R^6$;

R^5 is H, alkyl, aryl, heteroaryl, heterocyclyl or cycloalkyl; and

R^6 is selected from the group consisting of H, alkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, wherein each of said alkyl, heteroarylalkyl, aryl, heteroaryl and arylalkyl can be unsubstituted or optionally substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl, cycloalkyl, CF_3, OCF_3, CN, $-OR^5$, $-NR^5R^6$, $-CH_2OR^5$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ and $-N(R^5)C(O)NR^5R^6$;

R^7 is selected from the group consisting of alkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, wherein each of said alkyl, heteroarylalkyl, aryl, heteroaryl and arylalkyl can be unsubstituted or optionally substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl, cycloalkyl, CF_3, OCF_3, CN, $-OR^5$, $-NR^5R^6$, $-CH_2OR^5$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ and $-N(R^5)C(O)NR^5R^6$;

R^8 is selected from the group consisting of R^6, $-C(O)NR^5R^6$, $-S(O_2)NR^5R^6$, $-C(O)R^7$, $-C(O_2)R^6$, $-S(O_2)R^7$ and $-(CH_2)$-aryl;

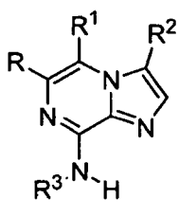
R^9 is selected from the group consisting of halogen, CN, NR^5R^6, $-C(O_2)R^6$, $-C(O)NR^5R^6$, $-OR^6$, $-C(O)R^7$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$,

$-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$and $-N(R^5)C(O)NR^5R^6$;

m is 0 to 4; and

p is 0-3;

i. A compound of Formula I:



Formula I

or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, wherein:

R is H, CN, $-NR^5R^6$, cycloalkyl, cycloalkenyl, heterocyclenyl, heteroaryl, $-C(O)NR^5R^6$, $-N(R^5)C(O)R^6$, heterocyclyl, heteroaryl substituted with $(CH_2)_{1-3}$ NR^5R^6, unsubstituted alkyl, or alkyl substituted with one or more moieties which can be the same or different each moiety being independently selected from the group consisting of $-OR^5$, heterocyclyl, $-N(R^5)C(O)N(R^5R^6)$, $-N(R^5)-C(O)OR^6$, $-(CH_2)_{1-3}-N(R^5R^6)$ and $-NR^5R^6$;

R^1 is H, halo, aryl or heteroaryl, wherein each of said aryl and heteroaryl can be unsubstituted or substituted with one or more moieties which can be the same or different each moiety being independently selected from the group consisting of halo, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, $-CH_2OR^5$, $-C(O)NR^5R^6$, -C(O)OH, $-C(O)NH_2$, $-NR^5R^6$ (wherein the R^5 and R^6, together with the N of said $-NR^5R^6$, form a heterocyclyl ring), $-S(O)R^5$, $-S(O_2)R^5$, -CN, -CHO, $-SR^5$, $-C(O)OR^5$, $-C(O)R^5$ and $-OR^5$;

R^2 is H, halo, aryl, arylalkyl or heteroaryl, wherein each of said aryl, arylalkyl and heteroaryl can be unsubstituted or optionally independently be substituted with one or more moieties which can be the same or different each moiety being independently selected from the group consisting of halo, amide, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, -C(O)OH, $-C(O)NH_2$, $-NR^5R^6$ (wherein the R^5 and R^6, together with the N of said $-NR^5R^6$, form a heterocyclyl ring), -CN, arylalkyl, $-CH_2OR^5$, $-S(O)R^5$, $-S(O_2)R^5$, -CN, -CHO, $-SR^5$, $-C(O)OR^5$, $-C(O)R^5$, heteroaryl and heterocyclyl;

R^3 is heterocyclyl–$(CR^7R^8)_n$-X, heterocyclenyl–$(CR^7R^8)_n$-X, heteroaryl–$(CR^7R^8)_n$-X or aryl–

$(CR^7R^8)_n$-X wherein each of the heterocyclyl-, heterocyclenyl-, heteroaryl- or aryl-moieties of said R^3 can be unsubstituted or substituted with one or more moieties, independently selected from the group consisting of $-CONR^5R^6$, $-OR^5$ and alkyl,

n is 1-6,

X is selected from the group consisting of, $-NR^5R^6$, $-OR^5$, $-SO-R^5$ and $-SR^5$,

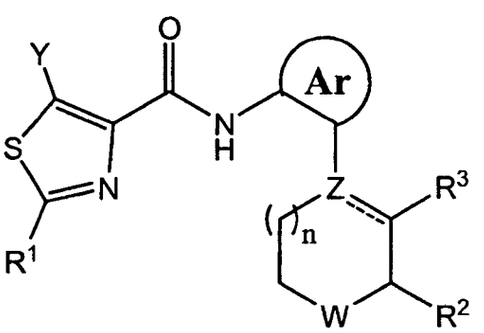
R^7 and R^8 are each independently hydrogen or alkyl;

R^5 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkoxyalkyl, -alkyl-S-alkyl, aminoalkyl, aryl, heteroaryl, heterocyclenyl, heterocycloalkyl, cycloalkyl, cycloalkenyl, heterocyclylalkoxyl, -S-alkylheterocyclyl, heterocyclyl, heterocyclenyl, alkylN(alkyl)$_2$, alkylNH(alkyl), alkylN(alkenyl)2, -alkylN(alkoxyl)2, -alkyl-SH and hydroxyalkyl, wherein each of said aryl, heteroaryl, heterocyclenyl, heterocycloalkyl, cycloalkyl, cycloalkenyl, heterocyclylalkoxyl, -S-alkylheterocyclyl, heterocyclyl, heterocyclenyl can be unsubstituted or substituted with one or more moieties independently selected from the group consisting of alkyl, alkyl, alkenyl, aryl, cycloalkenyl, cycloalkyl, arylalkyl, cycloalkenylalkyl, cycloalkylalkyl, heteroaryl, heterocyclenyl, heterocyclyl, heteroarylalkyl, heterocyclenylalkyl, heterocycloalkylalkyl, alkoxyalkyl, -alkyl-S-alkyl, -alkylSH, alkoxyl, -S-alkyl, hydroxyalkyl, and aminoalkyl;

R^6 is selected from the group consisting of hydrogen, alkyl, alkenyl, aryl, cycloalkenyl, cycloalkyl, arylalkyl, cycloalkenylalkyl, cycloalkylalkyl, heteroaryl, heterocyclenyl, heterocyclyl, heteroarylalkyl, heterocyclenylalkyl, heterocycloalkylalkyl, alkoxyalkyl, -alkyl-S-alkyl, -alkylSH, alkoxyl, -S-alkyl, hydroxyalkyl, and aminoalkyl, wherein each of said aryl, cycloalkenyl, cycloalkyl, arylalkyl, cycloalkenylalkyl, cycloalkylalkyl, heteroaryl, heterocyclenyl, heterocyclyl, heteroarylalkyl, heterocyclenylalkyl, heterocycloalkylalkyl can be unsubstituted or substituted with one or more moieties independently selected from the group consisting of alkyl, alkyl, alkenyl, aryl, cycloalkenyl, cycloalkyl, arylalkyl, cycloalkenylalkyl, cycloalkylalkyl, heteroaryl, heterocyclenyl, heterocyclyl, heteroarylalkyl, heterocyclenylalkyl, heterocycloalkylalkyl, alkoxyalkyl, -alkyl-S-alkyl, -alkylSH, alkoxyl, -S-alkyl, hydroxyalkyl, and aminoalkyl;

further wherein in any -NR^5R^6 in Formula I, said R^5 and R^6 can optionally be joined together with the N of said -NR^5R^6 to form a cyclic ring or bridged cyclic ring, wherein each of said cyclic ring or bridged cyclic ring, can be unsubstituted or substituted with one or more moieties, which can be the same or different, independently selected from the group consisting of hydroxyl, -SH, alkyl, alkenyl, hydroxyalkyl, -alkyl-SH, alkoxyl, -S-alkyl, -CO_2-alkyl, -CO_2-alkenyl, arylalkyl, cycloalkenylalkyl, cycloalkylalkyl, heteroarylalkyl, heterocyclenylalkyl, heterocycloalkylalkyl, heteroaryl, aryl, cycloalkenyl, cycloalkyl, spiroheterocyclyl, spiroheterocyclenyl, spiroheteroaryl, spirocyclyl, spirocyclenyl, spiroaryl, alkoxyalkyl, -alkyl-S-alkyl, heterocyclyl, and heterocyclenyl;

j. A compound having the formula:



(J)

or a pharmaceutically acceptable salt, solvate, ester, prodrug or stereoisomer thereof, wherein the dashed lines indicate an optional and additional bond, and wherein:

R^1 is nitrogen-containing heteroaryl, nitrogen-containing heterocyclyl, nitrogen-containing benzofused heteroaryl or nitrogen-containing benzofused heterocyclyl, wherein R^1 is joined to the rest of the compound of formula (I) via a ring nitrogen atom, and wherein one or more ring carbon atoms of a nitrogen-containing heteroaryl, nitrogen-containing heterocyclyl, nitrogen-containing benzofused heteroaryl or nitrogen-containing benzofused heterocyclyl group can be substituted with up to 5 substituents, which may be the same or different, and are independently selected from alkyl, aryl, halo, -OH, -O-alkyl, -O-aryl, -$N(R^8)_2$, -CF_3, -NO_2, -$C(O)R^8$, -$C(O)OR^8$, -$C(O)N(R^8)_2$, -$OC(O)R^8$ or -$NHC(O)R^8$;

R^2 is –H, -alkyl, –NH_2 or –CH_2NH_2;

R^3 is –H, -alkyl, $–NH_2$ or $–CH_2NH_2$;

each occurrence of R^4 is independently –H, -alkyl, $–NH_2$, -OH, -alkylene-OH, $–CH_2NH_2$, $-C(O)R^5$, $-C(O)NH_2$, -C(O)NH-alkyl, $-C(O)N(alkyl)_2$, $-NHC(O)R^6$ or $–NHS(O)_2R^6$;

R^5 is –H, -alkyl, -aryl, -heteroaryl, -NHOH;

R^6 is –H, -alkyl or $–CF_3$;

R^7 is –H, -OH, $-C_1$-C_6 alkyl, $-O-(C_1$-C_6 alkyl), or $–CF_3$;

R^8 is –H, alkyl, aryl, heterocyclyl, heteroaryl or cycloalkyl;

Ar is -arylene- or -heteroarylene-, wherein the arylene or heteroarylene is joined via 2 of its adjacent ring carbon atoms, and wherein the -arylene- or -heteroarylene- can be substituted with up to 4 substituents, which may be the same or different, and are independently selected from –halo, alkyl, alkoxy, aryloxy, $-SR^8$, $-S(O)R^8$, $-S(O)_2R^8$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)N(R^8)_2$, $-NHC(O)R^8$, $-CF_3$, -CN or NO_2, and such that when Ar is tetrahydronaphthylene, R^1 and R^2 cannot both be hydrogen

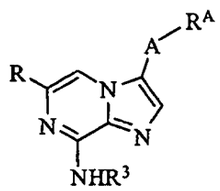
W is –NH- or $–C(R^4)_2$-, wherein both R^4 groups and the carbon atom to which they are attached can combine to form a five to seven membered heterocyclyl or heteroaryl group;

Y is –H, -halo, -alkyl or –CN;

Z is $–CR^7$- or –N-, when the optional additional bond is absent, and –C- when the optional additional bond is present;

n is an integer ranging from 0 to 2; and

(k) A compound of Formula K:



Formula K

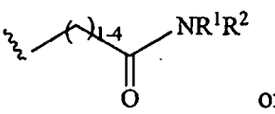
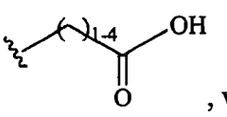
or a pharmaceutically acceptable salt, solvate, ester, prodrug or stereoisomer thereof, wherein:

R is H, halo or alkyl;

R^3 is heteroaryl-X, wherein X is heterocyclylalkyl- wherein said heterocyclyl can be unsubstituted or optionally substituted with 1-4 alkyl moieties;

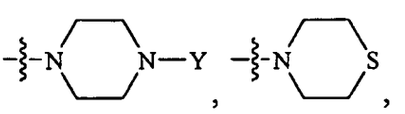
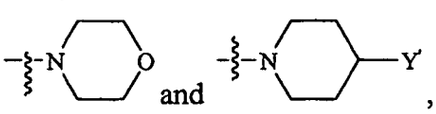
A is -aryl- , -heteroaryl-, $-N(R^1)$-aryl- or $-N(R^1)$-heteroaryl- , wherein each of said aryl and heteroaryl can be independently unsubstituted or optionally substituted with one or more

substituents, which substituents can be the same or different, each substituent being independently selected from the group consisting of alkyl, $-NO_2$, halo, hydroxy, trihaloalkyl, alkoxy, and dialkylamino;

R^A is $-(CH_2)_{1-4}$-heteroaryl,  or  , wherein said heteroaryl can optionally be fused with an aryl, wherein each of said aryl and heteroaryl can independently be optionally substituted with one or more moieties each moiety being independently selected from the group consisting of trihaloalkyl, $-NO_2$, halo, hydroxyalkyl, alkoxyalkyl and dialkylamino;

R^1 is H or alkyl;

R^2 is H, hydroxyalkyl-, arylalkyl-, heteroaryl, aryl, heteroarylalkyl-, alkyl, dialkylaminoalkyl-, alkylaminoalkyl-, cycloalkylalkyl-, cycloalkyl, heterocyclylalkyl- or heterocyclyl, wherein said aryl and aryl of arylalkyl can be unsubstituted or substituted with one or more moieties independently selected from the group consisting of trihaloalkyl, $-NO_2$, halo, hydroxyalkyl, alkoxyalkyl, dialkylamino and heterocyclylalkyl-, wherein said heterocyclylalkyl can be unsubstituted or substituted with alkyl or $-SO_2NH_2$; said heteroaryl and heteroaryl of heteroarylalkyl can be unsubstituted or substituted with one or more moieties, each moiety being independently selected from the group consisting of hydroxyalkyl, alkoxy, alkyl, halo, hydroxyl, and $-NO_2$; and said cycloalkyl is unsubstituted or substituted with hydroxyl; or

R^1 and R^2 together with the N to which each is attached, form a heterocyclic group selected from the group consisting of  ,  and , wherein

Y is alkoxyalkyl, hydroxyalkyl, dialkylaminoalkyl or alkyl, further wherein Y' is hydroxyl.

4. The method of claim 3, wherein endoreduplication in cancer cells results in death of the cancer cell, wherein said cancer cell is selected from the group consisting of tumor of the bladder, breast (including BRCA-mutated breast cancer), colorectal, colon, kidney, liver, lung (including small cell lung cancer and non-small cell lung cancer), head and neck, esophagus,

bladder, gall bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, and skin, including squamous cell carcinoma;

leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T- cell lymphoma, Hodgkins lymphoma, non-Hodgkins lymphoma, hairy cell lymphoma, mantle cell lymphoma, myeloma and Burkett's lymphoma;

chronic lymphocytic leukemia ("CLL"),

acute and chronic myelogenous leukemia, myelodysplastic syndrome and promyelocytic leukemia;

fibrosarcoma, rhabdomyosarcoma;

mantle cell lymphoma, myeloma;

astrocytoma, neuroblastoma, glioblastoma, malignant glial tumors, hepatocellular carcinoma, gastrointestinal stromal tumors ("GIST") and schwannomas;

melanoma, multiple myeloma, seminoma, teratocarcinoma, osteosarcoma, xenoderoma pigmentosum, keratoctanthoma, thyroid follicular cancer and Kaposi's sarcoma.

5. The method of claim 4, wherein said cancer cell is selected from the group consisting of colon cancer cell, breast cancer cell, lung cancer cell, prostrate cancer cell, and ovarian cancer cell.

6. The method of claim 3, wherein said pretreatment of cancer cells with at least one of said anti-mitotic agents is for at least about 12-24 hours.

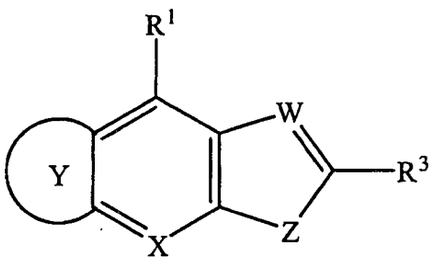
7. The method of claim 6, wherein said pretreatment of cancer cells with at least one of said anti-mitotic agents is for at least about 16 hours.

8. The method of claim 6, wherein after said pretreatment of cancer cells with said antimotic agent, the cancer cells are exposed to at least one aurora kinase inhibitor for about 2-12 hours.

9. The method of claim 7, wherein after said pretreatment of cancer cells with said antimotic agent, the cancer cells are exposed to at least one aurora kinase inhibitor for about 4 hours.

10. A method of retarding the growth of a tumor in vivo comprising the steps of (a) first administering to tumor in vivo at least one anti-mitotic agent selected from the group consisting of a taxane, paclitaxel, docetaxel, a Cenp-E Inhibitor, Abraxane, Epothilone, Monastrol, a KSP inhibitor, Ispinesib and compounds represented by Formulas A-D shown in paragraphs a-d below:

a. A compound represented by the structural Formula A:



Formula A

or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:

ring Y is a 5- to 6-membered aryl or a 5- or 6-membered heteroaryl fused as shown in Formula A, wherein in said aryl and heteroaryl each substitutable ring carbon is independently substituted with R^2 and each substitutable ring nitrogen is independently substituted with R^6;

W is N or $C(R^{12})$;

X is N or N-oxide;

Z is S, S(=O) or $S(=O)_2$;

R^1 is H, alkyl, alkoxy, hydroxy, halo, -CN, $-S(O)_m$-alkyl, $-C(O)NR^9R^{10}$, $-(CR^9R^{10})_{1-6}OH$, or $-NR^4(CR^9R^{10})_{1-2}OR^9$;

each R^2 is independently selected from the group consisting of H, halo, alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, $-(CR^{10}R^{11})_{0-6}-OR^7$, $-C(O)R^4$, $-C(S)R^4$, $-C(O)OR^7$, $-C(S)OR^7$, $-OC(O)R^7$, $-OC(S)R^7$, $-C(O)NR^4R^5$, $-C(S)NR^4R^5$, $-C(O)NR^4OR^7$, $-C(S)NR^4OR^7$, $-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, -CN, $-OCF_3$, $-SCF_3$, $-C(=NR^7)NR^4$, $-C(O)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}OR^7$, $-C(S)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(S)NR^7(CH_2)_{1-10}OR^7$, haloalkyl and alkylsilyl, wherein each of said alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl or heteroaralkyl is independently optionally substituted with 1-5 R^9 moieties;

each R^3 is independently selected from the group consisting of H, halo, alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, $-(CR^{10}R^{11})_{0-6}-OR^7$, $-C(O)R^4$, $-C(S)R^4$, $-C(O)OR^7$, $-C(S)OR^7$, $-OC(O)R^7$,

$-OC(S)R^7$, $-C(O)NR^4R^5$, $-C(S)NR^4R^5$, $-C(O)NR^4OR^7$, $-C(S)NR^4OR^7$, $-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, $-CN$, $-OCF_3$, $-SCF_3$, $-C(=NR^7)NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}OR^7$, $-C(S)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(S)NR^7(CH_2)_{1-10}OR^7$, haloalkyl and alkylsilyl, wherein each of said alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl or heteroaralkyl is independently optionally substituted with 1-5 R^9 moieties;

each R^4 and R^5 is independently selected from the group consisting of H, alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, $-OR^7$, $-C(O)R^7$, and $-C(O)OR^7$, wherein each of said alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl is optionally substituted with 1-4 R^8 moieties;

or R^4 and R^5, when attached to the same nitrogen atom, are optionally taken together with the nitrogen atom to which they are attached to form a 3-6 membered heterocyclic ring having 0-2 additional heteroatoms selected from N, O or S;

each R^6 is independently selected from the group consisting of H, alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroaralkyl, $-(CH_2)_{1-6}CF_3$, $-C(O)R^7$, $-C(O)OR^7$ and $-SO_2R^7$;

each R^7 is independently selected from the group consisting of H, alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, and heteroaralkyl, wherein each member of R^7 except H is optionally substituted with 1-4 R^8 moieties;

each R^8 is independently selected from the group consisting of halo, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-NO_2$, $-OR^{10}$, $-(C_1\text{-}C_6$ alkyl$)\text{-}OR^{10}$, $-CN$, $-NR^{10}R^{11}$, $-C(O)R^{10}$, $-C(O)OR^{10}$, $-C(O)NR^{10}R^{11}$, $-CF_3$, $-OCF_3$, $-CF_2CF_3$, $-C(=NOH)R^{10}$, $-N(R^{10})C(O)R^{11}$, $-C(=NR^{10})NR^{10}R^{11}$, and $-NR^{10}C(O)OR^{11}$, wherein each of said alkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally independently substituted with 1-3 moieties selected from the group consisting of halo, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-NO_2$, $-OR^{10}$, $-(C_1\text{-}C_6$ alkyl$)\text{-}OR^{10}$, $-CN$, $-NR^{10}R^{11}$, $-C(O)OR^{10}$, $-C(O)NR^{10}R^{11}$, $-CF^3$, $-OCF_3$, $-NR^{10}C(O)OR^{11}$, and

$-NR^{10}C(O)R^{40}$;

or two R^8 groups, when attached to the same carbon atom, are optionally taken together with the carbon atom to which they are attached to form a C=O or a C=S group;

each R^9 is independently selected from the group consisting of H, alkyl, alkoxy, OH, CN, halo, $-(CR^{10}R^{11})_{0-4}NR^4R^5$, haloalkyl, hydroxyalkyl, alkoxyalkyl, $-C(O)NR^4R^5$, $-C(O)OR^7$, $-OC(O)NR^4R^5$, $-NR^4C(O)R^5$, and $-NR^4C(O)NR^4R^5$;

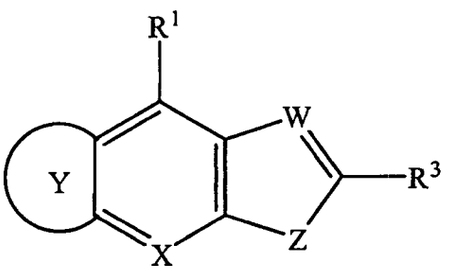
each R^{10} is independently H or alkyl; or R^9 and R^{10}, when attached to the same nitrogen atom, are optionally taken together with the nitrogen atom to which they are attached to form a 3-6 membered heterocyclic ring having 0-2 additional heteroatoms selected from N, O or S;

each R^{11} is independently H or alkyl; or R^{10} and R^{11}, when attached to the same nitrogen atom, are optionally taken together with the nitrogen atom to which they are attached to form a 3-6 membered heterocyclic ring having 0-2 additional heteroatoms selected from N, O or S;

each R^{12} is independently selected from the group consisting of H, halo, alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, $-(CR^{10}R^{11})_{0-6}-OR^7$, $-C(O)R^4$, $-C(S)R^4$, $-C(O)OR^7$, $-C(S)OR^7$, $-OC(O)R^7$, $-OC(S)R^7$, $-C(O)NR^4R^5$, $-C(S)NR^4R^5$, $-C(O)NR^4OR^7$, $-C(S)NR^4OR^7$, $-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, -CN, $-OCF_3$, $-SCF_3$, $-C(=NR^7)NR^4$, $-C(O)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}OR^7$, $-C(S)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(S)NR^7(CH_2)_{1-10}OR^7$, haloalkyl and alkylsilyl, wherein each of said alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl or heteroaralkyl is independently optionally substituted with 1-5 R^9 moieties; and

R^{40} is selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl, wherein each of said cycloalkyl, heterocyclyl, aryl and heteroaryl are optionally independently substituted with 1-3 moieties independently selected from the group consisting of -CN, -OH, halo, alkyl, haloalkyl, alkoxy, and $-NR^{10}R^{11}$;

b. A compound represented by the structural Formula B:



Formula B

or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:

ring Y is a 5- to 7-membered ring selected from the group consisting of cycloalkyl, cycloalkenyl, heterocyclyl or heterocyclenyl fused as shown in Formula B, wherein in each of said 5- to 7-membered ring, each substitutable ring carbon is independently substituted with 1-2 R^2 moieties and each substitutable ring heteroatom is independently substituted with R^6;

W is N or $C(R^{12})$;

X is N or N-oxide;

Z is S, S(=O) or $S(=O)_2$;

R^1 is H, alkyl, alkoxy, hydroxy, halo, -CN, $-S(O)_m$-alkyl, $-C(O)NR^9R^{10}$, $-(CR^9R^{10})_{1-6}OH$, or $-NR^4(CR^9R^{10})_{1-2}OR^9$; wherein m is 0 to 2;

each R^2 is independently selected from the group consisting of H, halo, alkyl, cycloalkyl, alkylsilyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, heteroaryl, $-(CR^{10}R^{11})_{0-6}-OR^7$, $-C(O)R^4$, $-C(S)R^4$, $-C(O)OR^7$, $-C(S)OR^7$, $-OC(O)R^7$, $-OC(S)R^7$, $-C(O)NR^4R^5$, $-C(S)NR^4R^5$, $-C(O)NR^4OR^7$, $-C(S)NR^4OR^7$, $-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, -CN, $-OCF_3$, $-SCF_3$, $-C(=NR^7)NR^4$, $-C(O)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}OR^7$, $-C(S)NR^7(CH_2)_{1-10}NR^4R^5$, and $-C(S)NR^7(CH_2)_{1-10}OR^7$, wherein each of said alkyl, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, and heteroaryl is independently optionally substituted with 1-5 R^9 moieties;

or two R^2s on the same carbon atom are optionally taken together with the carbon atom to which they are attached to form a C=O, a C=S or an ethylenedioxy group;

R^3 is independently selected from the group consisting of H, halo, alkyl, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, heteroaryl, $-(CR^{10}R^{11})_{0-6}-OR^7$, $-C(O)R^4$, -

$C(S)R^4$, -$C(O)OR^7$, -$C(S)OR^7$, -$OC(O)R^7$, -$OC(S)R^7$, -$C(O)NR^4R^5$, -$C(S)NR^4R^5$, -$C(O)NR^4OR^7$, -$C(S)NR^4OR^7$, -$C(O)NR^7NR^4R^5$, -$C(S)NR^7NR^4R^5$, -$C(S)NR^4OR^7$, -$C(O)SR^7$, -NR^4R^5, -$NR^4C(O)R^5$, -$NR^4C(S)R^5$, -$NR^4C(O)OR^7$, -$NR^4C(S)OR^7$, -$OC(O)NR^4R^5$, -$OC(S)NR^4R^5$, -$NR^4C(O)NR^4R^5$, -$NR^4C(S)NR^4R^5$, -$NR^4C(O)NR^4OR^7$, -$NR^4C(S)NR^4OR^7$, -$(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, -$S(O)_{1-2}NR^4R^5$, -$N(R^7)SO_2R^7$, -$S(O)_{1-2}NR^5OR^7$, -CN, -$C(=NR^7)NR^4R^5$, -$C(O)N(R^7)$-$(CR^{40}R^{41})_{1-5}$-$C(=NR^7)NR^4R^5$, -$C(O)N(R^7)(CR^{40}R^{41})_{1-5}$-$NR^4R^5$, -$C(O)N(R^7)(CR^{40}R^{41})_{1-5}$-$C(O)$-$NR^4R^5$, -$C(O)N(R^7)(CR^{40}R^{41})_{1-5}$-$OR^7$, -$C(S)NR^7(CH_2)_{1-5}NR^4R^5$, and -$C(S)NR^7(CH_2)_{1-5}OR^7$, wherein each of said alkyl, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, and heteroaryl is independently optionally substituted with 1-5 R^9 moieties;

each of R^4 and R^5 is independently selected from the group consisting of H, alkyl, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, heteroaryl, -OR^7, -$C(O)R^7$, and -$C(O)OR^7$, wherein each of said alkyl, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, and heteroaryl, is optionally substituted with 1-4 R^8 moieties;

or R^4 and R^5, when attached to the same nitrogen atom, are optionally taken together with the nitrogen atom to which they are attached to form a 3-6 membered heterocyclic ring having 0-2 additional heteroatoms selected from N, O or S;

each R^6 is independently selected from the group consisting of H, alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroaralkyl, -$(CH_2)_{1-6}CF_3$, -$C(O)R^7$, –$C(O)OR^7$ and –SO_2R^7;

each R^7 is independently selected from the group consisting of H, alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, and heteroaralkyl, wherein each member of R^7 except H is optionally substituted with 1-4 R^8 moieties;

each R^8 is independently selected from the group consisting of halo, alkyl, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, heteroaryl, -NO_2, -OR^{10}, -(C_1-C_6 alkyl)-OR^{10}, –CN, –$NR^{10}R^{11}$, –$C(O)R^{10}$, -$C(O)OR^{10}$, -$C(O)NR^{10}R^{11}$, -CF_3, –OCF_3, –CF_2CF_3, –$C(=NOH)R^{10}$, –$N(R^{10})C(O)R^{11}$, -$C(=NR^{10})NR^{10}R^{11}$, and -$NR^{10}C(O)OR^{11}$; wherein said each of said alkyl, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, and heteroaryl is independently optionally substituted with 1-4 R^{42} moieties; wherein when each of said cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, and heteroaryl contains two

radicals on adjacent carbon atoms anywhere within said cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, and heteroaryl, such radicals may optionally and independently in each occurrence, be taken together with the carbon atoms to which they are attached, to form a five- or six-membered carbocyclic or heterocyclic ring;

or two R^8 groups, when attached to the same carbon, are optionally taken together with the carbon atom to which they are attached to form a C=O or a C=S group;

each R^9 is independently selected from the group consisting of H, alkyl, alkoxy, OH, CN, halo, $-(CR^{10}R^{11})_{0-4}NR^4R^5$, haloalkyl, hydroxyalkyl, alkoxyalkyl, $-C(O)NR^4R^5$, $-C(O)OR^7$, $-OC(O)NR^4R^5$, $-NR^4C(O)R^5$, and $-NR^4C(O)NR^4R^5$;

each R^{10} is independently H or alkyl; or R^9 and R^{10}, when attached to the same nitrogen atom, are optionally taken together with the nitrogen atom to which they are attached to form a 3-6 membered heterocyclic ring having 0-2 additional heteroatoms selected from N, O or S;

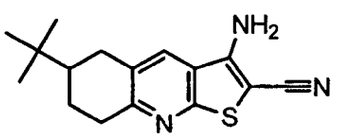
each R^{11} is independently H, alkyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heterocyclenyl, or heteroaryl; or R^{10} and R^{11}, when attached to the same nitrogen atom, are optionally taken together with the nitrogen atom to which they are attached to form a 3-6 membered heterocyclic ring having 0-2 additional heteroatoms selected from N, O or S; wherein each of said R^{11} alkyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heterocyclenyl, and heteroaryl is independently optionally substituted with 1-3 moieties selected from the group consisting of –CN, -OH, $-NH_2$, -N(H)alkyl, $-N(alkyl)_2$, halo, haloalkyl, CF_3, alkyl, hydroxyalkyl, alkoxy, aryl, aryloxy, and heteroaryl;

each R^{12} is independently selected from the group consisting of H, halo, alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, $-(CR^{10}R^{11})_{0-6}-OR^7$, $-C(O)R^4$, $-C(S)R^4$, $-C(O)OR^7$, $-C(S)OR^7$, $-OC(O)R^7$, $-OC(S)R^7$, $-C(O)NR^4R^5$, $-C(S)NR^4R^5$, $-C(O)NR^4OR^7$, $-C(S)NR^4OR^7$, $-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, -CN, $-OCF_3$, $-SCF_3$, $-C(=NR^7)NR^4$, $-C(O)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}OR^7$, $-C(S)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(S)NR^7(CH_2)_{1-10}OR^7$, haloalkyl and alkylsilyl, wherein each of said alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl or heteroaralkyl is independently optionally substituted with 1-5 R^9 moieties;

R^{40} and R^{41} can be the same or different, each being independently selected from the group consisting of H, alkyl, aryl, heteroaryl, heterocyclyl, heterocyclenyl, cycloalkyl and cycloalkenyl;

each R^{42} is independently selected from the group consisting of halo, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-NO_2$, $-OR^{10}$, $-(C_1-C_6\ alkyl)-OR^{10}$, $-CN$, $-NR^{10}R^{11}$, $-C(O)R^{10}$, $-C(O)OR^{10}$, $-C(O)NR^{10}R^{11}$, $-CF_3$, $-OCF_3$, $-N(R^{10})C(O)R^{11}$, and $-NR^{10}C(O)OR^{11}$;

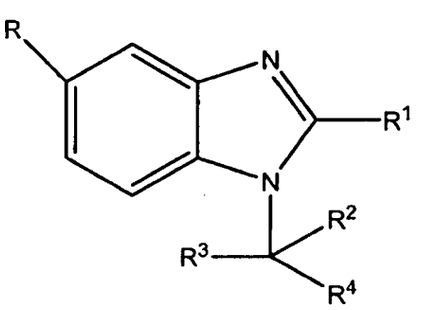
with the proviso that when W is $C(R^{12})$, R^{12} and R^3 are optionally taken together, with the two ring carbon atoms to which they are attached to form a 6-membered ring selected from the group consisting of cycloalkenyl, aryl, heteroaryl, heterocyclyl and heterocyclenyl, wherein said 6-membered ring is optionally substituted with 1-3 moieties independently selected from oxo, thioxo, $-OR^{11}$, $-NR^{10}R^{11}$, $-C(O)R^{11}$, $-C(O)OR^{11}$, $-C(O)N(R^{10})(R^{11})$, or $-N(R^{10})C(O)R^{11}$;

c. 

Formula C

or a pharmaceutically acceptable salt, solvate, or ester thereof; and

d. A compound of Formula D



Formula D

or a pharmaceutically acceptable salt, solvate, or ester thereof, wherein:

R is selected from the group consisting of H, alkyl, cyano, haloalkyl, halo, —SH, -S-alkyl, -S-haloalkyl, $-S(=O)_2$alkyl, $-S(=O)_2OH$, $-S(=O)_2NH_2$, $-S(=O)_2NH$(alkyl), $S(=O)_2NH$(cycloalkyl), $-S(=O)_2N(alkyl)_2$, $-S(=O)_2$heterocyclyl, $-S(=O)_2$heteroaryl, cycloalkyl, aryl, heterocyclyl, heteroaryl, -NHC(=O)alkyl, $-C(=O)NH_2$, –C(=O)NH(alkyl), -C(=O)NH(cycloalkyl), $-C(=O)N(alkyl)_2$, –C(=O)OH, –

C(=O)Oalkyl, -C(=O)heterocyclyl, -C(=O)NH(aryl), wherein when each of said cycloalkyl, aryl, heterocyclyl, heteroaryl, and the "heterocyclyl" and "aryl" portions of said R groups has two substituents on adjacent carbon atoms, said substituents, may optionally be taken together with the carbon atoms to which they are attached to form a five- to six-membered cycloalkyl, aryl, heterocyclyl, heterocyclenyl, or heteroaryl ring; wherein each of the aforementioned R alkyl, aryl, cycloalkyl, heterocyclyl, and heteroaryl, and the "alkyl", "cycloalkyl", "heterocyclyl", and "aryl" portions of said R groups, optionally with said five- to six-membered aryl, heterocyclyl, heterocyclenyl, or heteroaryl ring, is optionally substituted with 1-3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, hydroxyl, cyano, halo, haloalkyl, haloalkoxy, -C(O)OH, -C(=O)Oalkyl, and -C(O)NH_2;

R^1 is selected from the group consisting of alkyl, heterocyclyl, -C(=O)aryl, -NH_2, -NH(alkyl), -NH(cycloalkyl), -N(alkyl)(cycloalkyl), -NH(heterocyclyl), -N(alkyl)(heterocyclyl), N(alkyl)$_2$, -NH(aryl), -N(alkyl)(aryl), -N(aryl)$_2$, -NH(heteroaryl), -N(alkyl)(heteroaryl), -NHC(=O)-alkyl, -N(alkyl)C(=O)-alkyl, -NHC(=O)Oalkyl, -N(alkyl)C(=O)O-alkyl, wherein each of the aforesaid alkyl, heterocyclyl, and the "alkyl", "cycloalkyl", "aryl", and "heteroaryl" portions of said R^1 groups is optionally substituted with 1-3 substituents independently selected from the group consisting of halo, heterocyclyl, aryl, heteroaryl, haloalkyl, haloalkoxy, aryloxy, cyano, –SH, -S-alkyl, -S-haloalkyl, -S(=O)$_2$alkyl, -S(=O)$_2$OH, -S(=O)$_2$$NH_2$, -S(=O)$_2$NH(alkyl), S(=O)$_2$NH(cycloalkyl), -S(=O)$_2$N(alkyl)$_2$, -S(=O)$_2$heterocyclyl, -S(=O)$_2$heteroaryl, hydroxy, alkyl, alkenyl, alkynyl, -NH_2, -NH(alkyl), -N(alkyl)$_2$, alkoxy, -NHC(=O)alkyl, -C(=O)H, -C(=O)alkyl, -C(=O)aryl, , -C(=O)heteroaryl, -C(=O)Oalkyl, -C(=O)NH_2, -C(O)NHalkyl, -C(=O)N(alkyl)$_2$; wherein when each of said heterocyclyl, aryl and heteroaryl has two substituents on adjacent carbon atoms, said substituents, may optionally be taken together with the carbon atoms to which they are attached to form a five to six-membered aryl, heterocyclyl, heterocyclenyl, or heteroaryl ring;

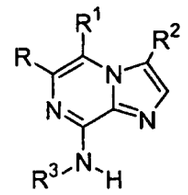
R^2 and R^3 independently are H or alkyl, or -C(R^2)(R^3)- is absent;

R^4 is selected from the group consisting of alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl, wherein when each of said cycloalkyl, heterocyclyl, aryl, and heteroaryl has two substituents on adjacent carbon atoms, said substituents, may optionally be

taken together with the carbon atoms to which they are attached to form a five to six-membered aryl, heterocyclyl, heterocyclenyl, or heteroaryl ring; wherein each of the aforementioned R^4 alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl, optionally with said five to six-membered aryl, heterocyclyl, heterocyclenyl, or heteroaryl ring is optionally substituted with 1-3 substituents independently selected from the group consisting of cyano, halo, haloalkyl, alkyl, alkoxy, hydroxyl, haloalkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-S(=O)_2$alkyl, $-S(=O)_2NH_2$, $-S(=O)_2NH$(alkyl), $-S(=O)_2N(alkyl)_2$, -S-alkyl, -S-haloalkyl, $-C(=O)OH$, $-NH_2$, -NH(alkyl), $-N(alkyl)_2$, and $-C(=O)O$alkyl;

and (b) subsequently administering to said tumor at least one aurora kinase inhibitor, wherein said aurora kinase inhibitor is selected from the group consisting of a compound represented by Formulas E-K shown below in paragraphs e-k:

e. A compound represented by the structural Formula E:



Formula E

or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, wherein:

R is H, CN, $-NR^5R^6$, cycloalkyl, cycloalkenyl, heterocyclenyl, heteroaryl, $-C(O)NR^5R^6$, $-N(R^5)C(O)R^6$, heterocyclyl, heteroaryl substituted with $(CH_2)_{1-3}$ NR^5R^6, unsubstituted alkyl, or alkyl substituted with one or more moieties which can be the same or different each moiety being independently selected from the group consisting of $-OR^5$, heterocyclyl, $-N(R^5)C(O)N(R^5R^6)$, $-N(R^5)$-$C(O)OR^6$, $-(CH_2)_{1-3}$-$N(R^5R^6)$ and $-NR^5R^6$;

R^1 is H, halo, aryl or heteroaryl, wherein each of said aryl and heteroaryl can be unsubstituted or substituted with one or more moieties which can be the same or different each moiety being independently selected from the group consisting of halo, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, $-CH_2OR^5$, $-C(O)NR^5R^6$, -C(O)OH, $-C(O)NH_2$, $-NR^5R^6$ (wherein the R^5 and R^6, together with the N of said

$-NR^5R^6$, form a heterocyclyl ring), $-S(O)R^5$, $-S(O_2)R^5$, -CN, -CHO, $-SR^5$, $-C(O)OR^5$, $-C(O)R^5$ and $-OR^5$;

R^2 is H, halo, aryl, arylalkyl or heteroaryl, wherein each of said aryl, arylalkyl and heteroaryl can be unsubstituted or optionally independently be substituted with one or more moieties which can be the same or different each moiety being independently selected from the group consisting of halo, amide, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, $-C(O)OH$, $-C(O)NH_2$, $-NR^5R^6$ (wherein the R^5 and R^6, together with the N of said $-NR^5R^6$, form a heterocyclyl ring), -CN, arylalkyl, $-CH_2OR^5$, $-S(O)R^5$, $-S(O_2)R^5$, -CN, -CHO, $-SR^5$, $-C(O)OR^5$, $-C(O)R^5$, heteroaryl and heterocyclyl;

R^3 is H, alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl, wherein:

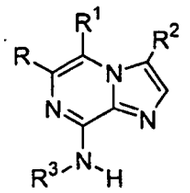
- said alkyl shown above for R^3 can be unsubstituted or substituted with one or more moieties which can be the same or different each moiety being independently selected from the group consisting of $-OR^5$, alkoxy, heteroaryl, and $-NR^5R^6$;
- said aryl shown above for R^3 is unsubstituted, or optionally substituted, or optionally fused, with halo, heteroaryl, heterocyclyl, cycloalkyl or heteroarylalkyl, wherein each of said heteroaryl, heterocyclyl, cycloalkyl and heteroarylalkyl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different each moiety being independently selected from alkyl, $-OR^5$, $-N(R^5R^6)$ and $-S(O_2)R^5$; and
- said heteroaryl shown above for R^3 can be unsubstituted or optionally substituted, or optionally fused, with one or more moieties which can be the same or different with each moiety being independently selected from the group consisting of halo, amino, alkoxycarbonyl, $-OR^5$, alkyl, -CHO, $-NR^5R^6$, $-S(O_2)N(R^5R^6)$, $-C(O)N(R^5R^6)$, $-SR^5$, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclenyl, and heterocyclyl;

R^5 is H, alkyl, aminoalkyl, aryl, heteroaryl, heterocyclyl or cycloalkyl; and

R^6 is H, alkyl, aryl, arylalkyl, heteroaryl, heterocyclyl or cycloalkyl;

further wherein in any $-NR^5R^6$ in Formula I, said R^5 and R^6 can optionally be joined together with the N of said $-NR^5R^6$ to form a cyclic ring;

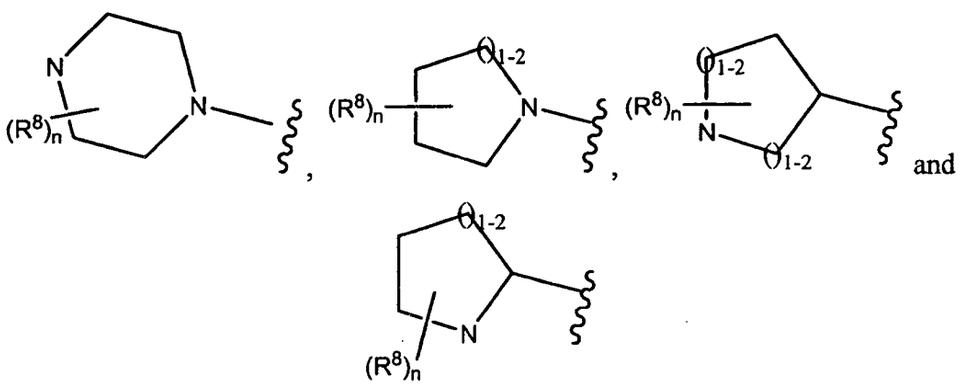
f. A compound represented by the structural formula:



Formula F

or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, wherein:

R is selected from the group consisting of H, halogen, aryl, heteroaryl, cycloalkyl, arylalkyl, heterocyclyl, heterocyclylalkyl, alkenyl, alkynyl, $-C(O)R^7$,



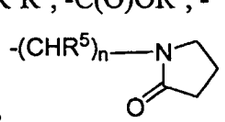
and

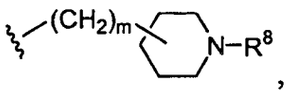
wherein each of said aryl, heteroaryl, cycloalkyl, arylalkyl, alkenyl, heterocyclyl and the heterocyclyl moieties whose structures are shown immediately above for R can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, cycloalkyl, CF_3, CN, $-OCF_3$, $-OR^6$, $-C(O)R^7$, $-NR^5R^6$, $-C(O_2)R^6$, $-C(O)NR^5R^6$, $-(CHR^5)_nOR^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ and $-N(R^5)C(O)NR^5R^6$;

R^1 is H, halogen or alkyl;

R^2 is alkyl;

R^3 is selected from the group consisting of H, aryl, heteroaryl, heterocyclyl, $-(CHR^5)_n$-aryl, $-(CHR^5)_n$-heteroaryl, $-(CHR^5)_n-OR^6$, $-S(O_2)R^6$, $-C(O)R^6$, $-S(O_2)NR^5R^6$, $-C(O)OR^6$, $-C(O)NR^5R^6$, cycloalkyl, $-CH(aryl)_2$, $-(CH_2)_m-NR^8$, $-(CHR^5)_n-CH(aryl)_2$,



and  , wherein each of said aryl, heteroaryl and heterocyclyl can be substituted or optionally substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl, cycloalkyl, CF_3, CN, $-OCF_3$, $-OR^5$, $-NR^5R^6$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^6$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ and $-N(R^5)C(O)NR^5R^6$;

R^5 is H or alkyl;

R^6 is selected from the group consisting of H, alkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, wherein each of said alkyl, heteroarylalkyl, aryl, heteroaryl and arylalkyl can be unsubstituted or optionally substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl, cycloalkyl, CF_3, OCF_3, CN, $-OR^5$, $-NR^5R^6$, $-CH_2OR^5$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ and $-N(R^5)C(O)NR^5R^6$;

R^7 is selected from the group consisting of alkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, wherein each of said alkyl, heteroarylalkyl, aryl, heteroaryl and arylalkyl can be unsubstituted or optionally substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl, cycloalkyl, CF_3, OCF_3, CN, $-OR^5$, $-NR^5R^6$, $-CH_2OR^5$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ and $-N(R^5)C(O)NR^5R^6$;

R^8 is selected from the group consisting of R^6, $-C(O)NR^5R^6$, $-S(O_2)NR^5R^6$, $-C(O)R^7$, $-C(O_2)R^6$, $-S(O_2)R^7$ and $-(CH_2)$-aryl;

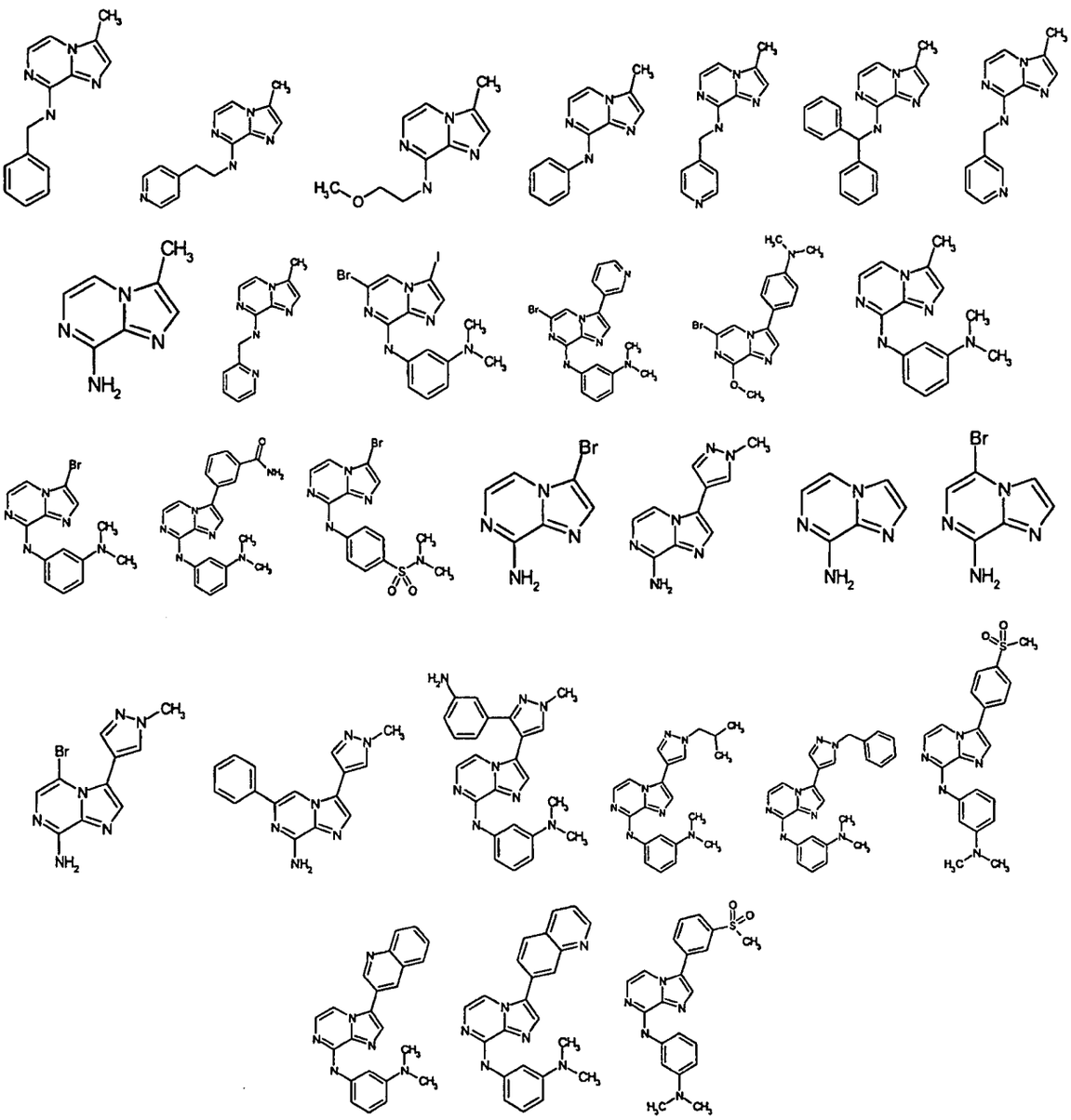
R^9 is selected from the group consisting of halogen, CN, NR^5R^6, $-C(O_2)R^6$, $-C(O)NR^5R^6$, $-OR^6$, $-C(O)R^7$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$and $-N(R^5)C(O)NR^5R^6$;

m is 0 to 4;

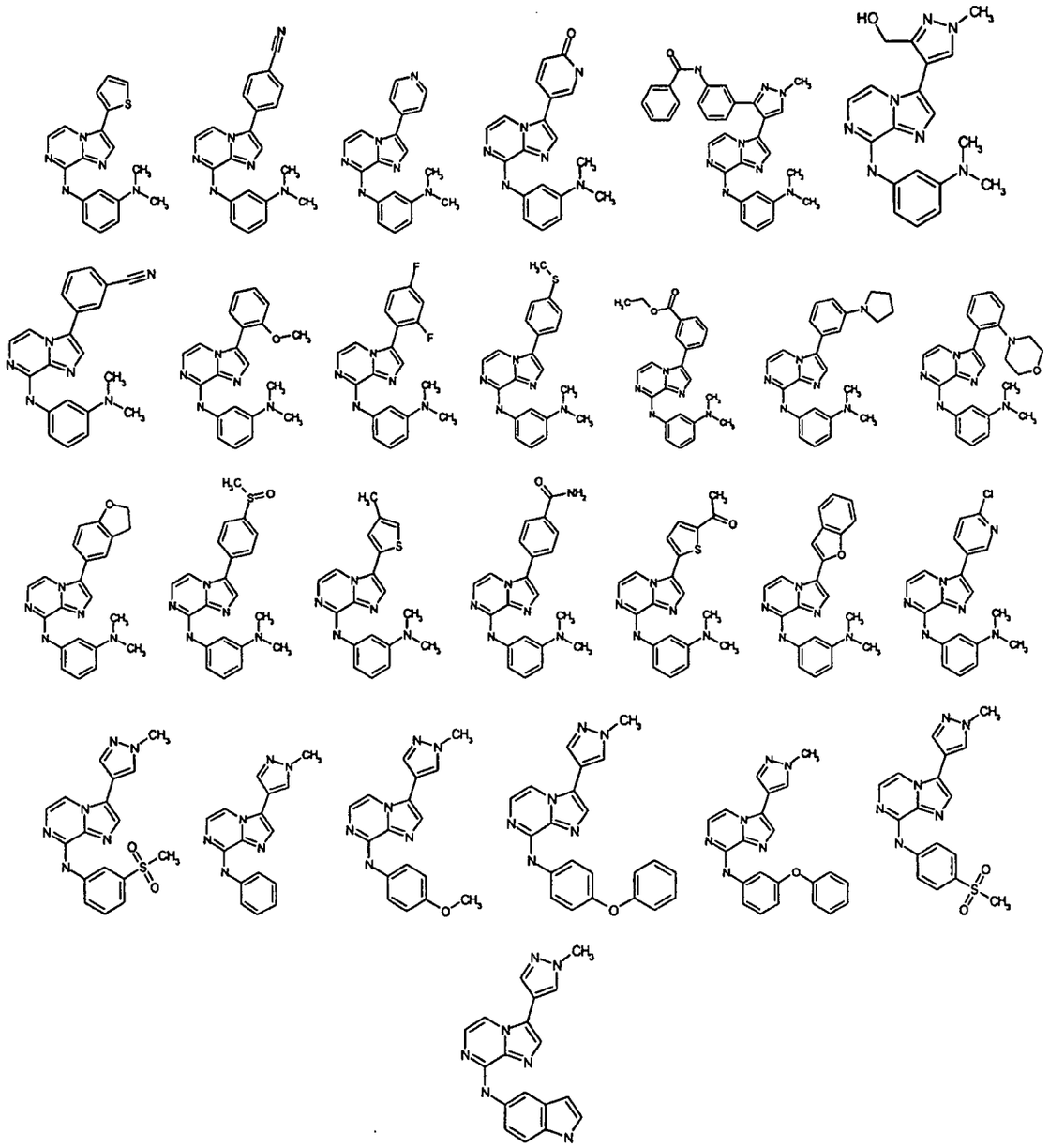
n is 1-4; and

p is 0-3;

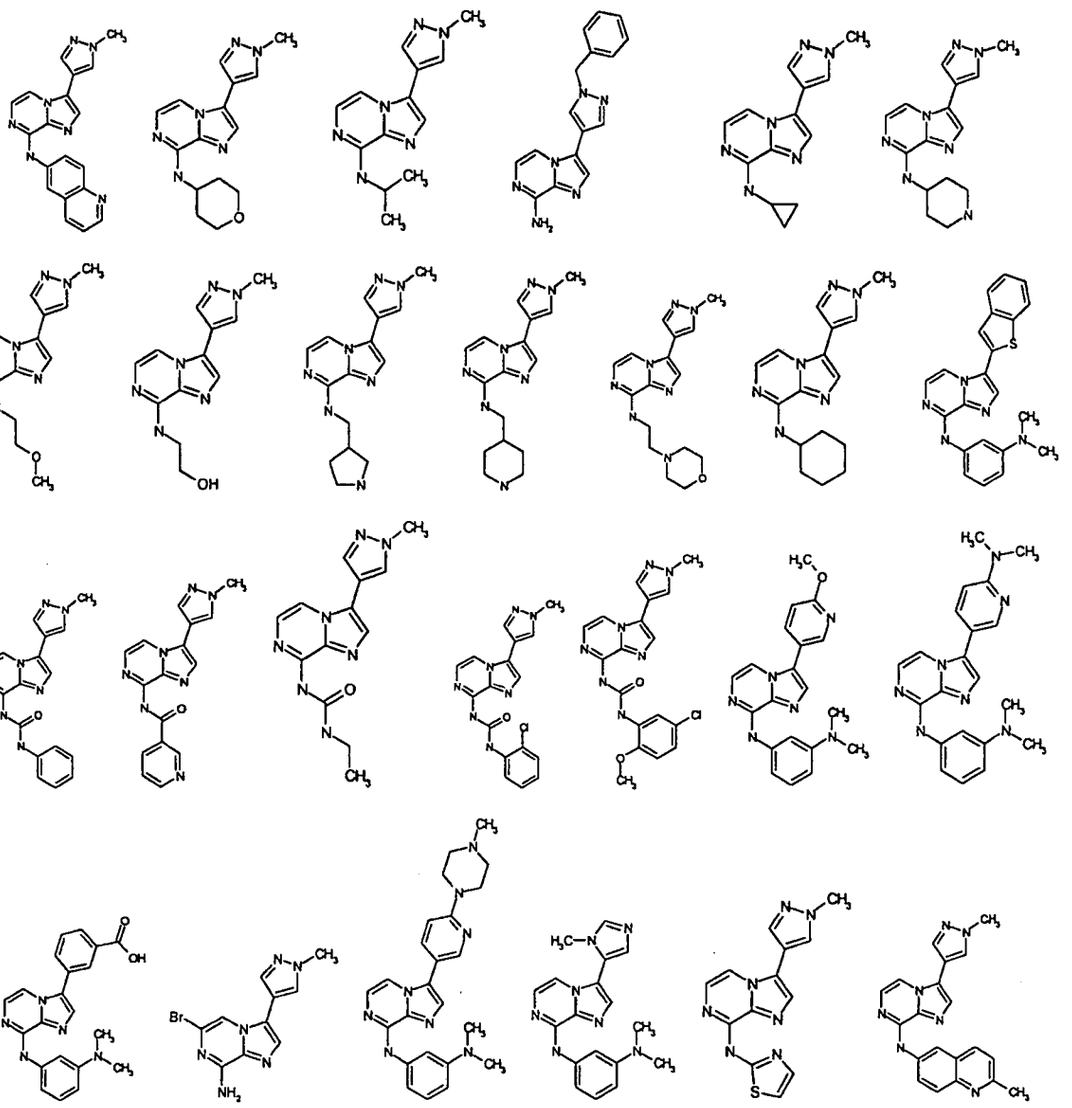
g. A compound selected from the compounds of the formulas:



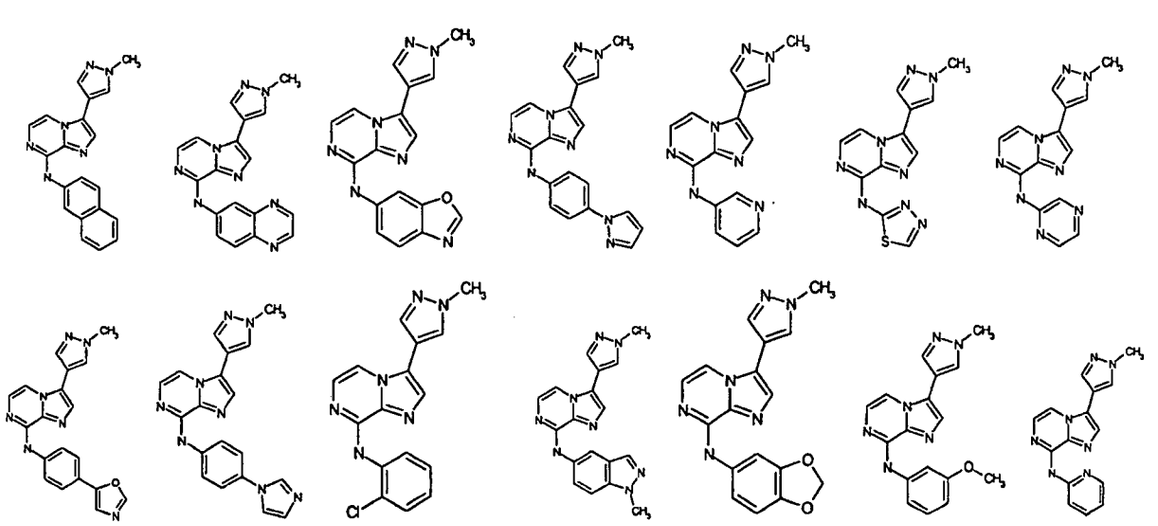
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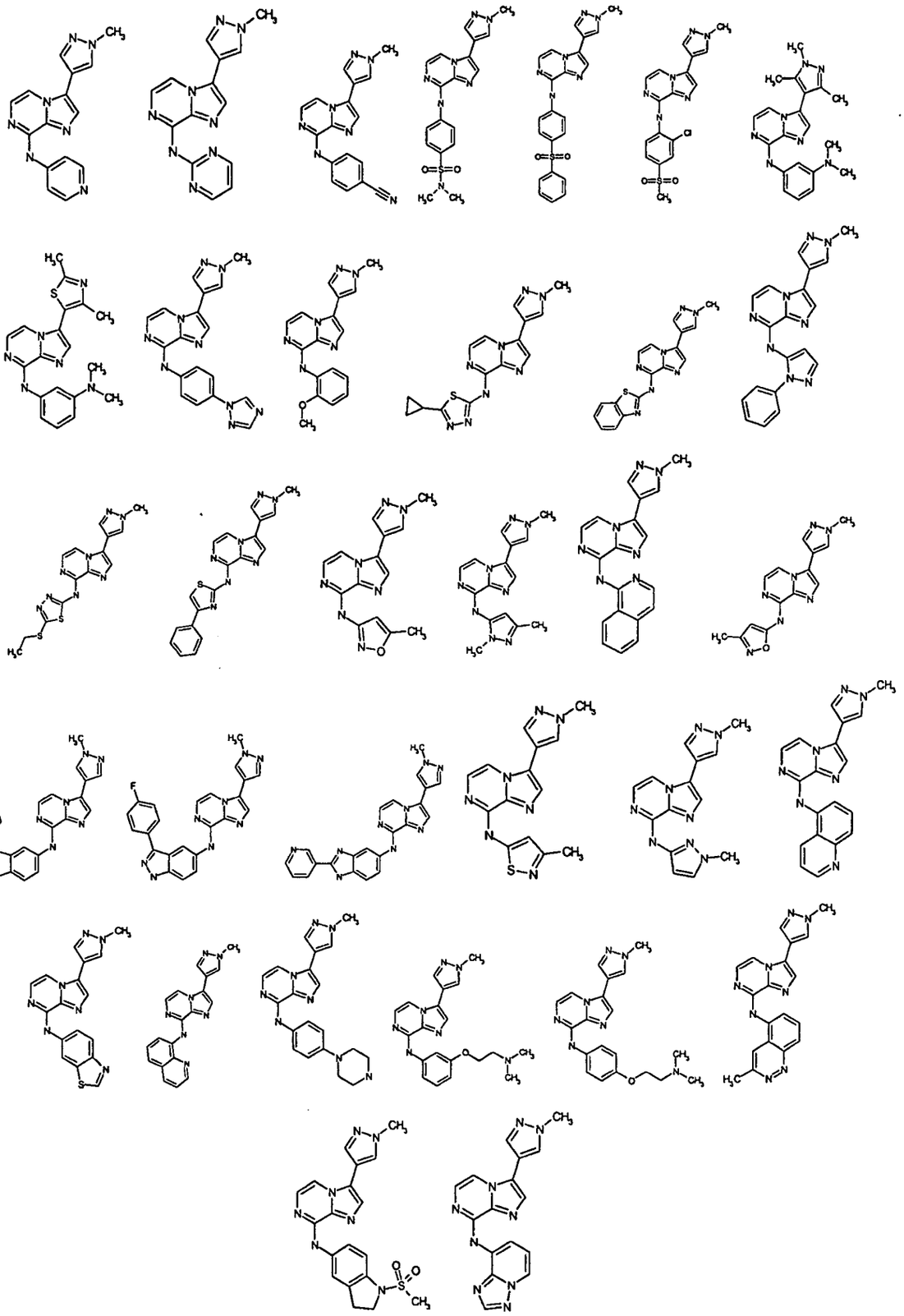


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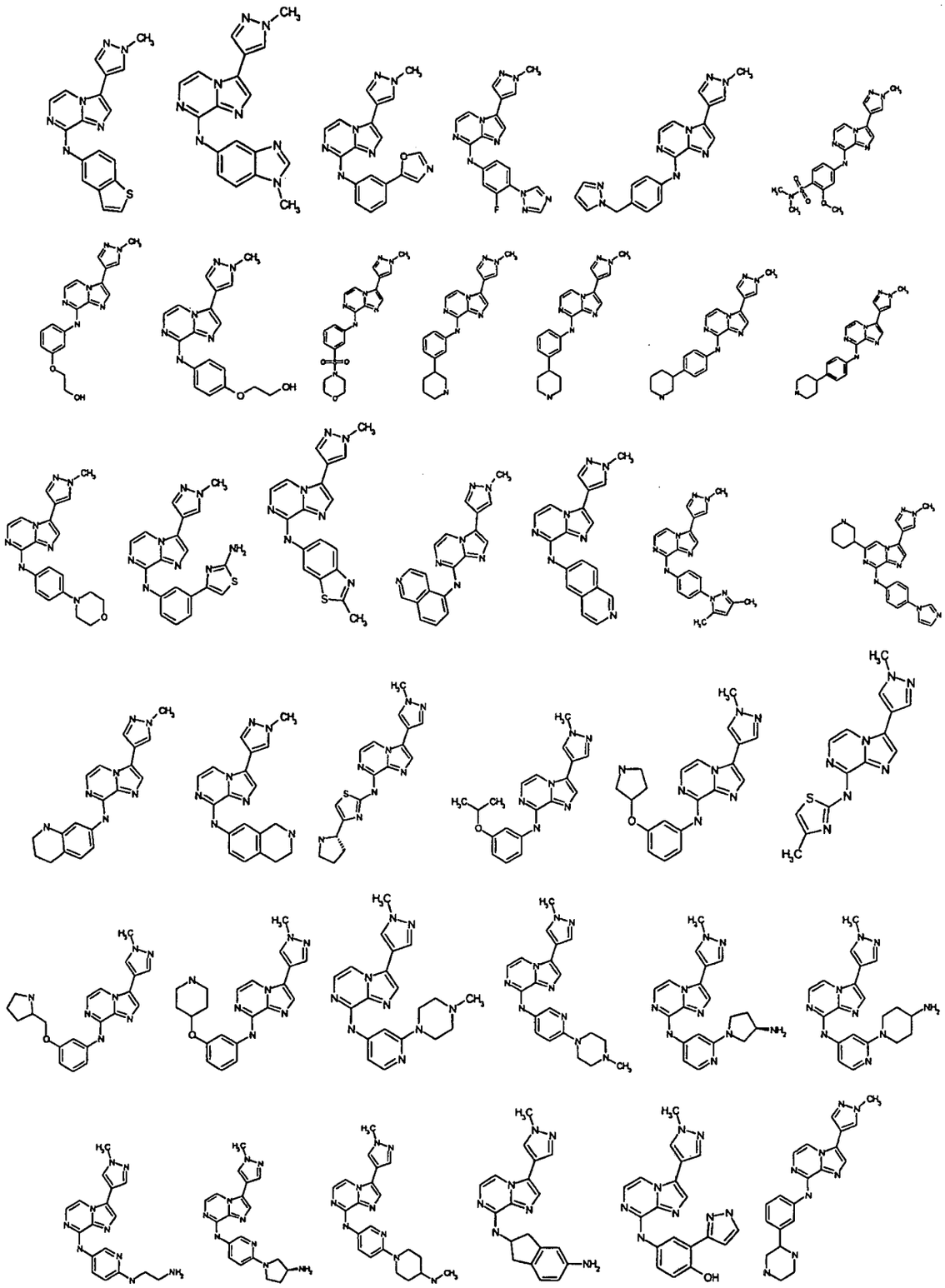


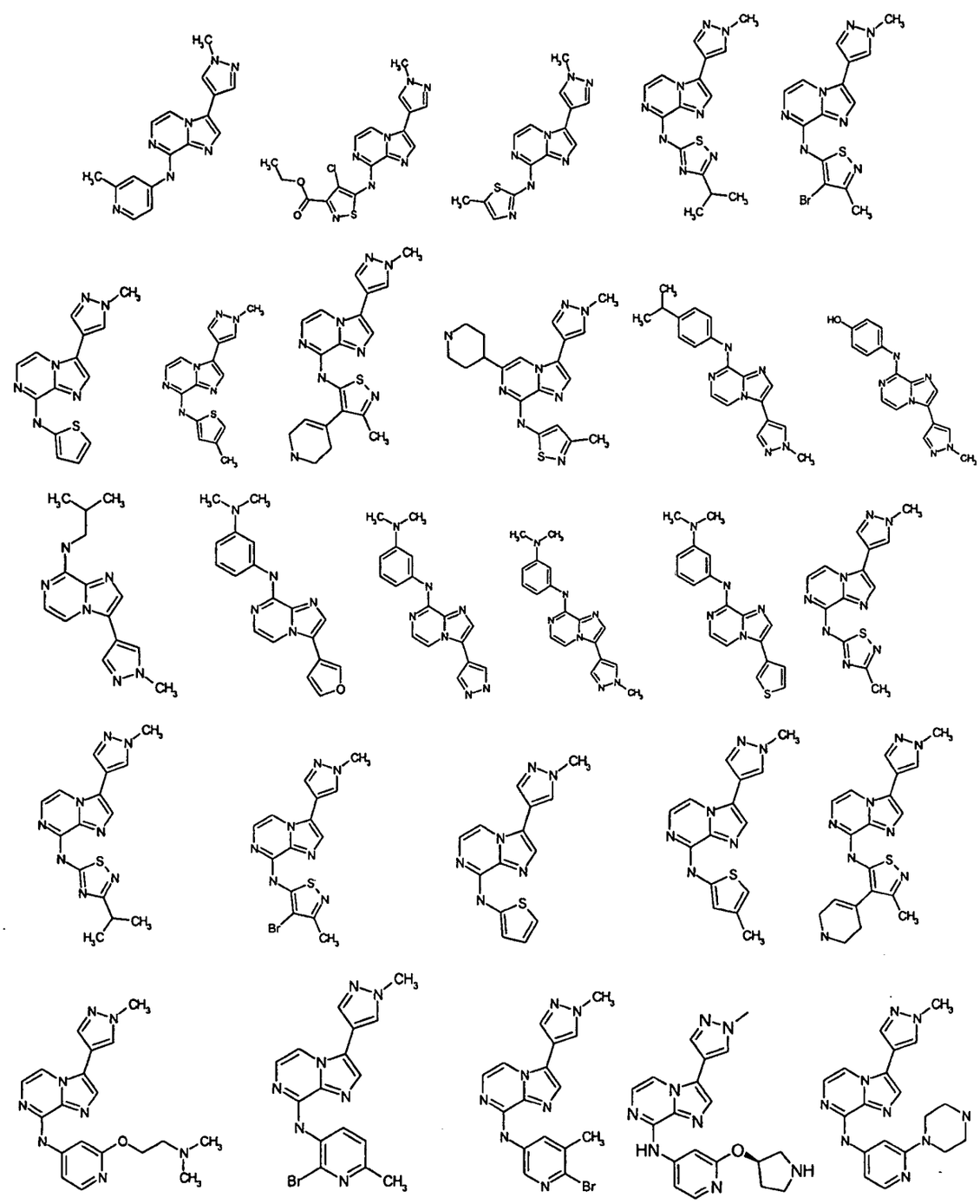
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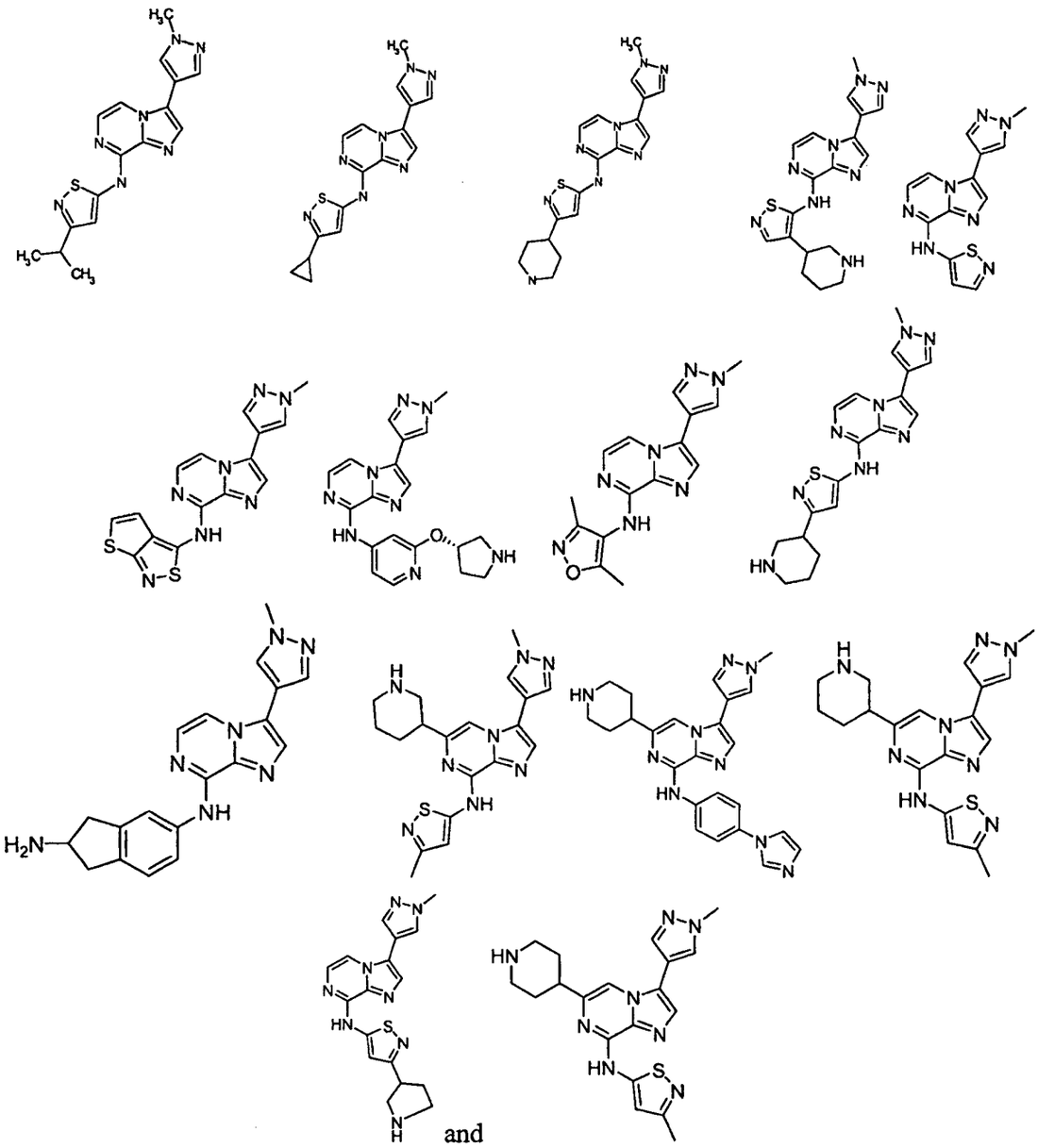


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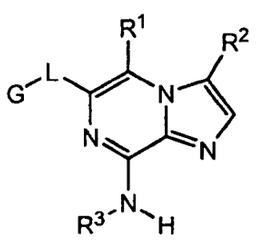
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and

or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof;

h. A compound of the formula:



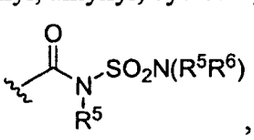
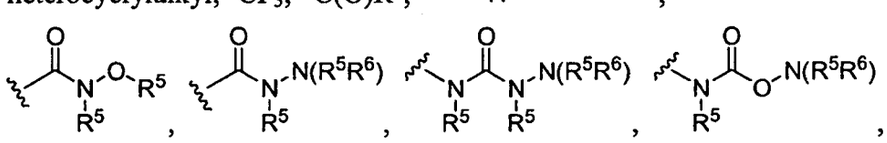
Formula H

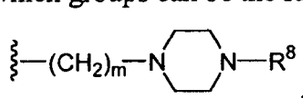
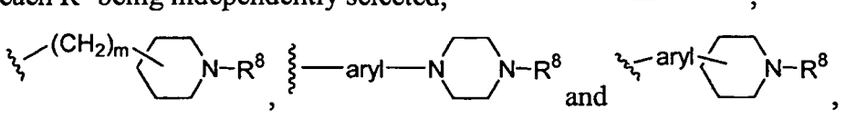
or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, wherein:

L is selected from the group consisting of S, S(O) and $S(O_2)$;

G is alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclenyl or heterocyclyl, wherein each of said alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclenyl or heterocyclyl can be unsubstituted or optionally independently substituted with one or more moieties which are independently selected from the group consisting of $-OR^5$, halo, -CN, $-C(O)NR^5R^6$, $-N(H)-C(O)R^5$, $-N(H)-C(O)-NR^5R^6$, $-S(O_2)NR^5R^6$, $-NR^5R^6$, $-C(O)R^5$, $-C(O_2)R^5$, $-SR^5$, $-S(O)R^5$, $-S(O_2)R^5$;

R^1 is H, halo, alkyl, aryl or heteroaryl, wherein each of said alkyl, aryl and heteroaryl can be unsubstituted or substituted with one or more moieties which can be the same or different each moiety being independently selected from the group consisting of halo, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C(O)NR^5R^6$ and $-OR^5$;

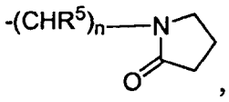
R^2 is selected from the group consisting of H, R^9, alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclylalkyl, $-CF_3$, $-C(O)R^7$,  , 

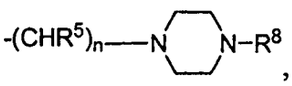
alkyl substituted with 1-6 R^9 groups which groups can be the same or different with each R^9 being independently selected,  , 

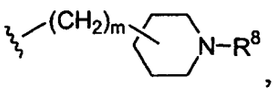
wherein each of the above-said aryl, heteroaryl, cycloalkyl, arylalkyl and heterocyclyl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halo, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, CF_3, CN, $-OCF_3$, $-OR^6$, $-C(O)R^7$, $-NR^5R^6$, $-C(O_2)R^6$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$,

$-N(R^5)C(O)R^7$ and $-N(R^5)C(O)NR^5R^6$;

R^3 is selected from the group consisting of H, alkyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroarylalkyl, cycloalkylalkyl, heterocyclylalkyl,



,


, $-(CHR^5)_n-OR^6$, $-S(O_2)R^6$, $-C(O)R^6$, $-S(O_2)NR^5R^6$, $-C(O)OR^6$, $-C(O)NR^5R^6$, cycloalkyl, $-CH(aryl)_2$, $-CH(heteroaryl)_2$, $-(CH_2)_m-NR^8$, and


, wherein each of said alkyl, aryl, heteroaryl and heterocyclyl can be substituted or optionally substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halo, alkyl, aryl, cycloalkyl, CF_3, CN, $-OCF_3$, $-OR^5$, $-NR^5R^6$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^6$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ and $-N(R^5)C(O)NR^5R^6$;

R^5 is H, alkyl, aryl, heteroaryl, heterocyclyl or cycloalkyl; and

R^6 is selected from the group consisting of H, alkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, wherein each of said alkyl, heteroarylalkyl, aryl, heteroaryl and arylalkyl can be unsubstituted or optionally substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl, cycloalkyl, CF_3, OCF_3, CN, $-OR^5$, $-NR^5R^6$, $-CH_2OR^5$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ and $-N(R^5)C(O)NR^5R^6$;

R^7 is selected from the group consisting of alkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, wherein each of said alkyl, heteroarylalkyl, aryl, heteroaryl and arylalkyl can be unsubstituted or optionally substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl, cycloalkyl, CF_3, OCF_3, CN, $-OR^5$, $-NR^5R^6$, $-CH_2OR^5$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ and $-N(R^5)C(O)NR^5R^6$;

R^8 is selected from the group consisting of R^6, $-C(O)NR^5R^6$, $-S(O_2)NR^5R^6$, $-C(O)R^7$, $-C(O_2)R^6$, $-S(O_2)R^7$ and $-(CH_2)$-aryl;

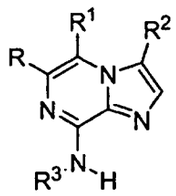
R^9 is selected from the group consisting of halogen, CN, NR^5R^6, $-C(O_2)R^6$, $-C(O)NR^5R^6$, $-OR^6$, $-C(O)R^7$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$,

$-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$and $-N(R^5)C(O)NR^5R^6$;

m is 0 to 4; and

p is 0-3;

i. A compound of Formula I:



Formula I

or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, wherein:

R is H, CN, $-NR^5R^6$, cycloalkyl, cycloalkenyl, heterocyclenyl, heteroaryl, $-C(O)NR^5R^6$, $-N(R^5)C(O)R^6$, heterocyclyl, heteroaryl substituted with $(CH_2)_{1-3}$ NR^5R^6, unsubstituted alkyl, or alkyl substituted with one or more moieties which can be the same or different each moiety being independently selected from the group consisting of $-OR^5$, heterocyclyl, $-N(R^5)C(O)N(R^5R^6)$, $-N(R^5)-C(O)OR^6$, $-(CH_2)_{1-3}-N(R^5R^6)$ and $-NR^5R^6$;

R^1 is H, halo, aryl or heteroaryl, wherein each of said aryl and heteroaryl can be unsubstituted or substituted with one or more moieties which can be the same or different each moiety being independently selected from the group consisting of halo, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, $-CH_2OR^5$, $-C(O)NR^5R^6$, -C(O)OH, $-C(O)NH_2$, $-NR^5R^6$ (wherein the R^5 and R^6, together with the N of said $-NR^5R^6$, form a heterocyclyl ring), $-S(O)R^5$, $-S(O_2)R^5$, -CN, -CHO, $-SR^5$, $-C(O)OR^5$, $-C(O)R^5$ and $-OR^5$;

R^2 is H, halo, aryl, arylalkyl or heteroaryl, wherein each of said aryl, arylalkyl and heteroaryl can be unsubstituted or optionally independently be substituted with one or more moieties which can be the same or different each moiety being independently selected from the group consisting of halo, amide, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, -C(O)OH, $-C(O)NH_2$, $-NR^5R^6$ (wherein the R^5 and R^6, together with the N of said $-NR^5R^6$, form a heterocyclyl ring), -CN, arylalkyl, $-CH_2OR^5$, $-S(O)R^5$, $-S(O_2)R^5$, -CN, -CHO, $-SR^5$, $-C(O)OR^5$, $-C(O)R^5$, heteroaryl and heterocyclyl;

R^3 is heterocyclyl–$(CR^7R^8)_n$-X, heterocyclenyl–$(CR^7R^8)_n$-X, heteroaryl–$(CR^7R^8)_n$-X or aryl–

$(CR^7R^8)_n$-X wherein each of the heterocyclyl-, heterocyclenyl-, heteroaryl- or aryl- moieties of said R^3 can be unsubstituted or substituted with one or more moieties, independently selected from the group consisting of $-CONR^5R^6$, $-OR^5$ and alkyl,

n is 1-6,

X is selected from the group consisting of, $-NR^5R^6$, $-OR^5$, $-SO-R^5$ and $-SR^5$,

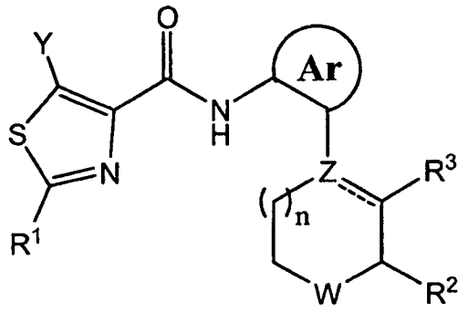
R^7 and R^8 are each independently hydrogen or alkyl;

R^5 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkoxyalkyl, -alkyl-S-alkyl, aminoalkyl, aryl, heteroaryl, heterocyclenyl, heterocycloalkyl, cycloalkyl, cycloalkenyl, heterocyclylalkoxyl, -S-alkylheterocyclyl, heterocyclyl, heterocyclenyl, alkylN(alkyl)$_2$, alkylNH(alkyl), alkylN(alkenyl)2, -alkylN(alkoxyl)2, -alkyl-SH and hydroxyalkyl, wherein each of said aryl, heteroaryl, heterocyclenyl, heterocycloalkyl, cycloalkyl, cycloalkenyl, heterocyclylalkoxyl, -S-alkylheterocyclyl, heterocyclyl, heterocyclenyl can be unsubstituted or substituted with one or more moieties independently selected from the group consisting of alkyl, alkyl, alkenyl, aryl, cycloalkenyl, cycloalkyl, arylalkyl, cycloalkenylalkyl, cycloalkylalkyl, heteroaryl, heterocyclenyl, heterocyclyl, heteroarylalkyl, heterocyclenylalkyl, heterocycloalkylalkyl, alkoxyalkyl, -alkyl-S-alkyl, -alkylSH, alkoxyl, -S-alkyl, hydroxyalkyl, and aminoalkyl;

R^6 is selected from the group consisting of hydrogen, alkyl, alkenyl, aryl, cycloalkenyl, cycloalkyl, arylalkyl, cycloalkenylalkyl, cycloalkylalkyl, heteroaryl, heterocyclenyl, heterocyclyl, heteroarylalkyl, heterocyclenylalkyl, heterocycloalkylalkyl, alkoxyalkyl, -alkyl-S-alkyl, -alkylSH, alkoxyl, -S-alkyl, hydroxyalkyl, and aminoalkyl, wherein each of said aryl, cycloalkenyl, cycloalkyl, arylalkyl, cycloalkenylalkyl, cycloalkylalkyl, heteroaryl, heterocyclenyl, heterocyclyl, heteroarylalkyl, heterocyclenylalkyl, heterocycloalkylalkyl can be unsubstituted or substituted with one or more moieties independently selected from the group consisting of alkyl, alkyl, alkenyl, aryl, cycloalkenyl, cycloalkyl, arylalkyl, cycloalkenylalkyl, cycloalkylalkyl, heteroaryl, heterocyclenyl, heterocyclyl, heteroarylalkyl, heterocyclenylalkyl, heterocycloalkylalkyl, alkoxyalkyl, -alkyl-S-alkyl, -alkylSH, alkoxyl, -S-alkyl, hydroxyalkyl, and aminoalkyl;

further wherein in any -NR^5R^6 in Formula I, said R^5 and R^6 can optionally be joined together with the N of said -NR^5R^6 to form a cyclic ring or bridged cyclic ring, wherein each of said cyclic ring or bridged cyclic ring, can be unsubstituted or substituted with one or more moieties, which can be the same or different, independently selected from the group consisting of hydroxyl, -SH, alkyl, alkenyl, hydroxyalkyl, -alkyl-SH, alkoxyl, -S-alkyl, -CO_2-alkyl, -CO_2-alkenyl, arylalkyl, cycloalkenylalkyl, cycloalkylalkyl, heteroarylalkyl, heterocyclenylalkyl, heterocycloalkylalkyl, heteroaryl, aryl, cycloalkenyl, cycloalkyl, spiroheterocyclyl, spiroheterocyclenyl, spiroheteroaryl, spirocyclyl, spirocyclenyl, spiroaryl, alkoxyalkyl, -alkyl-S-alkyl, heterocyclyl, and heterocyclenyl;

j. A compound having the formula:



(J)

or a pharmaceutically acceptable salt, solvate, ester, prodrug or stereoisomer thereof, wherein the dashed lines indicate an optional and additional bond, and wherein:

R^1 is nitrogen-containing heteroaryl, nitrogen-containing heterocyclyl, nitrogen-containing benzofused heteroaryl or nitrogen-containing benzofused heterocyclyl, wherein R^1 is joined to the rest of the compound of formula (I) via a ring nitrogen atom, and wherein one or more ring carbon atoms of a nitrogen-containing heteroaryl, nitrogen-containing heterocyclyl, nitrogen-containing benzofused heteroaryl or nitrogen-containing benzofused heterocyclyl group can be substituted with up to 5 substituents, which may be the same or different, and are independently selected from alkyl, aryl, halo, -OH, -O-alkyl, -O-aryl, -$N(R^8)_2$, -CF_3, -NO_2, -$C(O)R^8$, -$C(O)OR^8$, -$C(O)N(R^8)_2$, -$OC(O)R^8$ or -$NHC(O)R^8$;

R^2 is –H, -alkyl, –NH_2 or –CH_2NH_2;

R^3 is –H, -alkyl, $–NH_2$ or $–CH_2NH_2$;

each occurrence of R^4 is independently –H, -alkyl, $–NH_2$, -OH, -alkylene-OH, $–CH_2NH_2$, $-C(O)R^5$, $-C(O)NH_2$, -C(O)NH-alkyl, $-C(O)N(alkyl)_2$, $-NHC(O)R^6$ or $–NHS(O)_2R^6$;

R^5 is –H, -alkyl, -aryl, -heteroaryl, -NHOH;

R^6 is –H, -alkyl or $–CF_3$;

R^7 is –H, -OH, $-C_1$-C_6 alkyl, $-O-(C_1$-C_6 alkyl), or $–CF_3$;

R^8 is –H, alkyl, aryl, heterocyclyl, heteroaryl or cycloalkyl;

Ar is -arylene- or -heteroarylene-, wherein the arylene or heteroarylene is joined via 2 of its adjacent ring carbon atoms, and wherein the -arylene- or -heteroarylene- can be substituted with up to 4 substituents, which may be the same or different, and are independently selected from –halo, alkyl, alkoxy, aryloxy, $-SR^8$, $-S(O)R^8$, $-S(O)_2R^8$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)N(R^8)_2$, $-NHC(O)R^8$, $-CF_3$, -CN or NO_2, and such that when Ar is tetrahydronaphthylene, R^1 and R^2 cannot both be hydrogen

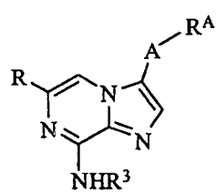
W is –NH- or $–C(R^4)_2$-, wherein both R^4 groups and the carbon atom to which they are attached can combine to form a five to seven membered heterocyclyl or heteroaryl group;

Y is –H, -halo, -alkyl or –CN;

Z is $–CR^7$- or –N-, when the optional additional bond is absent, and –C- when the optional additional bond is present;

n is an integer ranging from 0 to 2; and

(k) A compound of Formula K:



Formula K

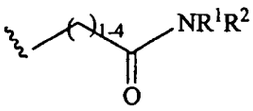
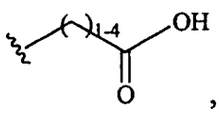
or a pharmaceutically acceptable salt, solvate, ester, prodrug or stereoisomer thereof, wherein:

R is H, halo or alkyl;

R^3 is heteroaryl-X, wherein X is heterocyclylalkyl- wherein said heterocyclyl can be unsubstituted or optionally substituted with 1-4 alkyl moieties;

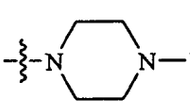
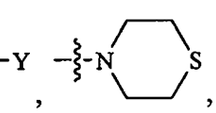
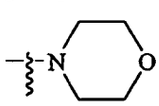
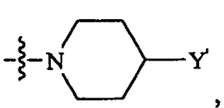
A is -aryl- , -heteroaryl-, $-N(R^1)$-aryl- or $-N(R^1)$-heteroaryl- , wherein each of said aryl and heteroaryl can be independently unsubstituted or optionally substituted with one or more

substituents, which substituents can be the same or different, each substituent being independently selected from the group consisting of alkyl, $-NO_2$, halo, hydroxy, trihaloalkyl, alkoxy, and dialkylamino;

R^A is $-(CH_2)_{1-4}$-heteroaryl,  or  , wherein said heteroaryl can optionally be fused with an aryl, wherein each of said aryl and heteroaryl can independently be optionally substituted with one or more moieties each moiety being independently selected from the group consisting of trihaloalkyl, $-NO_2$, halo, hydroxyalkyl, alkoxyalkyl and dialkylamino;

R^1 is H or alkyl;

R^2 is H, hydroxyalkyl-, arylalkyl-, heteroaryl, aryl, heteroarylalkyl-, alkyl, dialkylaminoalkyl-, alkylaminoalkyl-, cycloalkylalkyl-, cycloalkyl, heterocyclylalkyl- or heterocyclyl, wherein said aryl and aryl of arylalkyl can be unsubstituted or substituted with one or more moieties independently selected from the group consisting of trihaloalkyl, $-NO_2$, halo, hydroxyalkyl, alkoxyalkyl, dialkylamino and heterocyclylalkyl-, wherein said heterocyclylalkyl can be unsubstituted or substituted with alkyl or $-SO_2NH_2$; said heteroaryl and heteroaryl of heteroarylalkyl can be unsubstituted or substituted with one or more moieties, each moiety being independently selected from the group consisting of hydroxyalkyl, alkoxy, alkyl, halo, hydroxyl, and $-NO_2$; and said cycloalkyl is unsubstituted or substituted with hydroxyl; or

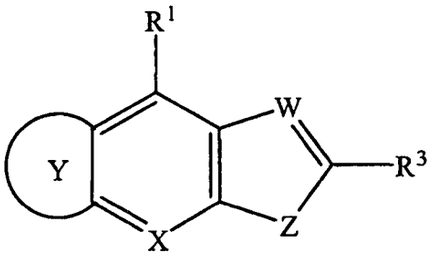
R^1 and R^2 together with the N to which each is attached, form a heterocyclic group selected from the group consisting of  ,  ,  and  , wherein

Y is alkoxyalkyl, hydroxyalkyl, dialkylaminoalkyl or alkyl, further wherein Y' is hydroxyl.

11. A method of inducing polyploidy in cancer cells comprising the steps of first administering to a cancer cell in vivo at least one anti-mitotic agent selected from the group consisting of a taxane, paclitaxel, docetaxel, a Cenp-E Inhibitor, Abraxane, Epothilone,

Monastrol, KSP inhibitors including Ispinesib SB-715992 (Cytokinetics), and compounds represented by Formulas A-D shown in paragraphs a-d below:

a. A compound represented by the structural Formula A:



Formula A

or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:

ring Y is a 5- to 6-membered aryl or a 5- or 6-membered heteroaryl fused as shown in Formula A, wherein in said aryl and heteroaryl each substitutable ring carbon is independently substituted with R^2 and each substitutable ring nitrogen is independently substituted with R^6;

W is N or $C(R^{12})$;

X is N or N-oxide;

Z is S, S(=O) or $S(=O)_2$;

R^1 is H, alkyl, alkoxy, hydroxy, halo, -CN, $-S(O)_m$-alkyl, $-C(O)NR^9R^{10}$, $-(CR^9R^{10})_{1-6}OH$, or $-NR^4(CR^9R^{10})_{1-2}OR^9$;

each R^2 is independently selected from the group consisting of H, halo, alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, $-(CR^{10}R^{11})_{0-6}-OR^7$, $-C(O)R^4$, $-C(S)R^4$, $-C(O)OR^7$, $-C(S)OR^7$, $-OC(O)R^7$, $-OC(S)R^7$, $-C(O)NR^4R^5$, $-C(S)NR^4R^5$, $-C(O)NR^4OR^7$, $-C(S)NR^4OR^7$, $-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, -CN, $-OCF_3$, $-SCF_3$, $-C(=NR^7)NR^4$, $-C(O)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}OR^7$, $-C(S)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(S)NR^7(CH_2)_{1-10}OR^7$, haloalkyl and alkylsilyl, wherein each of said alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl or heteroaralkyl is independently optionally substituted with 1-5 R^9 moieties;

each R^3 is independently selected from the group consisting of H, halo, alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, $-(CR^{10}R^{11})_{0-6}-OR^7$, $-C(O)R^4$, $-C(S)R^4$, $-C(O)OR^7$, $-C(S)OR^7$, $-OC(O)R^7$, $-OC(S)R^7$, $-C(O)NR^4R^5$, $-C(S)NR^4R^5$, $-C(O)NR^4OR^7$, $-C(S)NR^4OR^7$, $-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, -CN, $-OCF_3$, $-SCF_3$, $-C(=NR^7)NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}OR^7$, $-C(S)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(S)NR^7(CH_2)_{1-10}OR^7$, haloalkyl and alkylsilyl, wherein each of said alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl or heteroaralkyl is independently optionally substituted with 1-5 R^9 moieties;

each R^4 and R^5 is independently selected from the group consisting of H, alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, $-OR^7$, $-C(O)R^7$, and $-C(O)OR^7$, wherein each of said alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl is optionally substituted with 1-4 R^8 moieties;

or R^4 and R^5, when attached to the same nitrogen atom, are optionally taken together with the nitrogen atom to which they are attached to form a 3-6 membered heterocyclic ring having 0-2 additional heteroatoms selected from N, O or S;

each R^6 is independently selected from the group consisting of H, alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroaralkyl, $-(CH_2)_{1-6}CF_3$, $-C(O)R^7$, $-C(O)OR^7$ and $-SO_2R^7$;

each R^7 is independently selected from the group consisting of H, alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, and heteroaralkyl, wherein each member of R^7 except H is optionally substituted with 1-4 R^8 moieties;

each R^8 is independently selected from the group consisting of halo, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-NO_2$, $-OR^{10}$, $-(C_1-C_6$ alkyl$)-OR^{10}$, –CN, $-NR^{10}R^{11}$, $-C(O)R^{10}$, $-C(O)OR^{10}$, $-C(O)NR^{10}R^{11}$, $-CF_3$, $-OCF_3$, $-CF_2CF_3$, $-C(=NOH)R^{10}$, $-N(R^{10})C(O)R^{11}$, $-C(=NR^{10})NR^{10}R^{11}$, and $-NR^{10}C(O)OR^{11}$, wherein each of said alkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally independently

substituted with 1-3 moieties selected from the group consisting of halo, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-NO_2$, $-OR^{10}$, $-(C_1-C_6\ alkyl)-OR^{10}$, -CN, $-NR^{10}R^{11}$, $-C(O)OR^{10}$, $-C(O)NR^{10}R^{11}$, $-CF^3$, $-OCF_3$, $-NR^{10}C(O)OR^{11}$, and $-NR^{10}C(O)R^{40}$;

or two R^8 groups, when attached to the same carbon atom, are optionally taken together with the carbon atom to which they are attached to form a C=O or a C=S group;

each R^9 is independently selected from the group consisting of H, alkyl, alkoxy, OH, CN, halo, $-(CR^{10}R^{11})_{0-4}NR^4R^5$, haloalkyl, hydroxyalkyl, alkoxyalkyl, $-C(O)NR^4R^5$, $-C(O)OR^7$, $-OC(O)NR^4R^5$, $-NR^4C(O)R^5$, and $-NR^4C(O)NR^4R^5$;

each R^{10} is independently H or alkyl; or R^9 and R^{10}, when attached to the same nitrogen atom, are optionally taken together with the nitrogen atom to which they are attached to form a 3-6 membered heterocyclic ring having 0-2 additional heteroatoms selected from N, O or S;

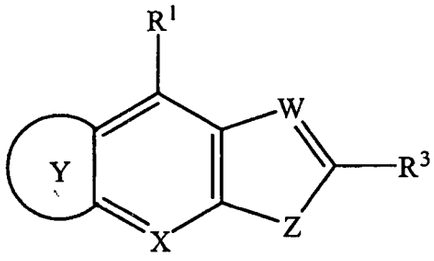
each R^{11} is independently H or alkyl; or R^{10} and R^{11}, when attached to the same nitrogen atom, are optionally taken together with the nitrogen atom to which they are attached to form a 3-6 membered heterocyclic ring having 0-2 additional heteroatoms selected from N, O or S;

each R^{12} is independently selected from the group consisting of H, halo, alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, $-(CR^{10}R^{11})_{0-6}-OR^7$, $-C(O)R^4$, $-C(S)R^4$, $-C(O)OR^7$, $-C(S)OR^7$, $-OC(O)R^7$, $-OC(S)R^7$, $-C(O)NR^4R^5$, $-C(S)NR^4R^5$, $-C(O)NR^4OR^7$, $-C(S)NR^4OR^7$, $-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, -CN, $-OCF_3$, $-SCF_3$, $-C(=NR^7)NR^4$, $-C(O)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}OR^7$, $-C(S)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(S)NR^7(CH_2)_{1-10}OR^7$, haloalkyl and alkylsilyl, wherein each of said alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl or heteroaralkyl is independently optionally substituted with 1-5 R^9 moieties; and

R^{40} is selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl, wherein each of said cycloalkyl, heterocyclyl, aryl and heteroaryl are

optionally independently substituted with 1-3 moieties independently selected from the group consisting of -CN, -OH, halo, alkyl, haloalkyl, alkoxy, and $-NR^{10}R^{11}$;

b. A compound represented by the structural Formula B:



Formula B

or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:

ring Y is a 5- to 7-membered ring selected from the group consisting of cycloalkyl, cycloalkenyl, heterocyclyl or heterocyclenyl fused as shown in Formula B, wherein in each of said 5- to 7-membered ring, each substitutable ring carbon is independently substituted with 1-2 R^2 moieties and each substitutable ring heteroatom is independently substituted with R^6;

W is N or $C(R^{12})$;

X is N or N-oxide;

Z is S, S(=O) or $S(=O)_2$;

R^1 is H, alkyl, alkoxy, hydroxy, halo, -CN, $-S(O)_m$-alkyl, $-C(O)NR^9R^{10}$, $-(CR^9R^{10})_{1-6}OH$, or $-NR^4(CR^9R^{10})_{1-2}OR^9$; wherein m is 0 to 2;

each R^2 is independently selected from the group consisting of H, halo, alkyl, cycloalkyl, alkylsilyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, heteroaryl, $-(CR^{10}R^{11})_{0-6}-OR^7$, $-C(O)R^4$, $-C(S)R^4$, $-C(O)OR^7$, $-C(S)OR^7$, $-OC(O)R^7$, $-OC(S)R^7$, $-C(O)NR^4R^5$, $-C(S)NR^4R^5$, $-C(O)NR^4OR^7$, $-C(S)NR^4OR^7$, $-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, -CN, $-OCF_3$, $-SCF_3$, $-C(=NR^7)NR^4$, $-C(O)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}OR^7$, $-C(S)NR^7(CH_2)_{1-10}NR^4R^5$, and $-C(S)NR^7(CH_2)_{1-10}OR^7$, wherein each of said alkyl, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, and heteroaryl is independently optionally substituted with 1-5 R^9 moieties;

or two R^2s on the same carbon atom are optionally taken together with the carbon atom to which they are attached to form a C=O, a C=S or an ethylenedioxy group;

R^3 is independently selected from the group consisting of H, halo, alkyl, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, heteroaryl, $-(CR^{10}R^{11})_{0-6}-OR^7$, $-C(O)R^4$, $-C(S)R^4$, $-C(O)OR^7$, $-C(S)OR^7$, $-OC(O)R^7$, $-OC(S)R^7$, $-C(O)NR^4R^5$, $-C(S)NR^4R^5$, $-C(O)NR^4OR^7$, $-C(S)NR^4OR^7$, $-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, -CN, $-C(=NR^7)NR^4R^5$, $-C(O)N(R^7)-(CR^{40}R^{41})_{1-5}-C(=NR^7)NR^4R^5$, $-C(O)N(R^7)(CR^{40}R^{41})_{1-5}-NR^4R^5$, $-C(O)N(R^7)(CR^{40}R^{41})_{1-5}-C(O)-NR^4R^5$, $-C(O)N(R^7)(CR^{40}R^{41})_{1-5}-OR^7$, $-C(S)NR^7(CH_2)_{1-5}NR^4R^5$, and $-C(S)NR^7(CH_2)_{1-5}OR^7$, wherein each of said alkyl, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, and heteroaryl is independently optionally substituted with 1-5 R^9 moieties;

each of R^4 and R^5 is independently selected from the group consisting of H, alkyl, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, heteroaryl, $-OR^7$, $-C(O)R^7$, and $-C(O)OR^7$, wherein each of said alkyl, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, and heteroaryl, is optionally substituted with 1-4 R^8 moieties;

or R^4 and R^5, when attached to the same nitrogen atom, are optionally taken together with the nitrogen atom to which they are attached to form a 3-6 membered heterocyclic ring having 0-2 additional heteroatoms selected from N, O or S;

each R^6 is independently selected from the group consisting of H, alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroaralkyl, $-(CH_2)_{1-6}CF_3$, $-C(O)R^7$, $-C(O)OR^7$ and $-SO_2R^7$;

each R^7 is independently selected from the group consisting of H, alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, and heteroaralkyl, wherein each member of R^7 except H is optionally substituted with 1-4 R^8 moieties;

each R^8 is independently selected from the group consisting of halo, alkyl, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, heteroaryl, $-NO_2$, $-OR^{10}$, $-(C_1-C_6$ alkyl$)-OR^{10}$, $-CN$, $-NR^{10}R^{11}$, $-C(O)R^{10}$, $-C(O)OR^{10}$, $-C(O)NR^{10}R^{11}$, $-CF_3$, $-OCF_3$, $-CF_2CF_3$, $-$

$C(=NOH)R^{10}$, $-N(R^{10})C(O)R^{11}$, $-C(=NR^{10})NR^{10}R^{11}$, and $-NR^{10}C(O)OR^{11}$; wherein said each of said alkyl, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, and heteroaryl is independently optionally substituted with 1-4 R^{42} moieties; wherein when each of said cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, and heteroaryl contains two radicals on adjacent carbon atoms anywhere within said cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, and heteroaryl, such radicals may optionally and independently in each occurrence, be taken together with the carbon atoms to which they are attached, to form a five- or six-membered carbocyclic or heterocyclic ring;

or two R^8 groups, when attached to the same carbon, are optionally taken together with the carbon atom to which they are attached to form a C=O or a C=S group;

each R^9 is independently selected from the group consisting of H, alkyl, alkoxy, OH, CN, halo, $-(CR^{10}R^{11})_{0-4}NR^4R^5$, haloalkyl, hydroxyalkyl, alkoxyalkyl, $-C(O)NR^4R^5$, $-C(O)OR^7$, $-OC(O)NR^4R^5$, $-NR^4C(O)R^5$, and $-NR^4C(O)NR^4R^5$;

each R^{10} is independently H or alkyl; or R^9 and R^{10}, when attached to the same nitrogen atom, are optionally taken together with the nitrogen atom to which they are attached to form a 3-6 membered heterocyclic ring having 0-2 additional heteroatoms selected from N, O or S;

each R^{11} is independently H, alkyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heterocyclenyl, or heteroaryl; or R^{10} and R^{11}, when attached to the same nitrogen atom, are optionally taken together with the nitrogen atom to which they are attached to form a 3-6 membered heterocyclic ring having 0-2 additional heteroatoms selected from N, O or S;

wherein each of said R^{11} alkyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heterocyclenyl, and heteroaryl is independently optionally substituted with 1-3 moieties selected from the group consisting of –CN, -OH, $-NH_2$, -N(H)alkyl, $-N(alkyl)_2$, halo, haloalkyl, CF_3, alkyl, hydroxyalkyl, alkoxy, aryl, aryloxy, and heteroaryl;

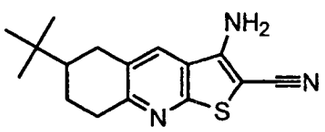
each R^{12} is independently selected from the group consisting of H, halo, alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, $-(CR^{10}R^{11})_{0-6}-OR^7$, $-C(O)R^4$, $-C(S)R^4$, $-C(O)OR^7$, $-C(S)OR^7$, $-OC(O)R^7$, $-OC(S)R^7$, $-C(O)NR^4R^5$, $-C(S)NR^4R^5$, $-C(O)NR^4OR^7$, $-C(S)NR^4OR^7$, $-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, -CN, $-OCF_3$, $-SCF_3$, $-C(=NR^7)NR^4$, $-C(O)NR^7(CH_2)_{1-}$

$_{10}NR^4R^5$, -C(O)$NR^7(CH_2)_{1-10}OR^7$, -C(S)$NR^7(CH_2)_{1-10}NR^4R^5$, -C(S)$NR^7(CH_2)_{1-10}OR^7$, haloalkyl and alkylsilyl, wherein each of said alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl or heteroaralkyl is independently optionally substituted with 1-5 R^9 moieties;

R^{40} and R^{41} can be the same or different, each being independently selected from the group consisting of H, alkyl, aryl, heteroaryl, heterocyclyl, heterocyclenyl, cycloalkyl and cycloalkenyl;

each R^{42} is independently selected from the group consisting of halo, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, -NO_2, -OR^{10}, -(C_1-C_6 alkyl)-OR^{10}, -CN, –$NR^{10}R^{11}$, –C(O)R^{10}, -C(O)OR^{10}, -C(O)$NR^{10}R^{11}$, -CF_3, –OCF_3, –N(R^{10})C(O)R^{11}, and -NR^{10}C(O)OR^{11};

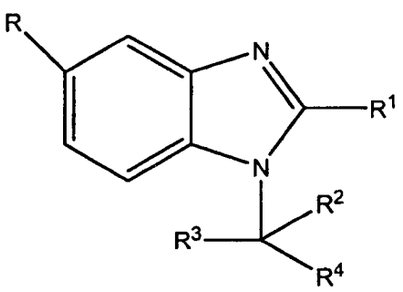
with the proviso that when W is C(R^{12}), R^{12} and R^3 are optionally taken together, with the two ring carbon atoms to which they are attached to form a 6-membered ring selected from the group consisting of cycloalkenyl, aryl, heteroaryl, heterocyclyl and heterocyclenyl, wherein said 6-membered ring is optionally substituted with 1-3 moieties independently selected from oxo, thioxo, -OR^{11}, -$NR^{10}R^{11}$, -C(O)R^{11}, -C(O)OR^{11}, -C(O)N(R^{10})(R^{11}), or -N(R^{10})C(O)R^{11};

c. 

Formula C

or a pharmaceutically acceptable salt, solvate, or ester thereof; and

d. A compound of Formula D



Formula D

or a pharmaceutically acceptable salt, solvate, or ester thereof, wherein:

R is selected from the group consisting of H, alkyl, cyano, haloalkyl, halo, –SH, -S-alkyl, -S-haloalkyl, -S(=O)$_2$alkyl, -S(=O)$_2$OH, -S(=O)$_2$NH$_2$, -S(=O)$_2$NH(alkyl), S(=O)$_2$NH(cycloalkyl), -S(=O)$_2$N(alkyl)$_2$, -S(=O)$_2$heterocyclyl, -S(=O)$_2$heteroaryl, cycloalkyl, aryl, heterocyclyl, heteroaryl, -NHC(=O)alkyl, –C(=O)NH$_2$, –C(=O)NH(alkyl), -C(=O)NH(cycloalkyl), -C(=O)N(alkyl)$_2$, –C(=O)OH, –C(=O)Oalkyl, -C(=O)heterocyclyl, -C(=O)NH(aryl), wherein when each of said cycloalkyl, aryl, heterocyclyl, heteroaryl, and the "heterocyclyl" and "aryl" portions of said R groups has two substituents on adjacent carbon atoms, said substituents, may optionally be taken together with the carbon atoms to which they are attached to form a five- to six-membered cycloalkyl, aryl, heterocyclyl, heterocyclenyl, or heteroaryl ring; wherein each of the aforementioned R alkyl, aryl, cycloalkyl, heterocyclyl, and heteroaryl, and the "alkyl", "cycloalkyl", "heterocyclyl", and "aryl" portions of said R groups, optionally with said five- to six-membered aryl, heterocyclyl, heterocyclenyl, or heteroaryl ring, is optionally substituted with 1-3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, hydroxyl, cyano, halo, haloalkyl, haloalkoxy, -C(O)OH, -C(=O)Oalkyl, and -C(O)NH$_2$;

R^1 is selected from the group consisting of alkyl, heterocyclyl, -C(=O)aryl, -NH$_2$, -NH(alkyl), -NH(cycloalkyl), -N(alkyl)(cycloalkyl), -NH(heterocyclyl), -N(alkyl)(heterocyclyl), N(alkyl)$_2$, -NH(aryl), -N(alkyl)(aryl), -N(aryl)$_2$, -NH(heteroaryl), -N(alkyl)(heteroaryl), -NHC(=O)-alkyl, -N(alkyl)C(=O)-alkyl, -NHC(=O)Oalkyl, -N(alkyl)C(=O)O-alkyl, wherein each of the aforesaid alkyl, heterocyclyl, and the "alkyl", "cycloalkyl", "aryl", and "heteroaryl" portions of said R^1 groups is optionally substituted with 1-3 substituents independently selected from the group consisting of halo, heterocyclyl, aryl, heteroaryl, haloalkyl, haloalkoxy, aryloxy, cyano, –SH, -S-alkyl, -S-haloalkyl, -S(=O)$_2$alkyl, -S(=O)$_2$OH, -S(=O)$_2$NH$_2$, -S(=O)$_2$NH(alkyl), S(=O)$_2$NH(cycloalkyl), -S(=O)$_2$N(alkyl)$_2$, -S(=O)$_2$heterocyclyl, -S(=O)$_2$heteroaryl, hydroxy, alkyl, alkenyl, alkynyl, -NH$_2$, -NH(alkyl), -N(alkyl)$_2$, alkoxy, -NHC(=O)alkyl, -C(=O)H, -C(=O)alkyl, -C(=O)aryl, , -C(=O)heteroaryl, -C(=O)Oalkyl, -C(=O)NH$_2$, -C(O)NHalkyl, -C(=O)N(alkyl)$_2$; wherein when each of said heterocyclyl, aryl and heteroaryl has two substituents on adjacent carbon atoms, said substituents, may optionally be taken together with the carbon atoms to which they

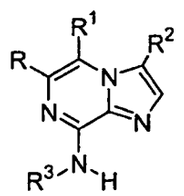
are attached to form a five to six-membered aryl, heterocyclyl, heterocyclenyl, or heteroaryl ring;

R^2 and R^3 independently are H or alkyl, or $-C(R^2)(R^3)-$ is absent;

R^4 is selected from the group consisting of alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl, wherein when each of said cycloalkyl, heterocyclyl, aryl, and heteroaryl has two substituents on adjacent carbon atoms, said substituents, may optionally be taken together with the carbon atoms to which they are attached to form a five to six-membered aryl, heterocyclyl, heterocyclenyl, or heteroaryl ring; wherein each of the aforementioned R^4 alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl, optionally with said five to six-membered aryl, heterocyclyl, heterocyclenyl, or heteroaryl ring is optionally substituted with 1-3 substituents independently selected from the group consisting of cyano, halo, haloalkyl, alkyl, alkoxy, hydroxyl, haloalkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-S(=O)_2$alkyl, $-S(=O)_2NH_2$, $-S(=O)_2NH$(alkyl), $-S(=O)_2N(alkyl)_2$, -S-alkyl, -S-haloalkyl, $-C(=O)OH$, $-NH_2$, -NH(alkyl), $-N(alkyl)_2$, and -C(=O)Oalkyl;

subsequently administering to said cancer cell at least one aurora kinase inhibitor, wherein said aurora kinase inhibitor is selected from the group consisting of a compound represented by Formulas E-K shown below in paragraphs e-k:

e. A compound represented by the structural Formula E:



Formula E

or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, wherein:

R is H, CN, $-NR^5R^6$, cycloalkyl, cycloalkenyl, heterocyclenyl, heteroaryl, $-C(O)NR^5R^6$, $-N(R^5)C(O)R^6$, heterocyclyl, heteroaryl substituted with $(CH_2)_{1-3}$ NR^5R^6, unsubstituted alkyl, or alkyl substituted with one or more moieties which can be the same or different each moiety being independently selected from the group consisting of $-OR^5$, heterocyclyl, $-N(R^5)C(O)N(R^5R^6)$, $-N(R^5)-C(O)OR^6$, $-(CH_2)_{1-3}-N(R^5R^6)$ and $-NR^5R^6$;

R^1 is H, halo, aryl or heteroaryl, wherein each of said aryl and heteroaryl can be unsubstituted or substituted with one or more moieties which can be the same or different each moiety being independently selected from the group consisting of halo, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, $-CH_2OR^5$, $-C(O)NR^5R^6$, -C(O)OH, -C(O)NH_2,

$-NR^5R^6$ (wherein the R^5 and R^6, together with the N of said $-NR^5R^6$, form a heterocyclyl ring), $-S(O)R^5$, $-S(O_2)R^5$, -CN, -CHO, $-SR^5$, $-C(O)OR^5$, $-C(O)R^5$ and $-OR^5$;

R^2 is H, halo, aryl, arylalkyl or heteroaryl, wherein each of said aryl, arylalkyl and heteroaryl can be unsubstituted or optionally independently be substituted with one or more moieties which can be the same or different each moiety being independently selected from the group consisting of halo, amide, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, -C(O)OH, $-C(O)NH_2$, $-NR^5R^6$ (wherein the R^5 and R^6, together with the N of said $-NR^5R^6$, form a heterocyclyl ring), -CN, arylalkyl, $-CH_2OR^5$, $-S(O)R^5$, $-S(O_2)R^5$, -CN, -CHO, $-SR^5$, $-C(O)OR^5$, $-C(O)R^5$, heteroaryl and heterocyclyl;

R^3 is H, alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl, wherein:

- said alkyl shown above for R^3 can be unsubstituted or substituted with one or more moieties which can be the same or different each moiety being independently selected from the group consisting of $-OR^5$, alkoxy, heteroaryl, and $-NR^5R^6$;
- said aryl shown above for R^3 is unsubstituted, or optionally substituted, or optionally fused, with halo, heteroaryl, heterocyclyl, cycloalkyl or heteroarylalkyl, wherein each of said heteroaryl, heterocyclyl, cycloalkyl and heteroarylalkyl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different each moiety being independently selected from alkyl, $-OR^5$, $-N(R^5R^6)$ and $-S(O_2)R^5$; and
- said heteroaryl shown above for R^3 can be unsubstituted or optionally substituted, or optionally fused, with one or more moieties which can be the same or different with each moiety being independently selected from the group consisting of halo, amino, alkoxycarbonyl, $-OR^5$, alkyl, -CHO, $-NR^5R^6$, $-S(O_2)N(R^5R^6)$, $-C(O)N(R^5R^6)$, $-SR^5$, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl,

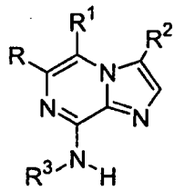
heterocyclenyl, and heterocyclyl;

R^5 is H, alkyl, aminoalkyl, aryl, heteroaryl, heterocyclyl or cycloalkyl; and

R^6 is H, alkyl, aryl, arylalkyl, heteroaryl, heterocyclyl or cycloalkyl;

further wherein in any $-NR^5R^6$ in Formula I, said R^5 and R^6 can optionally be joined together with the N of said $-NR^5R^6$ to form a cyclic ring;

f. A compound represented by the structural formula:

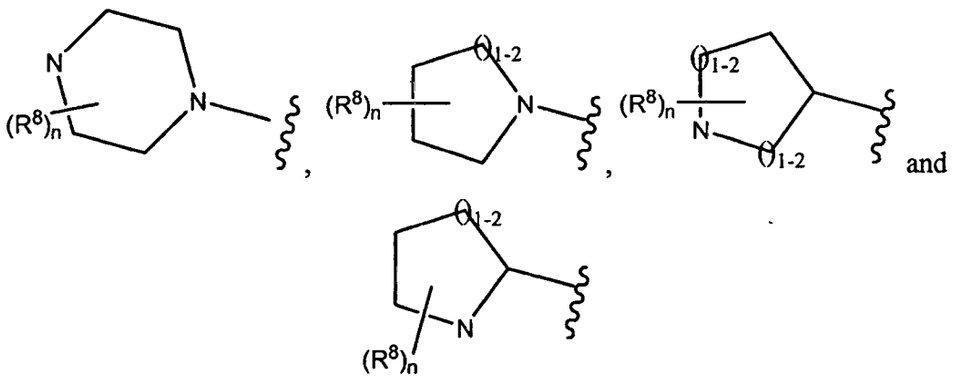


Formula F

or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, wherein:

R is selected from the group consisting of H, halogen, aryl, heteroaryl, cycloalkyl, arylalkyl, heterocyclyl, heterocyclylalkyl, alkenyl, alkynyl,

$-C(O)R^7$,

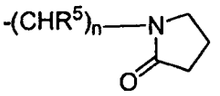


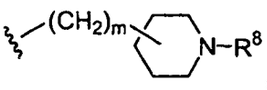
wherein each of said aryl, heteroaryl, cycloalkyl, arylalkyl, alkenyl, heterocyclyl and the heterocyclyl moieties whose structures are shown immediately above for R can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, cycloalkyl, CF_3, CN, $-OCF_3$,

$-OR^6$, $-C(O)R^7$, $-NR^5R^6$, $-C(O_2)R^6$, $-C(O)NR^5R^6$, $-(CHR^5)_nOR^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ and $-N(R^5)C(O)NR^5R^6$;

R^1 is H, halogen or alkyl;

R^2 is alkyl;

R^3 is selected from the group consisting of H, aryl, heteroaryl, heterocyclyl, -$(CHR^5)_n$-aryl, - $(CHR^5)_n$-heteroaryl, -$(CHR^5)_n$-OR^6, -$S(O_2)R^6$, -$C(O)R^6$, -$S(O_2)NR^5R^6$, -$C(O)OR^6$, -$C(O)NR^5R^6$, cycloalkyl, -$CH(aryl)_2$, –$(CH_2)_m$-NR^8, -$(CHR^5)_n$-$CH(aryl)_2$, 

and 

, wherein each of said aryl, heteroaryl and heterocyclyl can be substituted or optionally substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl, cycloalkyl, CF_3, CN, -OCF_3, -OR^5, -NR^5R^6, -$C(O_2)R^5$, -$C(O)NR^5R^6$, -SR^6, -$S(O_2)R^6$, -$S(O_2)NR^5R^6$, -$N(R^5)S(O_2)R^7$, -$N(R^5)C(O)R^7$ and -$N(R^5)C(O)NR^5R^6$;

R^5 is H or alkyl;

R^6 is selected from the group consisting of H, alkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, wherein each of said alkyl, heteroarylalkyl, aryl, heteroaryl and arylalkyl can be unsubstituted or optionally substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl, cycloalkyl, CF_3, OCF_3, CN, -OR^5, -NR^5R^6, -CH_2OR^5, -$C(O_2)R^5$, -$C(O)NR^5R^6$, -SR^6, -$S(O_2)R^7$, -$S(O_2)NR^5R^6$, -$N(R^5)S(O_2)R^7$, -$N(R^5)C(O)R^7$ and -$N(R^5)C(O)NR^5R^6$;

R^7 is selected from the group consisting of alkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, wherein each of said alkyl, heteroarylalkyl, aryl, heteroaryl and arylalkyl can be unsubstituted or optionally substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl, cycloalkyl, CF_3, OCF_3, CN, -OR^5, -NR^5R^6, -CH_2OR^5, -$C(O_2)R^5$, -$C(O)NR^5R^6$, -SR^6, -$S(O_2)R^7$, -$S(O_2)NR^5R^6$, -$N(R^5)S(O_2)R^7$, -$N(R^5)C(O)R^7$ and -$N(R^5)C(O)NR^5R^6$;

R^8 is selected from the group consisting of R^6, -$C(O)NR^5R^6$, -$S(O_2)NR^5R^6$, -$C(O)R^7$, -$C(O_2)R^6$, –$S(O_2)R^7$ and –(CH_2)-aryl;

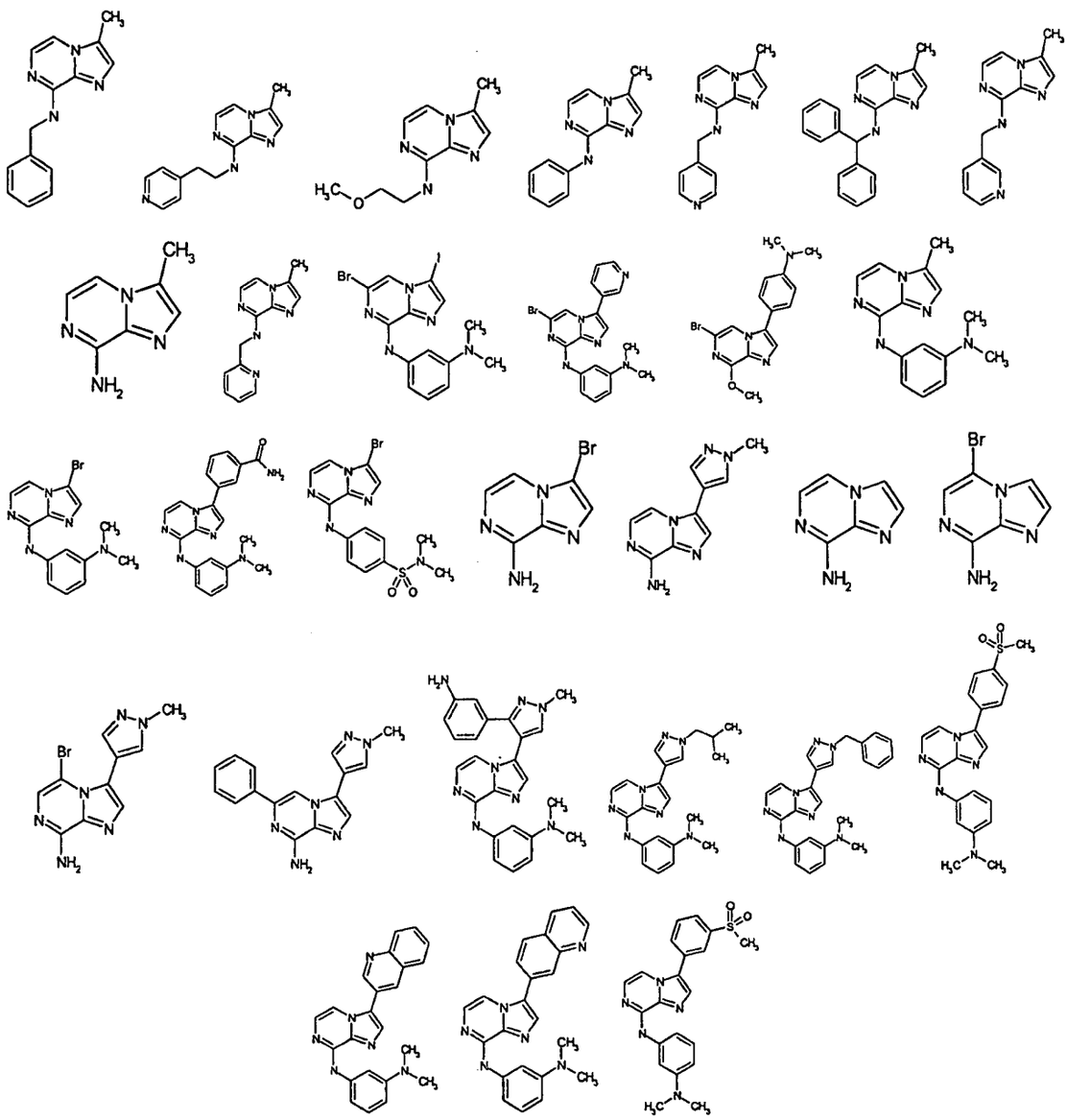
R^9 is selected from the group consisting of halogen, CN, NR^5R^6, -$C(O_2)R^6$, -$C(O)NR^5R^6$, -OR^6, -$C(O)R^7$, -SR^6, -$S(O_2)R^7$, -$S(O_2)NR^5R^6$, -$N(R^5)S(O_2)R^7$, -$N(R^5)C(O)R^7$and –$N(R^5)C(O)NR^5R^6$;

m is 0 to 4;

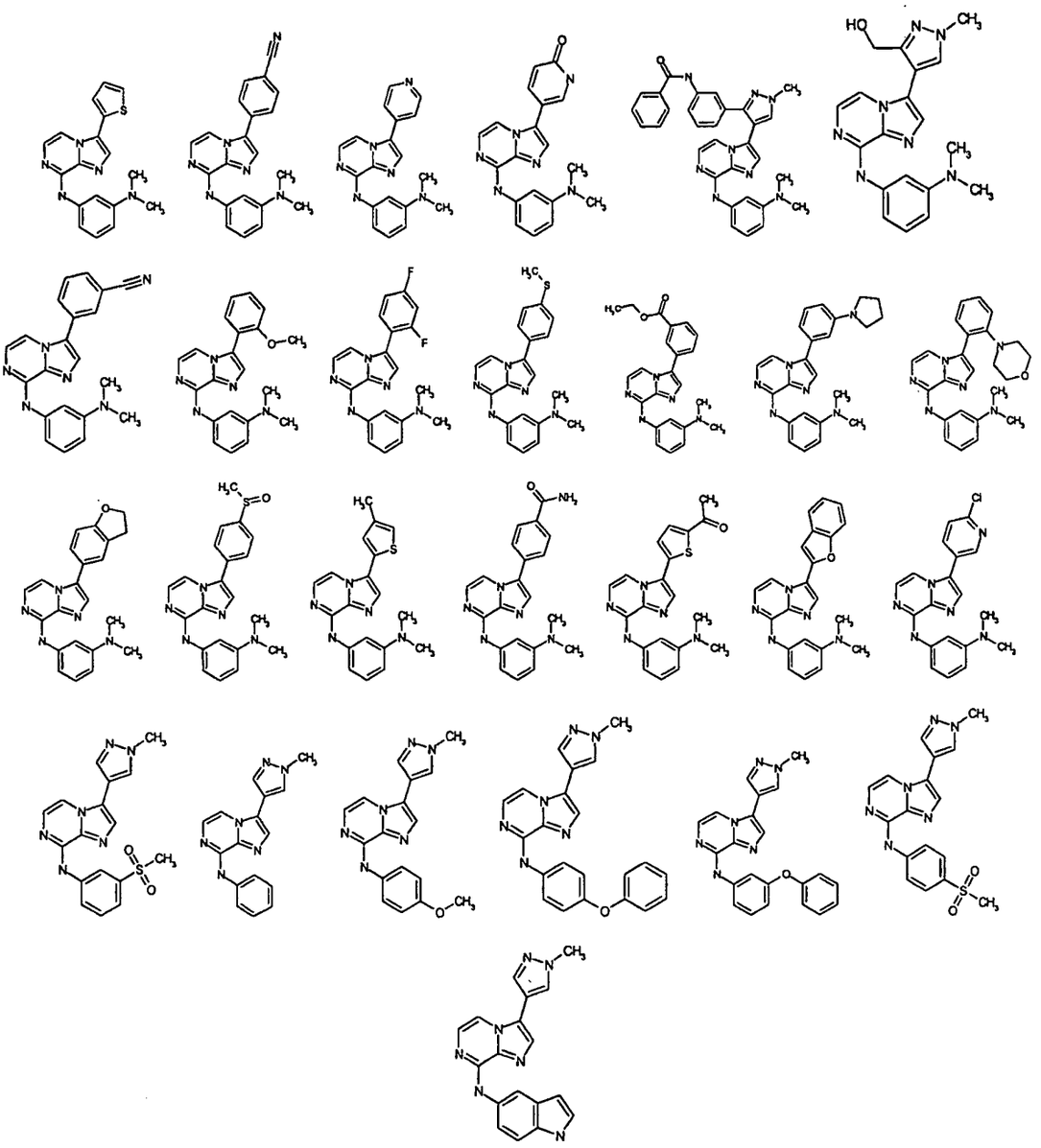
n is 1-4; and

p is 0-3;

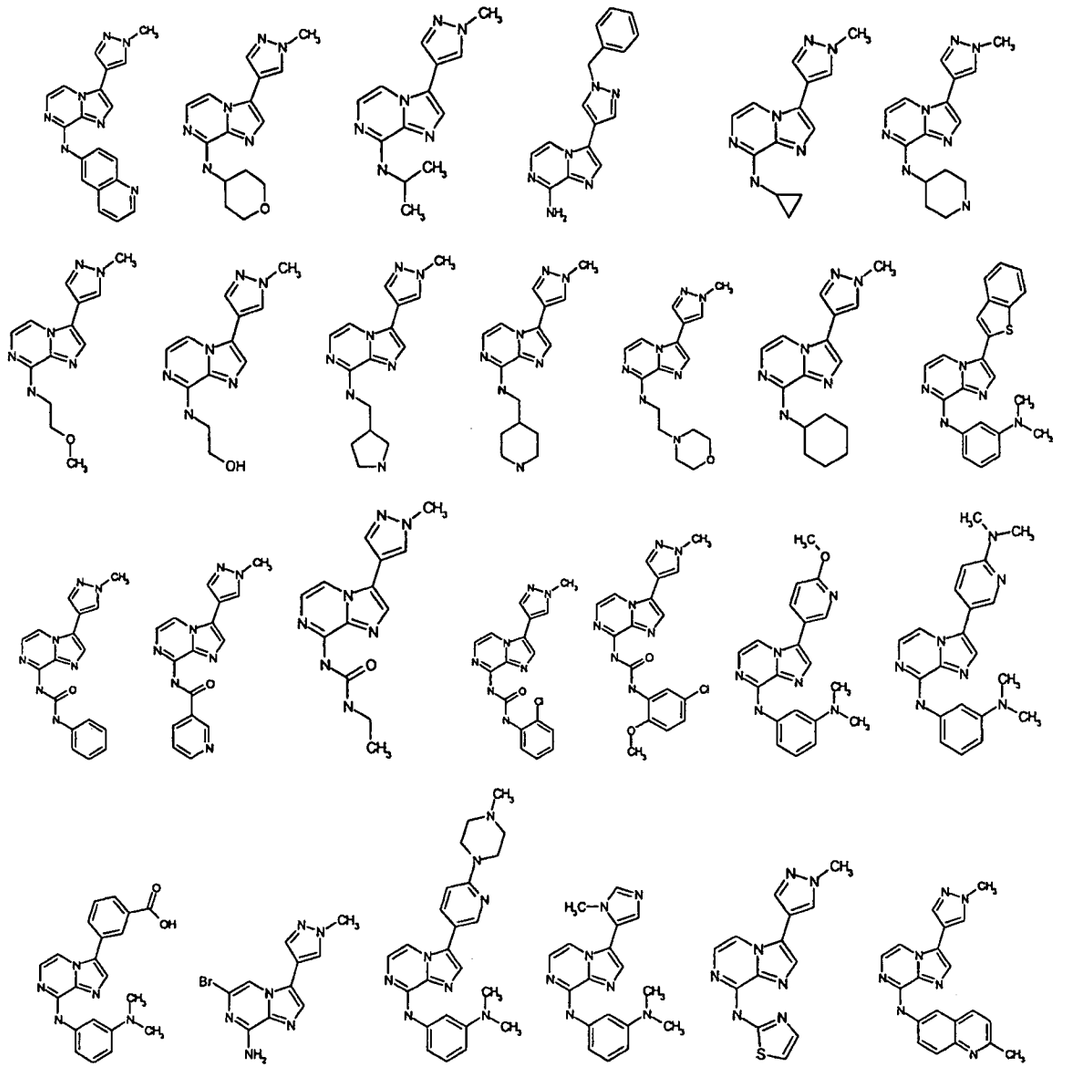
g. A compound selected from the compounds of the formulas:



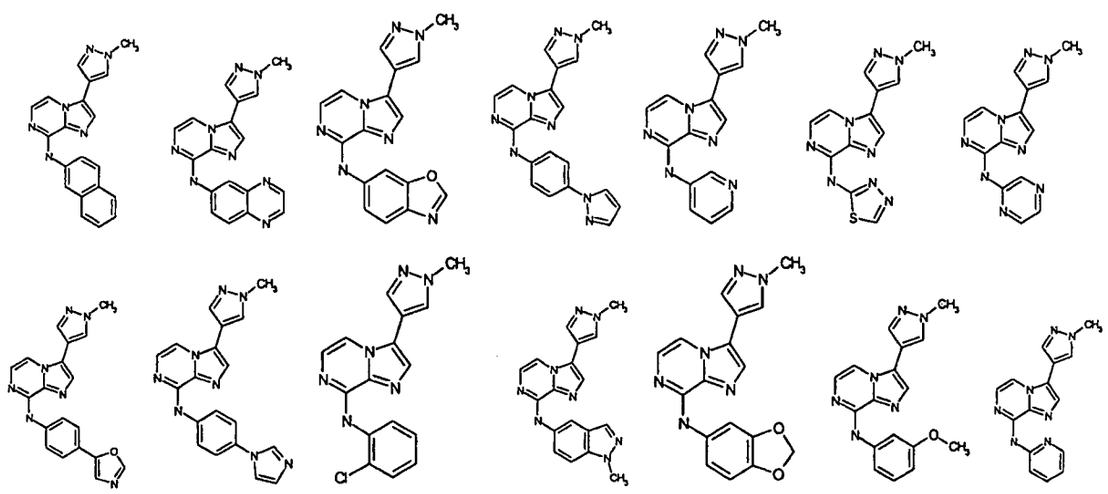
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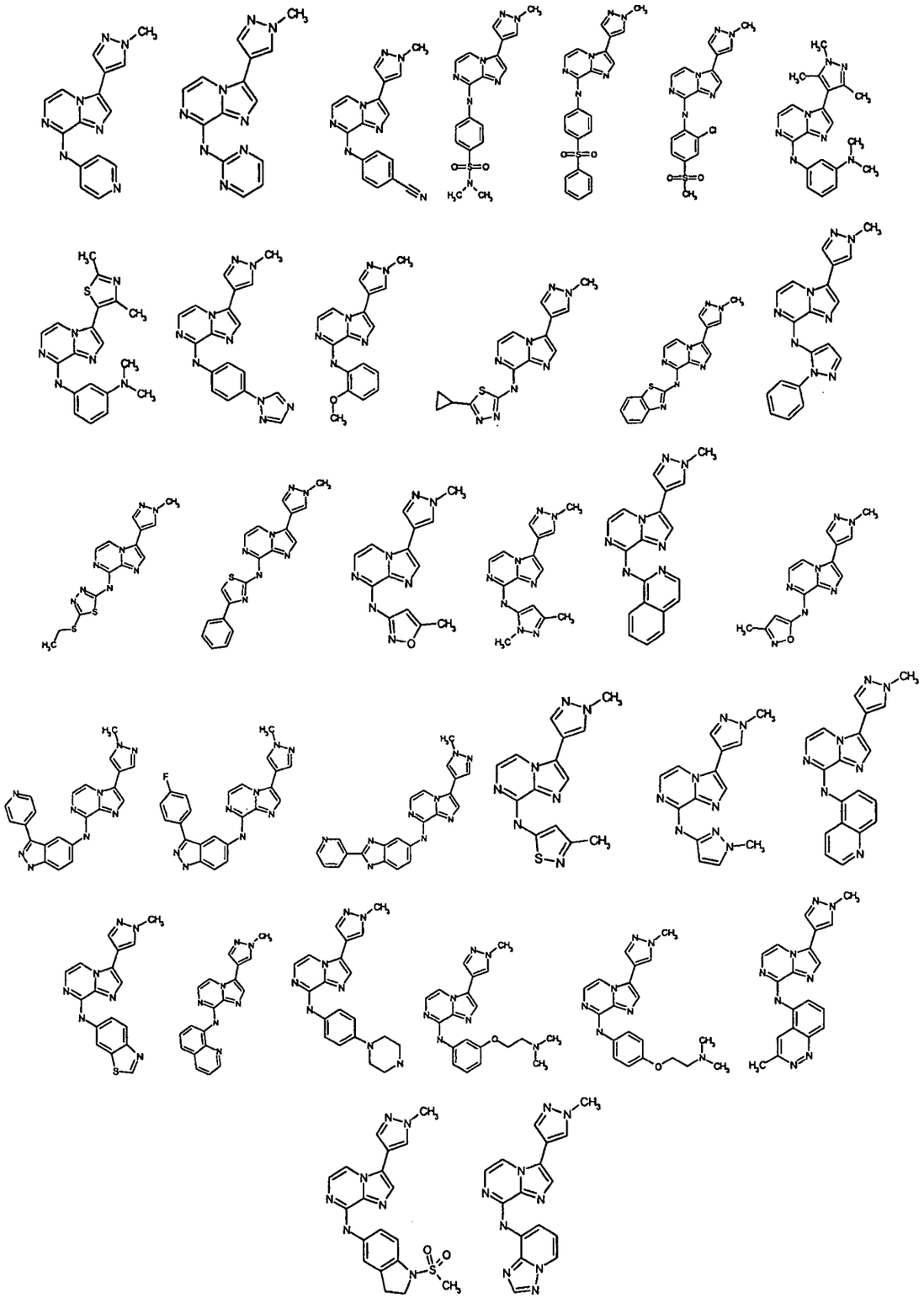


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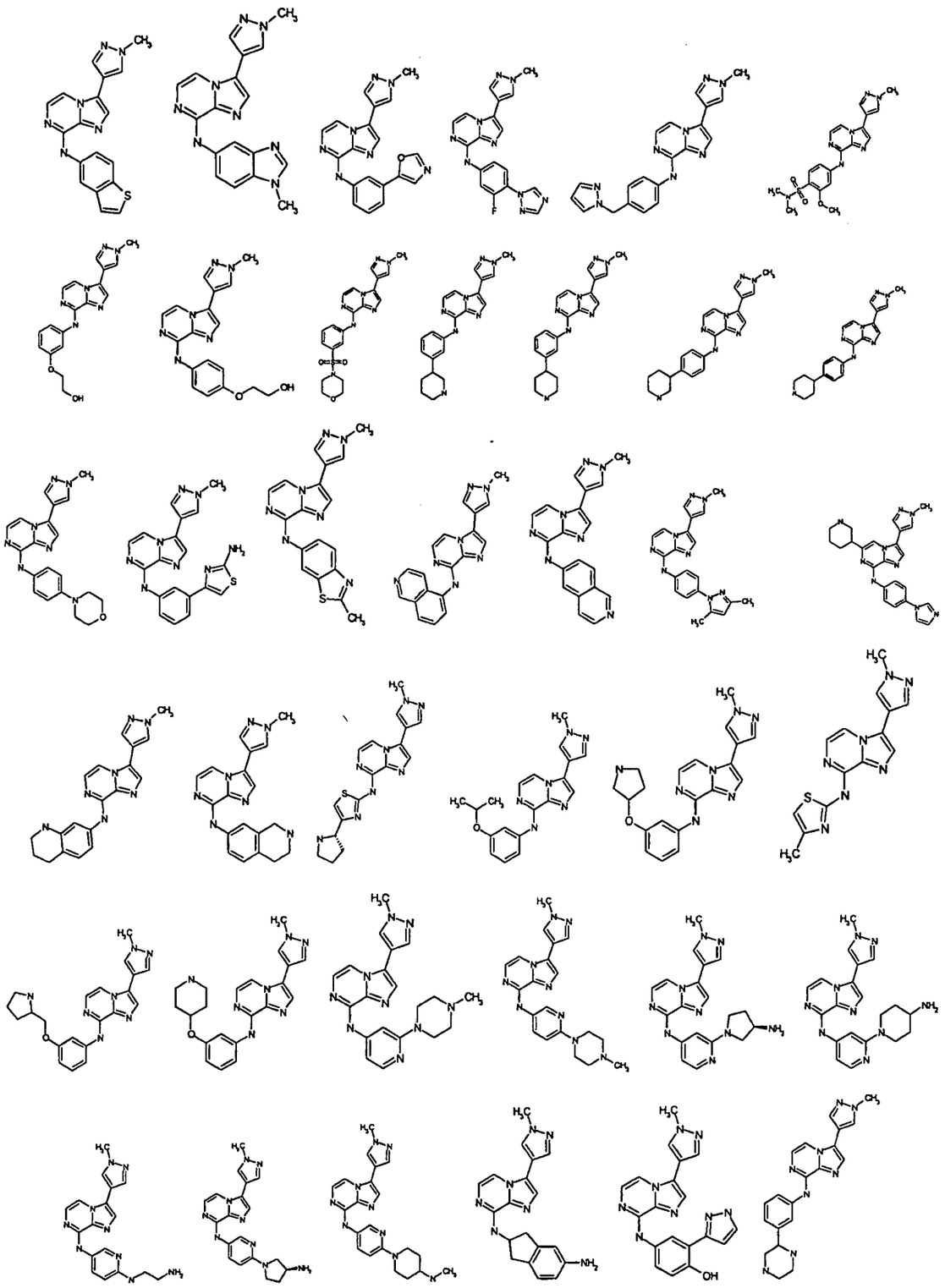


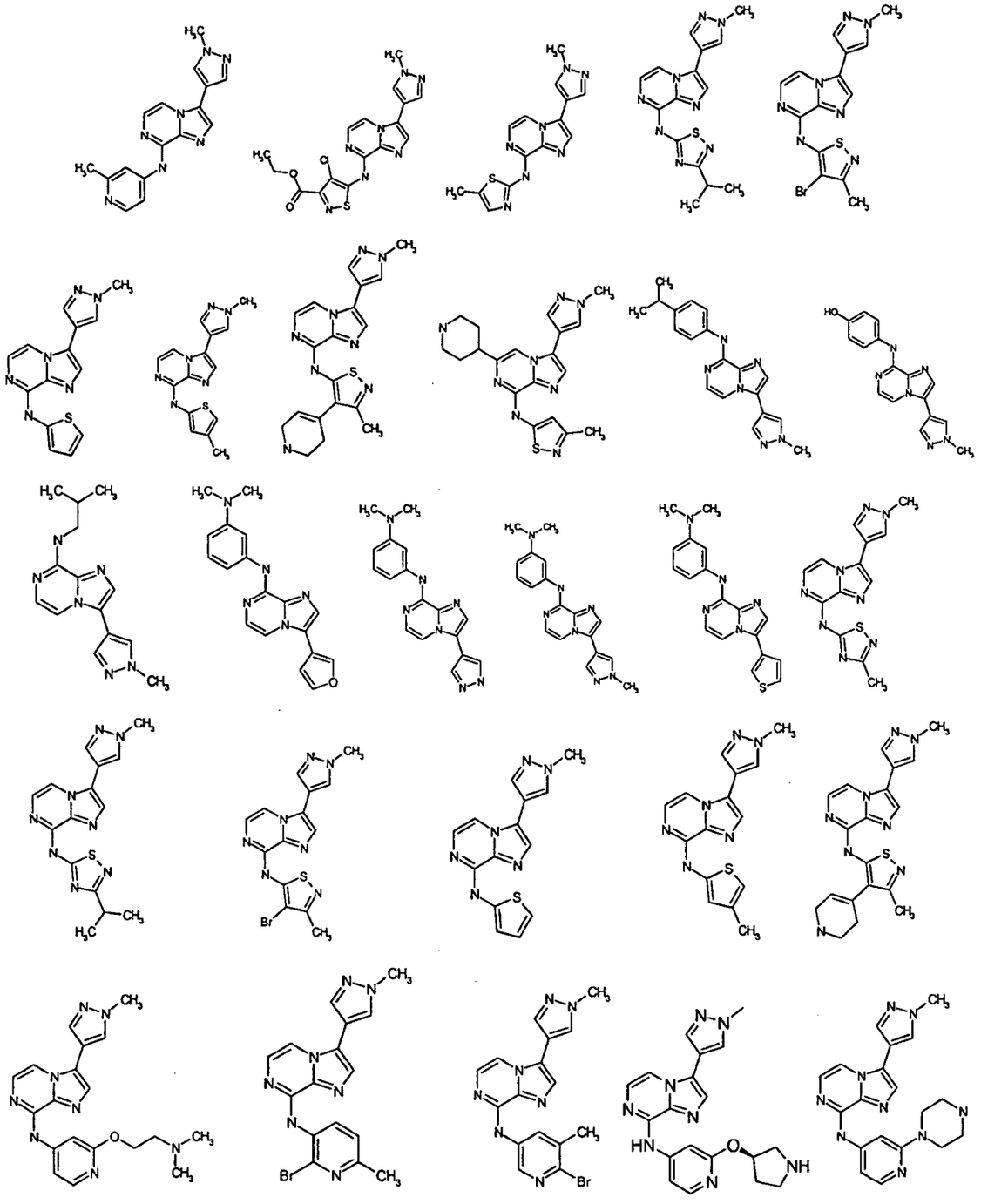
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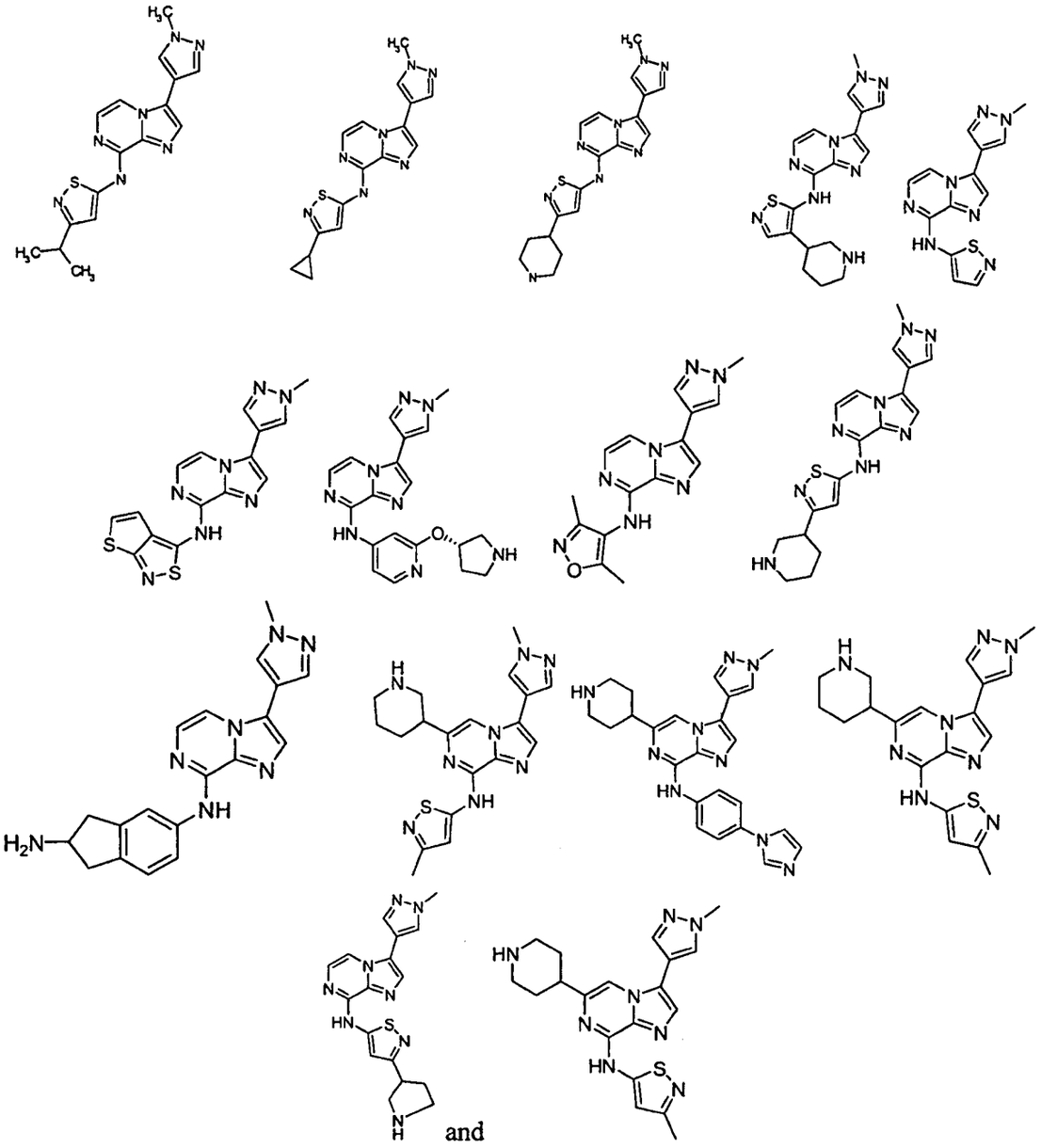


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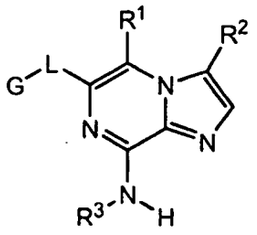
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and

or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof;

h. A compound of the formula:



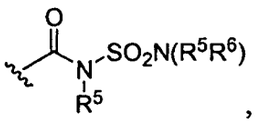
Formula H

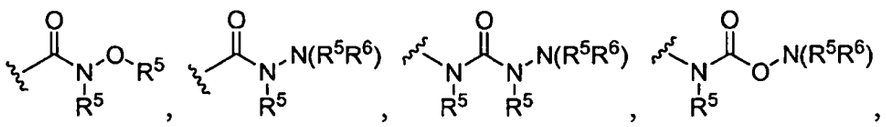
or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, wherein:

L is selected from the group consisting of S, S(O) and $S(O_2)$;

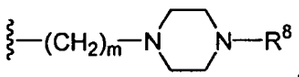
G is alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclenyl or heterocyclyl, wherein each of said alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclenyl or heterocyclyl can be unsubstituted or optionally independently substituted with one or more moieties which are independently selected from the group consisting of $-OR^5$, halo, -CN, $-C(O)NR^5R^6$, $-N(H)-C(O)R^5$,$-N(H)-C(O)-NR^5R^6$, $-S(O_2)NR^5R^6$, $-NR^5R^6$, $-C(O)R^5$, $-C(O_2)R^5$, $-SR^5$, $-S(O)R^5$, $-S(O_2)R^5$;

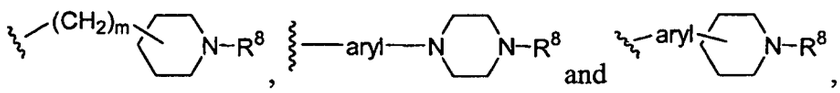
R^1 is H, halo, alkyl, aryl or heteroaryl, wherein each of said alkyl, aryl and heteroaryl can be unsubstituted or substituted with one or more moieties which can be the same or different each moiety being independently selected from the group consisting of halo, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C(O)NR^5R^6$ and $-OR^5$;

R^2 is selected from the group consisting of H, R^9, alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclylalkyl, $-CF_3$, $-C(O)R^7$, 

, 

,

alkyl substituted with 1-6 R^9 groups which groups can be the same or different with each R^9 being independently selected, 

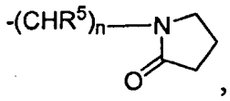
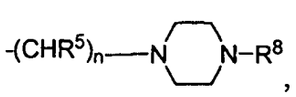
, 

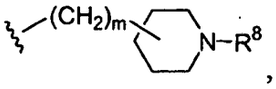
and ,

wherein each of the above-said aryl, heteroaryl, cycloalkyl, arylalkyl and heterocyclyl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halo, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, CF_3, CN, $-OCF_3$, $-OR^6$, $-C(O)R^7$, $-NR^5R^6$, $-C(O_2)R^6$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$,

$-N(R^5)C(O)R^7$ and $-N(R^5)C(O)NR^5R^6$;

R^3 is selected from the group consisting of H, alkyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroarylalkyl, cycloalkylalkyl, heterocyclylalkyl,



, $-(CHR^5)_n-OR^6$, $-S(O_2)R^6$, $-C(O)R^6$, $-S(O_2)NR^5R^6$, $-C(O)OR^6$, $-C(O)NR^5R^6$, cycloalkyl, $-CH(aryl)_2$, $-CH(heteroaryl)_2$, $-(CH_2)_m-NR^8$, and


, wherein each of said alkyl, aryl, heteroaryl and heterocyclyl can be substituted or optionally substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halo, alkyl, aryl, cycloalkyl, CF_3, CN, $-OCF_3$, $-OR^5$, $-NR^5R^6$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^6$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ and $-N(R^5)C(O)NR^5R^6$;

R^5 is H, alkyl, aryl, heteroaryl, heterocyclyl or cycloalkyl; and

R^6 is selected from the group consisting of H, alkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, wherein each of said alkyl, heteroarylalkyl, aryl, heteroaryl and arylalkyl can be unsubstituted or optionally substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl, cycloalkyl, CF_3, OCF_3, CN, $-OR^5$, $-NR^5R^6$, $-CH_2OR^5$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ and $-N(R^5)C(O)NR^5R^6$;

R^7 is selected from the group consisting of alkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, wherein each of said alkyl, heteroarylalkyl, aryl, heteroaryl and arylalkyl can be unsubstituted or optionally substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl, cycloalkyl, CF_3, OCF_3, CN, $-OR^5$, $-NR^5R^6$, $-CH_2OR^5$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ and $-N(R^5)C(O)NR^5R^6$;

R^8 is selected from the group consisting of R^6, $-C(O)NR^5R^6$, $-S(O_2)NR^5R^6$, $-C(O)R^7$, $-C(O_2)R^6$, $-S(O_2)R^7$ and $-(CH_2)$-aryl;

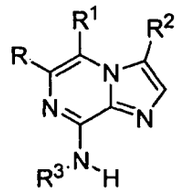
R^9 is selected from the group consisting of halogen, CN, NR^5R^6, $-C(O_2)R^6$, $-C(O)NR^5R^6$, $-OR^6$, $-C(O)R^7$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$,

$-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$and $-N(R^5)C(O)NR^5R^6$;

m is 0 to 4; and

p is 0-3;

i. A compound of Formula I:



Formula I

or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, wherein:

R is H, CN, $-NR^5R^6$, cycloalkyl, cycloalkenyl, heterocyclenyl, heteroaryl, $-C(O)NR^5R^6$, $-N(R^5)C(O)R^6$, heterocyclyl, heteroaryl substituted with $(CH_2)_{1-3}$ NR^5R^6, unsubstituted alkyl, or alkyl substituted with one or more moieties which can be the same or different each moiety being independently selected from the group consisting of $-OR^5$, heterocyclyl, $-N(R^5)C(O)N(R^5R^6)$, $-N(R^5)$-$C(O)OR^6$, $-(CH_2)_{1-3}$-$N(R^5R^6)$ and $-NR^5R^6$;

R^1 is H, halo, aryl or heteroaryl, wherein each of said aryl and heteroaryl can be unsubstituted or substituted with one or more moieties which can be the same or different each moiety being independently selected from the group consisting of halo, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, $-CH_2OR^5$, $-C(O)NR^5R^6$, -C(O)OH, $-C(O)NH_2$, $-NR^5R^6$ (wherein the R^5 and R^6, together with the N of said $-NR^5R^6$, form a heterocyclyl ring), $-S(O)R^5$, $-S(O_2)R^5$, -CN, -CHO, $-SR^5$, $-C(O)OR^5$, $-C(O)R^5$ and $-OR^5$;

R^2 is H, halo, aryl, arylalkyl or heteroaryl, wherein each of said aryl, arylalkyl and heteroaryl can be unsubstituted or optionally independently be substituted with one or more moieties which can be the same or different each moiety being independently selected from the group consisting of halo, amide, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, -C(O)OH, $-C(O)NH_2$, $-NR^5R^6$ (wherein the R^5 and R^6, together with the N of said $-NR^5R^6$, form a heterocyclyl ring), -CN, arylalkyl, $-CH_2OR^5$, $-S(O)R^5$, $-S(O_2)R^5$, -CN, -CHO, $-SR^5$, $-C(O)OR^5$, $-C(O)R^5$, heteroaryl and heterocyclyl;

R^3 is heterocyclyl–$(CR^7R^8)_n$-X, heterocyclenyl–$(CR^7R^8)_n$-X, heteroaryl–$(CR^7R^8)_n$-X or aryl–

$(CR^7R^8)_n$-X wherein each of the heterocyclyl-, heterocyclenyl-, heteroaryl- or aryl-moieties of said R^3 can be unsubstituted or substituted with one or more moieties, independently selected from the group consisting of $-CONR^5R^6$, $-OR^5$ and alkyl,

n is 1-6,

X is selected from the group consisting of, $-NR^5R^6$, $-OR^5$, $-SO-R^5$ and $-SR^5$,

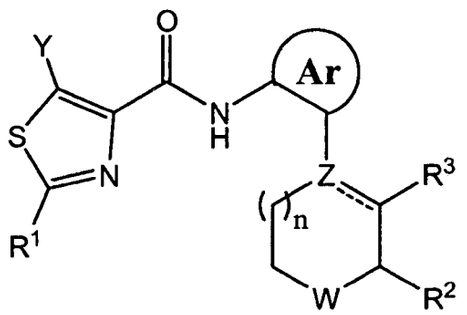
R^7 and R^8 are each independently hydrogen or alkyl;

R^5 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkoxyalkyl, -alkyl-S-alkyl, aminoalkyl, aryl, heteroaryl, heterocyclenyl, heterocycloalkyl, cycloalkyl, cycloalkenyl, heterocyclylalkoxyl, -S-alkylheterocyclyl, heterocyclyl, heterocyclenyl, alkylN(alkyl)$_2$, alkylNH(alkyl), alkylN(alkenyl)2, -alkylN(alkoxyl)2, -alkyl-SH and hydroxyalkyl, wherein each of said aryl, heteroaryl, heterocyclenyl, heterocycloalkyl, cycloalkyl, cycloalkenyl, heterocyclylalkoxyl, -S-alkylheterocyclyl, heterocyclyl, heterocyclenyl can be unsubstituted or substituted with one or more moieties independently selected from the group consisting of alkyl, alkyl, alkenyl, aryl, cycloalkenyl, cycloalkyl, arylalkyl, cycloalkenylalkyl, cycloalkylalkyl, heteroaryl, heterocyclenyl, heterocyclyl, heteroarylalkyl, heterocyclenylalkyl, heterocycloalkylalkyl, alkoxyalkyl, -alkyl-S-alkyl, -alkylSH, alkoxyl, -S-alkyl, hydroxyalkyl, and aminoalkyl;

R^6 is selected from the group consisting of hydrogen, alkyl, alkenyl, aryl, cycloalkenyl, cycloalkyl, arylalkyl, cycloalkenylalkyl, cycloalkylalkyl, heteroaryl, heterocyclenyl, heterocyclyl, heteroarylalkyl, heterocyclenylalkyl, heterocycloalkylalkyl, alkoxyalkyl, -alkyl-S-alkyl, -alkylSH, alkoxyl, -S-alkyl, hydroxyalkyl, and aminoalkyl, wherein each of said aryl, cycloalkenyl, cycloalkyl, arylalkyl, cycloalkenylalkyl, cycloalkylalkyl, heteroaryl, heterocyclenyl, heterocyclyl, heteroarylalkyl, heterocyclenylalkyl, heterocycloalkylalkyl can be unsubstituted or substituted with one or more moieties independently selected from the group consisting of alkyl, alkyl, alkenyl, aryl, cycloalkenyl, cycloalkyl, arylalkyl, cycloalkenylalkyl, cycloalkylalkyl, heteroaryl, heterocyclenyl, heterocyclyl, heteroarylalkyl, heterocyclenylalkyl, heterocycloalkylalkyl, alkoxyalkyl, -alkyl-S-alkyl, -alkylSH, alkoxyl, -S-alkyl, hydroxyalkyl, and aminoalkyl;

further wherein in any -NR^5R^6 in Formula I, said R^5 and R^6 can optionally be joined together with the N of said -NR^5R^6 to form a cyclic ring or bridged cyclic ring, wherein each of said cyclic ring or bridged cyclic ring, can be unsubstituted or substituted with one or more moieties, which can be the same or different, independently selected from the group consisting of hydroxyl, -SH, alkyl, alkenyl, hydroxyalkyl, -alkyl-SH, alkoxyl, -S-alkyl, -CO_2-alkyl, -CO_2-alkenyl, arylalkyl, cycloalkenylalkyl, cycloalkylalkyl, heteroarylalkyl, heterocyclenylalkyl, heterocycloalkylalkyl, heteroaryl, aryl, cycloalkenyl, cycloalkyl, spiroheterocyclyl, spiroheterocyclenyl, spiroheteroaryl, spirocyclyl, spirocyclenyl, spiroaryl, alkoxyalkyl, -alkyl-S-alkyl, heterocyclyl, and heterocyclenyl;

j. A compound having the formula:



(J)

or a pharmaceutically acceptable salt, solvate, ester, prodrug or stereoisomer thereof, wherein the dashed lines indicate an optional and additional bond, and wherein:

R^1 is nitrogen-containing heteroaryl, nitrogen-containing heterocyclyl, nitrogen-containing benzofused heteroaryl or nitrogen-containing benzofused heterocyclyl, wherein R^1 is joined to the rest of the compound of formula (I) via a ring nitrogen atom, and wherein one or more ring carbon atoms of a nitrogen-containing heteroaryl, nitrogen-containing heterocyclyl, nitrogen-containing benzofused heteroaryl or nitrogen-containing benzofused heterocyclyl group can be substituted with up to 5 substituents, which may be the same or different, and are independently selected from alkyl, aryl, halo, -OH, -O-alkyl, -O-aryl, -$N(R^8)_2$, -CF_3, -NO_2, -$C(O)R^8$, -$C(O)OR^8$, -$C(O)N(R^8)_2$, -$OC(O)R^8$ or -$NHC(O)R^8$;

R^2 is –H, -alkyl, –NH_2 or –CH_2NH_2;

R^3 is –H, -alkyl, $–NH_2$ or $–CH_2NH_2$;

each occurrence of R^4 is independently –H, -alkyl, $–NH_2$, -OH, -alkylene-OH, $–CH_2NH_2$, $-C(O)R^5$, $-C(O)NH_2$, -C(O)NH-alkyl, $-C(O)N(alkyl)_2$, $-NHC(O)R^6$ or $–NHS(O)_2R^6$;

R^5 is –H, -alkyl, -aryl, -heteroaryl, -NHOH;

R^6 is –H, -alkyl or $–CF_3$;

R^7 is –H, -OH, $-C_1$-C_6 alkyl, $-O-(C_1$-C_6 alkyl), or $–CF_3$;

R^8 is –H, alkyl, aryl, heterocyclyl, heteroaryl or cycloalkyl;

Ar is -arylene- or -heteroarylene-, wherein the arylene or heteroarylene is joined via 2 of its adjacent ring carbon atoms, and wherein the -arylene- or -heteroarylene- can be substituted with up to 4 substituents, which may be the same or different, and are independently selected from –halo, alkyl, alkoxy, aryloxy, $-SR^8$, $-S(O)R^8$, $-S(O)_2R^8$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)N(R^8)_2$, $-NHC(O)R^8$, $-CF_3$, -CN or NO_2, and such that when Ar is tetrahydronaphthylene, R^1 and R^2 cannot both be hydrogen

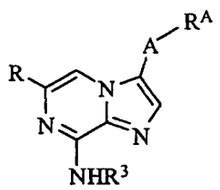
W is –NH- or $–C(R^4)_2$-, wherein both R^4 groups and the carbon atom to which they are attached can combine to form a five to seven membered heterocyclyl or heteroaryl group;

Y is –H, -halo, -alkyl or –CN;

Z is $–CR^7$- or –N-, when the optional additional bond is absent, and –C- when the optional additional bond is present;

n is an integer ranging from 0 to 2; and

(k) A compound of Formula K:



Formula K

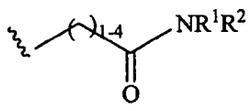
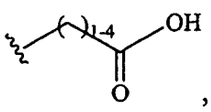
or a pharmaceutically acceptable salt, solvate, ester, prodrug or stereoisomer thereof, wherein:

R is H, halo or alkyl;

R^3 is heteroaryl-X, wherein X is heterocyclylalkyl- wherein said heterocyclyl can be unsubstituted or optionally substituted with 1-4 alkyl moieties;

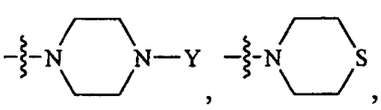
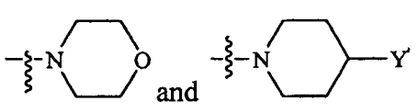
A is -aryl- , -heteroaryl-, $-N(R^1)$-aryl- or $-N(R^1)$-heteroaryl- , wherein each of said aryl and heteroaryl can be independently unsubstituted or optionally substituted with one or more

substituents, which substituents can be the same or different, each substituent being independently selected from the group consisting of alkyl, $-NO_2$, halo, hydroxy, trihaloalkyl, alkoxy, and dialkylamino;

R^A is $-(CH_2)_{1-4}$-heteroaryl,  or  , wherein said heteroaryl can optionally be fused with an aryl, wherein each of said aryl and heteroaryl can independently be optionally substituted with one or more moieties each moiety being independently selected from the group consisting of trihaloalkyl, $-NO_2$, halo, hydroxyalkyl, alkoxyalkyl and dialkylamino;

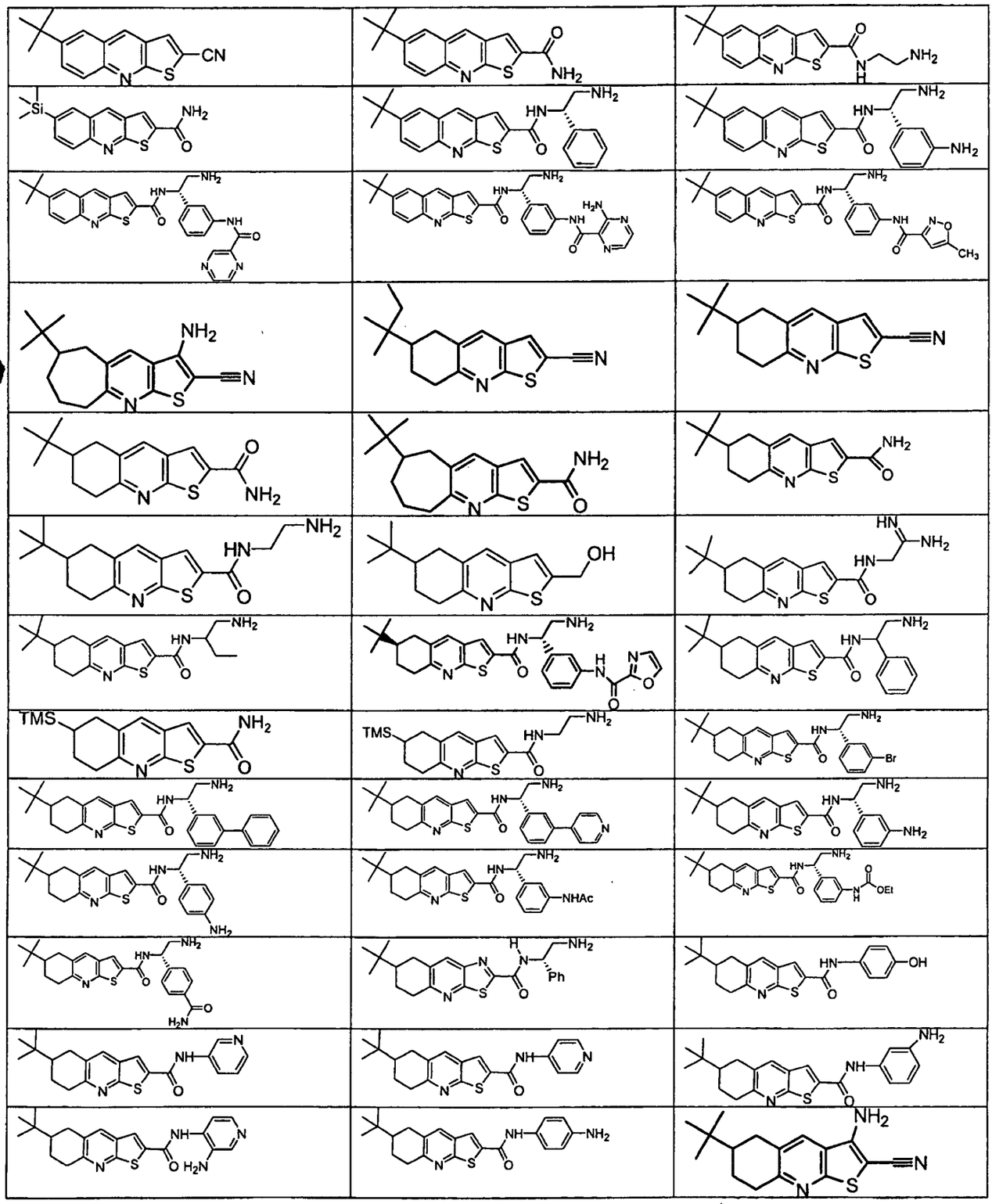
R^1 is H or alkyl;

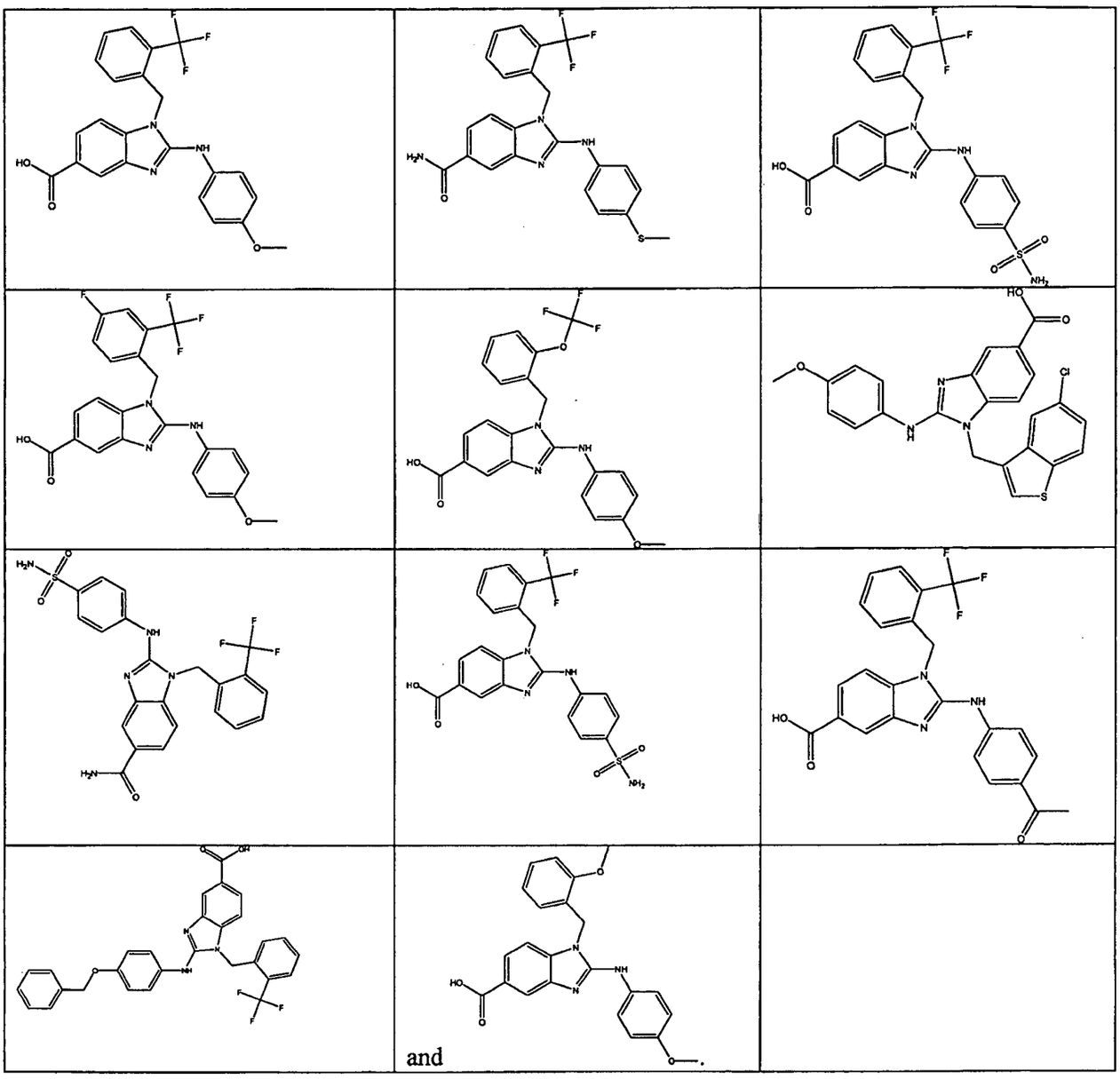
R^2 is H, hydroxyalkyl-, arylalkyl-, heteroaryl, aryl, heteroarylalkyl-, alkyl, dialkylaminoalkyl-, alkylaminoalkyl-, cycloalkylalkyl-, cycloalkyl, heterocyclylalkyl- or heterocyclyl, wherein said aryl and aryl of arylalkyl can be unsubstituted or substituted with one or more moieties independently selected from the group consisting of trihaloalkyl, $-NO_2$, halo, hydroxyalkyl, alkoxyalkyl, dialkylamino and heterocyclylalkyl-, wherein said heterocyclylalkyl can be unsubstituted or substituted with alkyl or $-SO_2NH_2$; said heteroaryl and heteroaryl of heteroarylalkyl can be unsubstituted or substituted with one or more moieties, each moiety being independently selected from the group consisting of hydroxyalkyl, alkoxy, alkyl, halo, hydroxyl, and $-NO_2$; and said cycloalkyl is unsubstituted or substituted with hydroxyl; or

R^1 and R^2 together with the N to which each is attached, form a heterocyclic group selected from the group consisting of  ,  , wherein

Y is alkoxyalkyl, hydroxyalkyl, dialkylaminoalkyl or alkyl, further wherein Y' is hydroxyl.

12. The pharmaceutical composition of claim 1, wherein said KSP inhibitor represented by Formulas A-D are selected from the group consisting of:

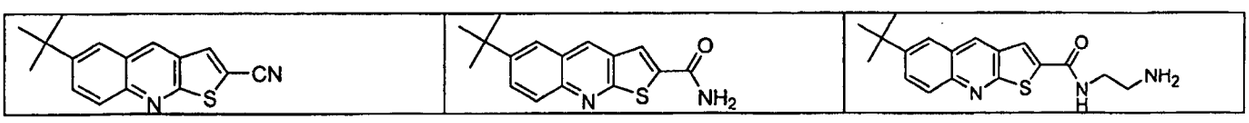


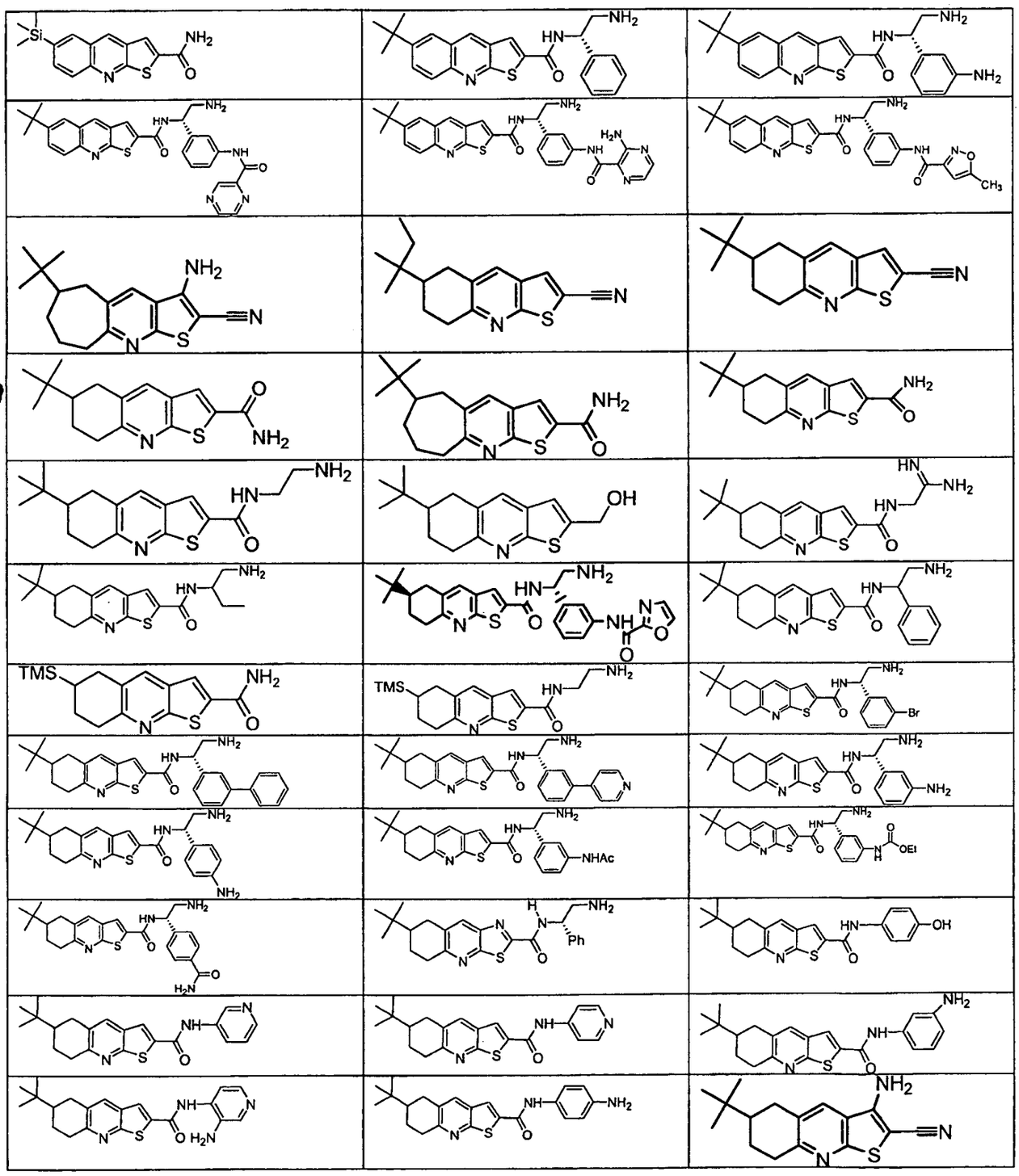


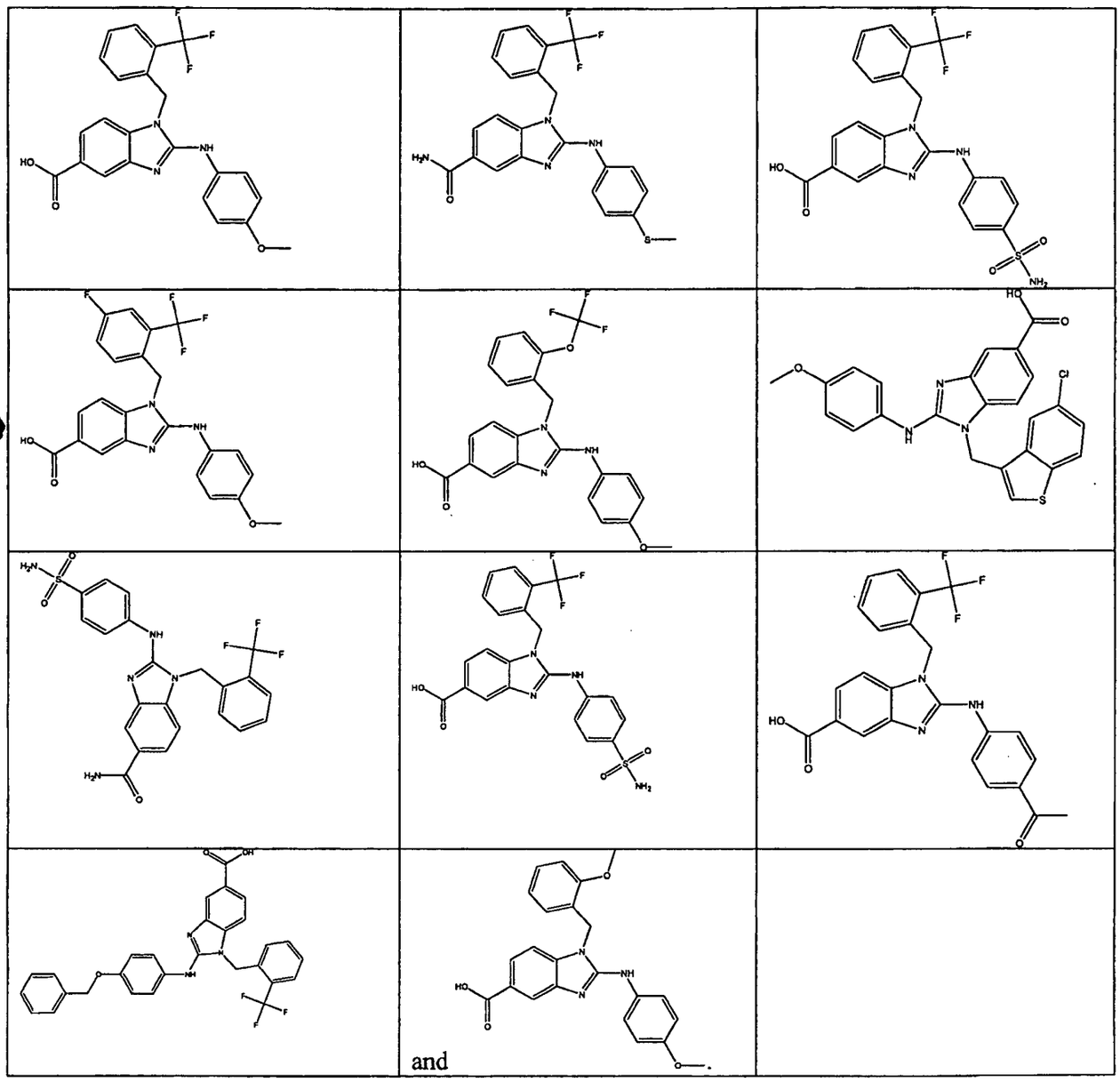
and

or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof.

13. The method of claim 2, wherein said KSP inhibitor represented by Formulas A-D are selected from the group consisting of:



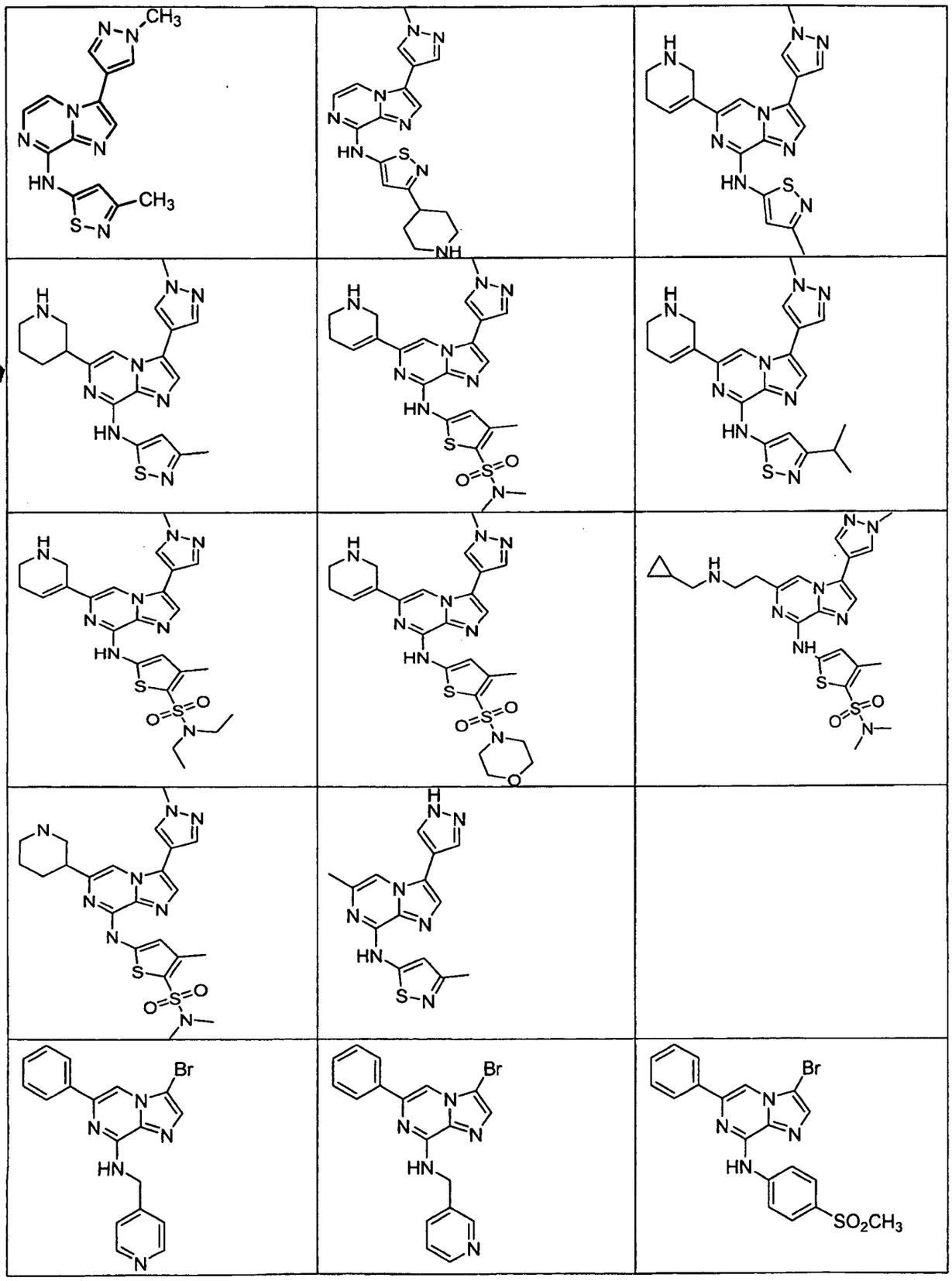


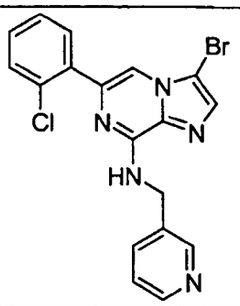
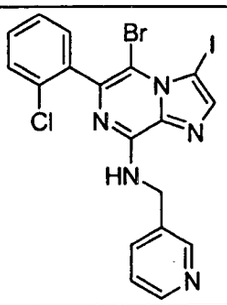
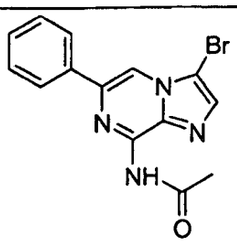
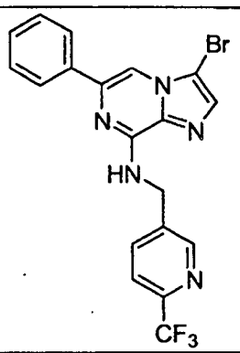
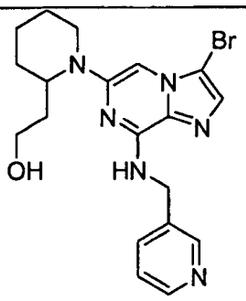
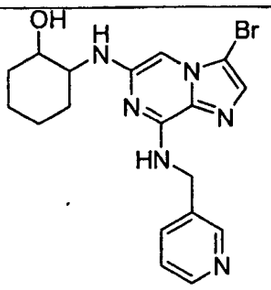
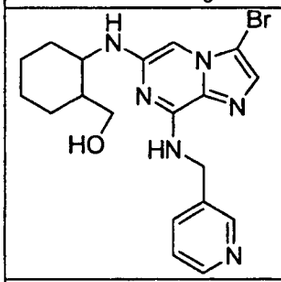
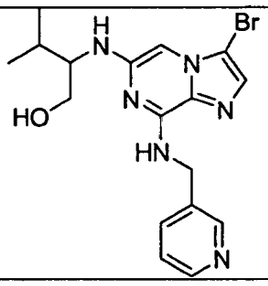
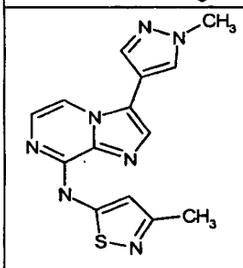
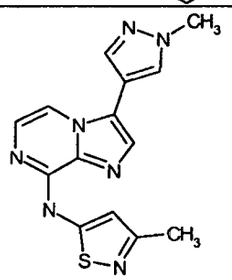
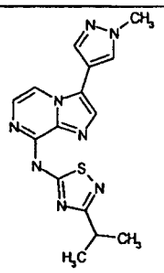
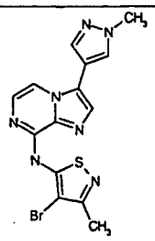
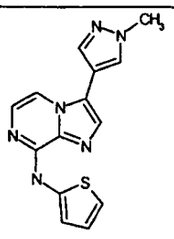
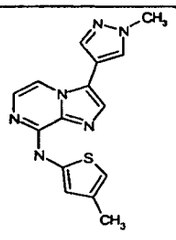


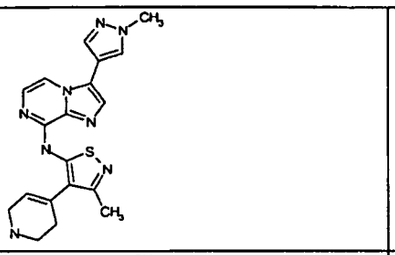
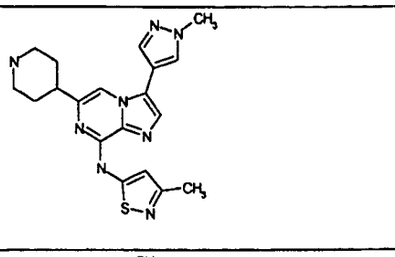
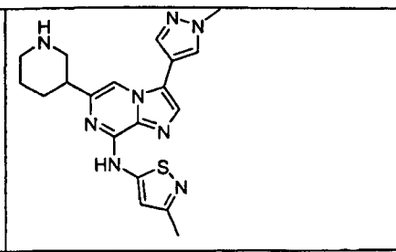
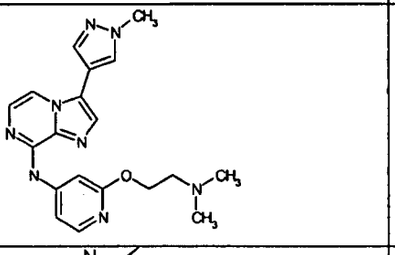
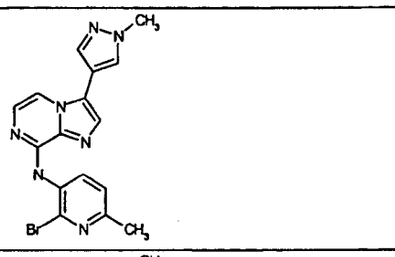
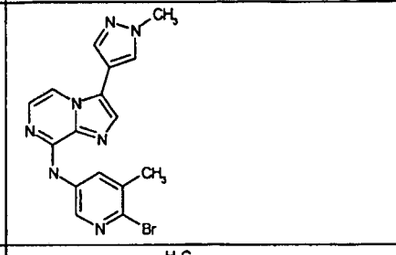
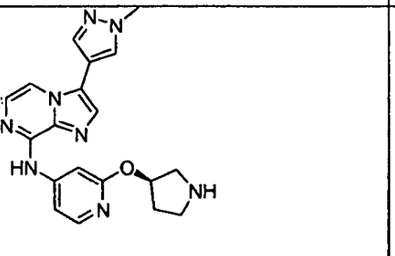
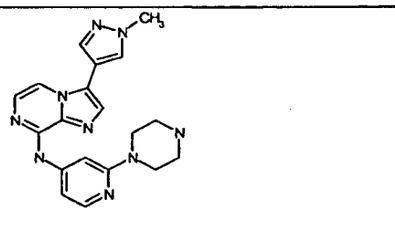
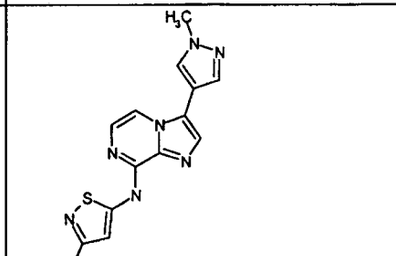
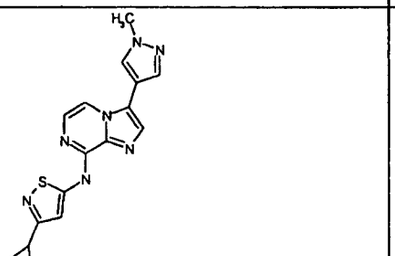
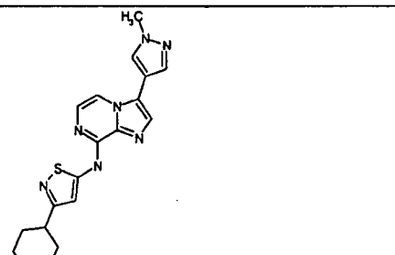
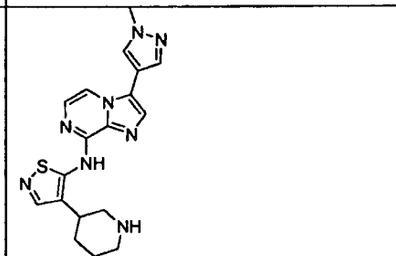
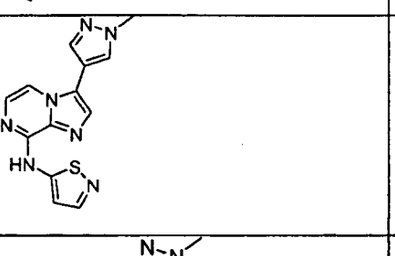
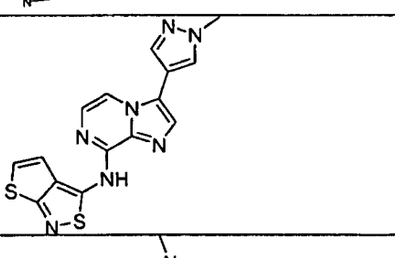
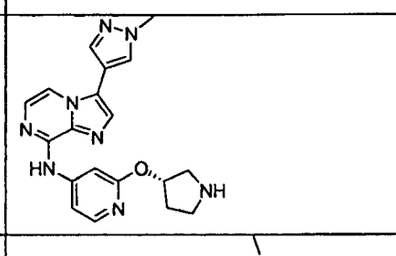
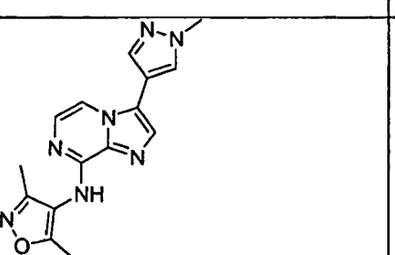
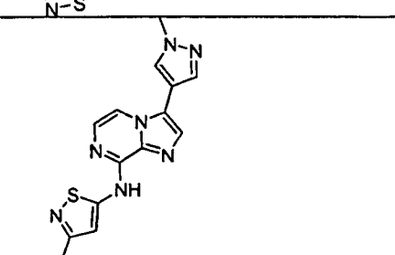
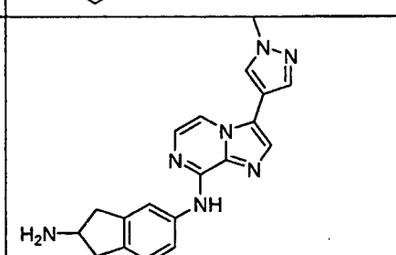
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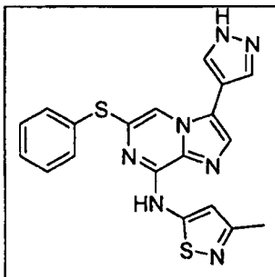
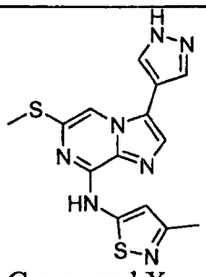
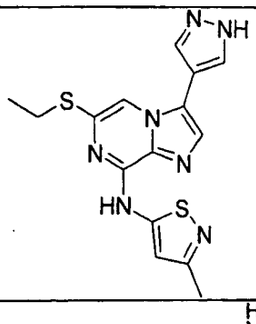
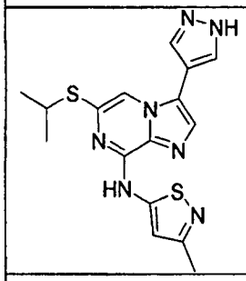
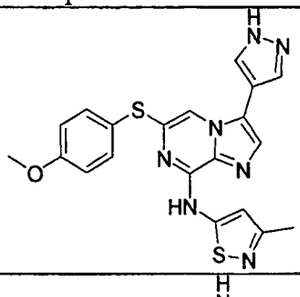
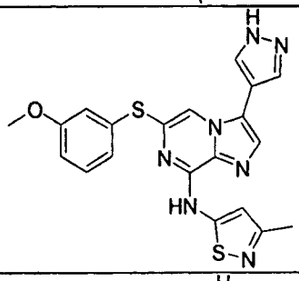
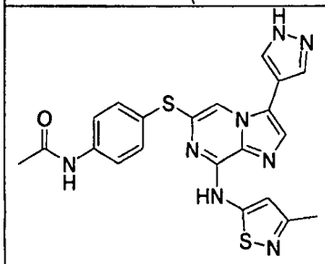
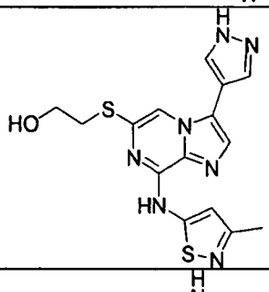
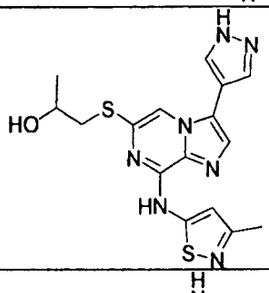
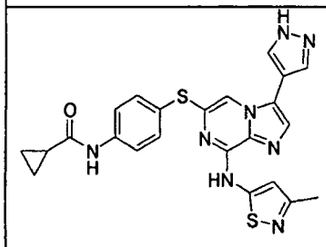
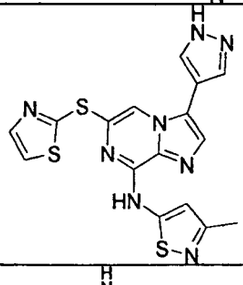
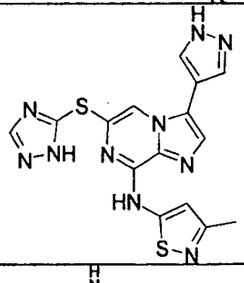
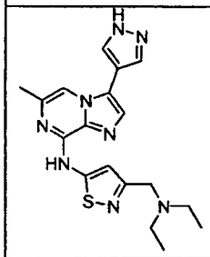
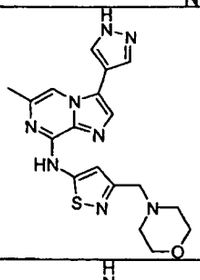
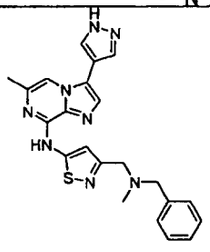
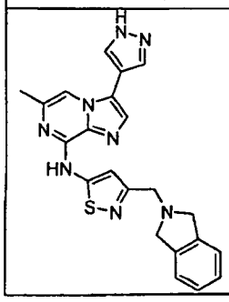
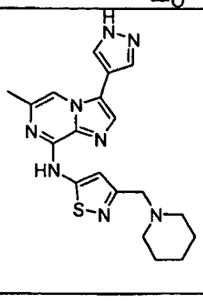
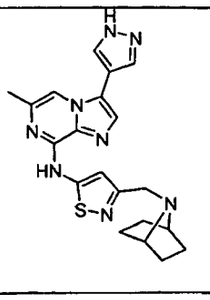
or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof.

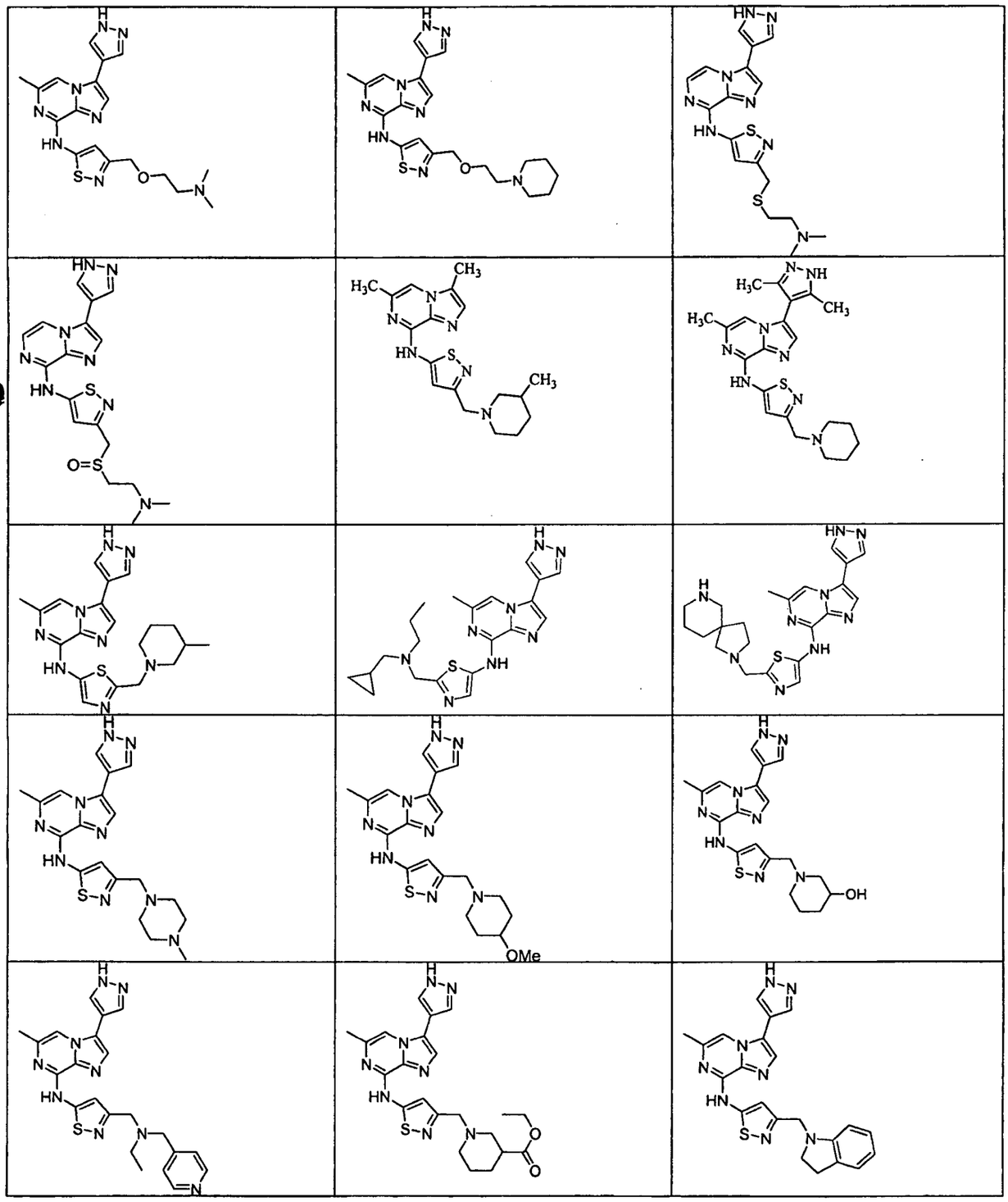
14. The pharmaceutical composition of claim 1, wherein said aurora kinase inhibitor, represented by Formulas E-K, are selected from the group consisting of:

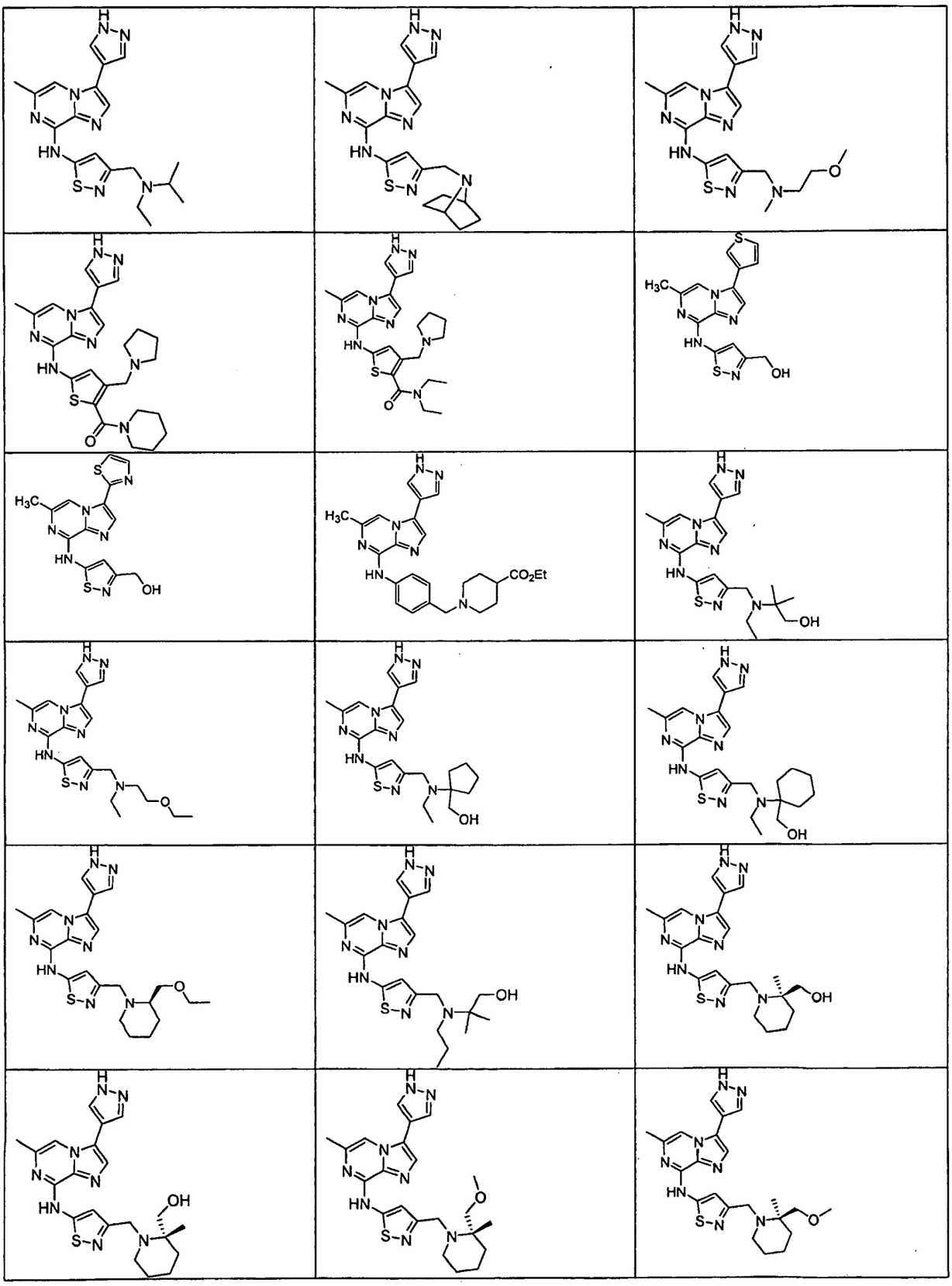


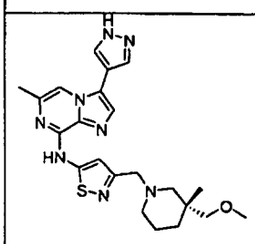
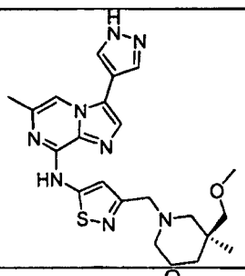
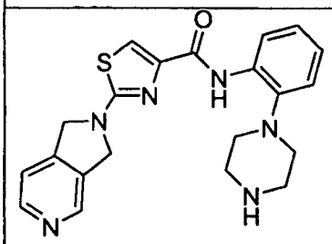
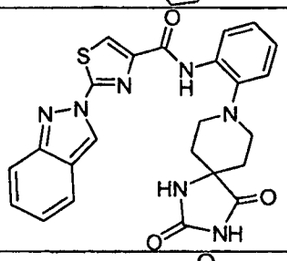
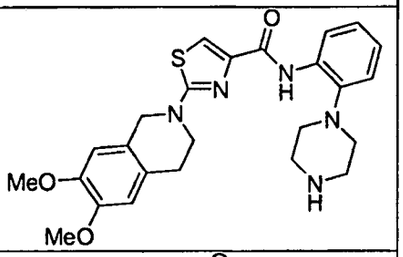
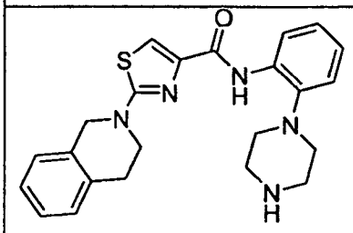
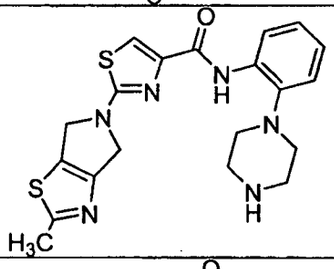
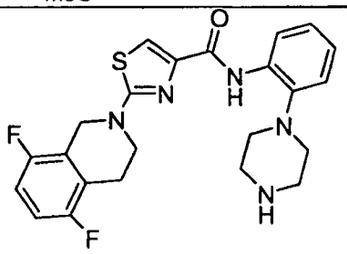
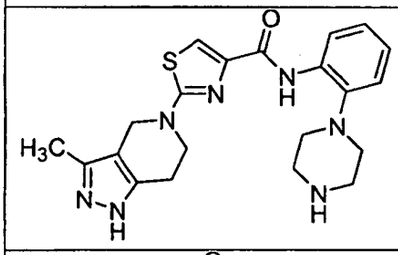
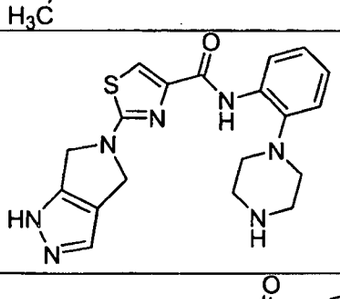
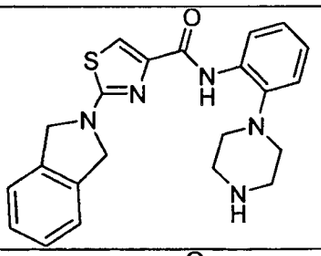
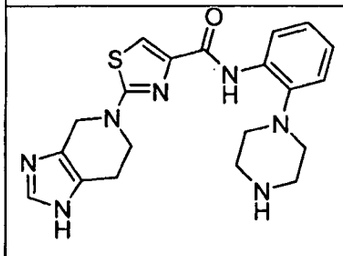
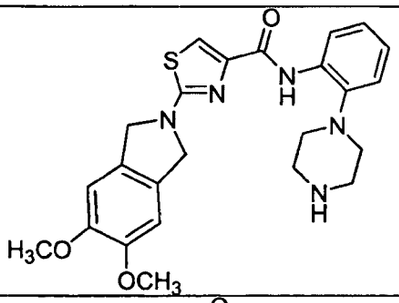
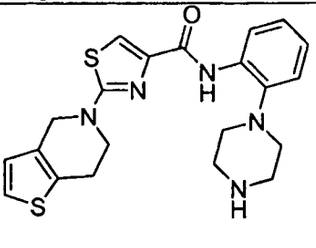
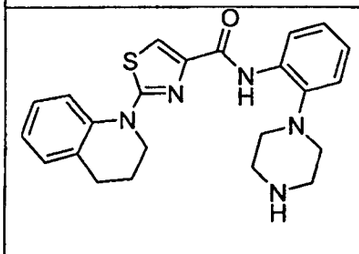
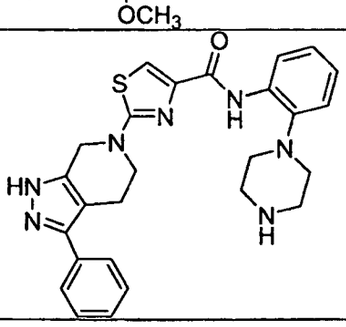
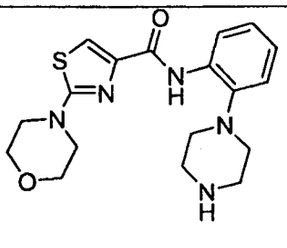
		
		
		
		
		

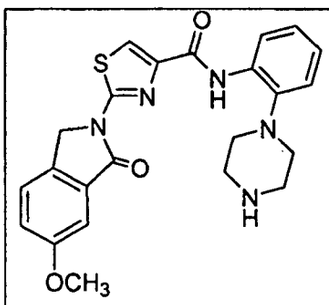
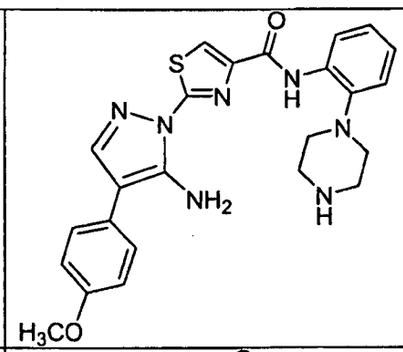
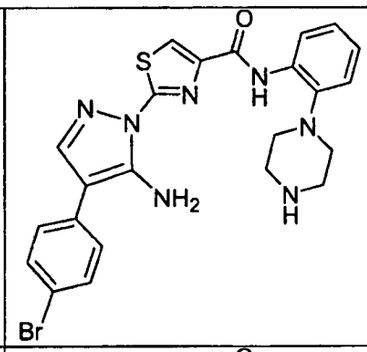
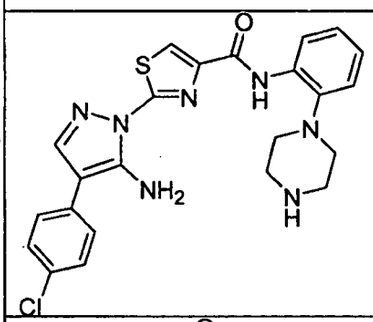
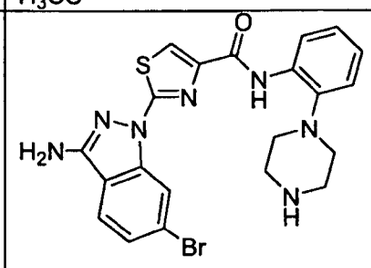
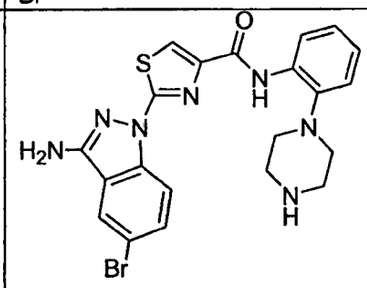
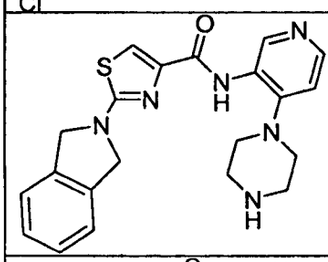
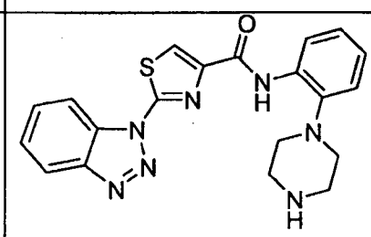
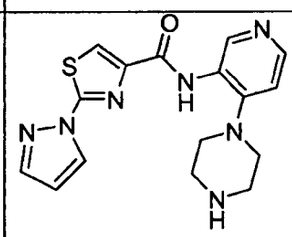
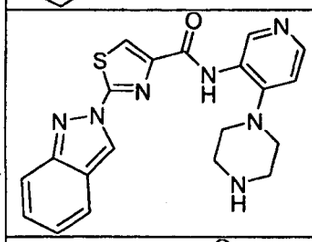
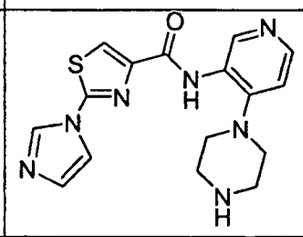
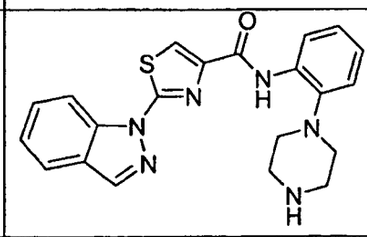
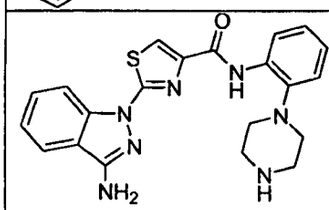
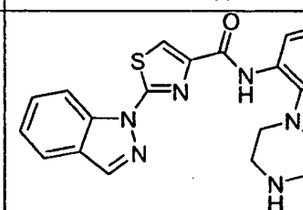
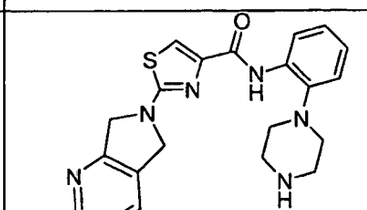
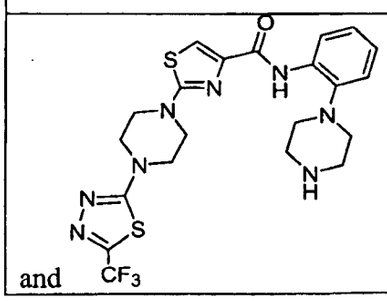
		
		
		
		
		
		

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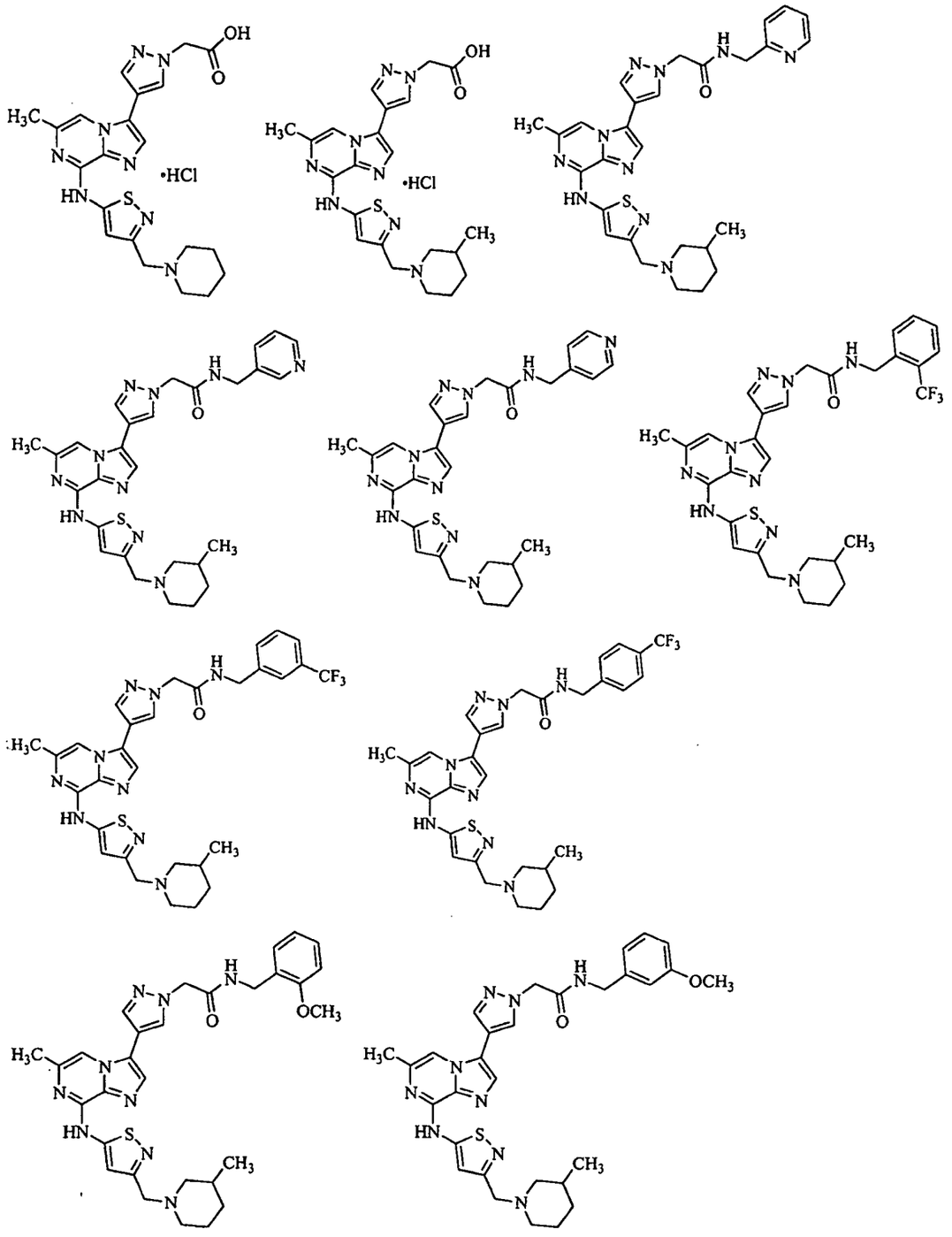




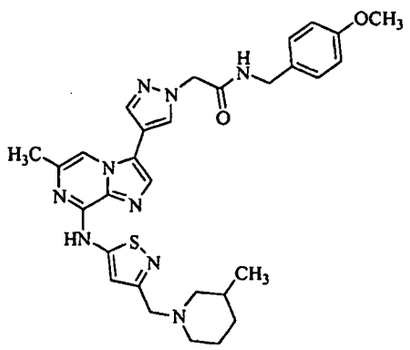
		
		
		
		
		
		

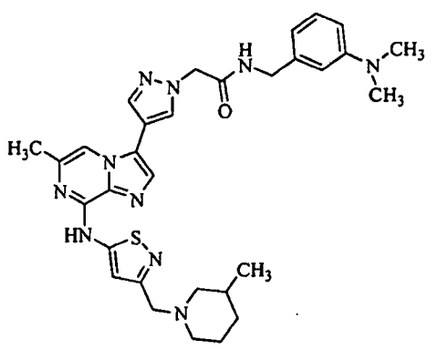
		
		
		
		
		
		

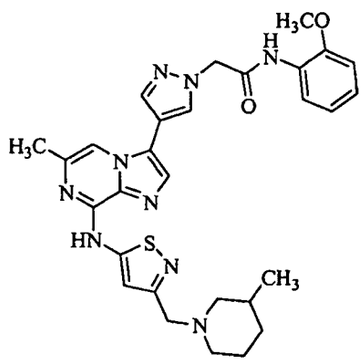
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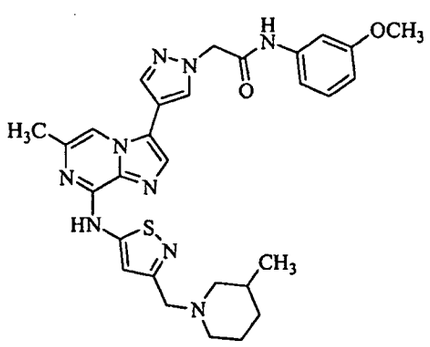


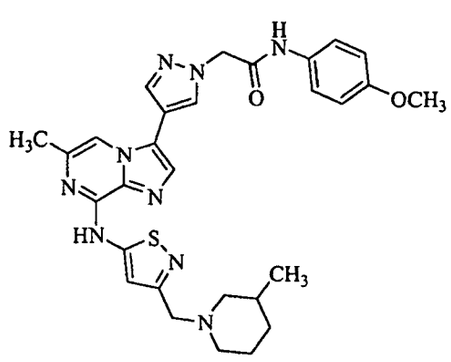
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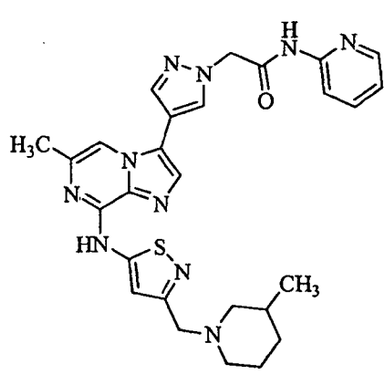


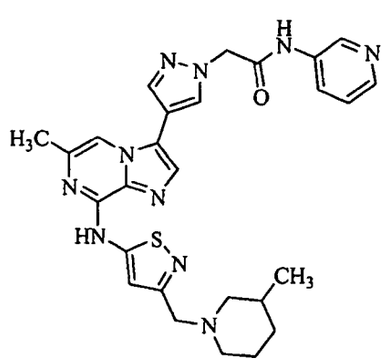


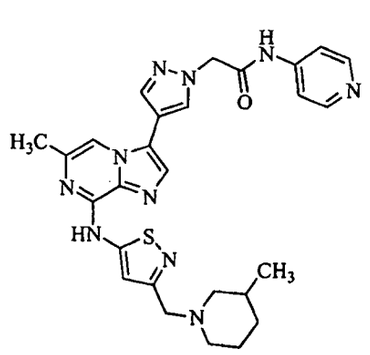


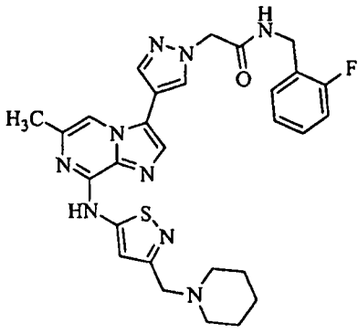


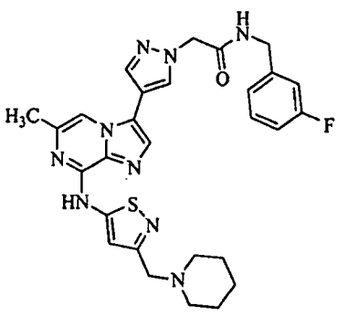


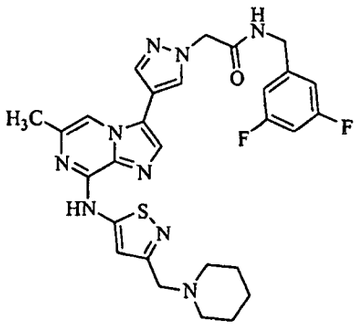


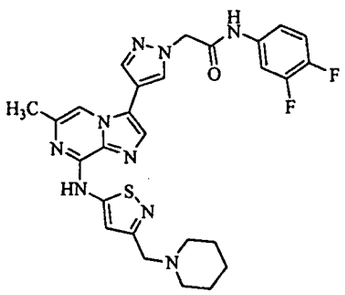


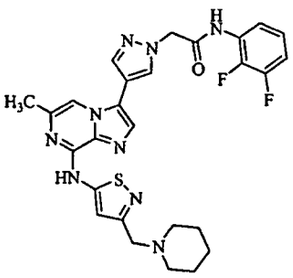


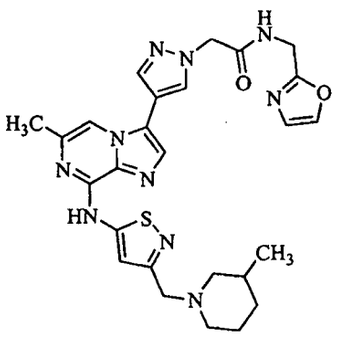


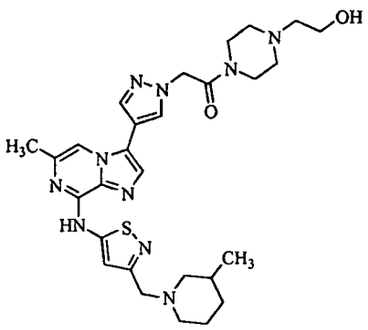


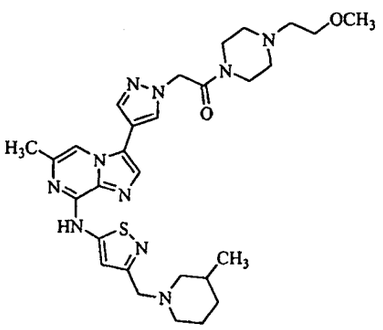


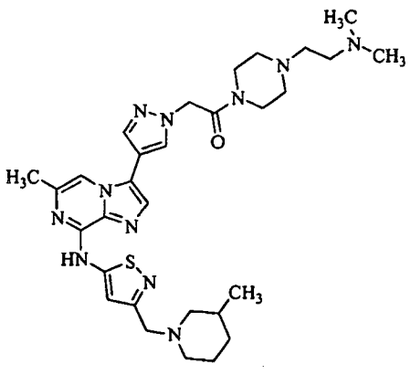


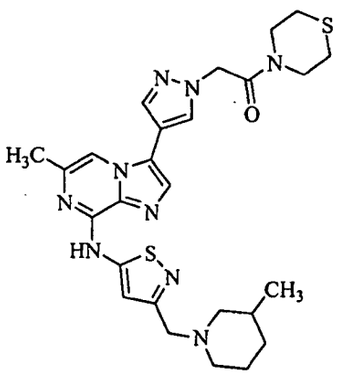


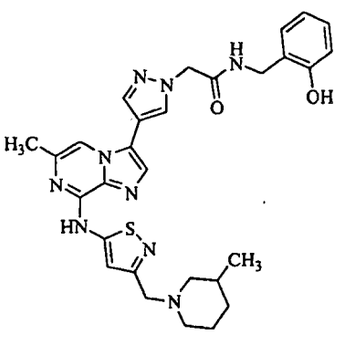


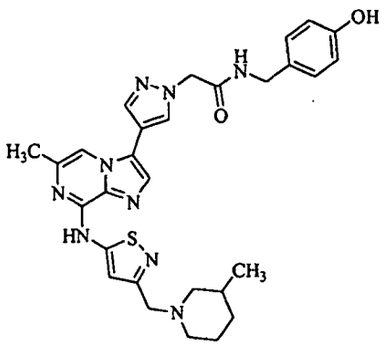
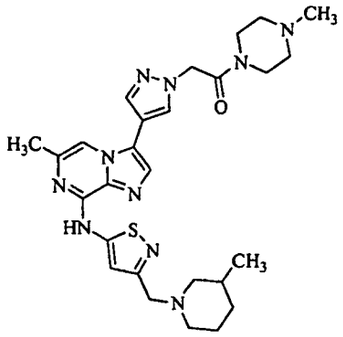
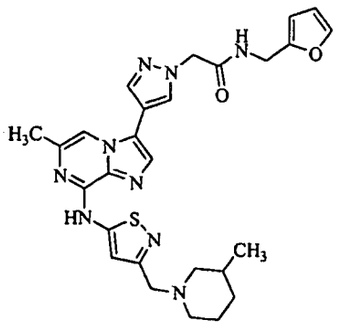
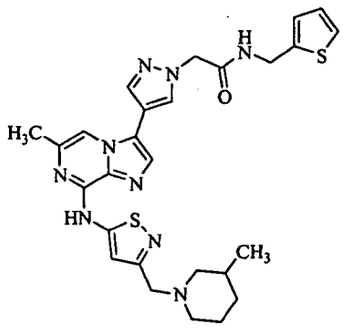
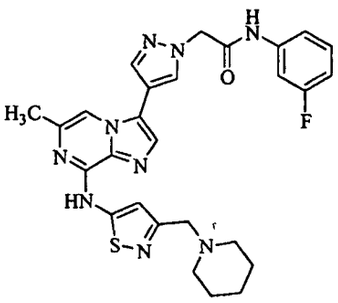
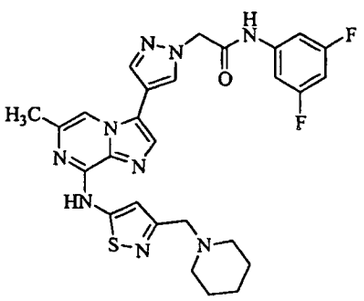
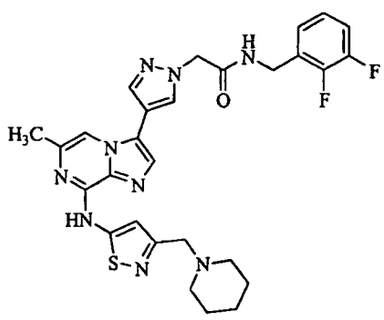
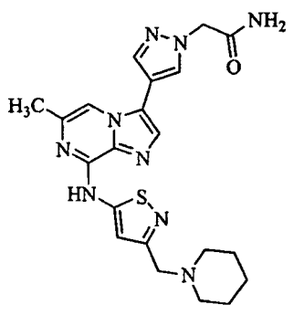
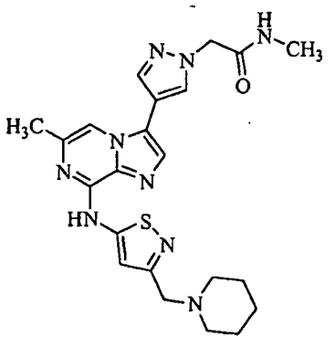
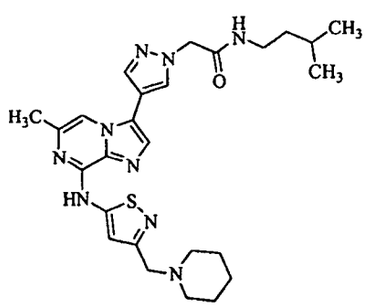
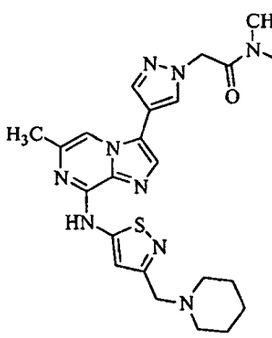
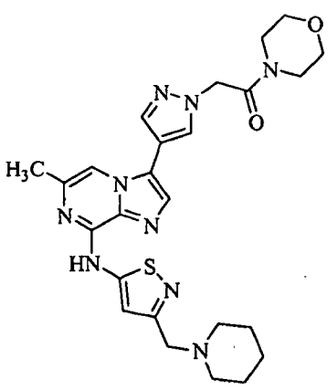


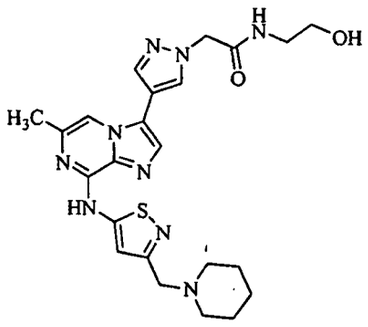


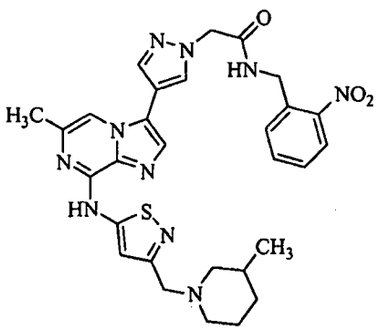


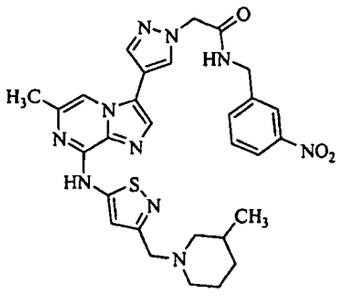


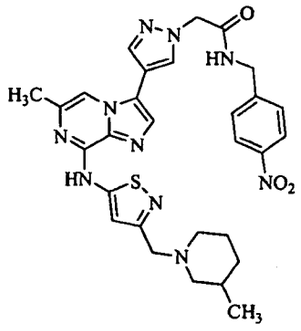


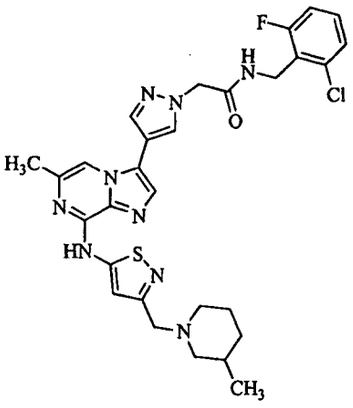













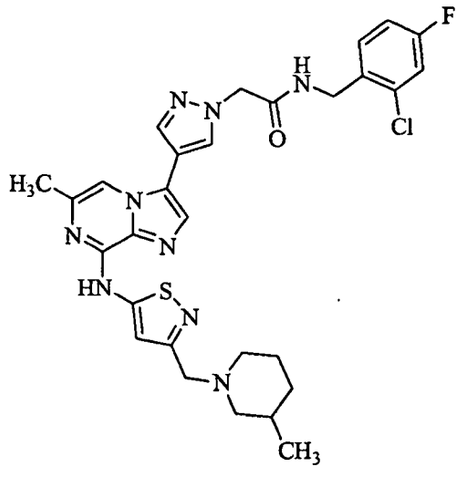


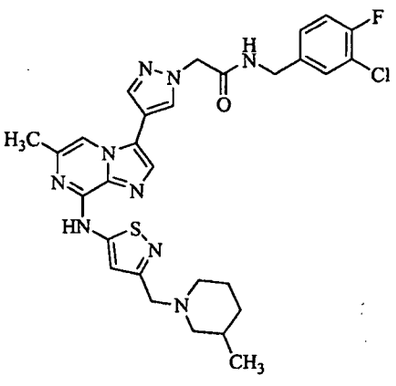


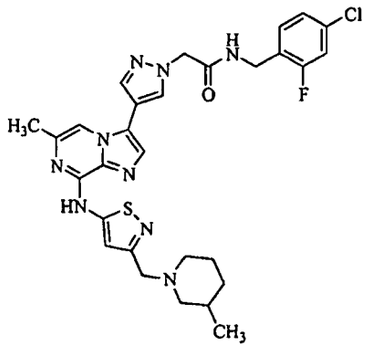


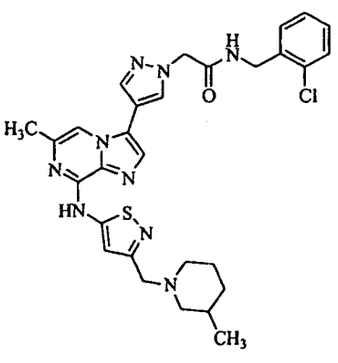


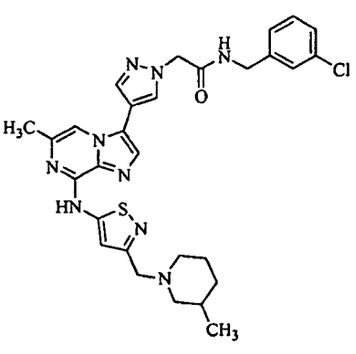


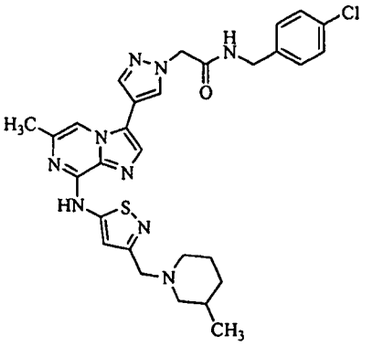


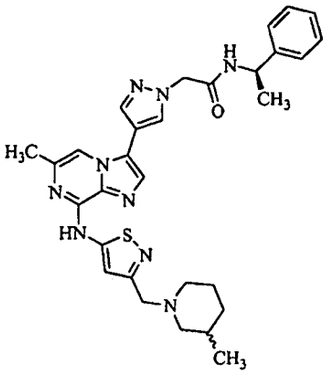


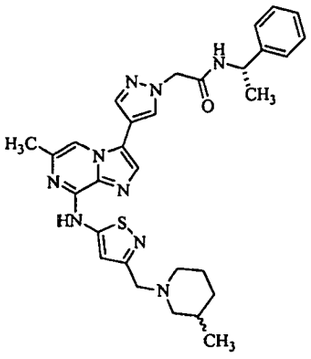


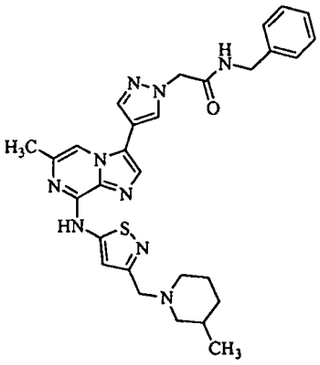


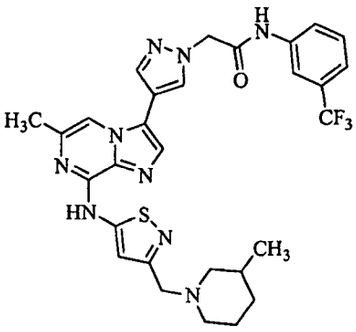


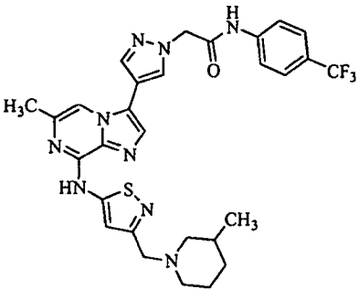


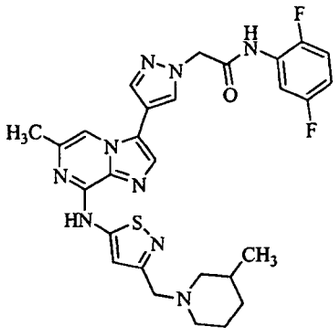


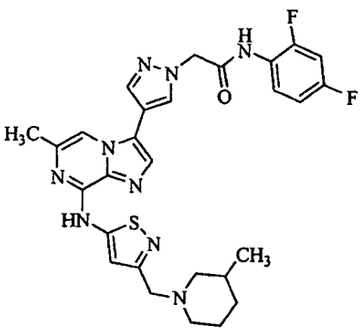


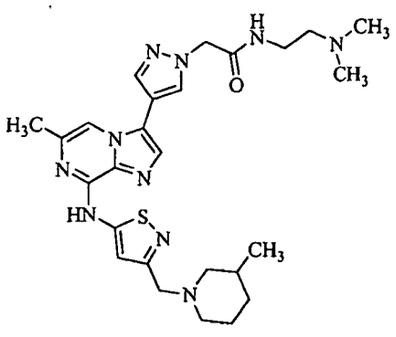


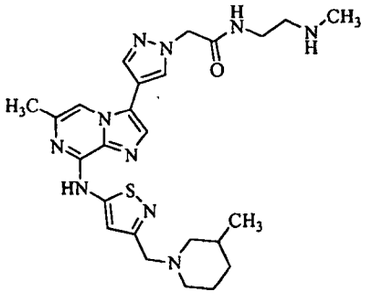


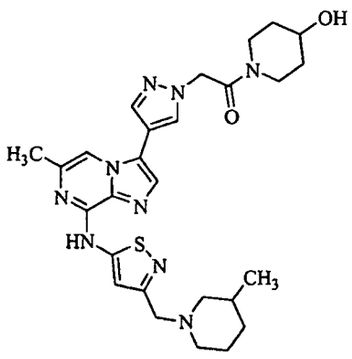


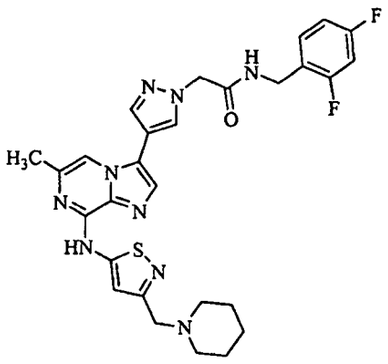


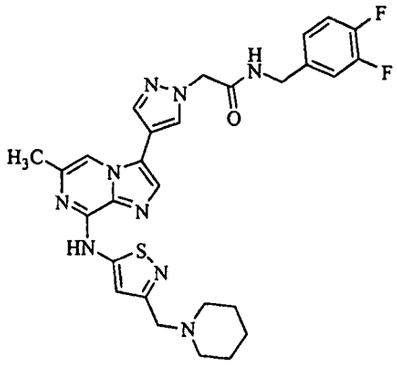


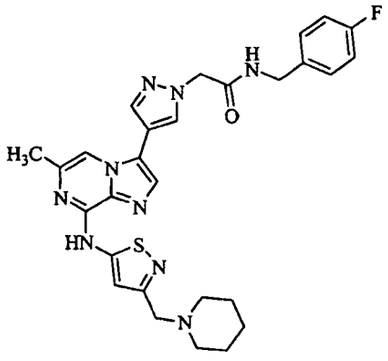


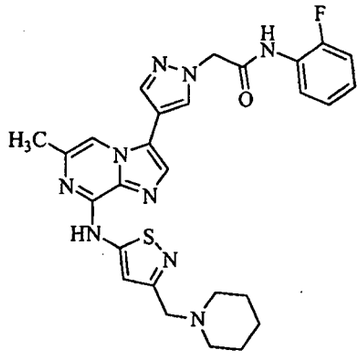


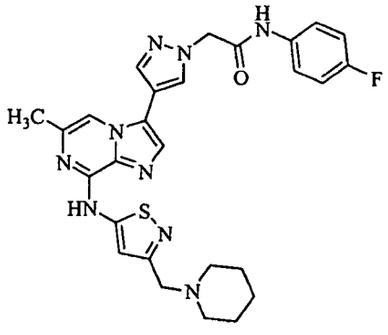


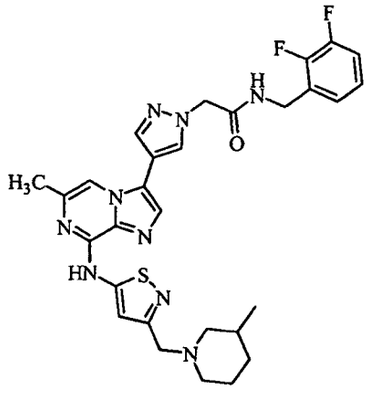


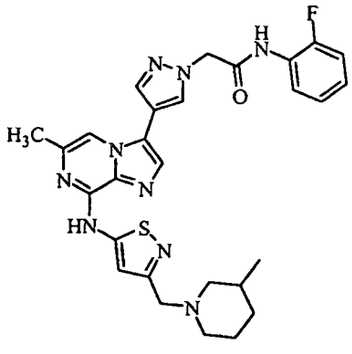


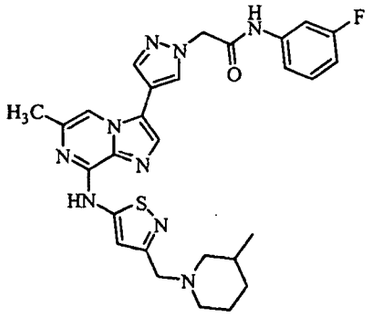


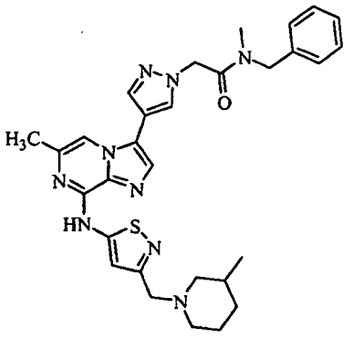


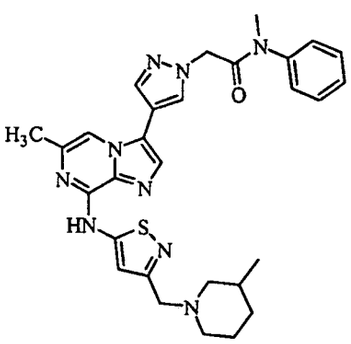


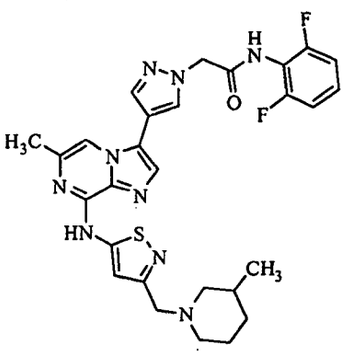


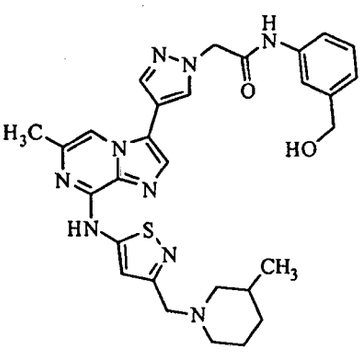


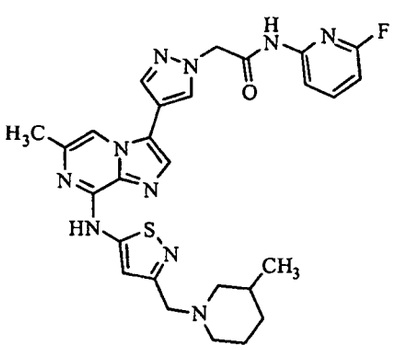


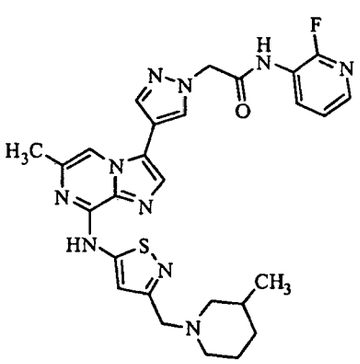


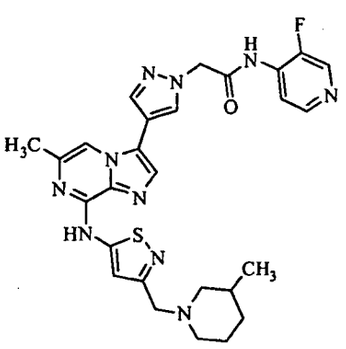


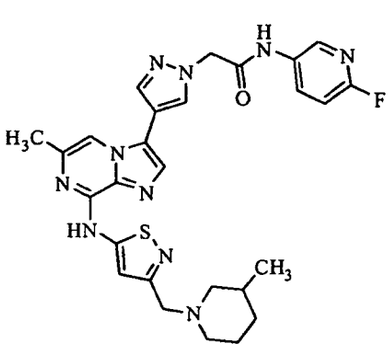


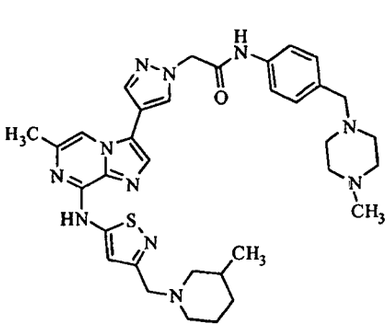


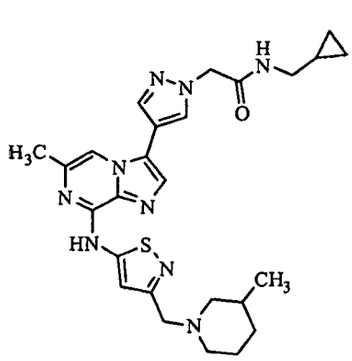


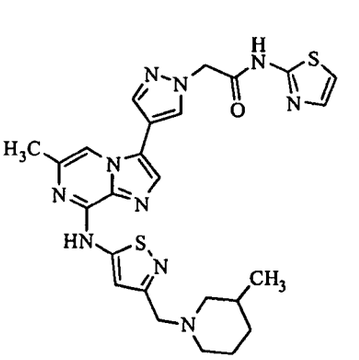


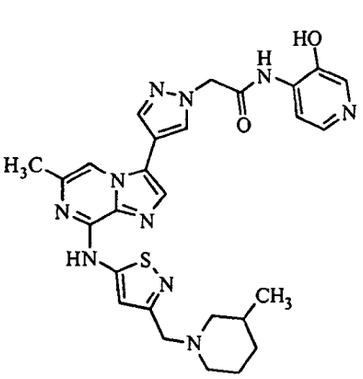


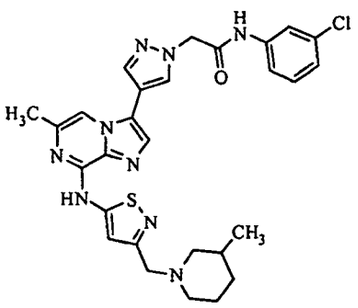


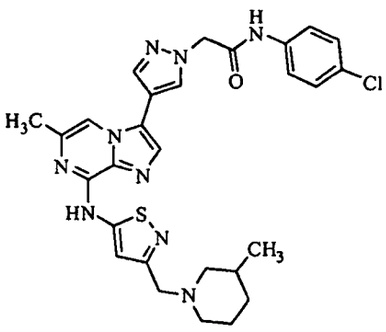


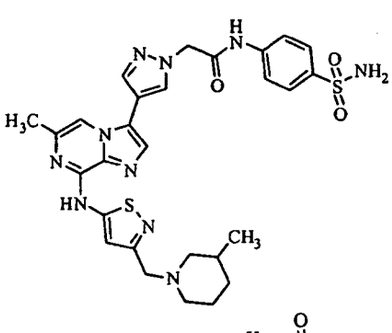


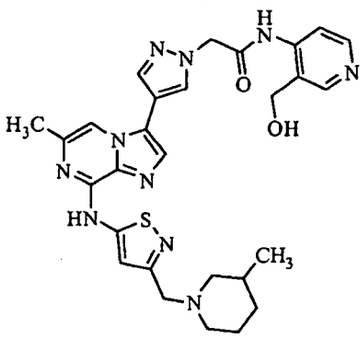


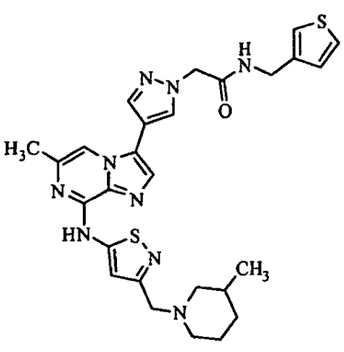


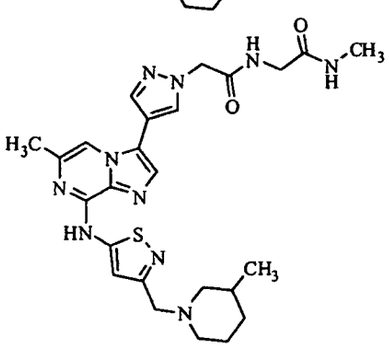


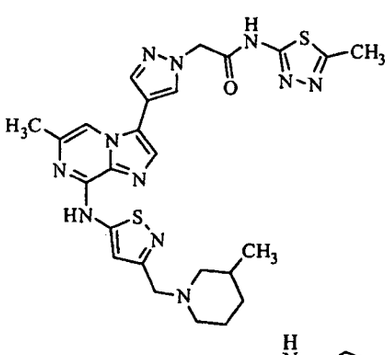


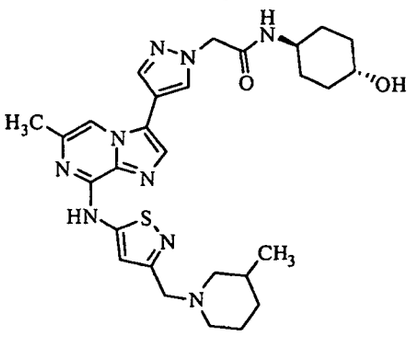


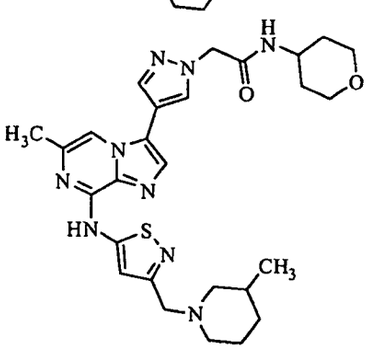


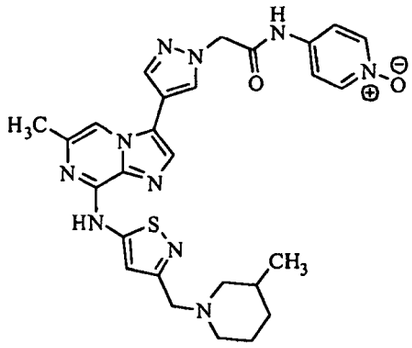


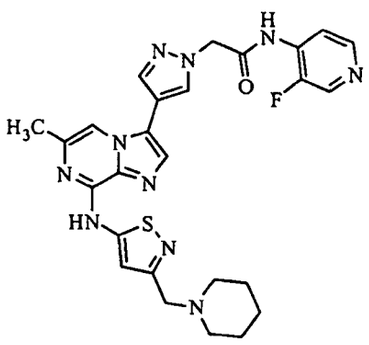


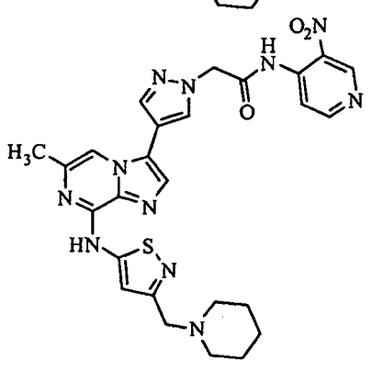


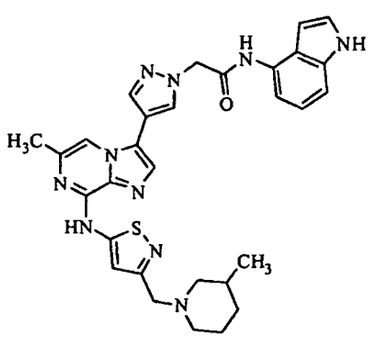


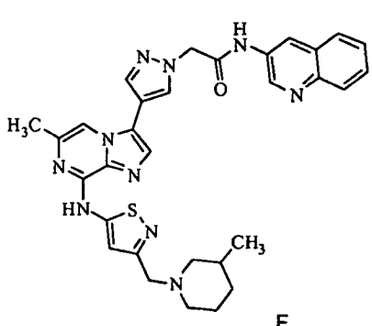


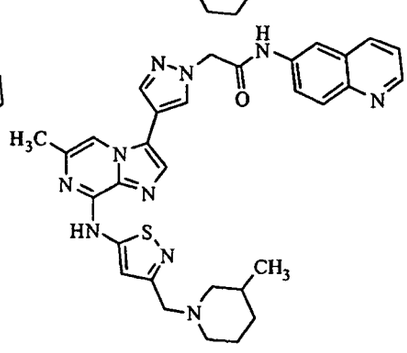


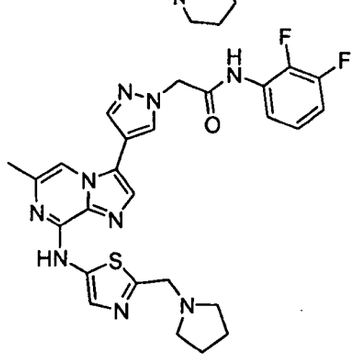


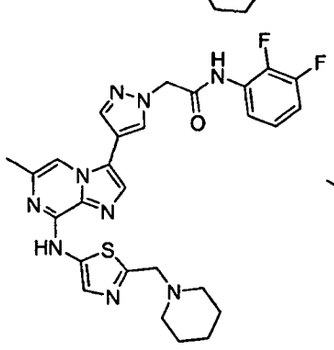


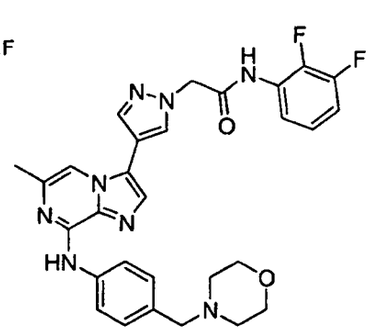


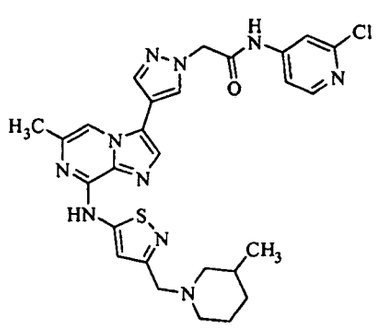


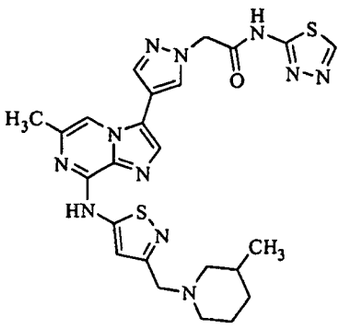


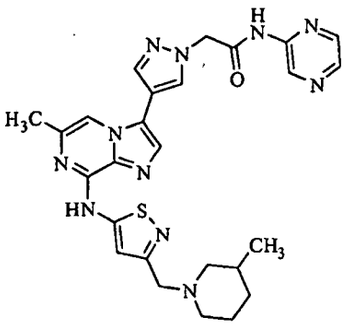


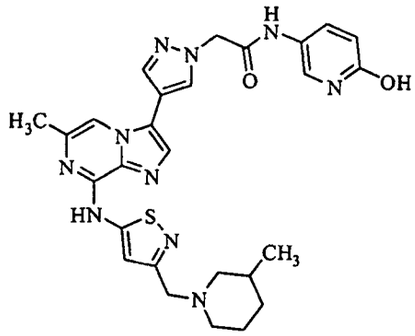


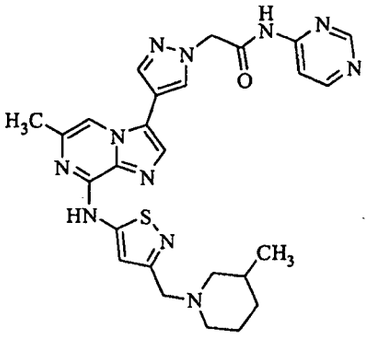


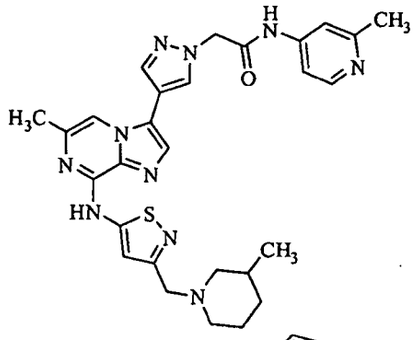


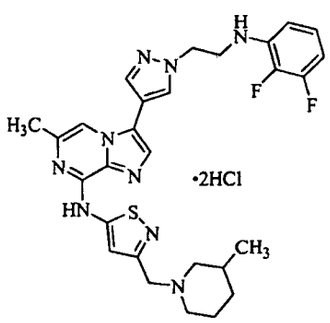


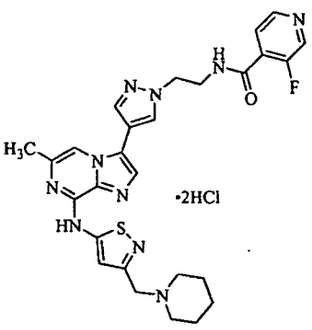


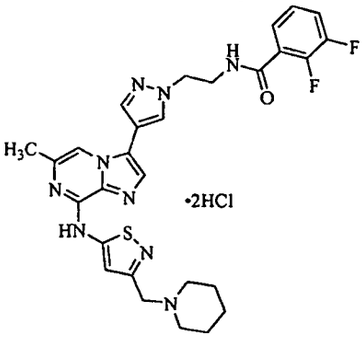


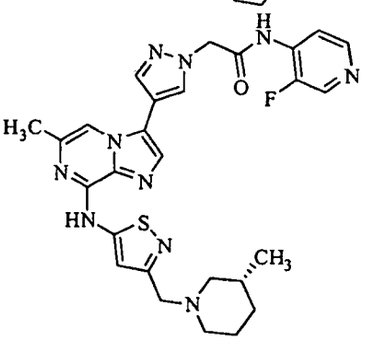


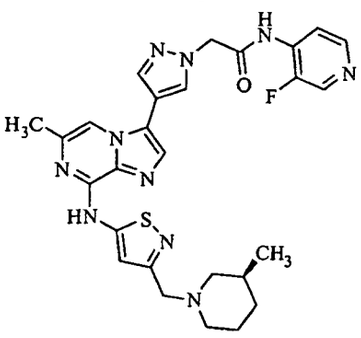


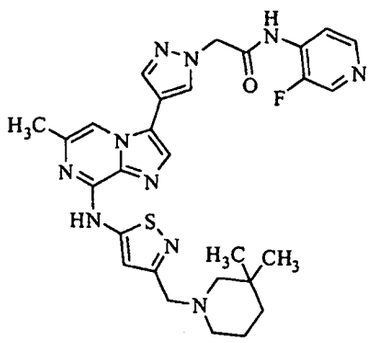

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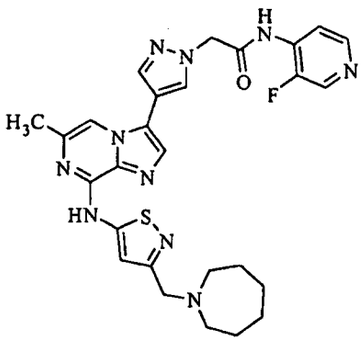

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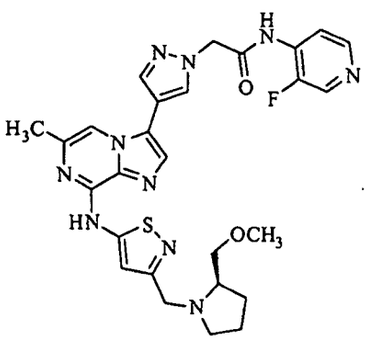

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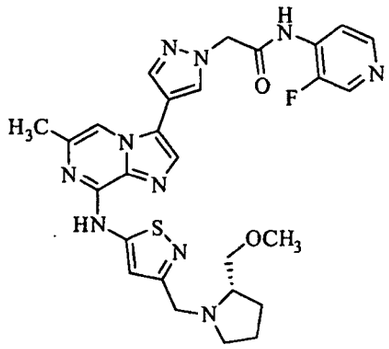


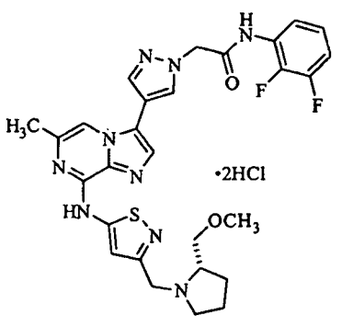


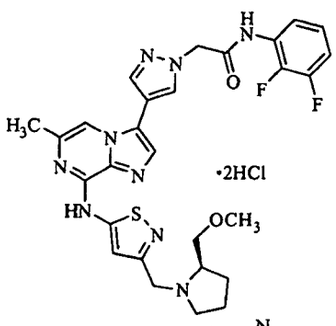


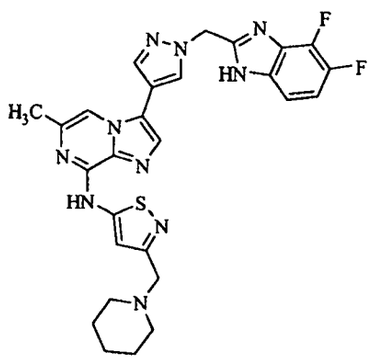


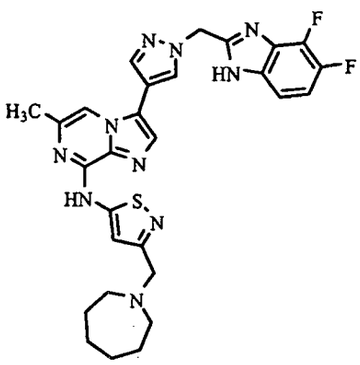


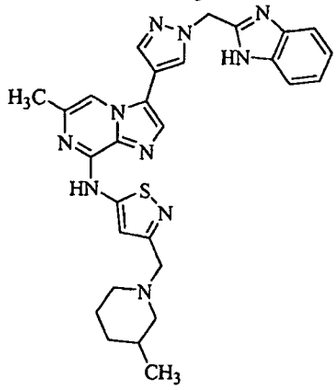


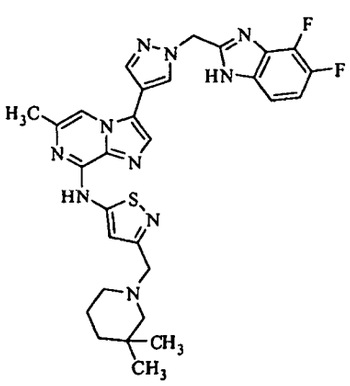

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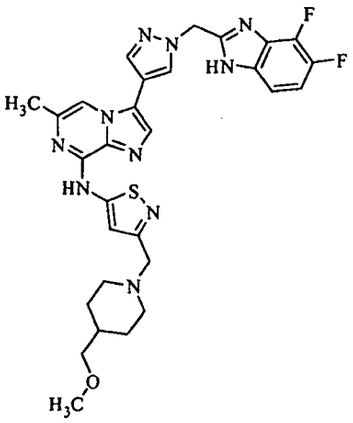

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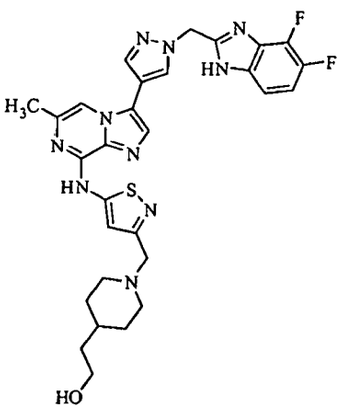


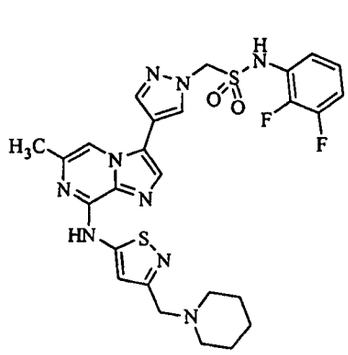
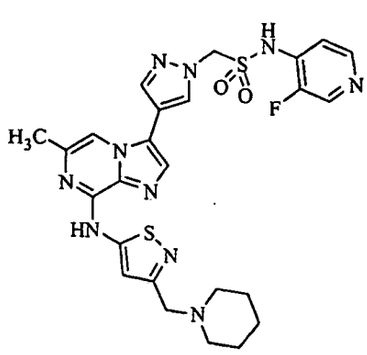
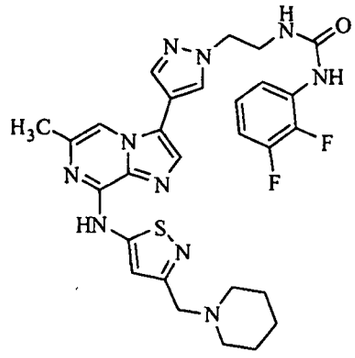
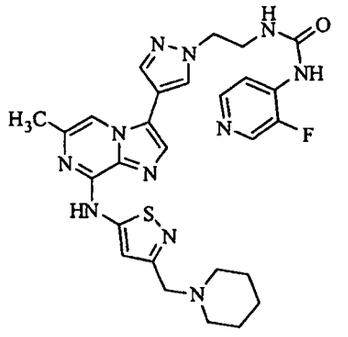
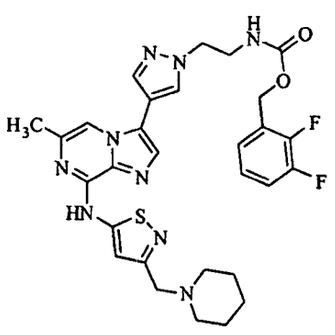
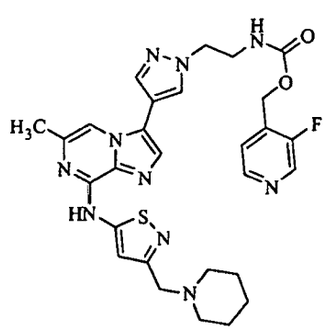
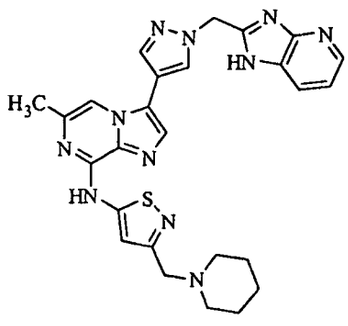
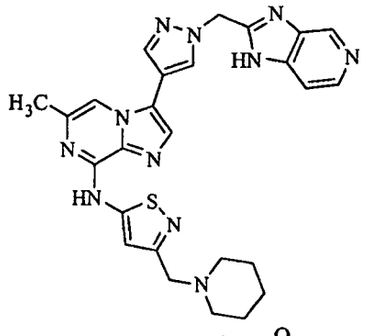
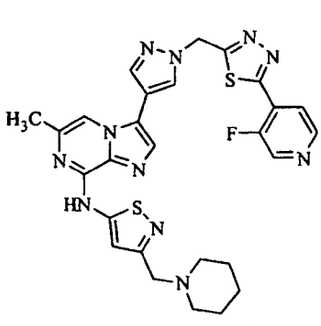
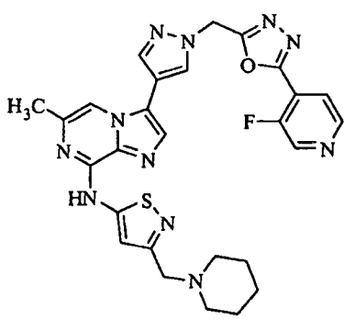
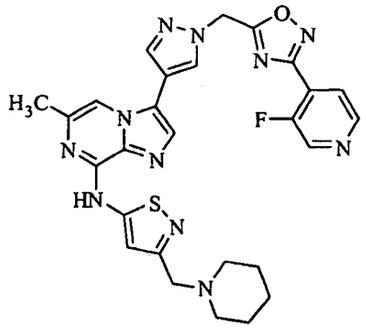
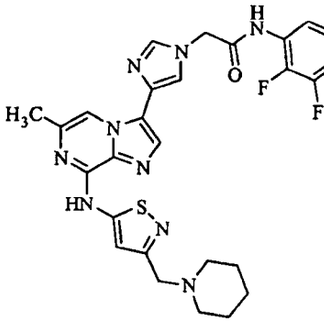


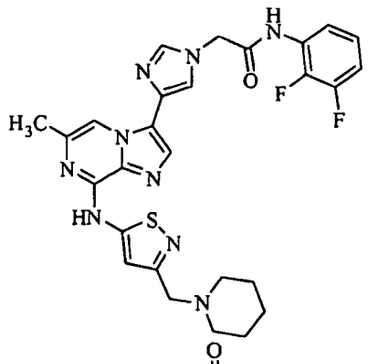


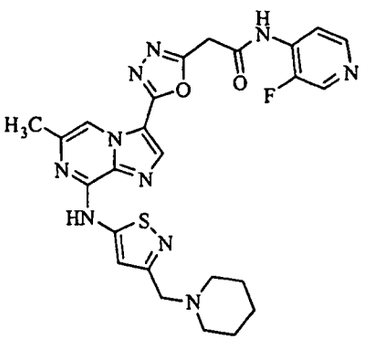


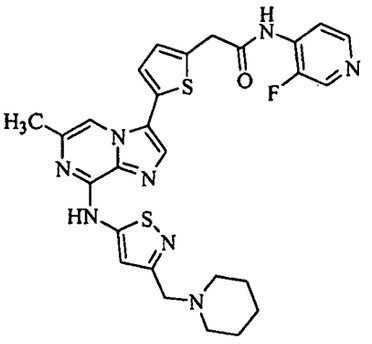


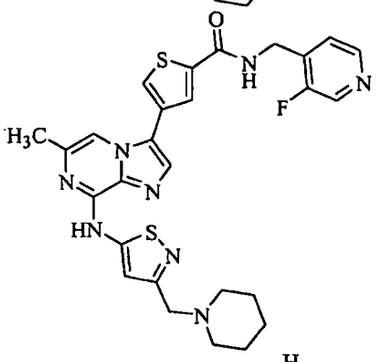


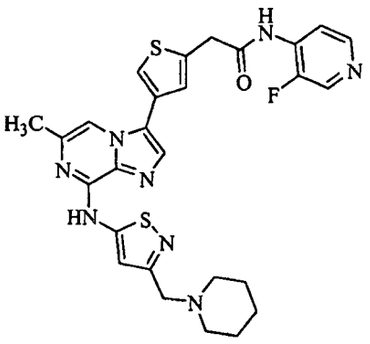













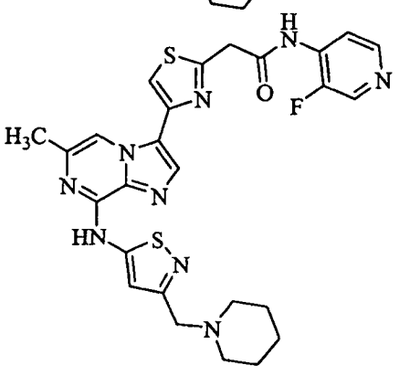


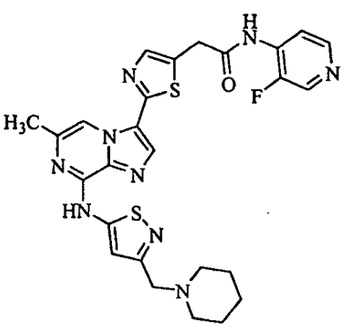


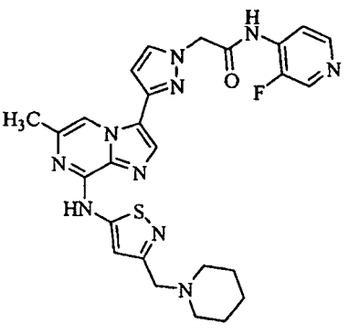


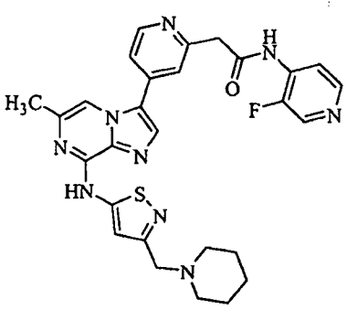


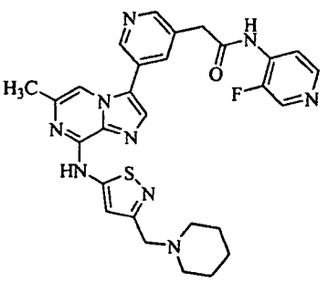


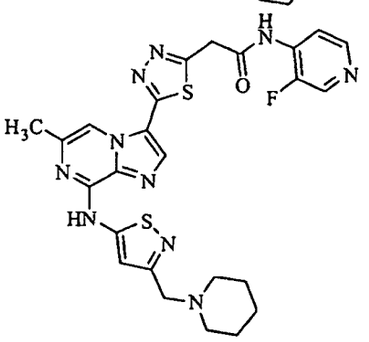


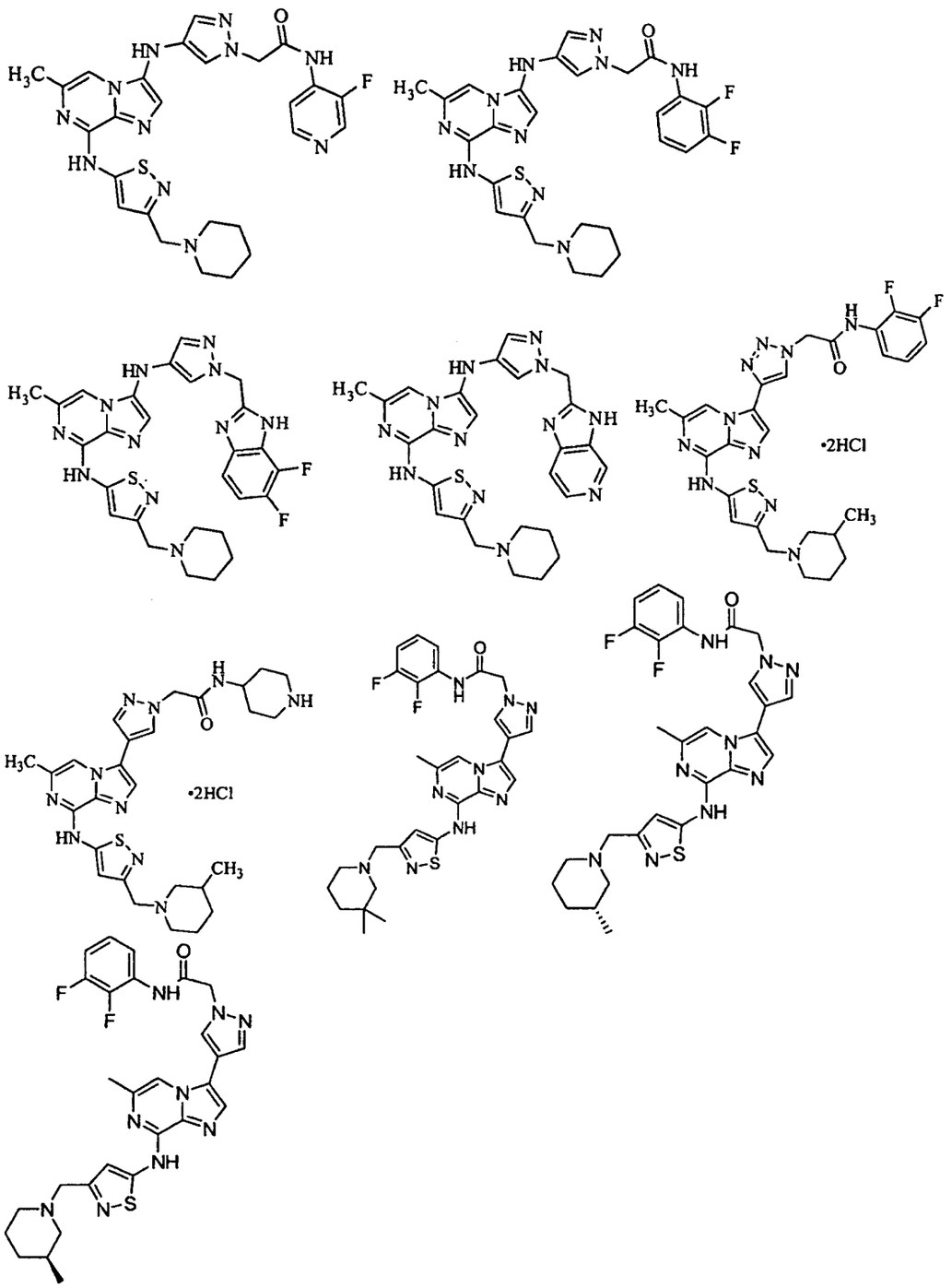






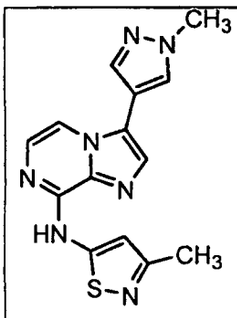
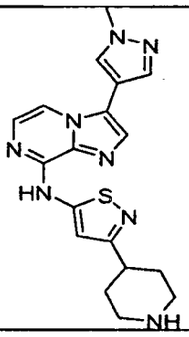
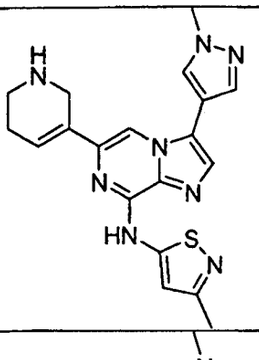
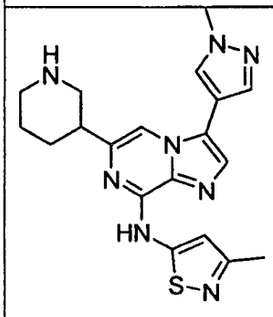
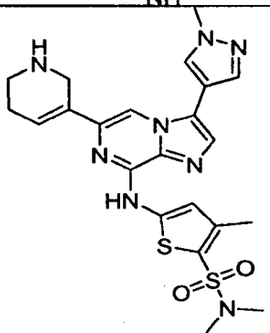
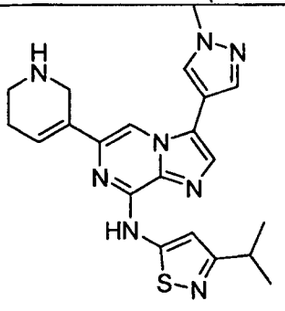
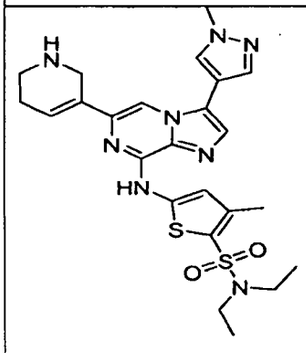
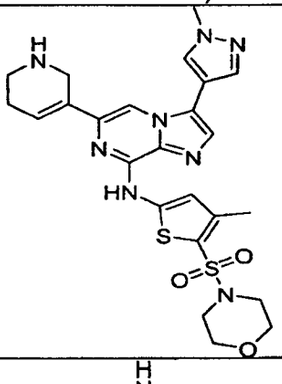
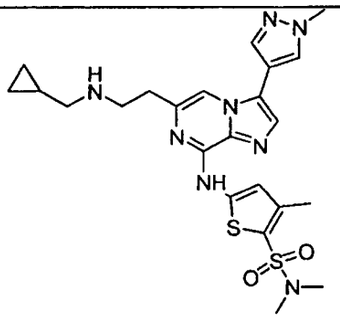
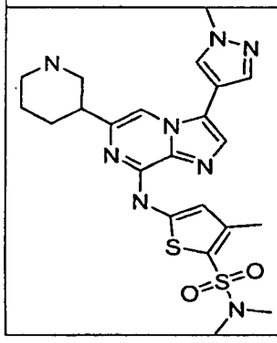
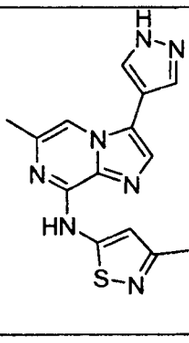


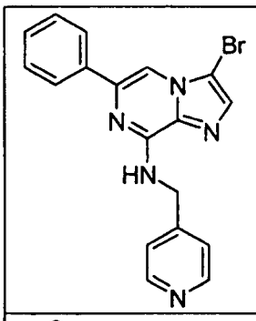
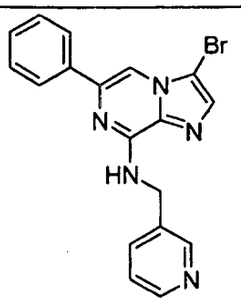
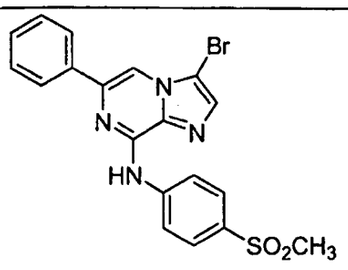
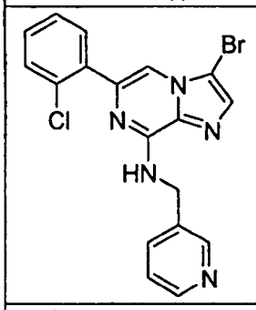
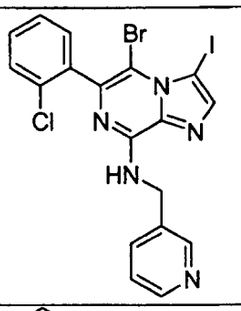
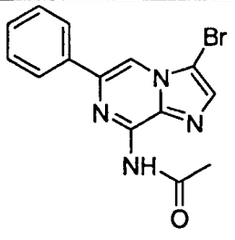
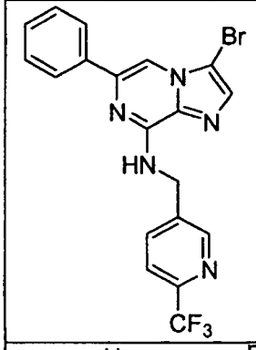
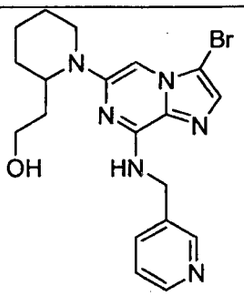
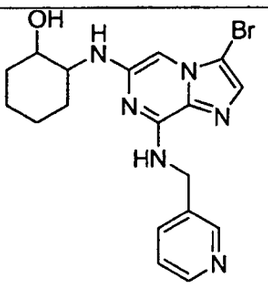
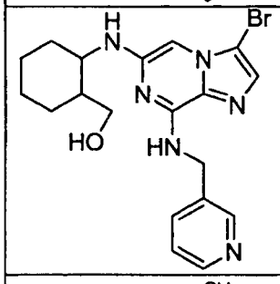
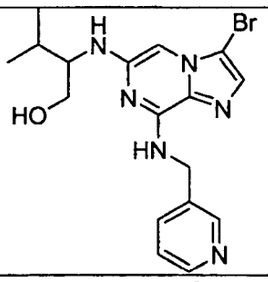
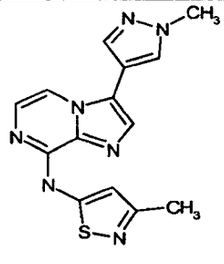
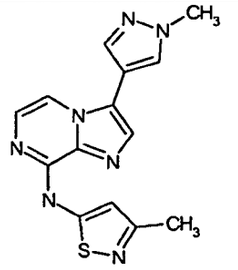
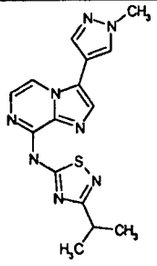




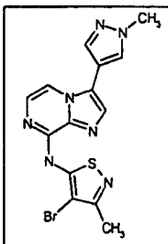
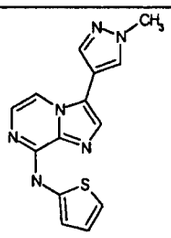
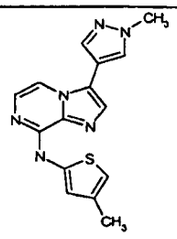
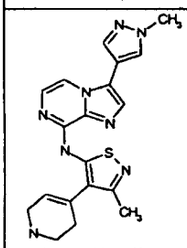
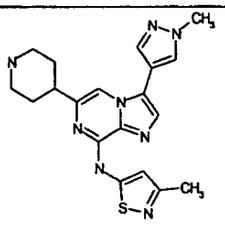
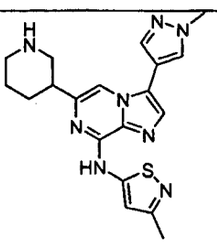
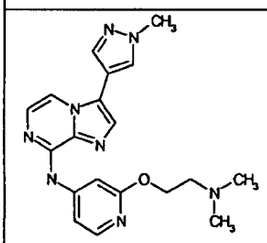
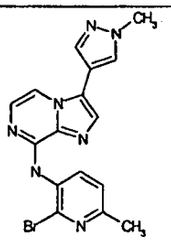
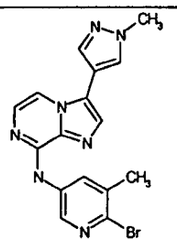
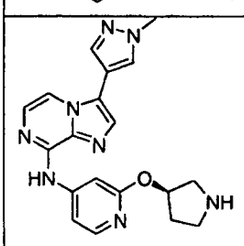
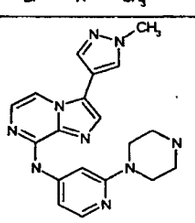
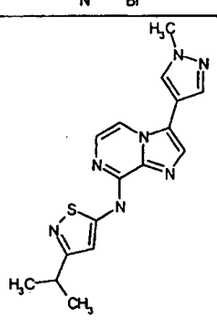
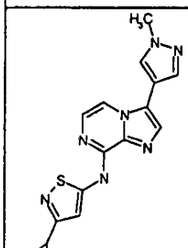
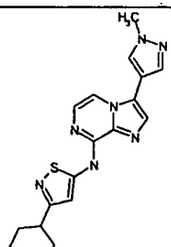
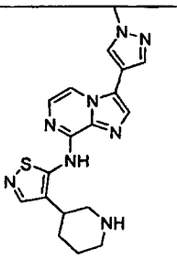
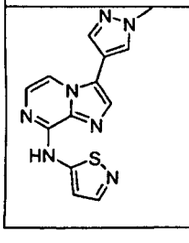
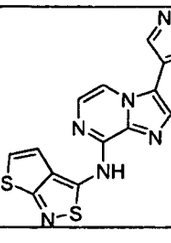
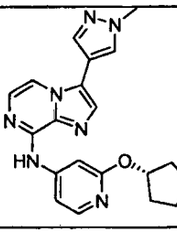
or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof.

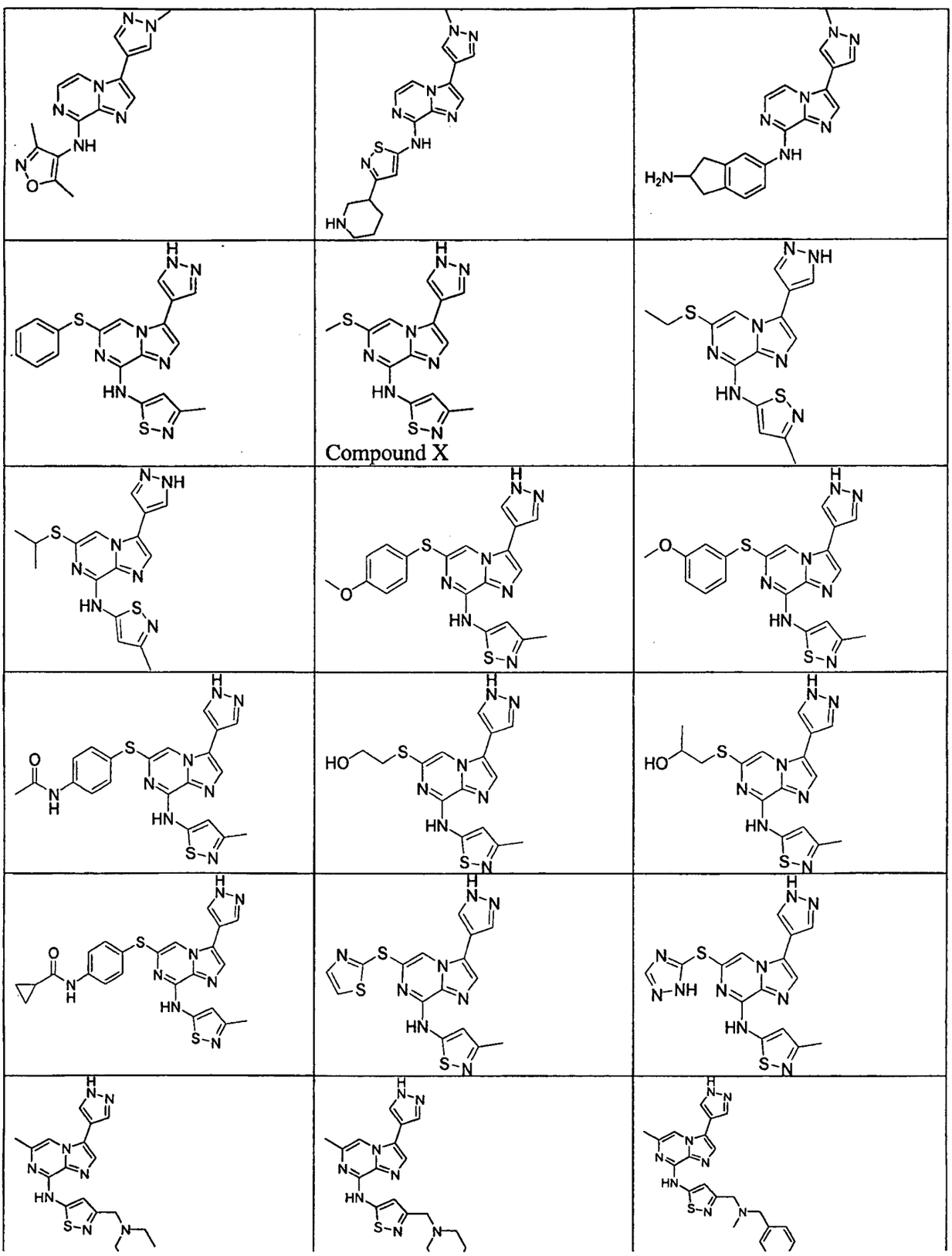
15. The method of claim 2, wherein said aurora kinase inhibitors represented by Formulas E-K are selected from the group consisting of:

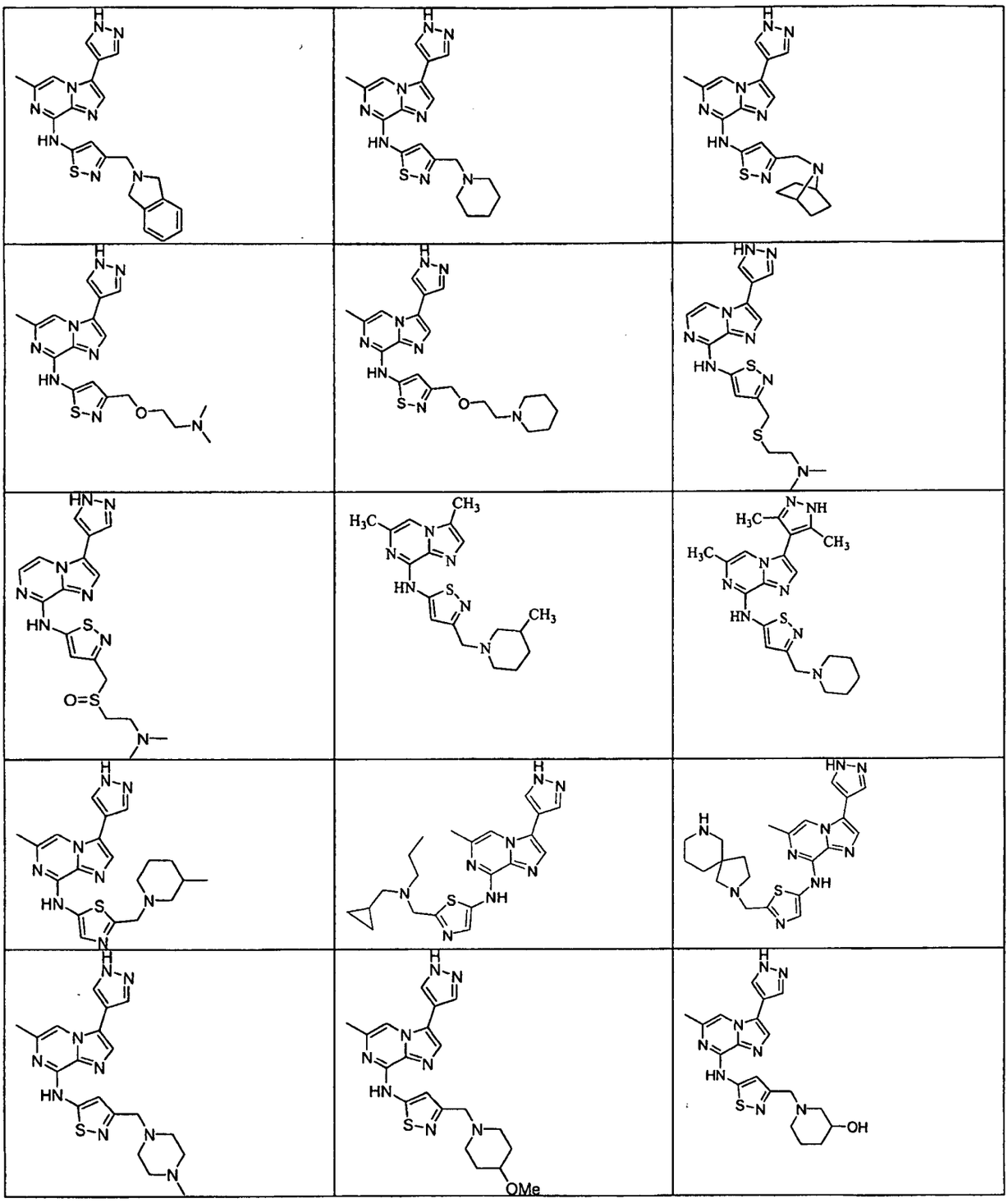
		
		
		
		

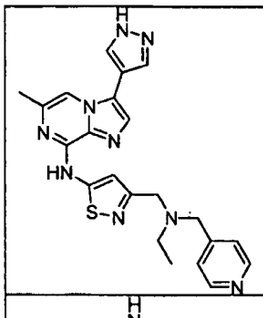
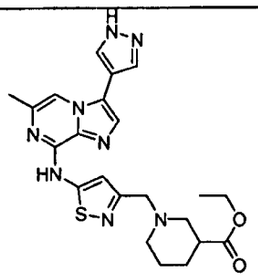
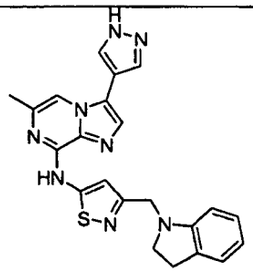
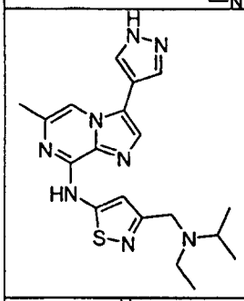
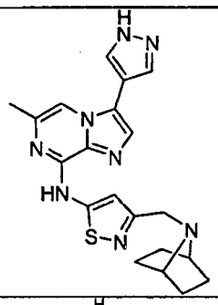
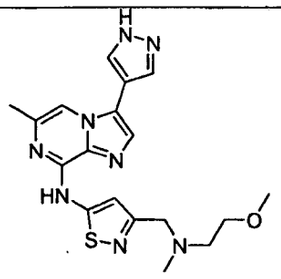
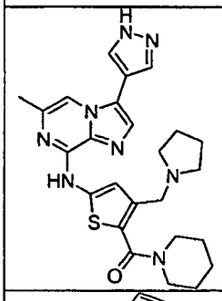
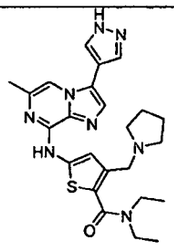
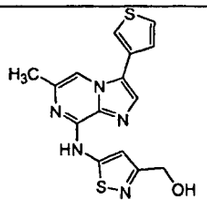
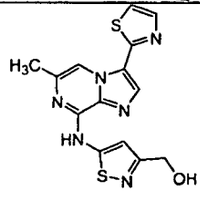
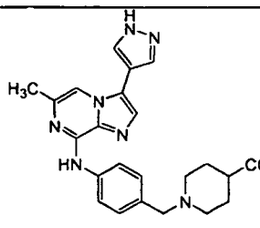
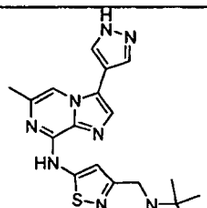
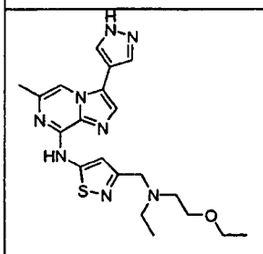
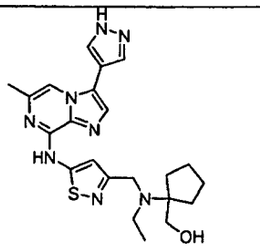
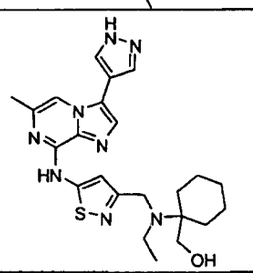
		
		
		
		
		

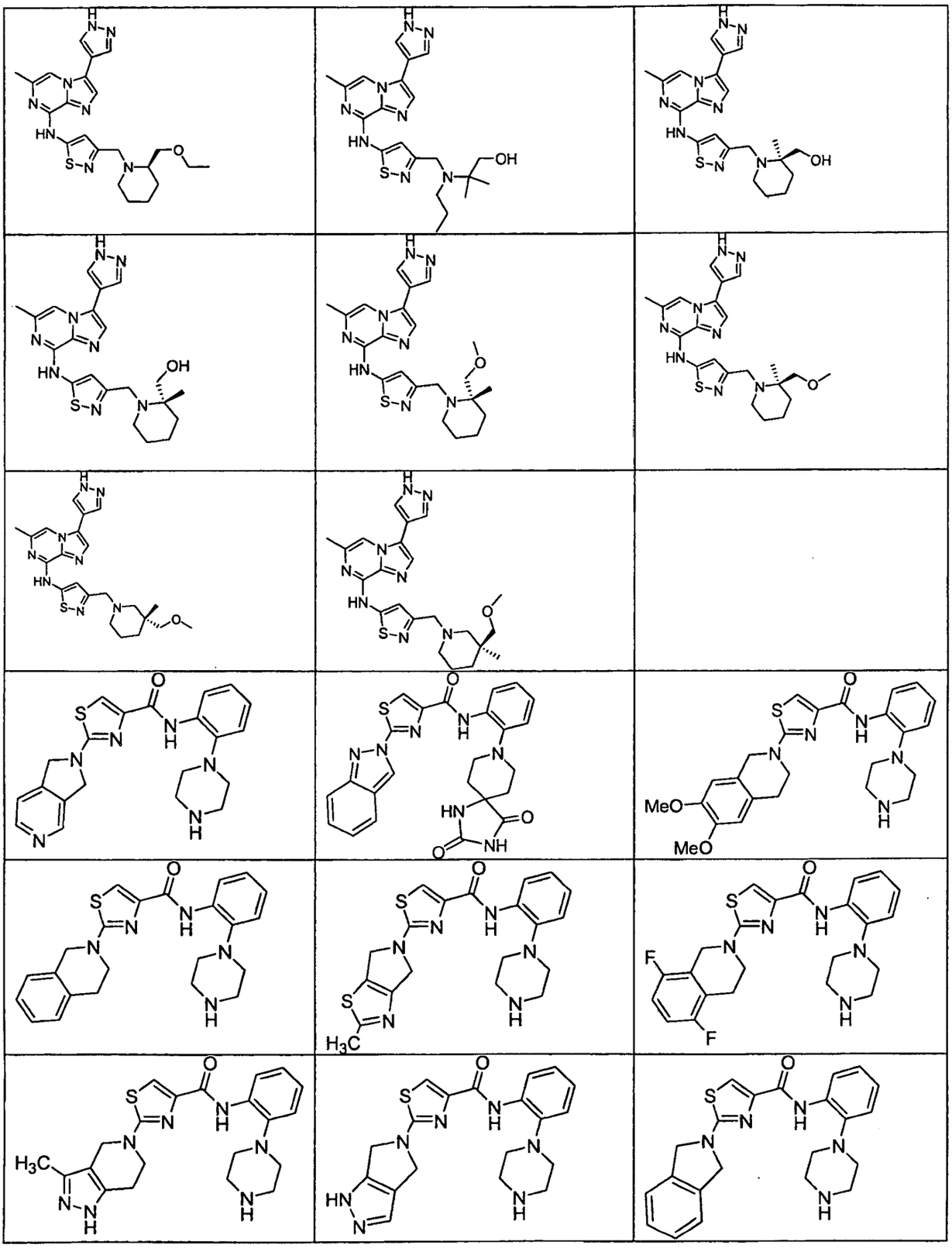
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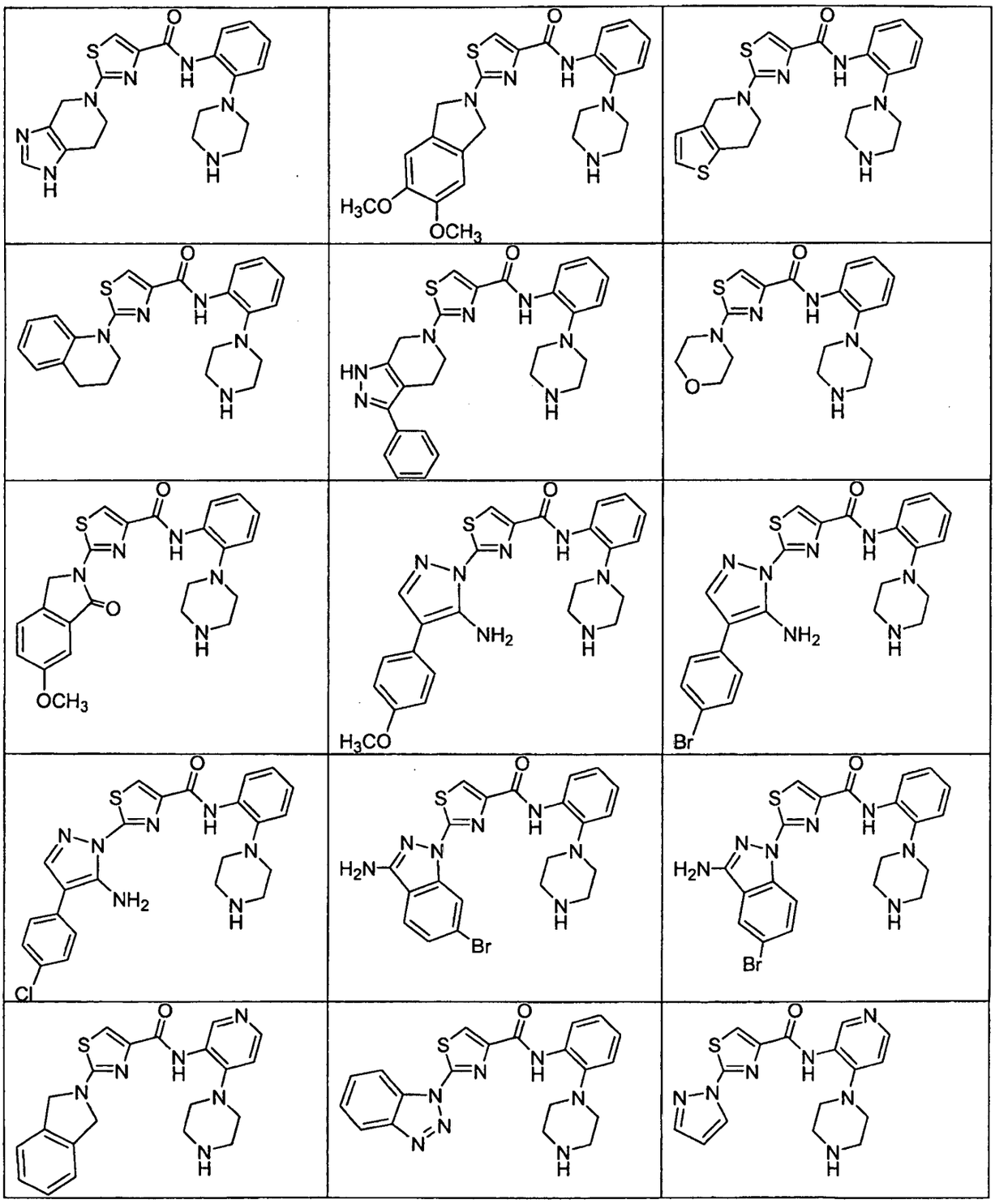
		
		
		
		
		
		

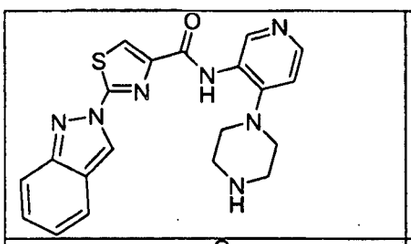
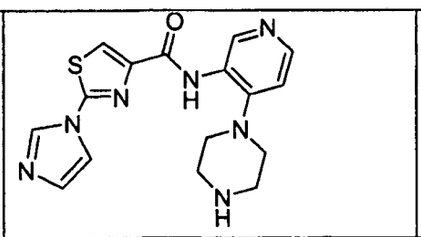
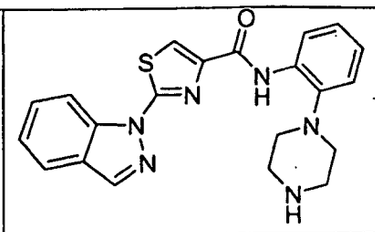
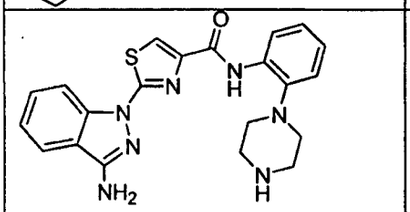
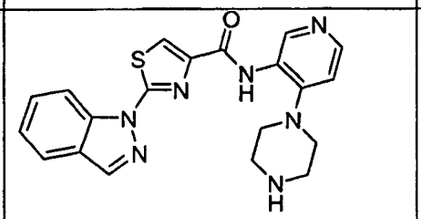
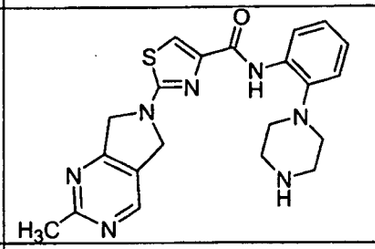
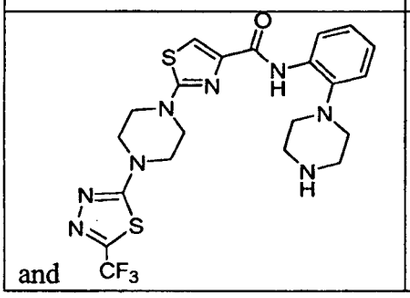

Compound X

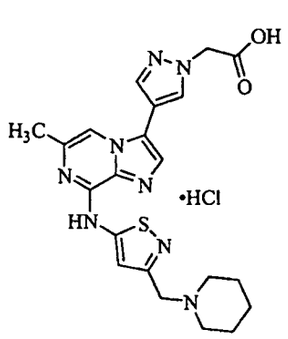


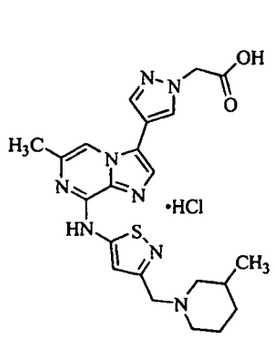
		
		
		
		
		

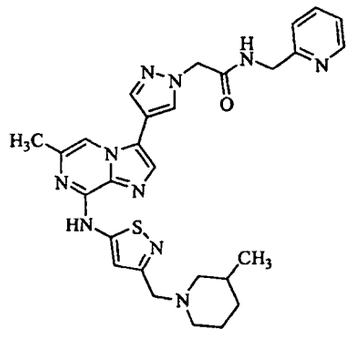


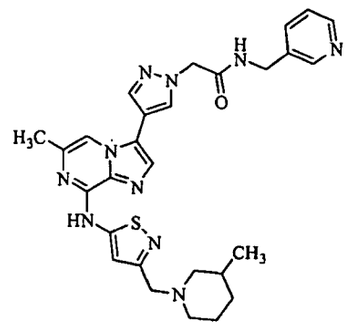


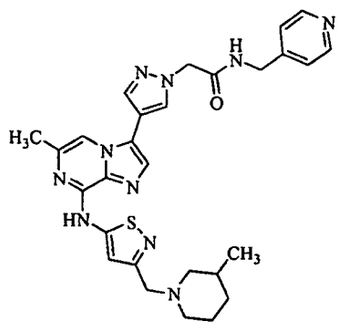
		
		
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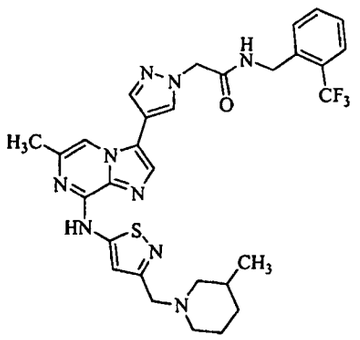


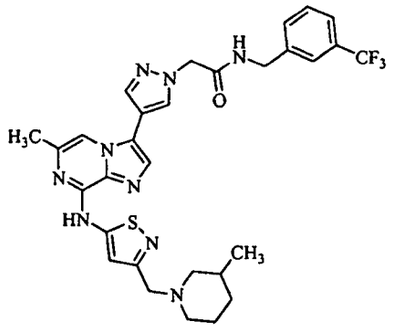


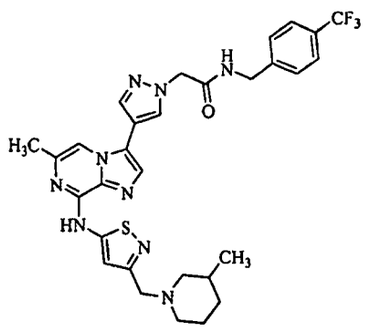


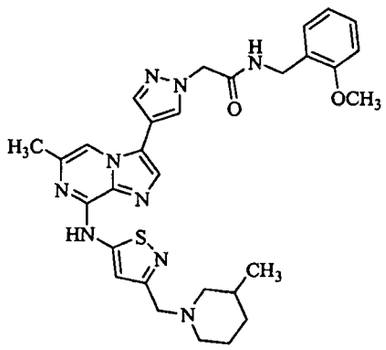


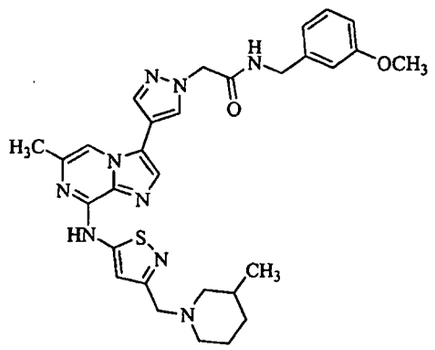


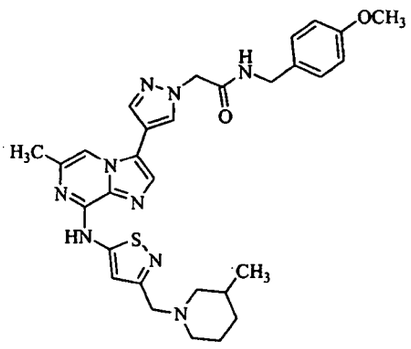


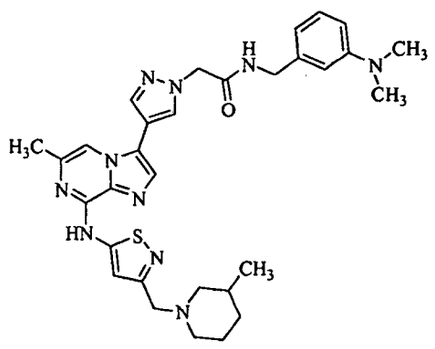


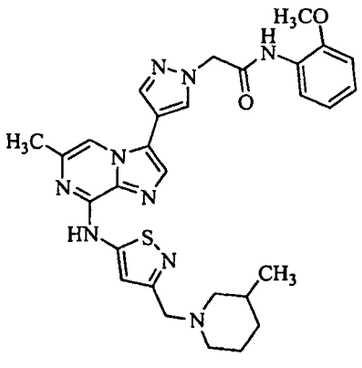


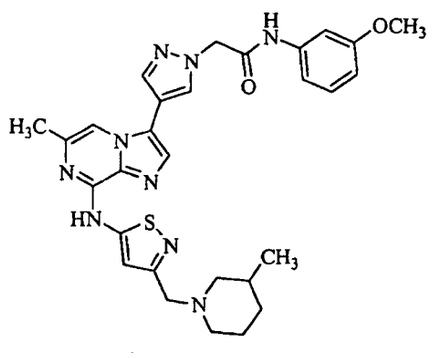


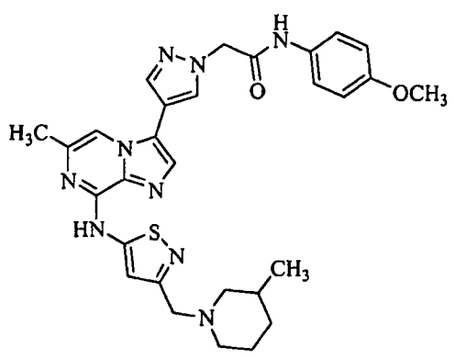


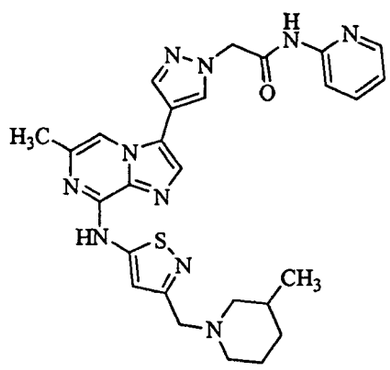


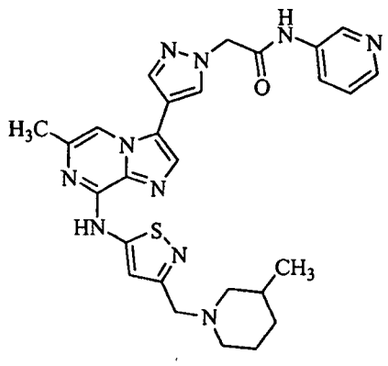


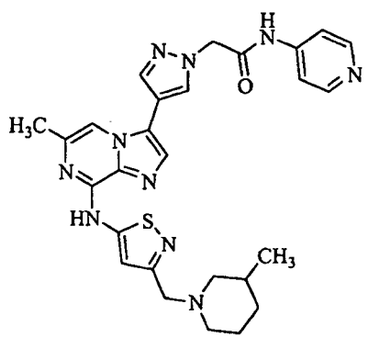


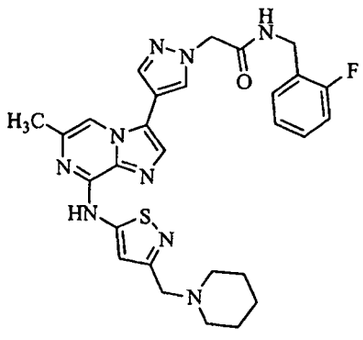


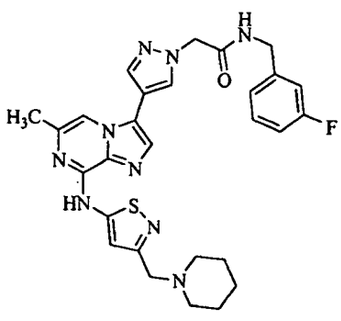


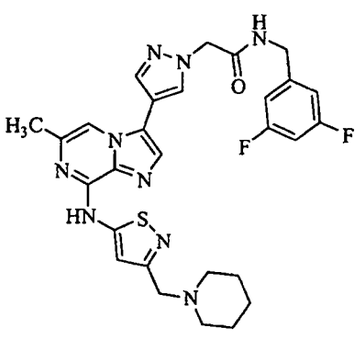


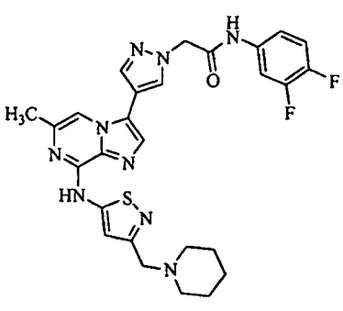


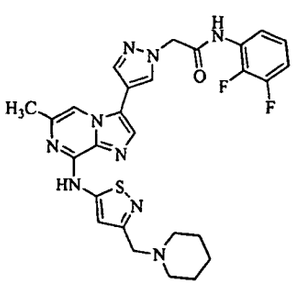


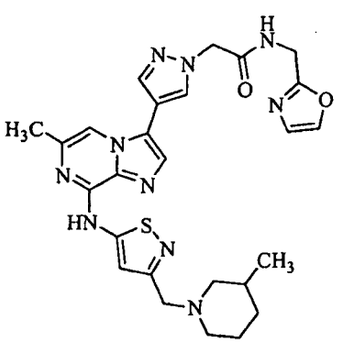


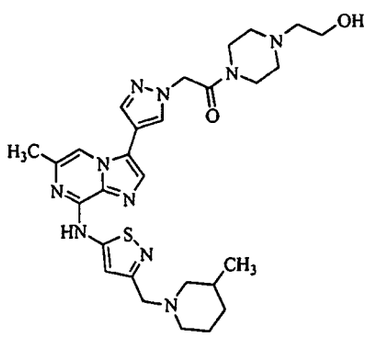


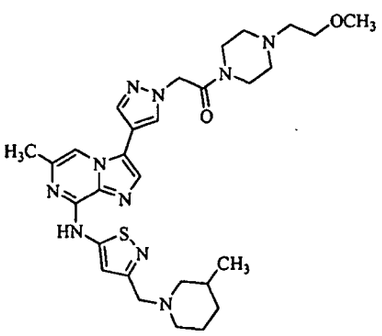


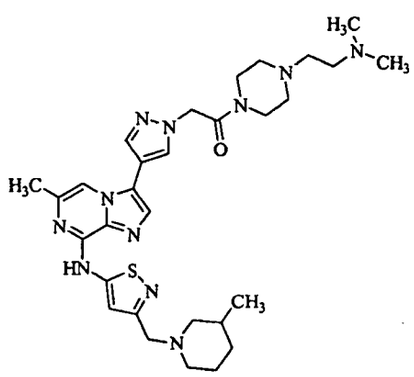


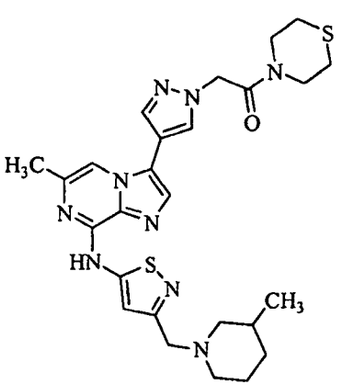


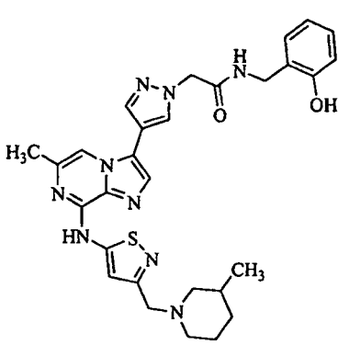


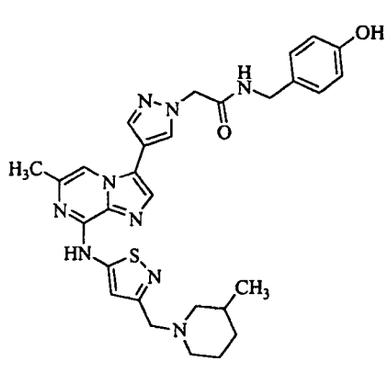


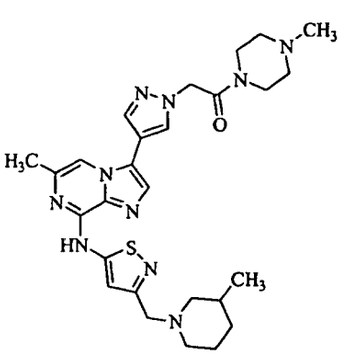


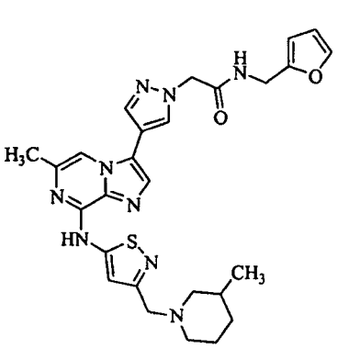


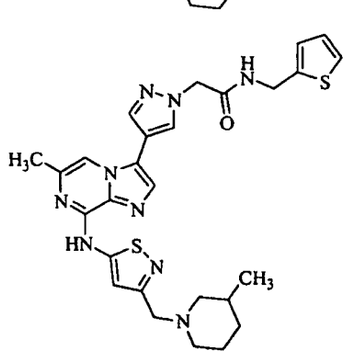


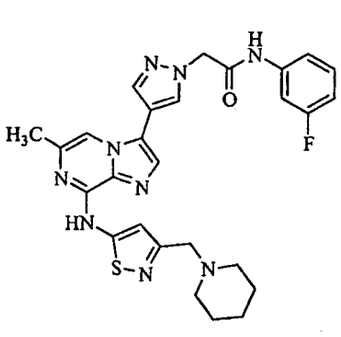


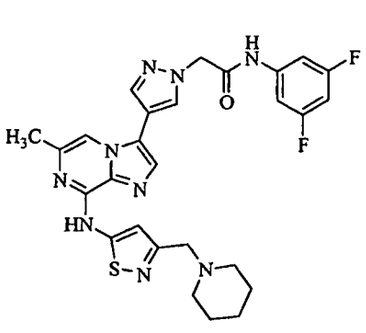


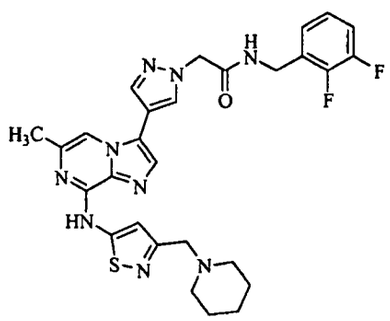


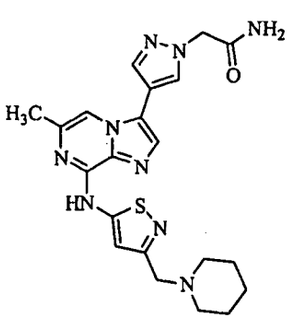


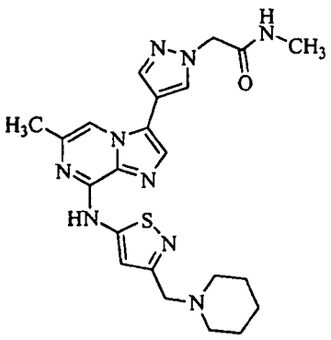


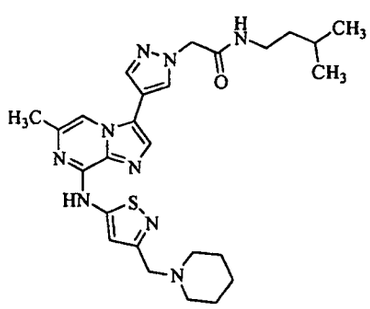


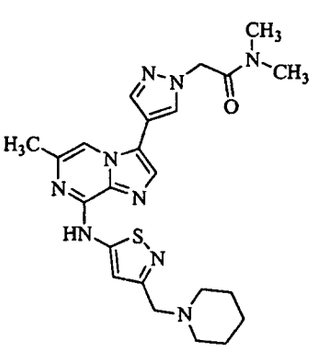


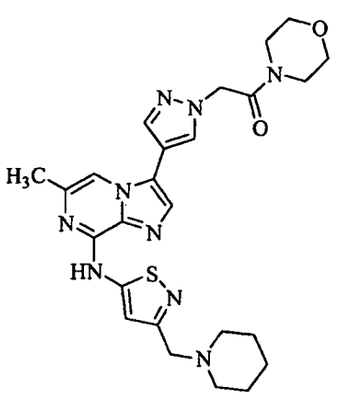


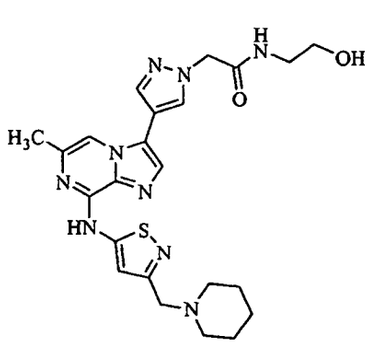


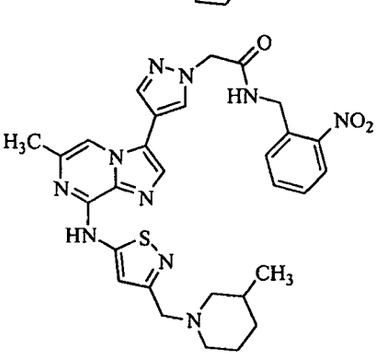


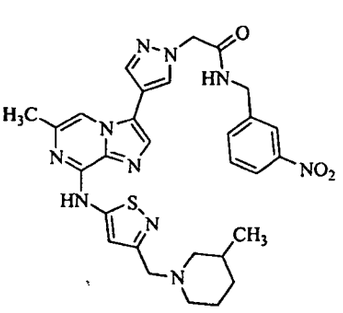


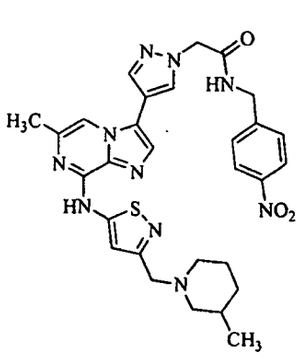


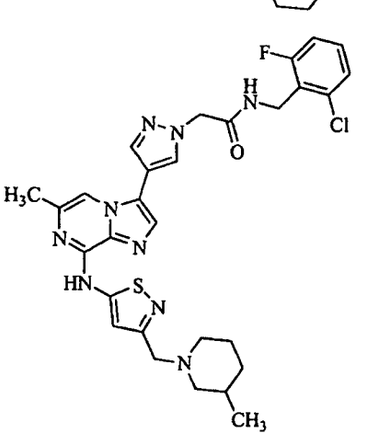


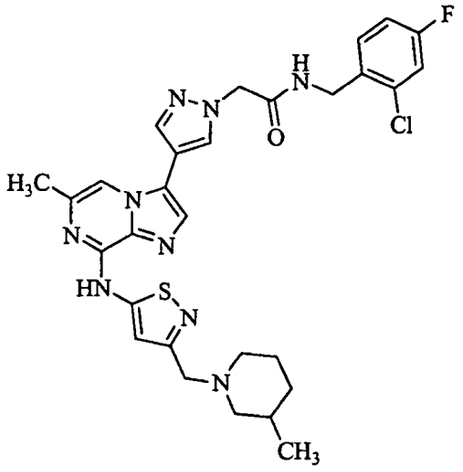


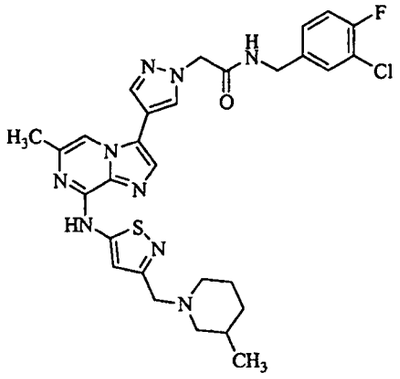


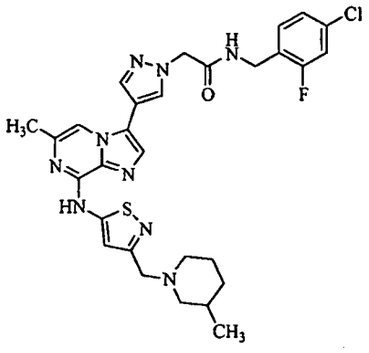


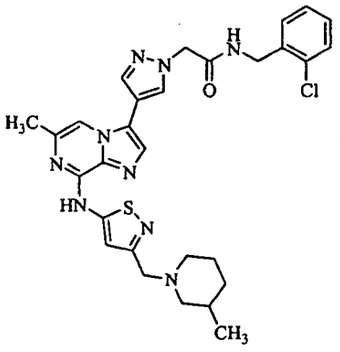


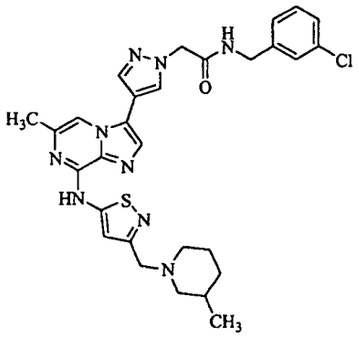


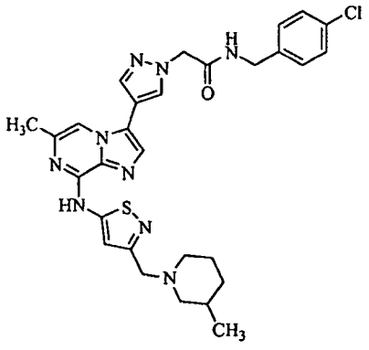


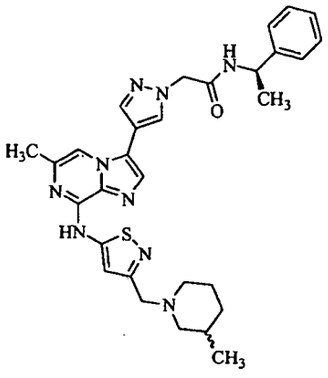


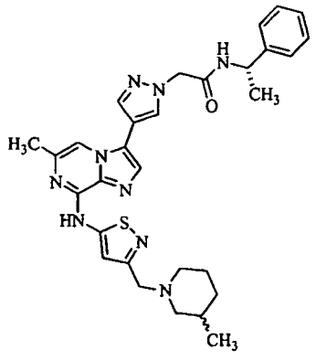


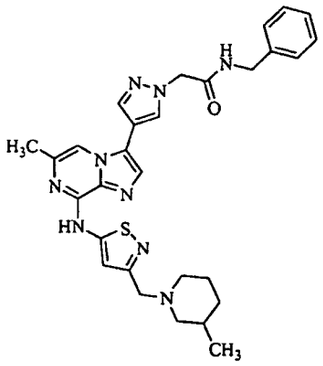


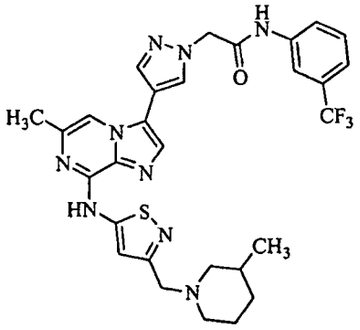


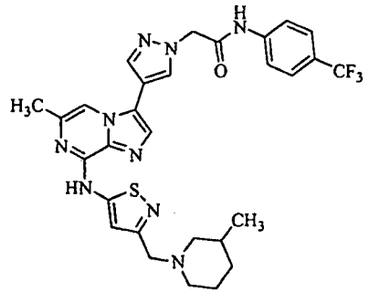


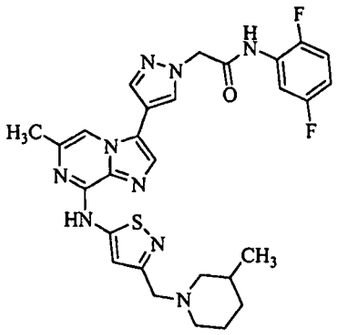


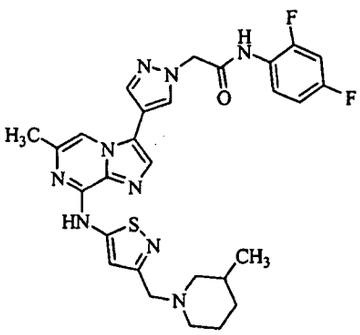


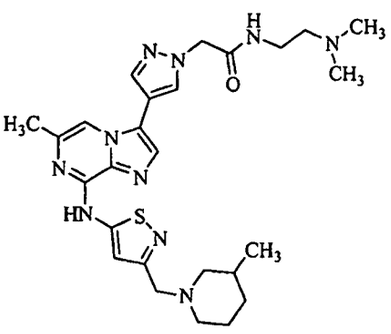


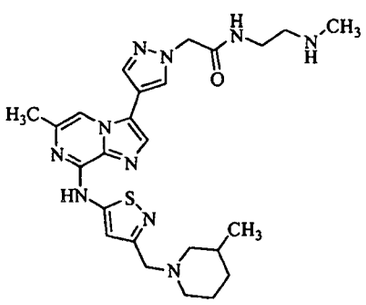


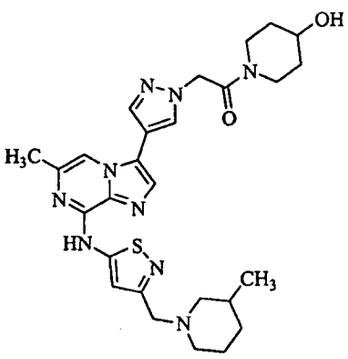


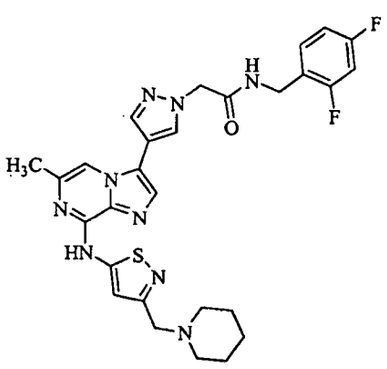


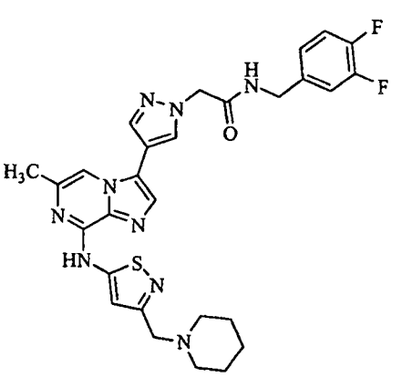


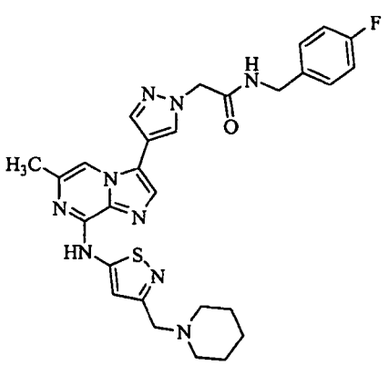


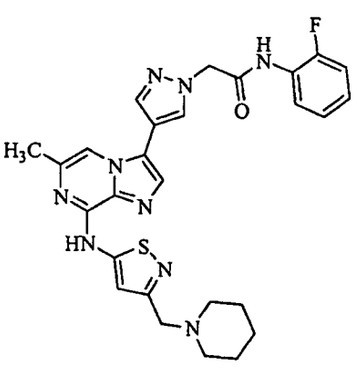


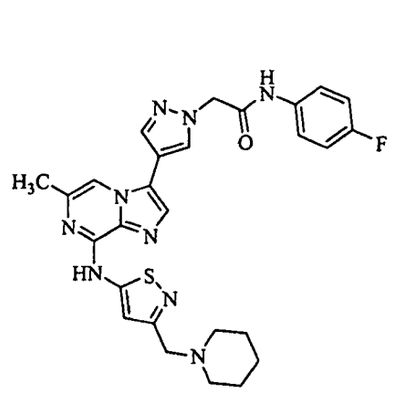


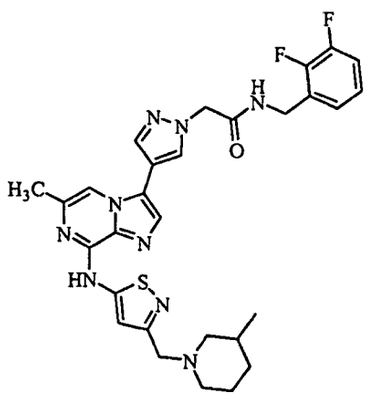


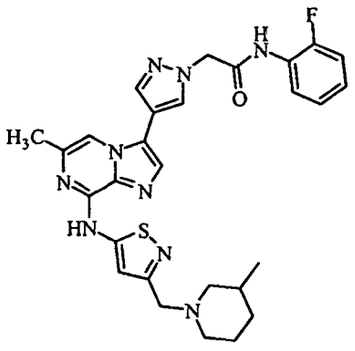


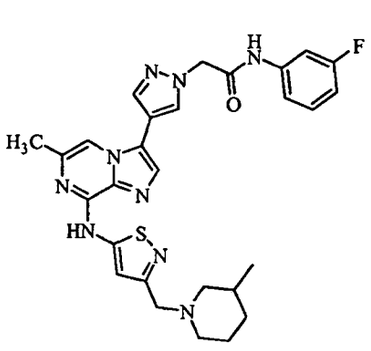


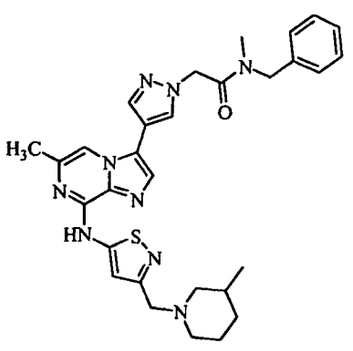


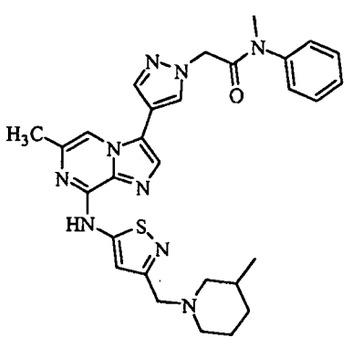


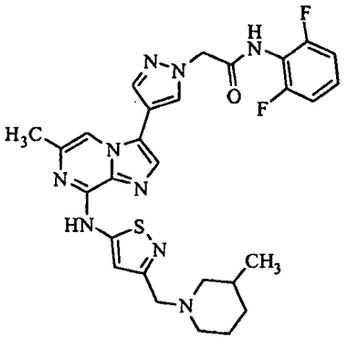


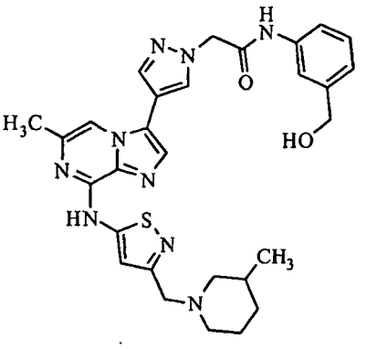


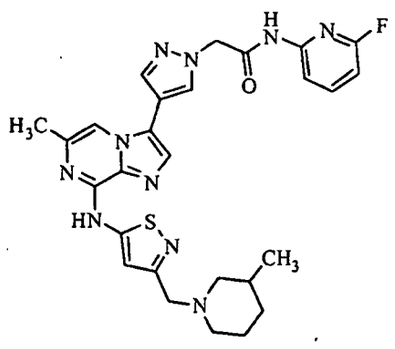


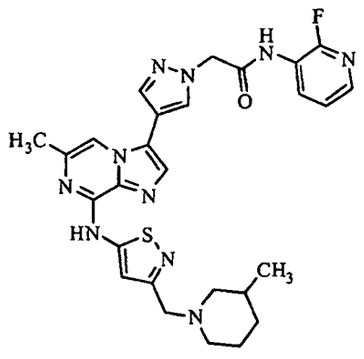


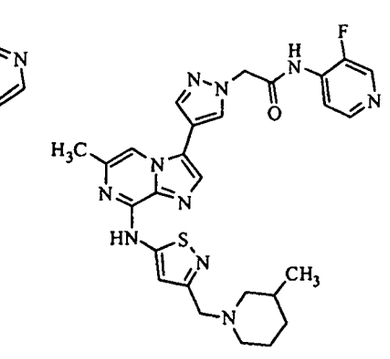


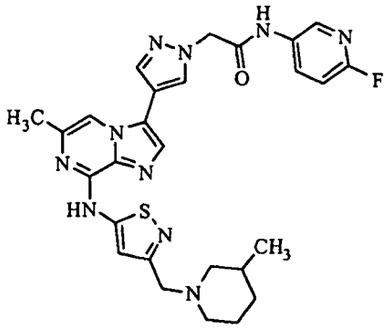


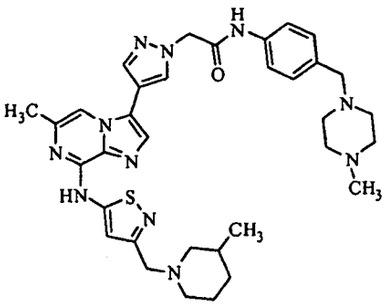


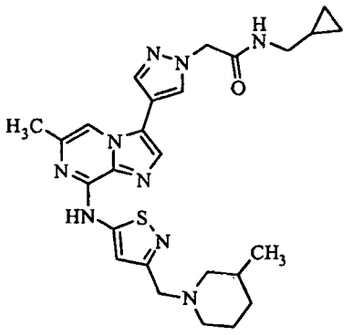


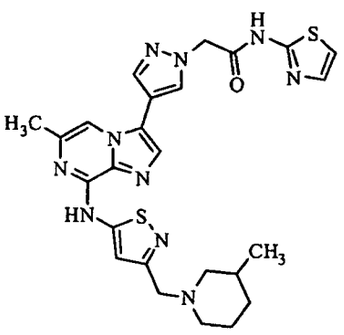


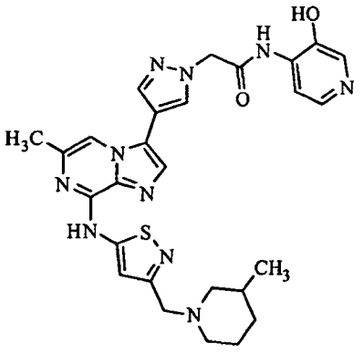


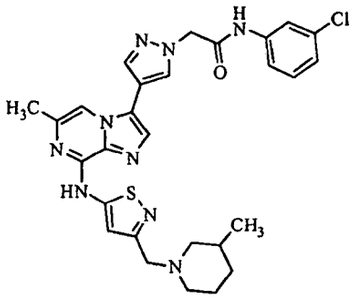


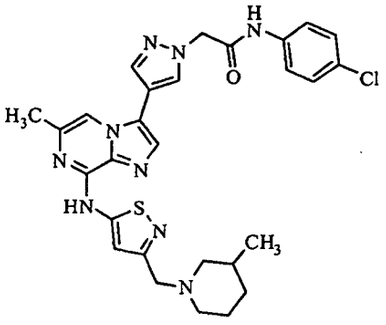


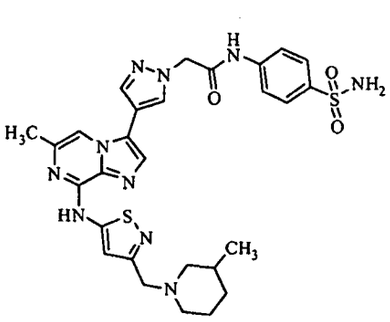


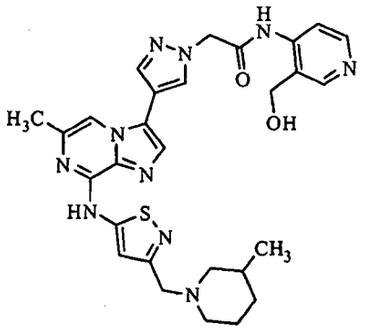


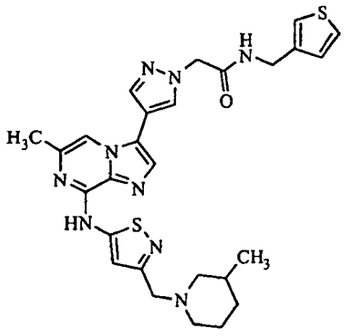


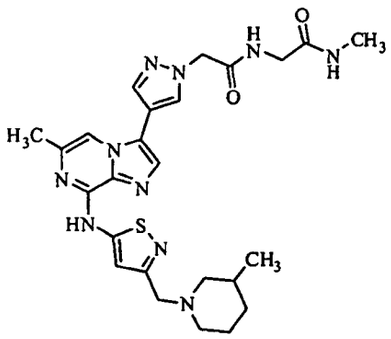


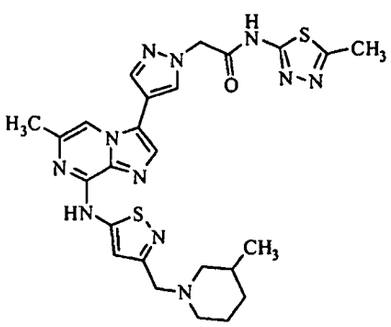


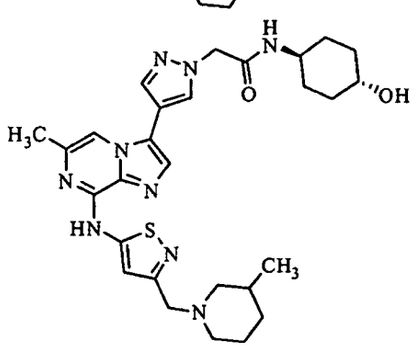


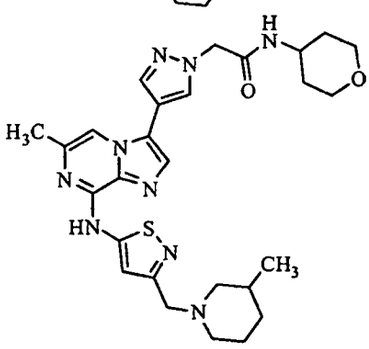


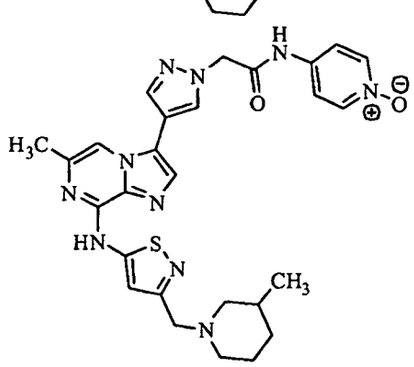


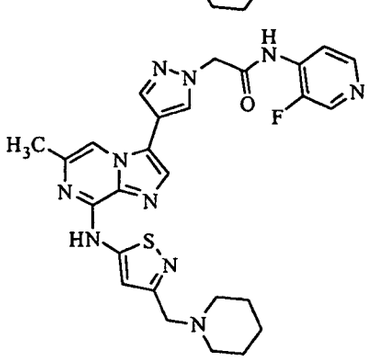


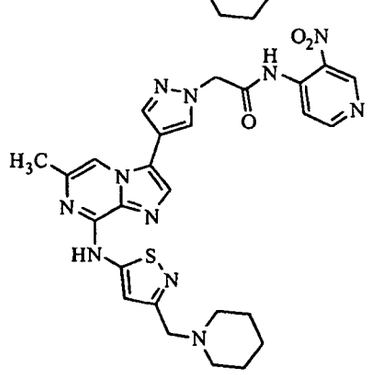


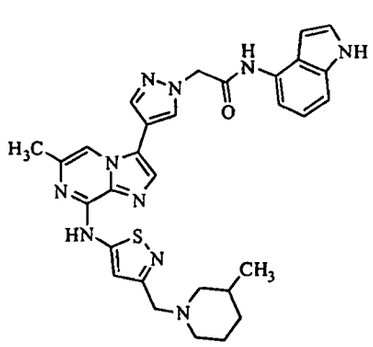


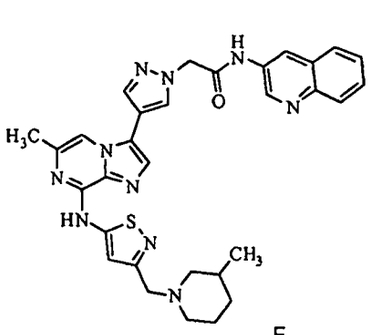


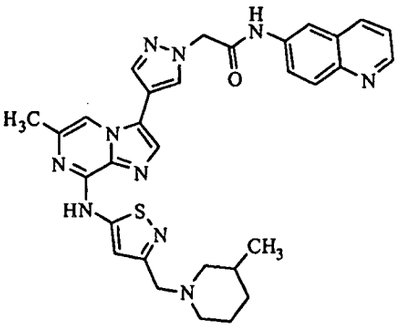


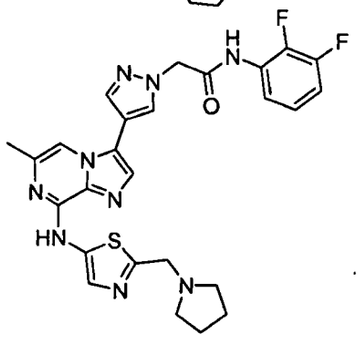


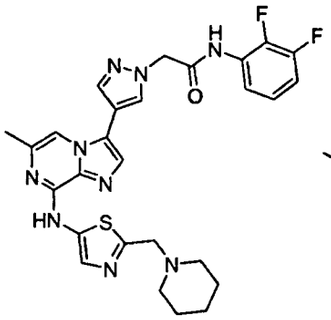


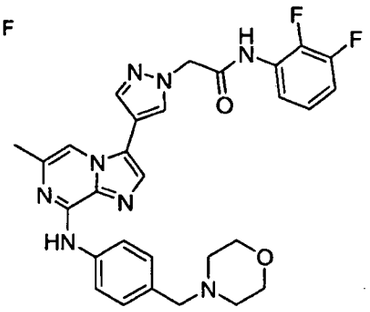


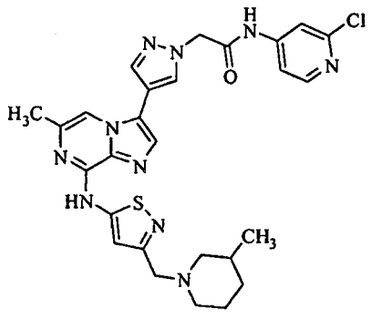


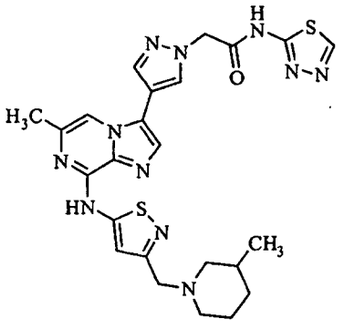


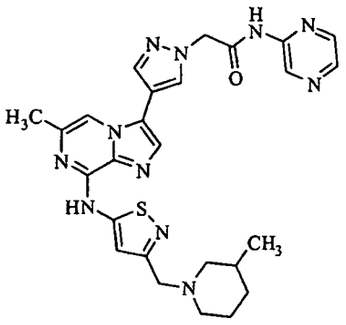


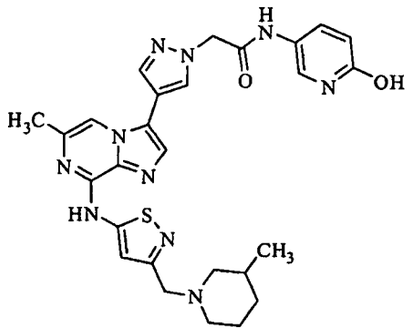


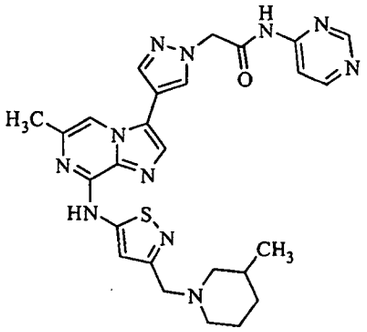


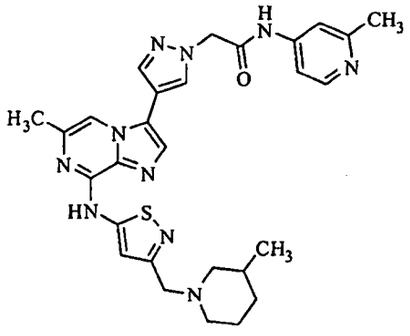


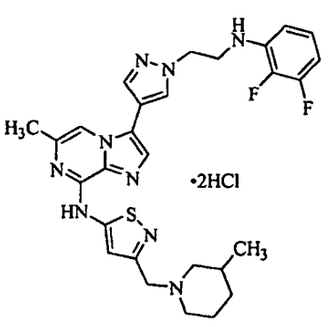


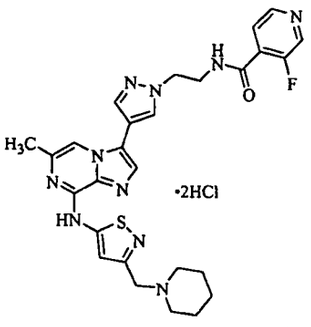




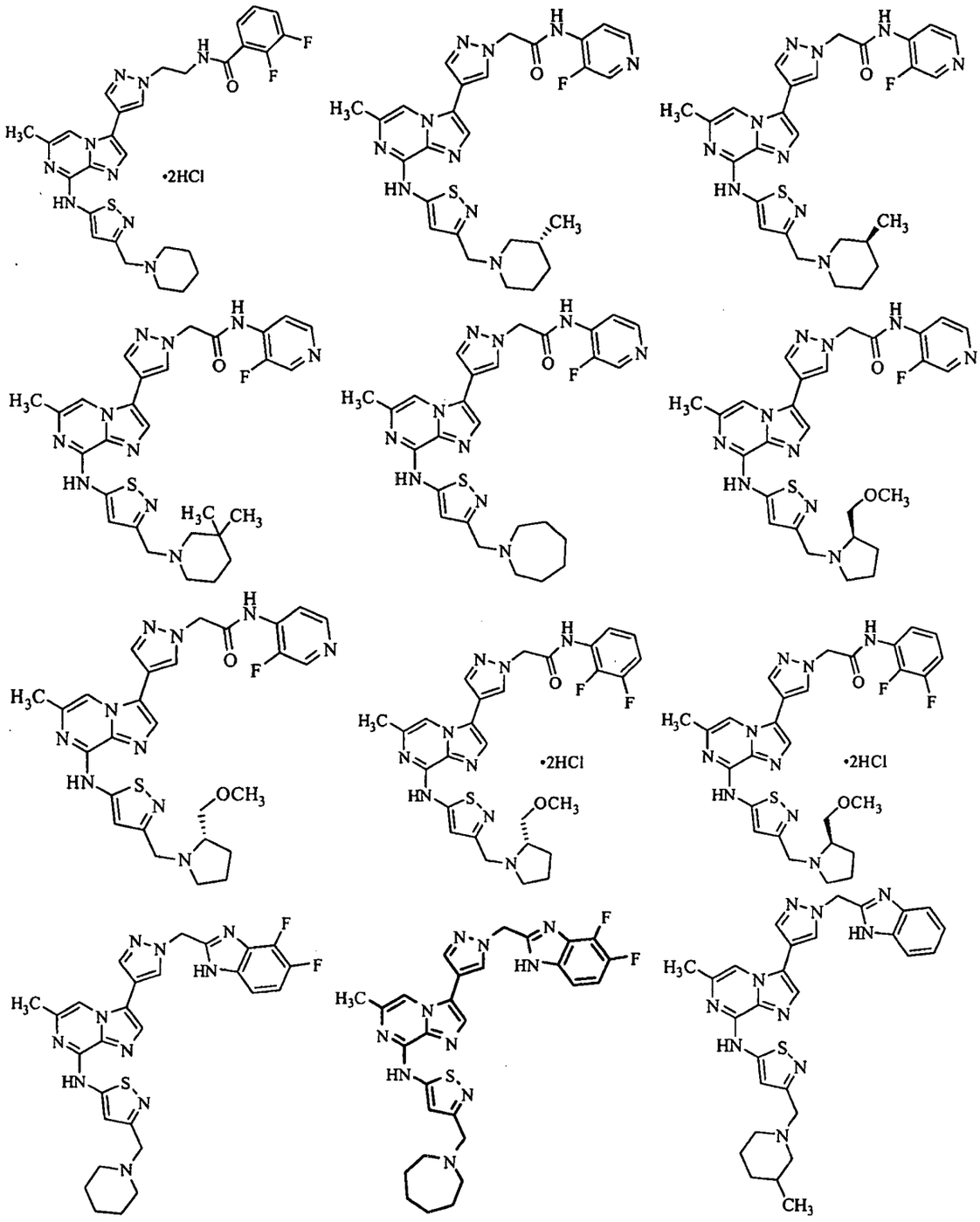


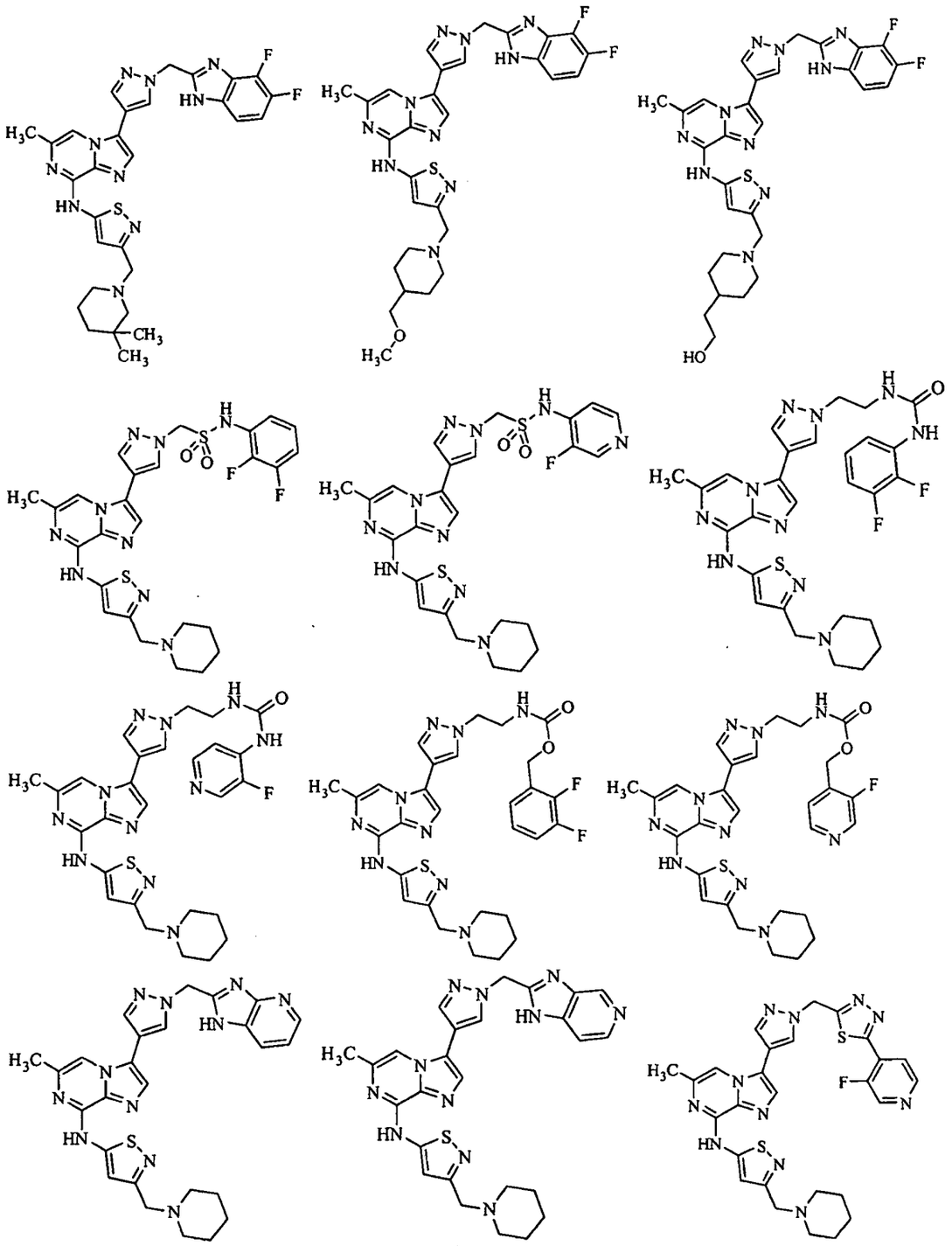


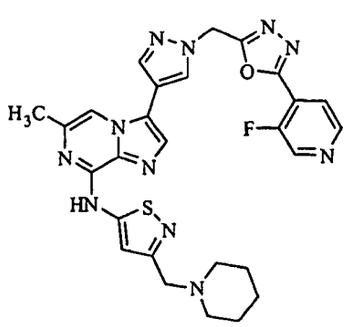


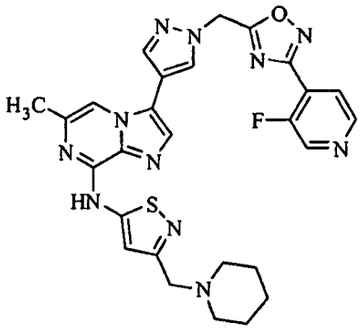


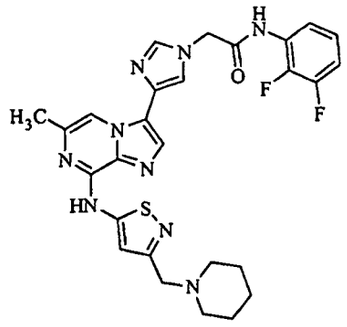
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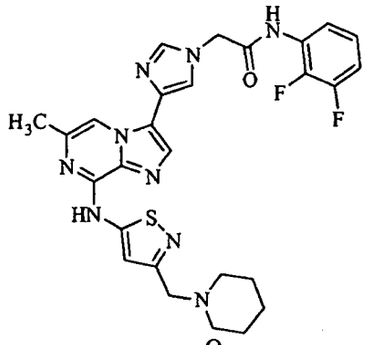


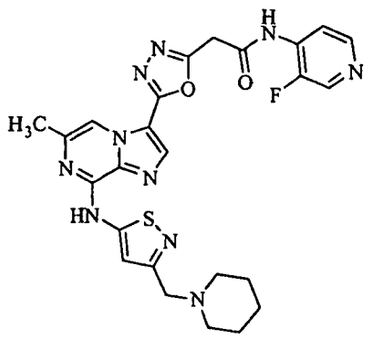


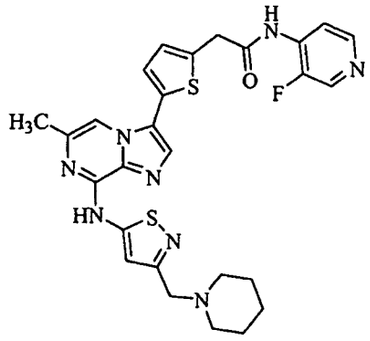


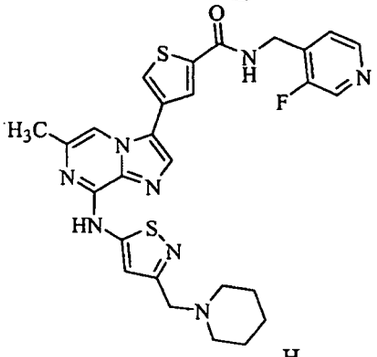


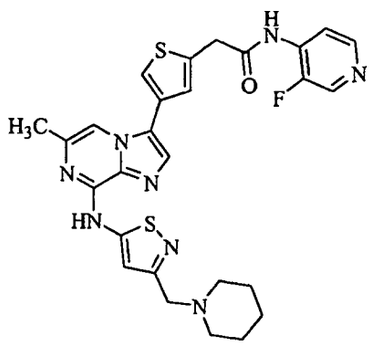


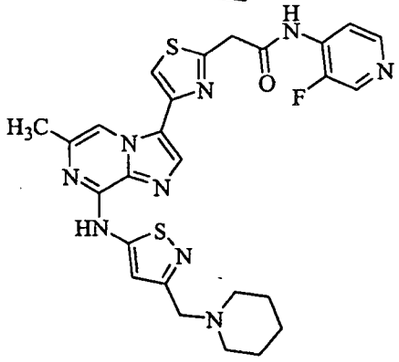


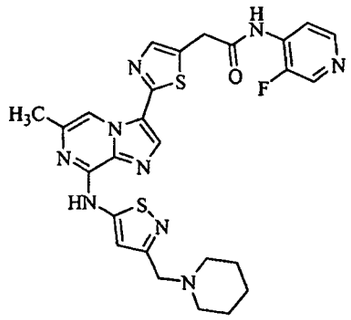


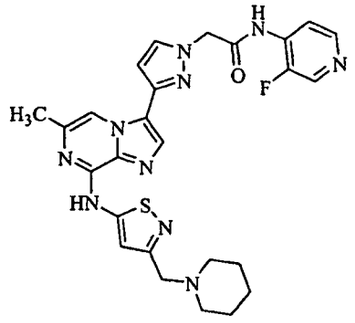


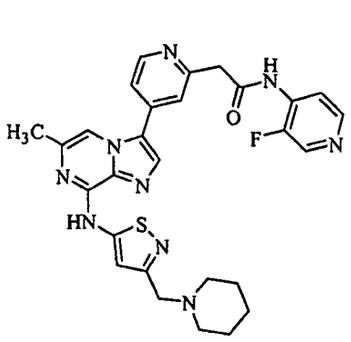


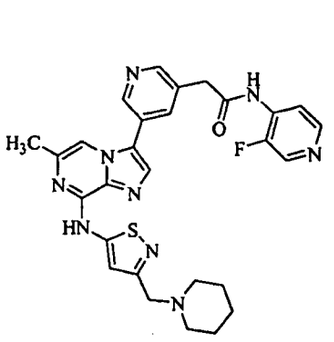


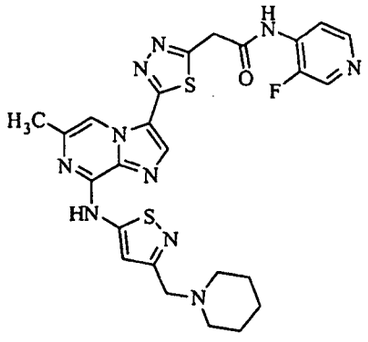


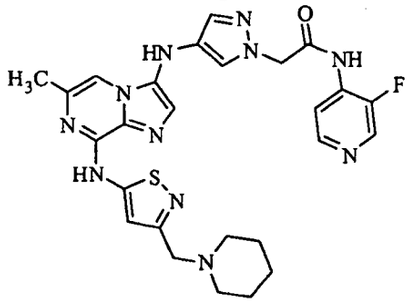


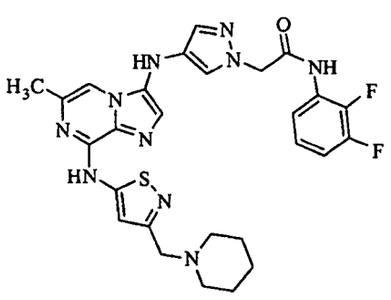


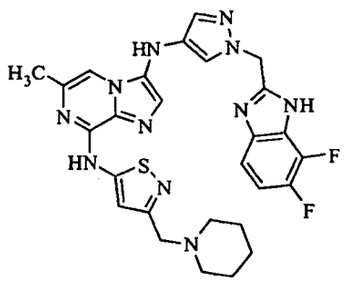


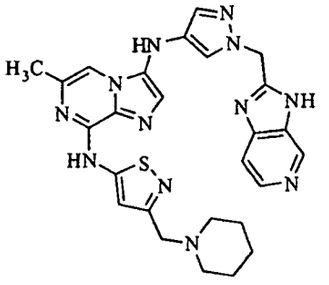


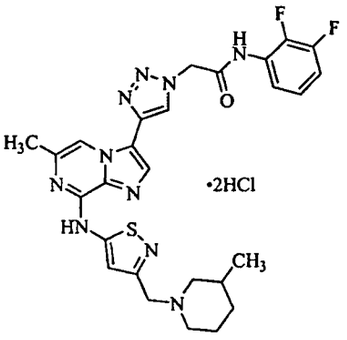


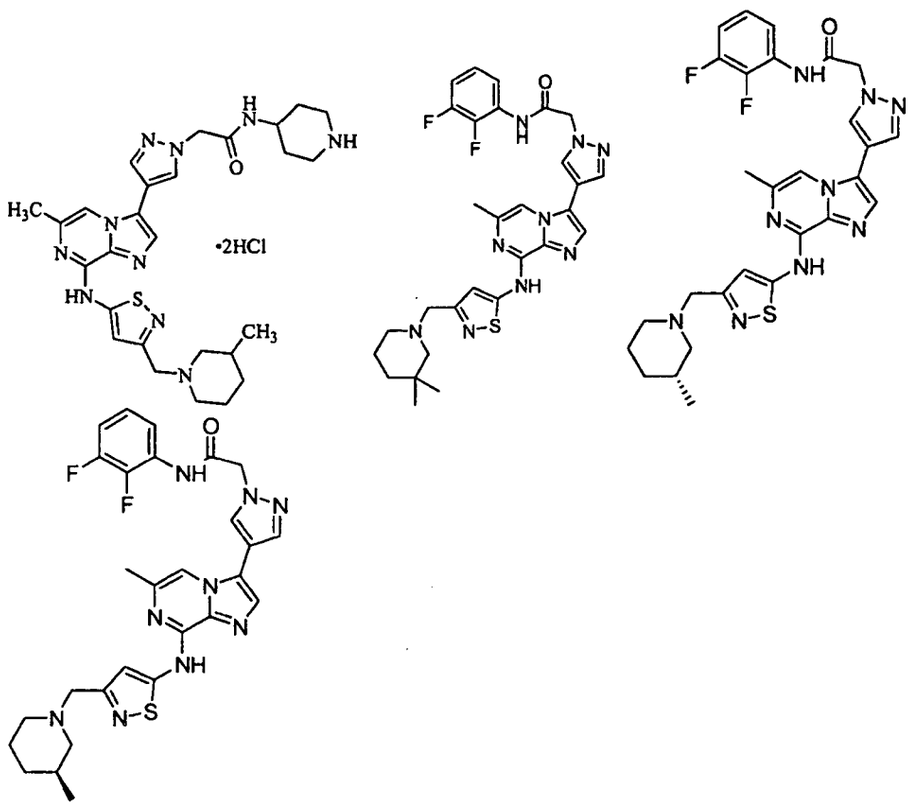









•2HCl



or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof.

16. The pharmaceutical composition of claim 1, further comprising a time release agent, wherein said aurora kinase inhibitor is released after the release of said anti-mitotic agent.

17. The pharmaceutical composition of claim 14, further comprising a time release agent, wherein said aurora kinase inhibitor is released after the release of said anti-mitotic agent.

18. A method of treating or ameliorating cancer comprising administering the pharmaceutical composition of claim 1.

19. A method of treating or ameliorating cancer comprising administering the pharmaceutical composition of claim 17.

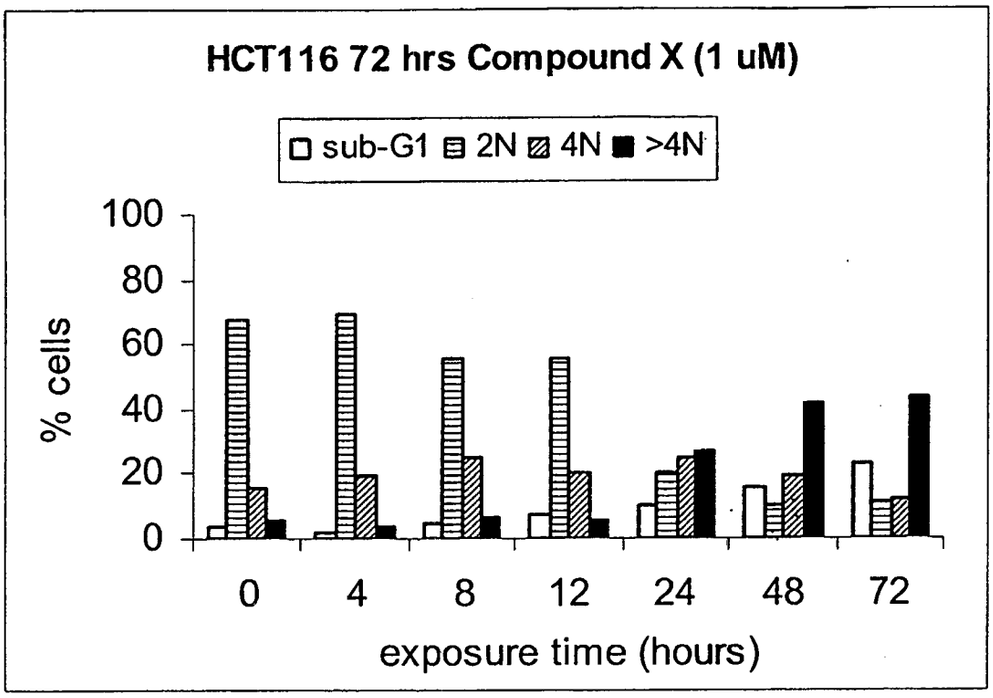

HCT116 72 hrs Compound X (1 uM)
sub-G1
2N
4N
>4N
100
80
60
40
20
0
% cells
0
4
8
12
24
48
72
exposure time (hours)

FIG. 1

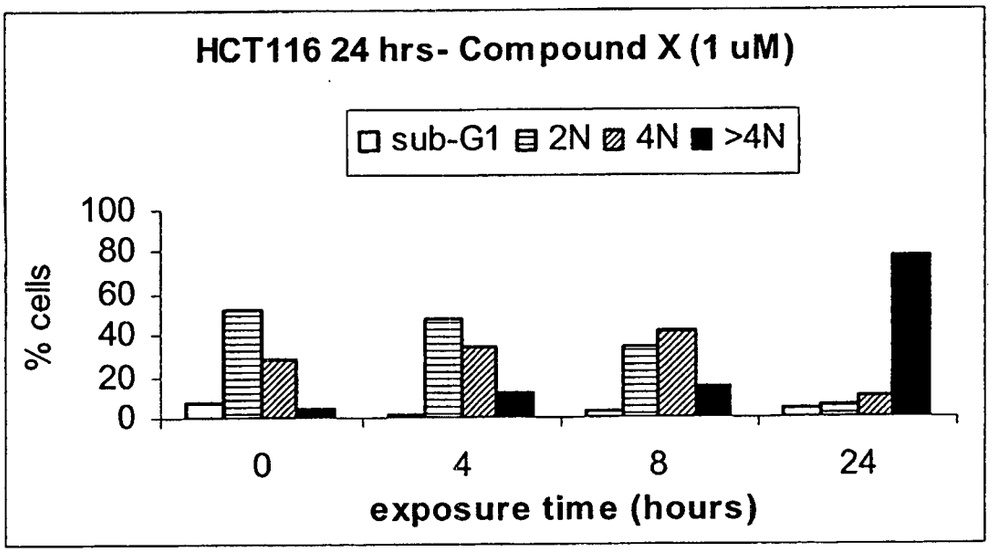

HCT116 24 hrs- Compound X (1 uM)
sub-G1
2N
4N
>4N
% cells
100
80
60
40
20
0
0
4
8
24
exposure time (hours)

FIG. 2

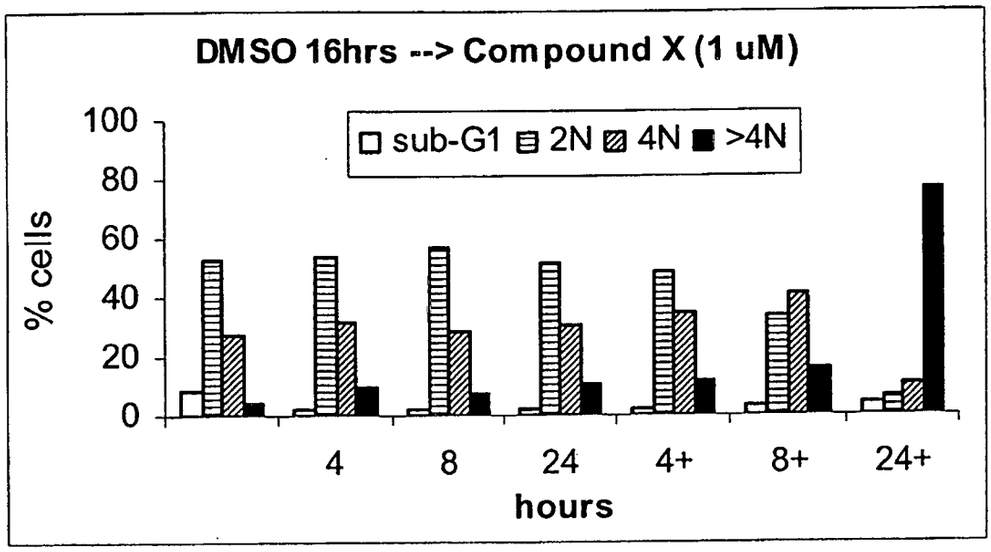

DMSO 16hrs --> Compound X (1 uM)
sub-G1
2N
4N
>4N
% cells
100
80
60
40
20
0
4
8
24
4+
8+
24+
hours

FIG. 3

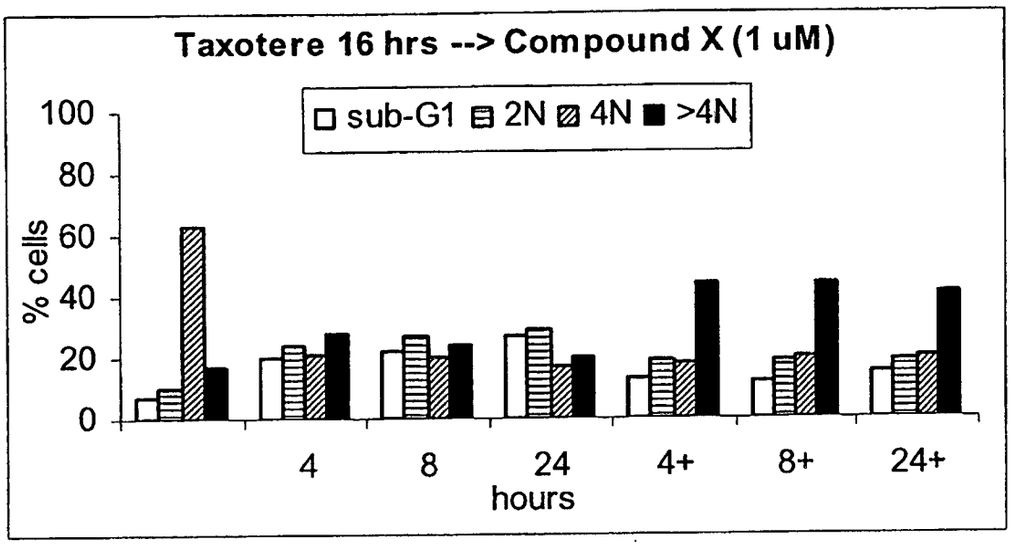

Taxotere 16 hrs --> Compound X (1 uM)
sub-G1
2N
4N
>4N
100
80
60
40
20
0
% cells
4
8
24
4+
8+
24+
hours

FIG. 4

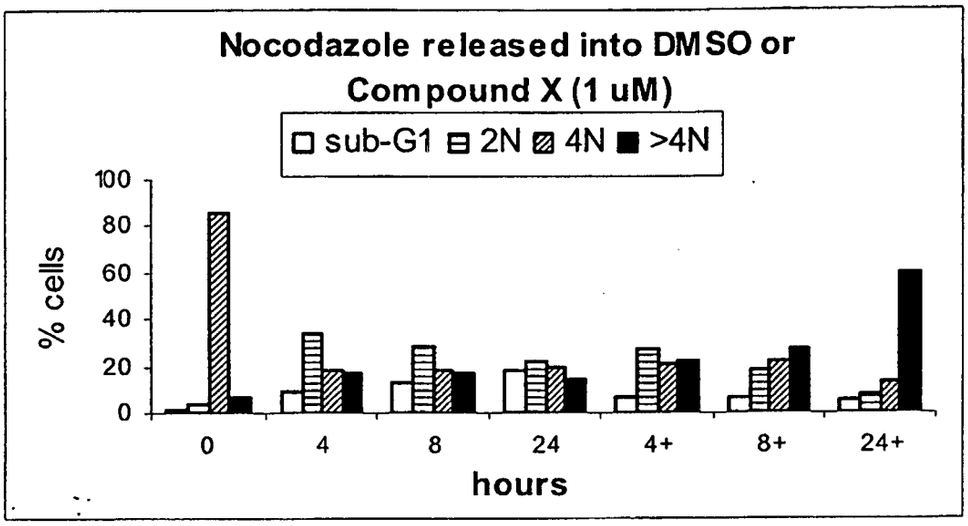

Nocodazole released into DMSO or Compound X (1 uM)
sub-G1 2N 4N >4N
% cells
100
80
60
40
20
0
0
4
8
24
4+
8+
24+
hours

FIG. 5

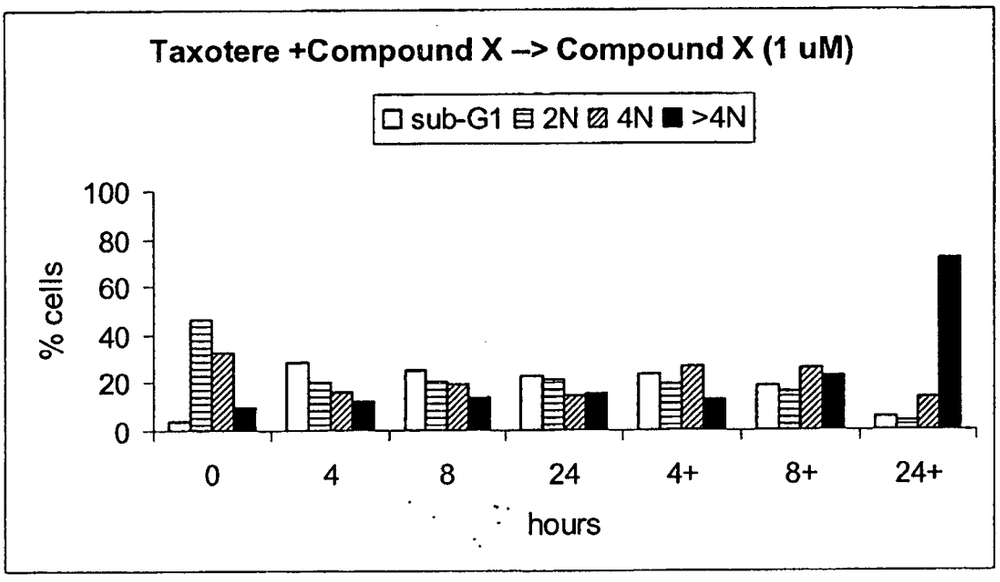

Taxotere +Compound X --> Compound X (1 uM)
sub-G1
2N
4N
>4N
% cells
100
80
60
40
20
0
0
4
8
24
4+
8+
24+
hours

FIG. 6

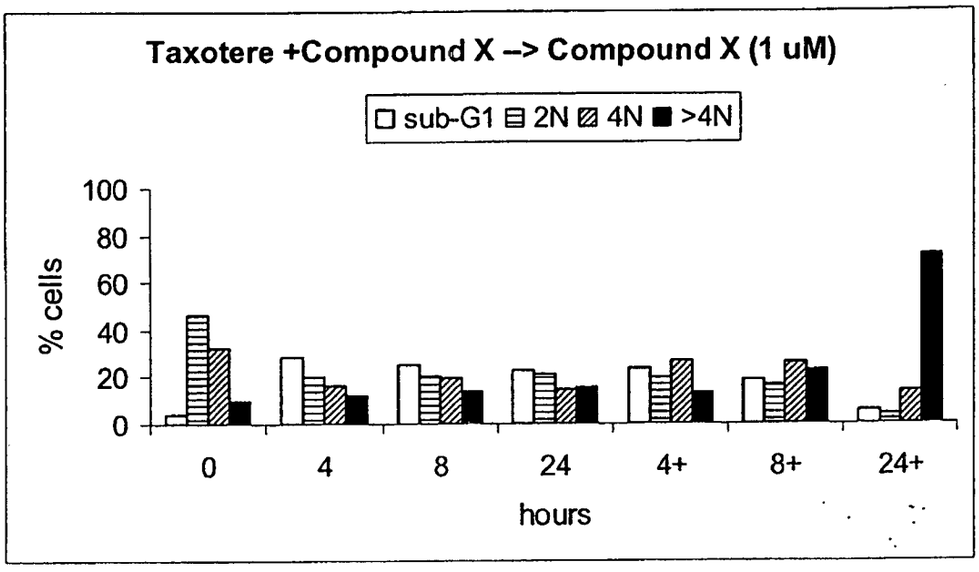

Taxotere +Compound X --> Compound X (1 uM)
sub-G1 2N 4N >4N
100
80
60
40
20
0
% cells
0
4
8
24
4+
8+
24+
hours

FIG. 7

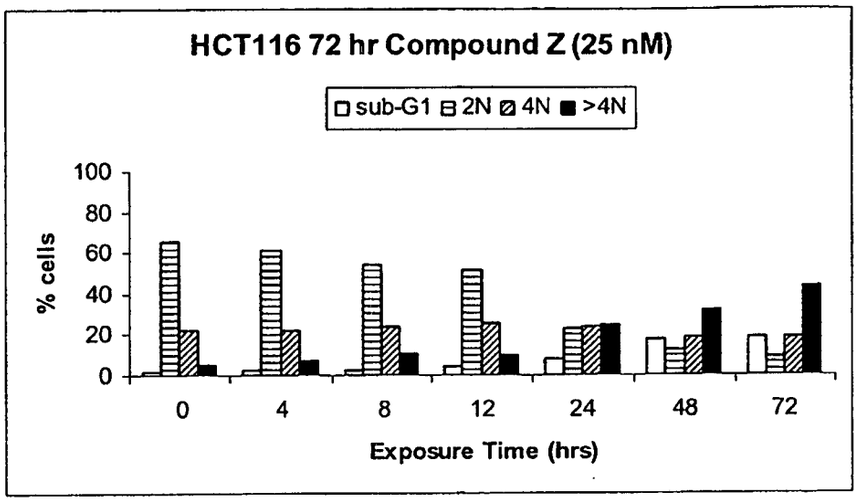

HCT116 72 hr Compound Z (25 nM)
sub-G1
2N
4N
>4N
% cells
100
80
60
40
20
0
0
4
8
12
24
48
72
Exposure Time (hrs)

FIG. 8

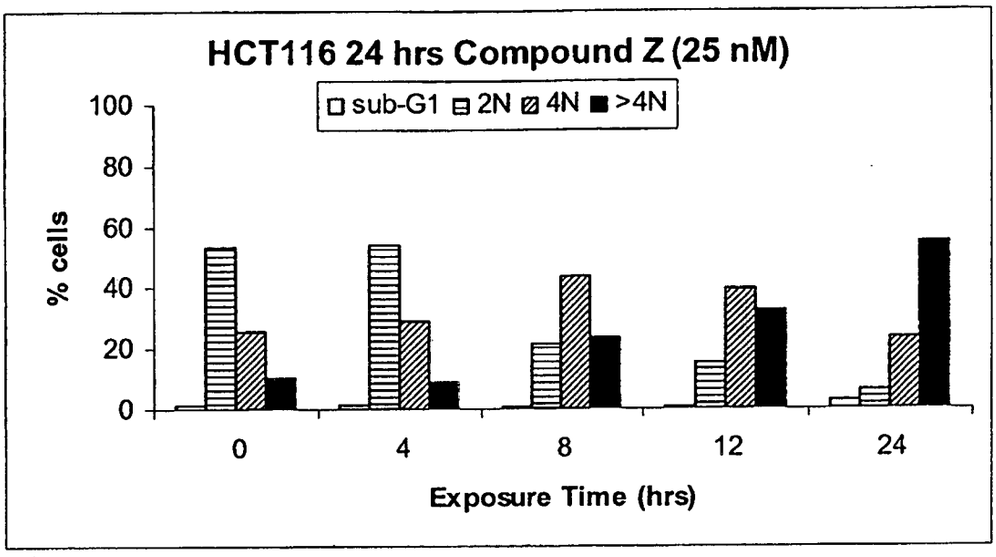

HCT116 24 hrs Compound Z (25 nM)
sub-G1
2N
4N
>4N
100
80
60
40
20
0
% cells
0
4
8
12
24
Exposure Time (hrs)

FIG. 9

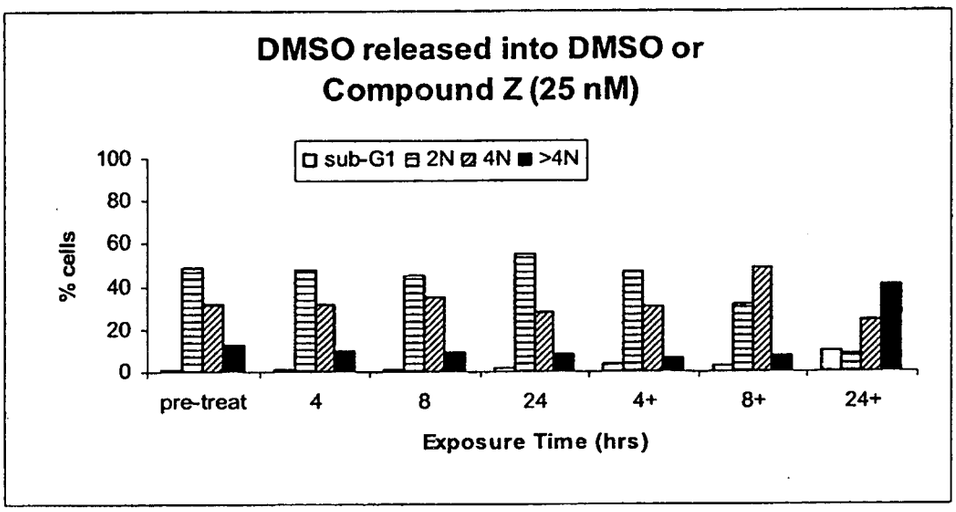

DMSO released into DMSO or
Compound Z (25 nM)
sub-G1
2N
4N
>4N
% cells
100
80
60
40
20
0
pre-treat
4
8
24
4+
8+
24+
Exposure Time (hrs)

FIG. 10

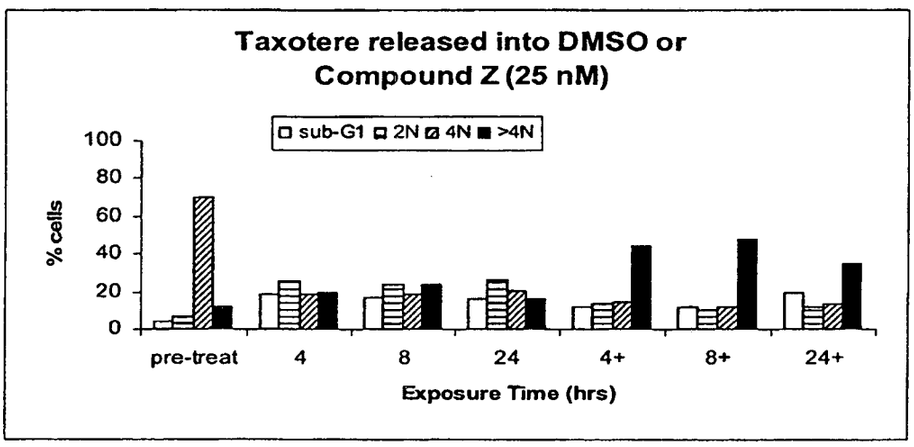

Taxotere released into DMSO or
Compound Z (25 nM)
sub-G1 2N 4N >4N
% cells
100
80
60
40
20
0
pre-treat
4
8
24
4+
8+
24+
Exposure Time (hrs)

FIG. 11

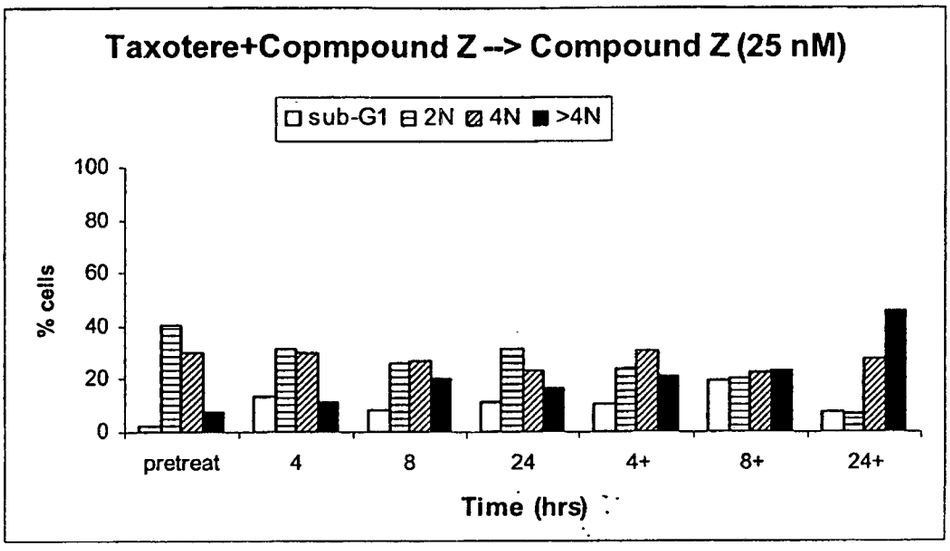

Taxotere+Copmpound Z --> Compound Z (25 nM)
sub-G1
2N
4N
>4N
100
80
60
40
20
0
% cells
pretreat
4
8
24
4+
8+
24+
Time (hrs)

FIG. 12

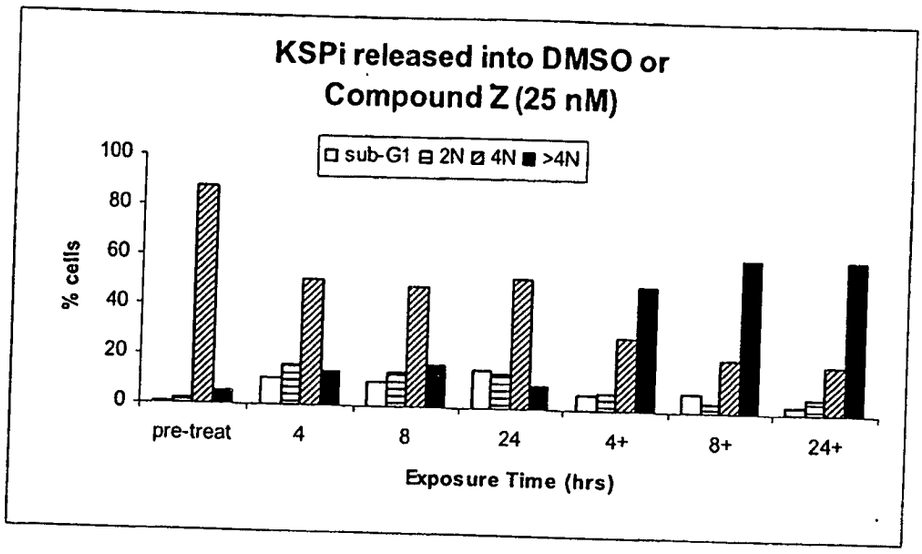

KSPi released into DMSO or
Compound Z (25 nM)
sub-G1 2N 4N >4N
% cells
100
80
60
40
20
0
pre-treat
4
8
24
4+
8+
24+
Exposure Time (hrs)

FIG. 13

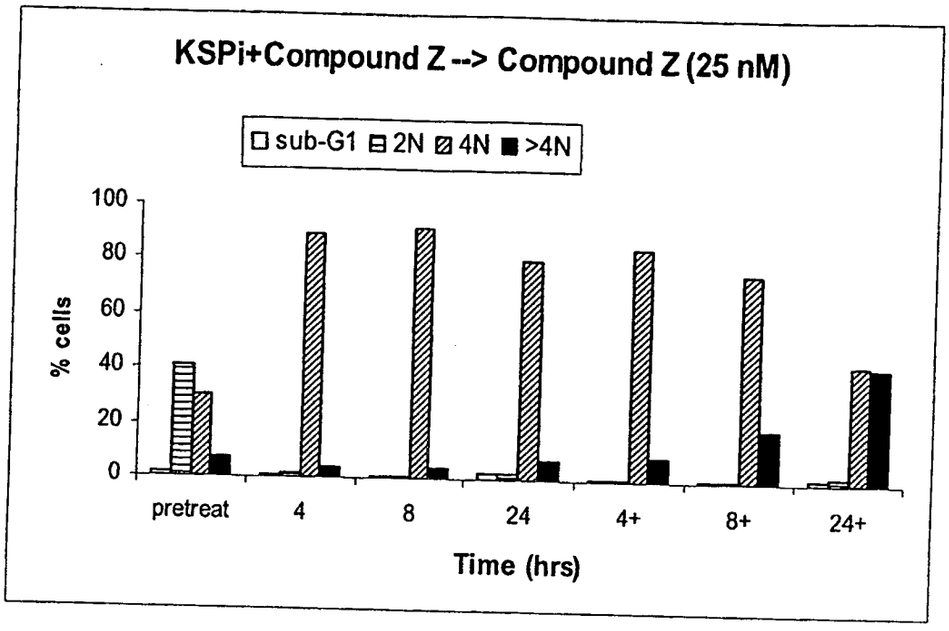

KSPi+Compound Z --> Compound Z (25 nM)
sub-G1
2N
4N
>4N
100
80
60
40
20
0
% cells
pretreat
4
8
24
4+
8+
24+
Time (hrs)

FIG. 14

6 COMBINACIÓN DE AGENTE ANTIMITÓTICO E INHIBIDOR DE AURORA QUINASA COMO TRATAMIENTO ANTICANCERÍGENO

CAMPO DE LA INVENCIÓN

La presente invención se refiere a un método para tratar el cáncer mediante un tratamiento previo con agentes antimitóticos seguido por inhibidores de aurora quinasa. La presente solicitud reivindica la prioridad de la Solicitud de Patente Provisional de EEUU, Serie Nº 60/953.087 presentada el 31 de julio de 2007.

ANTECEDENTES DE LA INVENCIÓN

Los taxanos tales como, por ejemplo, paclitaxel y docetaxel y los microtúbulos de interés de los alcaloides de la vinca, son responsables de la distribución de cromátidas hermanas duplicadas a cada una de las células hijas. La disrupción de microtúbulos puede inhibir la división celular e inducir la apoptosis.

Los inhibidores de la KSP interfieren en la función de las quinesinas mitotóticas y por lo tanto disgregan la mitosis normal y bloquean la división celular. La quinesina mitótica–KSP, conocida como Eg5, es necesaria para la separación del centrosoma. Las células en las cuales la función de la KSP está inhibida, se detienen en mitosis con los centrosomas no separados (Blangy y col., *Cell* 1995, 83: 1159–1169, Heald, R., *Cell* 2000, 102, 399). La detención mitótica produce la inhibición del crecimiento de las células tumorales. (Kaiser y col., *J. Biol. Chem.* 1999, 274: 18925–18931).

Al igual que el inhibidor de la KSP, los inhibidores de Cenp–E inhiben la separación de centrosomas mediante la inhibición de la proteína E asociada al

centrosoma produciendo la detención del ciclo celular con husos mitóticos bipolares y cromosomas mal alineados.

Ispinesib y Monastrol son inhibidores de la proteína de huso quinesina. Ellos causan la detención del ciclo celular mediante la disrupción de una proteína motora relacionada con quinesina que es necesaria para la formación de un huso bipolar. (Mayer y col., *Science* 1999, Vol. 286, No. 5441, 971–974).

Las aurora quinasas (Aurora–A, Aurora–B, Aurora–C) son proteínas serina/treonina quinasas que han estado involucradas en cánceres humanos tales como, por ejemplo, cáncer de colon, cáncer de mama y otros tumores sólidos. En diversos cánceres humanos se ha observado la sobreexpresión de Aurora A y/o Aurora B. En algunos casos, esto es el resultado de la amplificación génica. La sobreexpresión de Aurora quinasas está correlacionada con un mal pronóstico de supervivencia.

Las Aurora quinasas están involucradas en eventos de fosforilación que regulan el ciclo celular. La mala regulación del ciclo celular puede originar una proliferación celular y otras anormalidades. La Aurora A regula la maduración de centrómeros, entrada mitótica, conjunto de husos bipolares, y el alineamiento de cromosomas. La Aurora B regula la remodelación de la cromatina, la unión quinetocore–huso, y la citocinesis. La expresión de la Aurora C está limitada y se cree que su función es similar a la función de la Aurora B.

Se han desarrollado moléculas pequeñas que inhiben las Aurora quinasas como agentes anticancerígenos potenciales. VX–680 (Harrington 2004) y AT9283 son inhibidores dobles de la Aurora A/B. AZD1152 es un inhibidor selectivo de la Aurora B (Morlock 2006) y se divulga que MLN8054 es un inhibidor específico de la Aurora A (Manfredi 2007). Los compuestos que inhiben la Aurora B producen la inducción de la endorreduplicación, las células continúan a través del ciclo

celular sin someterse a citocinesis y acumulan ADN con contenido >4N (donde DNA 2N representa células en G1 y 4N representa células en mitosis).

Además se hace mención a R. R. Hoover. y M. W. Harding, *Journal of Clinical Oncology, 2007 American Society of Clinical Oncology Annual Meeting Proceedings Part I.* Vol. 25, No. 18S (Suplemento 20 de junio), 2007: 14069, que divulga el uso in vitro de un inhibidor reversible de quinasa (MK–0457) que selecciona como blanco la Aurora A, B y C en combinación consecutiva o simultánea con el agente microtúbulo de interés, Taxotero, en líneas celulares cancerígenas. Divulga que la sinergia se produce con la exposición consecutiva y no simultánea a ambos compuestos en los ensayos de viabilidad a corto plazo y que la sinergia se produce con la exposición simultánea en los ensayos de supervivencia a largo plazo.

Se hace mención a la inhibición de Aurora en combinación con taxanos en *Proceedings from the American Association for Cancer Research 2007 Annual Meeting* (18 de abril, 2007). P Phatak *y col.* (resumen Nº 5746) divulga la sinergia dependiente del programa de un inhibidor no específica de aurora quinasa (VE–465), que es similar a MK–0457, que está comúnmente en los ensayos clínicos, y paclitaxel en el cáncer de pulmón de células no pequeñas. Expone que VE–465 y paclitaxel exhiben sinergia dependiente del programa que produce la muerte celular mejorada dependiente de la línea celular. Asimismo, el Resumen Nº 4357 llegó a la conclusión de que la combinación de VX–680 y taxotero demostró una inhibición mejorada del crecimiento celular y el Resumen Nº 1819 llegó a la conclusión de que la combinación de VE–645 y taxol demostró una inhibición mejorada del crecimiento celular. El Resumen Nº 4359 y Nº 3263 llegaron a la conclusión de que AZD1152 en combinación con taxol demostró una inhibición mejorada del crecimiento celular.

Se hace referencia a la inhibición selectiva de la Aurora A y taxanos. Tanaka y col. (*Clinical Cancer Research* 2007; 13:1331) demostró que la Aurora A ARNsi en combinación con Taxotero dieron como resultado una apoptosis mejorada. Hata y col., (*Cancer Research* 2005; 65: 2899) demostraron que la Aurora A ARNsi en combinación con taxanos presentó una citotoxicidad mejorada. Ohkubo M y col., divulgaron en una patente que la combinación de aminopiridinas novedosas que tienen efectos inhibidores selectivos de la Aurora A con Taxol produjo una inhibición mejorada del crecimiento celular.

Yang y col., (*International Journal of Cancer* 2006; 119:2304) descubrió que la expresión ectópica de la Aurora A hace que las células sean resistentes a los agentes anticancerígenos tales como, por ejemplo, Taxol. Del mismo modo, Anand y col., (*Cancer Cell* 2003; 3:51) descubrió que la expresión elevada de la Aurora A causa resistencia a la apoptosis inducida por Taxol. Anand y col., (WO05/002571, presentada el 13 de enero de 2005), divulgó que la sobreexpresión de la Aurora A actúa de mediadora en la resistencia a los agentes anticancerígenos y la resistencia puede reducirse inhibiendo las Aurora quinasas o puede preverse midiendo la expresión o la actividad de las Aurora quinasas dentro de la célula.

SÍNTESIS DE LA INVENCIÓN

La presente invención provee una composición farmacéutica para tratar o paliar el cáncer, la cual comprende por lo menos un primer compuesto, que es un agente antimitótico y por lo menos un segundo compuesto, que es un inhibidor de la aurora quinasa.

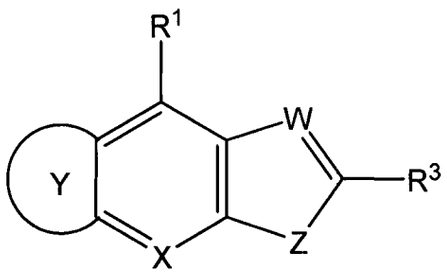
La presente invención además provee un método para tratar o paliar el cáncer, el cual comprende la administración a un mamífero que necesita dicho tratamiento de una cantidad de por lo menos un primer compuesto agente

antimitótico, seguido por una cantidad de por lo menos un segundo compuesto, que es un inhibidor de la aurora quinasa. Las secciones siguientes describen el agente antimitótico y el inhibidor de la aurora quinasa más detalladamente.

Algunos ejemplos no restrictivos de agentes antimitóticos útiles en la presente invención incluyen:

Taxanos, paclitaxel, docetaxel, Inhibidor de Cenp–E (tales como, por ejemplo, GSK–923295), Abraxano, Epotilona, Monastrol, e inhibidores de KSP. Algunos ejemplos no restrictivos de inhibidores útiles de KSP incluyen Ispinesib SB–715992 (Cytokinetics), así como también los compuestos de las Fórmulas A–D indicadas en los párrafos a–d que aparecen a continuación:

a. Un compuesto representado por la Fórmula estructural A:



Fórmula A

o una sal, solvato o éster del mismo, aceptables para uso farmacéutico, en el cual:

el anillo Y es un arilo de 5 a 6 miembros o un heteroarilo de 5 o 6 miembros fusionado como se indica en la Fórmula A, en el cual en dicho arilo y heteroarilo, cado carbono sustituible del anillo está sustituido en forma independiente con R^2 y cada nitrógeno sustituible del anillo está sustituido en forma independiente con R^6;

W es N o $C(R^{12})$;

X es N o N–óxido;

Z es S, S(=O) o $S(=O)_2$;

R^1 es H, alquilo, alcoxi, hidroxi, halo, –CN, $–S(O)_m–$alquilo, $–C(O)NR^9R^{10}$, $–(CR^9R^{10})_{1–6}OH$, o $–NR^4(CR^9R^{10})_{1–2}OR^9$;

cada R^2 está seleccionado en forma independiente entre el grupo integrado por H, halo, alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo, heteroaralquilo, $-(CR^{10}R^{11})_{0-6}-OR^7$, $-C(O)R^4$, $-C(S)R^4$, $-C(O)OR^7$, $-C(S)OR^7$, $-OC(O)R^7$, $-OC(S)R^7$, $-C(O)NR^4R^5$, $-C(S)NR^4R^5$, $-C(O)NR^4OR^7$, $-C(S)NR^4OR^7$, $-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, $-CN$, $-OCF_3$, $-SCF_3$, $-C(=NR^7)NR^4$, $-C(O)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}OR^7$, $-C(S)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(S)NR^7(CH_2)_{1-10}OR^7$, haloalquilo y alquilsililo, en el cual cada uno de dicho alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo o heteroaralquilo está sustituido en forma opcional e independiente con 1–5 restos de R^9;

cada R^3 está seleccionado en forma independiente entre el grupo integrado por H, halo, alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo, heteroaralquilo, $-(CR^{10}R^{11})_{0-6}-OR^7$, $-C(O)R^4$, $-C(S)R^4$, $-C(O)OR^7$, $-C(S)OR^7$, $-OC(O)R^7$, $-OC(S)R^7$, $-C(O)NR^4R^5$, $-C(S)NR^4R^5$, $-C(O)NR^4OR^7$, $-C(S)NR^4OR^7$, $-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, $-CN$, $-OCF_3$, $-SCF_3$, $-C(=NR^7)NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}OR^7$, $-C(S)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(S)NR^7(CH_2)_{1-10}OR^7$, haloalquilo y alquilsililo, en el cual cada uno de dicho alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo,

aralquilo, heteroarilo o heteroaralquilo está sustituido en forma opcional e independiente con 1–5 restos R^9;

cada R^4 y R^5 está seleccionado en forma independiente entre el grupo integrado por H, alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo, heteroaralquilo, $-OR^7$, $-C(O)R^7$, y $-C(O)OR^7$, en el cual cada uno de dicho alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo, o heteroaralquilo está sustituido en forma opcional con 1–4 restos de R^8;

o R^4 y R^5, cuando están unidos al mismo átomo de nitrógeno, se toman en forma opcional junto con el átomo de nitrógeno al cual están unidos para formar un anillo heterocíclico de 3–6 miembros que tiene 0–2 heteroátomos adicionales seleccionados entre N, O o S;

cada R^6 está seleccionado en forma independiente entre el grupo integrado por H, alquilo, arilo, aralquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, heteroarilo, heteroaralquilo, $-(CH_2)_{1-6}CF_3$, $-C(O)R^7$, $-C(O)OR^7$ y $-SO_2R^7$;

cada R^7 está seleccionado en forma independiente entre el grupo integrado por H, alquilo, arilo, aralquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, heteroarilo, y heteroaralquilo, en el cual cada miembro de R^7 excepto H está sustituido en forma opcional con 1–4 restos de R^8;

cada R^8 está seleccionado en forma independiente entre el grupo integrado por halo, alquilo, cicloalquilo, heterociclilo, arilo, heteroarilo, $-NO_2$, $-OR^{10}$, $-$(alquilo C_1–C_6)$-OR^{10}$, $-CN$, $-NR^{10}R^{11}$, $-C(O)R^{10}$, $-C(O)OR^{10}$, $-C(O)NR^{10}R^{11}$, $-CF_3$, $-OCF_3$, $-CF_2CF_3$, $-C(=NOH)R^{10}$, $-N(R^{10})C(O)R^{11}$, $-C(=NR^{10})NR^{10}R^{11}$, y $-NR^{10}C(O)OR^{11}$, en el cual cada uno de dicho alquilo, cicloalquilo, heterociclilo, arilo, y heteroarilo está sustituido en forma opcional e independiente con 1–3 restos seleccionados entre el grupo integrado por halo, alquilo, cicloalquilo,

heterociclilo, arilo, heteroarilo, $-NO_2$, $-OR^{10}$, $-$(alquilo C_1–C_6)$-OR^{10}$, $-CN$, $-NR^{10}R^{11}$, $-C(O)OR^{10}$, $-C(O)NR^{10}R^{11}$, $-CF^3$, $-OCF_3$, $-NR^{10}C(O)OR^{11}$, y $-NR^{10}C(O)R^{40}$;

o dos grupos R^8, cuando están unidos al mismo átomo de carbono, se toman en forma opcional junto con el átomo de carbono al cual están unidos para formar un grupo C=O o un grupo C=S;

cada R^9 está seleccionado en forma independiente entre el grupo integrado por H, alquilo, alcoxi, OH, CN, halo, $-(CR^{10}R^{11})_{0-4}NR^4R^5$, haloalquilo, hidroxialquilo, alcoxialquilo, $-C(O)NR^4R^5$, $-C(O)OR^7$, $-OC(O)NR^4R^5$, $-NR^4C(O)R^5$, y $-NR^4C(O)NR^4R^5$;

cada R^{10} es en forma independiente H o alquilo; o R^9 y R^{10}, cuando están unidos al mismo átomo de nitrógeno, se toman en forma opcional junto con el átomo de nitrógeno al cual están unidos para formar un anillo heterocíclico de 3–6 miembros que tiene 0–2 heteroátomos adicionales seleccionados entre N, O o S;

cada R^{11} es en forma independiente H o alquilo; o R^{10} y R^{11}, cuando están unidos al mismo átomo de nitrógeno, se toman en forma opcional junto con el átomo de nitrógeno al cual están unidos para formar un anillo heterocíclico de 3–6 miembros que tiene 0–2 heteroátomos adicionales seleccionados entre N, O o S;

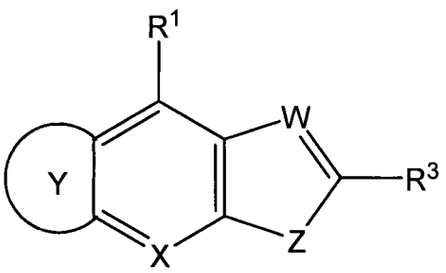
cada R^{12} está seleccionado en forma independiente entre el grupo integrado por H, halo, alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo, heteroaralquilo, $-(CR^{10}R^{11})_{0-6}-OR^7$, $-C(O)R^4$, $-C(S)R^4$, $-C(O)OR^7$, $-C(S)OR^7$, $-OC(O)R^7$, $-OC(S)R^7$, $-C(O)NR^4R^5$, $-C(S)NR^4R^5$, $-C(O)NR^4OR^7$, $-C(S)NR^4OR^7$, $-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, $-CN$, $-OCF_3$, $-SCF_3$, $-C(=NR^7)NR^4$,

$-C(O)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}OR^7$, $-C(S)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(S)NR^7(CH_2)_{1-10}OR^7$, haloalquilo y alquilsililo, en el cual cada uno de dicho alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo o heteroaralquilo está sustituido en forma opcional e independiente con 1–5 restos de R^9; y

R^{40} está seleccionado entre el grupo integrado por cicloalquilo, heterociclilo, arilo y heteroarilo, en el cual cada uno de dicho cicloalquilo, heterociclilo, arilo y heteroarilo está sustituido en forma opcional e independiente con 1–3 restos seleccionados en forma independiente entre el grupo integrado por –CN, –OH, halo, alquilo, haloalquilo, alcoxi, y $-NR^{10}R^{11}$.

Dichos compuestos de la Fórmula A en (a) se divulgan en WO 2006/098962, presentada el 7 de marzo de 2006, cuyo contenido se incorpora a la presente en su totalidad a modo de referencia;

b. Un compuesto representado por la Fórmula estructural B:



Fórmula B

o una sal, solvato o éster del mismo, aceptables para uso farmacéutico, en el cual:

el anillo Y es un anillo de 5 a 7 miembros seleccionado entre el grupo integrado por cicloalquilo, cicloalquenilo, heterociclilo o heterociclenilo fusionado como se indica en la Fórmula B, en el cual en cada uno de dicho anillo de 5 a 7 miembros, cada carbono sustituible en el anillo está sustituido en forma independiente con los restos 1–2 R^2 y cada heteroátomo sustituible en el anillo está sustituido en forma independiente con R^6;

W es N o $C(R^{12})$;

X es N o N–óxido;

Z es S, S(=O) o $S(=O)_2$;

R^1 es H, alquilo, alcoxi, hidroxi, halo, –CN, $–S(O)_m–$alquilo, $–C(O)NR^9R^{10}$, $–(CR^9R^{10})_{1–6}OH$, o $–NR^4(CR^9R^{10})_{1–2}OR^9$; en el cual m es 0 a 2;

cada R^2 está seleccionado en forma independiente entre el grupo integrado por H, halo, alquilo, cicloalquilo, alquilsililo, cicloalquenilo, heterociclilo, heterociclenilo, arilo, heteroarilo, $–(CR^{10}R^{11})_{0–6}–OR^7$, $–C(O)R^4$, $–C(S)R^4$, $–C(O)OR^7$, $–C(S)OR^7$, $–OC(O)R^7$, $–OC(S)R^7$, $–C(O)NR^4R^5$, $–C(S)NR^4R^5$, $–C(O)NR^4OR^7$, $–C(S)NR^4OR^7$, $–C(O)NR^7NR^4R^5$, $–C(S)NR^7NR^4R^5$, $–C(S)NR^4OR^7$, $–C(O)SR^7$, $–NR^4R^5$, $–NR^4C(O)R^5$, $–NR^4C(S)R^5$, $–NR^4C(O)OR^7$, $–NR^4C(S)OR^7$, $–OC(O)NR^4R^5$, $–OC(S)NR^4R^5$, $–NR^4C(O)NR^4R^5$, $–NR^4C(S)NR^4R^5$, $–NR^4C(O)NR^4OR^7$, $–NR^4C(S)NR^4OR^7$, $–(CR^{10}R^{11})_{0–6}SR^7$, SO_2R^7, $–S(O)_{1–2}NR^4R^5$, $–N(R^7)SO_2R^7$, $–S(O)_{1–2}NR^5OR^7$, –CN, $–OCF_3$, $–SCF_3$, $–C(=NR^7)NR^4$, $–C(O)NR^7(CH_2)_{1–10}NR^4R^5$, $–C(O)NR^7(CH_2)_{1–10}OR^7$, $–C(S)NR^7(CH_2)_{1–10}NR^4R^5$, y $–C(S)NR^7(CH_2)_{1–10}OR^7$, en el cual cada uno de dicho alquilo, cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, arilo, y heteroarilo está sustituido en forma opcional e independiente con 1–5 restos de R^9;

o dos R^2 en el mismo átomo de carbono se toman en forma opcional junto con el átomo de carbono al cual están unidos para formar un grupo C=O, C=S o un grupo etilendioxi;

R^3 está seleccionado en forma independiente entre el grupo integrado por H, halo, alquilo, cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, arilo, heteroarilo, $–(CR^{10}R^{11})_{0–6}–OR^7$, $–C(O)R^4$, $–C(S)R^4$, $–C(O)OR^7$, $–C(S)OR^7$, $–OC(O)R^7$, $–OC(S)R^7$, $–C(O)NR^4R^5$, $–C(S)NR^4R^5$, $–C(O)NR^4OR^7$, $–C(S)NR^4OR^7$, $–C(O)NR^7NR^4R^5$, $–C(S)NR^7NR^4R^5$, $–C(S)NR^4OR^7$, $–C(O)SR^7$, $–NR^4R^5$, $–NR^4C(O)R^5$, $–NR^4C(S)R^5$, $–NR^4C(O)OR^7$, $–NR^4C(S)OR^7$, $–OC(O)NR^4R^5$,

$-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, $-CN$, $-C(=NR^7)NR^4R^5$, $-C(O)N(R^7)-(CR^{40}R^{41})_{1-5}-C(=NR^7)NR^4R^5$, $-C(O)N(R^7)(CR^{40}R^{41})_{1-5}-NR^4R^5$, $-C(O)N(R^7)(CR^{40}R^{41})_{1-5}-C(O)-NR^4R^5$, $-C(O)N(R^7)(CR^{40}R^{41})_{1-5}-OR^7$, $-C(S)NR^7(CH_2)_{1-5}NR^4R^5$, y $-C(S)NR^7(CH_2)_{1-5}OR^7$, en el cual cada uno de dicho alquilo, cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, arilo, y heteroarilo está sustituido en forma opcional e independiente con 1–5 restos de R^9;

cada uno de R^4 y R^5 está seleccionado en forma independiente entre el grupo integrado por H, alquilo, cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, arilo, heteroarilo, $-OR^7$, $-C(O)R^7$, y $-C(O)OR^7$, en el cual cada uno de dicho alquilo, cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, arilo, y heteroarilo, está sustituido en forma opcional con 1–4 restos de R^8;

o R^4 y R^5, cuando están unidos al mismo átomo de nitrógeno, se toman en forma opcional junto con el átomo de nitrógeno al cual están unidos para formar un anillo heterocíclico de 3–6 miembros que tiene 0–2 heteroátomos adicionales seleccionados entre N, O o S;

cada R^6 está seleccionado en forma independiente entre el grupo integrado por H, alquilo, arilo, aralquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, heteroarilo, heteroaralquilo, $-(CH_2)_{1-6}CF_3$, $-C(O)R^7$, $-C(O)OR^7$ y $-SO_2R^7$;

cada R^7 está seleccionado en forma independiente entre el grupo integrado por H, alquilo, arilo, aralquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, heteroarilo, y heteroaralquilo, en el cual cada miembro de R^7 excepto H está sustituido en forma opcional con 1–4 restos de R^8;

cada R^8 está seleccionado en forma independiente entre el grupo integrado por halo, alquilo, cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, arilo,

heteroarilo, $-NO_2$, $-OR^{10}$, –(alquilo C_1–C_6)–OR^{10}, –CN, $-NR^{10}R^{11}$, $-C(O)R^{10}$, $-C(O)OR^{10}$, $-C(O)NR^{10}R^{11}$, $-CF_3$, $-OCF_3$, $-CF_2CF_3$, $-C(=NOH)R^{10}$, $-N(R^{10})C(O)R^{11}$, $-C(=NR^{10})NR^{10}R^{11}$, y $-NR^{10}C(O)OR^{11}$; en el cual cada uno de dicho alquilo, cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, arilo, y heteroarilo está sustituido en forma opcional e independiente con 1–4 restos R^{42}; en el cual cuando cada uno de dicho cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, arilo, y heteroarilo contiene dos radicales sobre átomos de carbono adyacentes en cualquier parte dentro de dicho cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, arilo, y heteroarilo, y dichos radicales pueden ser tomados en forma opcional e independiente en cada aparición, junto con los átomos de carbono a los cuales están unidos, para formar un anillo carbocíclico o heterocíclico de cinco o seis miembros;

o dos grupos R^8, cuando están unidos al mismo carbono, se toman en forma opcional junto con el átomo de carbono al cual están unidos para formar un grupo C=O o un grupo C=S;

cada R^9 está seleccionado en forma independiente entre el grupo integrado por H, alquilo, alcoxi, OH, CN, halo, $-(CR^{10}R^{11})_{0-4}NR^4R^5$, haloalquilo, hidroxialquilo, alcoxialquilo, $-C(O)NR^4R^5$, $-C(O)OR^7$, $-OC(O)NR^4R^5$, $-NR^4C(O)R^5$, y $-NR^4C(O)NR^4R^5$;

cada R^{10} es en forma independiente H o alquilo; o R^9 y R^{10}, cuando están unidos al mismo átomo de nitrógeno, se toman en forma opcional junto con el átomo de nitrógeno al cual están unidos para formar un anillo heterocíclico de 3–6 miembros que tiene 0–2 heteroátomos adicionales seleccionados entre N, O o S;

cada R^{11} es en forma independiente H, alquilo, cicloalquilo, cicloalquenilo, arilo, heterociclilo, heterociclenilo, o heteroarilo; o R^{10} y R^{11}, cuando están unidos al mismo átomo de nitrógeno, se toman en forma opcional junto con el átomo de nitrógeno al cual están unidos para formar un anillo heterocíclico de 3–6

miembros que tiene 0–2 heteroátomos adicionales seleccionados entre N, O o S; en el cual cada uno de dicho R^{11} alquilo, cicloalquilo, cicloalquenilo, arilo, heterociclilo, heterociclenilo, y heteroarilo está sustituido en forma opcional e independiente con 1–3 restos seleccionados entre el grupo integrado por –CN, –OH, $–NH_2$, –N(H)alquilo, $–N(alquilo)_2$, halo, haloalquilo, CF_3, alquilo, hidroxialquilo, alcoxi, arilo, ariloxi, y heteroarilo;

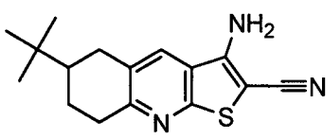
cada R^{12} está seleccionado en forma independiente entre el grupo integrado por H, halo, alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo, heteroaralquilo, $–(CR^{10}R^{11})_{0–6}–OR^7$, $–C(O)R^4$, $–C(S)R^4$, $–C(O)OR^7$, $–C(S)OR^7$, $–OC(O)R^7$, $–OC(S)R^7$, $–C(O)NR^4R^5$, $–C(S)NR^4R^5$, $–C(O)NR^4OR^7$, $–C(S)NR^4OR^7$, $–C(O)NR^7NR^4R^5$, $–C(S)NR^7NR^4R^5$, $–C(S)NR^4OR^7$, $–C(O)SR^7$, $–NR^4R^5$, $–NR^4C(O)R^5$, $–NR^4C(S)R^5$, $–NR^4C(O)OR^7$, $–NR^4C(S)OR^7$, $–OC(O)NR^4R^5$, $–OC(S)NR^4R^5$, $–NR^4C(O)NR^4R^5$, $–NR^4C(S)NR^4R^5$, $–NR^4C(O)NR^4OR^7$, $–NR^4C(S)NR^4OR^7$, $–(CR^{10}R^{11})_{0–6}SR^7$, SO_2R^7, $–S(O)_{1–2}NR^4R^5$, $–N(R^7)SO_2R^7$, $–S(O)_{1–2}NR^5OR^7$, –CN, $–OCF_3$, $–SCF_3$, $–C(=NR^7)NR^4$, $–C(O)NR^7(CH_2)_{1–10}NR^4R^5$, $–C(O)NR^7(CH_2)_{1–10}OR^7$, $–C(S)NR^7(CH_2)_{1–10}NR^4R^5$, $–C(S)NR^7(CH_2)_{1–10}OR^7$, haloalquilo y alquilsililo, en el cual cada uno de dicho alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo o heteroaralquilo está sustituido en forma opcional e independiente con 1–5 restos de R^9;

R^{40} y R^{41} pueden ser iguales o diferentes, estando cada uno seleccionado en forma independiente entre el grupo integrado por H, alquilo, arilo, heteroarilo, heterociclilo, heterociclenilo, cicloalquilo y cicloalquenilo;

cada R^{42} está seleccionado en forma independiente entre el grupo integrado por halo, alquilo, cicloalquilo, heterociclilo, arilo, heteroarilo, $–NO_2$, $–OR^{10}$, $–(C_1–C_6$ alkyl$)–OR^{10}$, –CN, $–NR^{10}R^{11}$, $–C(O)R^{10}$, $–C(O)OR^{10}$, $–C(O)NR^{10}R^{11}$, $–CF_3$, $–OCF_3$, $–N(R^{10})C(O)R^{11}$, y $–NR^{10}C(O)OR^{11}$;

con la condición de que cuando W es $C(R^{12})$, R^{12} y R^3 se toman en forma opcional junto, con los dos átomos de carbono en el anillo a los cuales están unidos para formar un anillo de 6 miembros seleccionado entre el grupo integrado por cicloalquenilo, arilo, heteroarilo, heterociclilo y heterociclenilo, en el cual dicho anillo de 6 miembros está sustituido en forma opcional con 1–3 restos seleccionados en forma independiente entre oxo, tioxo, $-OR^{11}$, $-NR^{10}R^{11}$, $-C(O)R^{11}$, $-C(O)OR^{11}$, $-C(O)N(R^{10})(R^{11})$, o $-N(R^{10})C(O)R^{11}$.

Dichos compuestos de la Fórmula B en (b) se divulgan en WO2006/098961, presentada el 7 de marzo de 2006, cuyo contenido se incorpora a la presente en su totalidad a modo de referencia;

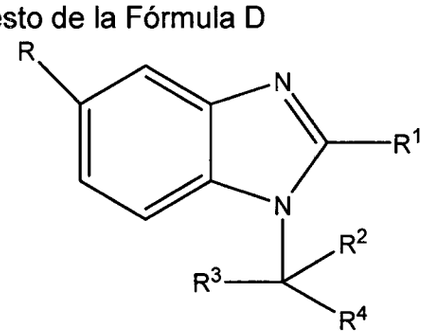
c. 

Fórmula C

o una sal, solvato, o éster del mismo, aceptables para uso farmacéutico.

Dichos compuestos de la Fórmula C en (c) se divulgan en la Publicación de EEUU Nº 2006/0258699, presentada el 7 de marzo de 2006, cuyo contenido se incorpora a la presente en su totalidad a modo de referencia; y

d. Un compuesto de la Fórmula D



Fórmula D

o una sal, solvato, o éster del mismo, aceptables para uso farmacéutico, en el cual:

R está seleccionado entre el grupo integrado por H, alquilo, ciano, haloalquilo, halo, —SH, –S–alquilo, –S–haloalquilo, $-S(=O)_2$alquilo, $-S(=O)_2OH$, $-S(=O)_2NH_2$, $-S(=O)_2$NH(alquilo), $S(=O)_2$NH(cicloalquilo), $-S(=O)_2$N(alquilo)$_2$, $-S(=O)_2$heterociclilo, $-S(=O)_2$heteroarilo, cicloalquilo, arilo, heterociclilo, heteroarilo, –NHC(=O)alquilo, $-C(=O)NH_2$, –C(=O)NH(alquilo), –C(=O)NH(cicloalquilo), –C(=O)N(alquilo)$_2$, –C(=O)OH, –C(=O)Oalquilo, –C(=O)heterociclilo, –C(=O)NH(arilo), en el cual cuando cada uno de dicho cicloalquilo, arilo, heterociclilo, heteroarilo, y las porciones "heterociclilo" y "arilo" de dichos grupos R tiene dos sustituyentes sobre átomos de carbono adyacentes, dichos sustituyentes en forma opcional junto con los átomos de carbono a los cuales están unidos pueden formar un anillo cicloalquilo, arilo, heterociclilo, heterociclenilo, o heteroarilo de cinco a seis miembros; en el cual cada uno de los R alquilo, arilo, cicloalquilo, heterociclilo, y heteroarilo anteriormente mencionados, y las porciones "alquilo", "cicloalquilo", "heterociclilo", y "arilo" de dichos grupos R, en forma opcional con dicho anillo arilo, heterociclilo, heterociclenilo, o heteroarilo de cinco a seis miembros, está sustituido en forma opcional con 1–3 sustituyentes seleccionados en forma independiente entre el grupo integrado por alquilo, alquenilo, alquinilo, hidroxilo, ciano, halo, haloalquilo, haloalcoxi, –C(O)OH, –C(=O)Oalquilo, y $-C(O)NH_2$;

R^1 está seleccionado entre el grupo integrado por alquilo, heterociclilo, –C(=O)arilo, $-NH_2$, –NH(alquilo), –NH(cicloalquilo), –N(alquilo)(cicloalquilo), –NH(heterociclilo),–N(alquil)(heterociclilo), N(alquilo)$_2$, –NH(arilo), –N(alquil)(arilo), –N(arilo)$_2$, –NH(heteroarilo), –N(alquil)(heteroarilo), –NHC(=O)–alquilo, –N(alquil)C(=O)–alquilo, –NHC(=O)Oalquilo, –N(alquil)C(=O)O–alquilo, en el cual cada uno de los alquilo, heterociclilo anteriormente mencionados, y las porciones "alquilo", "cicloalquilo", "arilo", y "heteroarilo" de dichos grupos R^1 está sustituido en forma opcional con 1–3 sustituyentes seleccionados en forma independiente

entre el grupo integrado por halo, heterociclilo, arilo, heteroarilo, haloalquilo, haloalcoxi, ariloxi, ciano, –SH, –S–alquilo, –S–haloalquilo, $–S(=O)_2$alquilo, $–S(=O)_2OH$, $–S(=O)_2NH_2$, $–S(=O)_2$NH(alquilo), $S(=O)_2$NH(cicloalquilo), $–S(=O)_2N$(alquilo)$_2$, $–S(=O)_2$heterociclilo, $–S(=O)_2$heteroarilo, hidroxi, alquilo, alquenilo, alquinilo, $–NH_2$, –NH(alquilo), –N(alquilo)$_2$, alcoxi, –NHC(=O)alquilo, –C(=O)H, –C(=O)alquilo, –C(=O)arilo, , –C(=O)heteroarilo, –C(=O)Oalquilo, $–C(=O)NH_2$, –C(O)NHalquilo, –C(=O)N(alquilo)$_2$; en el cual cuando cada uno de dicho heterociclilo, arilo y heteroarilo tiene dos sustituyentes sobre átomos de carbono adyacentes, dichos sustituyentes en forma opcional junto con los átomos de carbono a los cuales están unidos pueden formar un anillo arilo, heterociclilo, heterociclenilo, o heteroarilo de cinco a seis miembros;

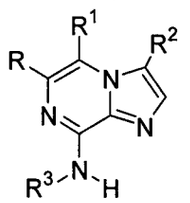
R^2 y R^3 son en forma independiente H o alquilo, o $–C(R^2)(R^3)–$ está ausente;

R^4 está seleccionado entre el grupo integrado por alquilo, cicloalquilo, heterociclilo, arilo y heteroarilo, en el cual cuando cada uno de dicho cicloalquilo, heterociclilo, arilo, y heteroarilo tiene dos sustituyentes sobre átomos de carbono adyacentes, dichos sustituyentes en forma opcional junto con los átomos de carbono a los cuales están unidos pueden formar un anillo arilo, heterociclilo, heterociclenilo, o heteroarilo de cinco a seis miembros; en el cual cada uno de los R^4 alquilo, cicloalquilo, heterociclilo, arilo y heteroarilo anteriormente mencionados, en forma opcional con dicho anillo arilo, heterociclilo, heterociclenilo, o heteroarilo de cinco a seis miembros está sustituido en forma opcional con 1–3 sustituyentes seleccionados en forma independiente entre el grupo integrado por ciano, halo, haloalquilo, alquilo, alcoxi, hidroxilo, haloalcoxi, cicloalquilo, heterociclilo, arilo, heteroarilo, $–S(=O)_2$alquilo, $–S(=O)_2NH_2$, $–S(=O)_2$NH(alquilo), $–S(=O)_2N$(alquilo)$_2$, –S–alquilo, –S–haloalquilo, –C(=O)OH, $–NH_2$, –NH(alquilo), –N(alquilo)$_2$, y –C(=O)Oalquilo.

Los compuestos representados en la presente solicitud por la Fórmula (d) se divulgan en PCT US2008/006472, presentada el 21 de mayo de 2008, cuyo contenido se incorpora a la presente en su totalidad a modo de referencia;

Algunos ejemplos no restrictivos de inhibidores de aurora quinasa apropiados, útiles en la presente invención, incluyen los compuestos representados por las Fórmulas E–K que se indican en los párrafos e–k que aparecen a continuación:

e. Un compuesto representado por la Fórmula estructural E:



Fórmula E

o una sal, solvato, éster o prodroga del mismo, aceptables para uso farmacéutico, en el cual:

R es H, CN, $-NR^5R^6$, cicloalquilo, cicloalquenilo, heterociclenilo, heteroarilo, $-C(O)NR^5R^6$, $-N(R^5)C(O)R^6$, heterociclilo, heteroarilo sustituido con $(CH_2)_{1-3}$ NR^5R^6, alquilo insustituido, o alquilo sustituido con uno o más restos que pueden ser iguales o diferentes donde cada resto está seleccionado en forma independiente entre el grupo integrado por $-OR^5$, heterociclilo, $-N(R^5)C(O)N(R^5R^6)$, $-N(R^5)-C(O)OR^6$, $-(CH_2)_{1-3}-N(R^5R^6)$ y $-NR^5R^6$;

R^1 es H, Halo, arilo o heteroarilo, en el cual cada uno de dicho arilo y heteroarilo puede estar insustituido o sustituido con uno o más restos que pueden ser iguales o diferentes, donde cada resto está seleccionado en forma independiente entre el grupo integrado por halo, alquilo, alquenilo, alquinilo, cicloalquilo, arilo, heteroarilo, heterociclilo, $-CH_2OR^5$, $-C(O)NR^5R^6$, $-C(O)OH$, $-C(O)NH_2$, $-NR^5R^6$ (en el cual R^5 y R^6, junto con el N de dicho $-NR^5R^6$, forman un anillo heterociclilo), $-S(O)R^5$, $-S(O_2)R^5$, $-CN$, $-CHO$, $-SR^5$, $-C(O)OR^5$, $-C(O)R^5$ y

$-OR^5$;

R^2 es H, halo, arilo, arilalquilo o heteroarilo, en el cual cada uno de dicho arilo, arilalquilo y heteroarilo puede estar insustituido o en forma opcional e independiente puede estar sustituido con uno o más restos que pueden ser iguales o diferentes donde cada resto está seleccionado en forma independiente entre el grupo integrado por halo, amida, alquilo, alquenilo, alquinilo, cicloalquilo, arilo, $-C(O)OH$, $-C(O)NH_2$, $-NR^5R^6$ (en el cual R^5 y R^6, junto con el N de dicho $-NR^5R^6$, forman un anillo heterociclilo), $-CN$, arilalquilo, $-CH_2OR^5$, $-S(O)R^5$, $-S(O_2)R^5$, $-CN$, $-CHO$, $-SR^5$, $-C(O)OR^5$, $-C(O)R^5$, heteroarilo y heterociclilo;

R^3 es H, alquilo, cicloalquilo, heterociclilo, arilo o heteroarilo, en el cual:

– dicho alquilo indicado anteriormente para R^3 puede estar insustituido o sustituido con uno o más restos que pueden ser iguales o diferentes donde cada resto está seleccionado en forma independiente entre el grupo integrado por $-OR^5$, alcoxi, heteroarilo, y $-NR^5R^6$;

– dicho arilo indicado anteriormente para R^3 es insustituido, o sustituido en forma opcional, o fusionado en forma opcional, con halo, heteroarilo, heterociclilo, cicloalquilo o heteroarilalquilo, en el cual cada uno de dicho heteroarilo, heterociclilo, cicloalquilo y heteroarilalquilo puede estar insustituido o sustituido en forma opcional e independiente con uno o más restos que pueden ser iguales o diferentes donde cada resto está seleccionado en forma independiente entre alquilo, $-OR^5$, $-N(R^5R^6)$ y $-S(O_2)R^5$; y

– dicho heteroarilo indicado anteriormente para R^3 puede estar insustituido o sustituido en forma opcional, o fusionado en forma opcional, con uno o más restos que pueden ser iguales o diferentes donde cada resto está seleccionado en forma independiente entre el grupo integrado por halo, amino, alcoxicarbonilo, $-OR^5$, alquilo, $-CHO$, $-NR^5R^6$, $-S(O_2)N(R^5R^6)$, $-C(O)N(R^5R^6)$, $-SR^5$, alquenilo, alquinilo, cicloalquilo, arilo, heteroarilo, heterociclenilo, y heterociclilo;

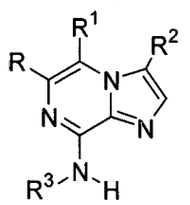
R^5 es H, alquilo, aminoalquilo, arilo, heteroarilo, heterociclilo o cicloalquilo, y

R^6 es H, alquilo, arilo, arilalquilo, heteroarilo, heterociclilo o cicloalquilo;

en el cual además en cualquier $-NR^5R^6$ en la Fórmula I, dicho R^5 y R^6 pueden estar unidos en forma opcional junto con el N de dicho $-NR^5R^6$ para formar un anillo cíclico.

Dichos compuestos de la Fórmula E en (e) se divulgan en WO2007/058942 presentada el 8 de noviembre de 2006, cuyo contenido se incorpora a la presente en su totalidad a modo de referencia;

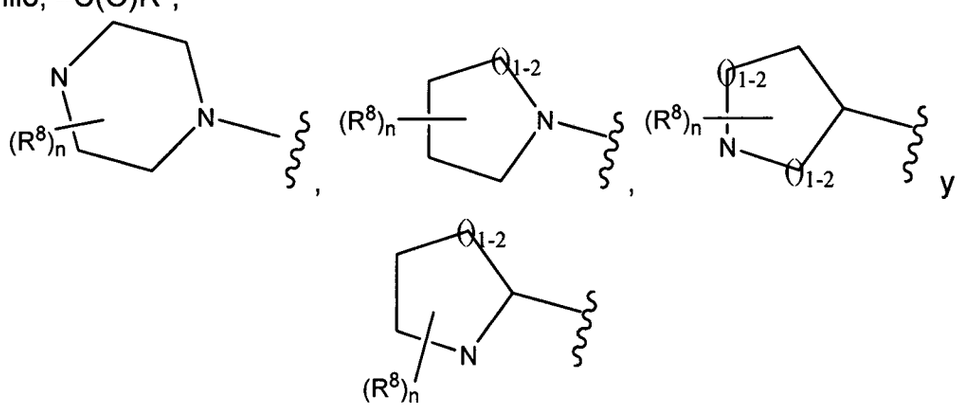
f. Un compuesto representado por la Fórmula estructural:



Fórmula F

o una sal, solvato, éster o prodroga del mismo, aceptables para uso farmacéutico, en el cual:

R está seleccionado entre el grupo integrado por H, halógeno, arilo, heteroarilo, cicloalquilo, arilalquilo, heterociclilo, heterociclilalquilo, alquenilo, alquinilo, $-C(O)R^7$,

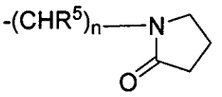
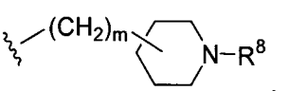


en el cual cada uno de dicho arilo, heteroarilo, cicloalquilo, arilalquilo, alquenilo, heterociclilo y los restos heterociclilo cuyas estructuras se indican inmediatamente con anterioridad para R pueden estar insustituidos o sustituidos en forma opcional

e independiente con uno o más restos que pueden ser iguales o diferentes, donde cada resto está seleccionado en forma independiente entre el grupo integrado por halógeno, alquilo, cicloalquilo, CF_3, CN, $-OCF_3$, $-OR^6$, $-C(O)R^7$, $-NR^5R^6$, $-C(O_2)R^6$, $-C(O)NR^5R^6$, $-(CHR^5)_nOR^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^6$;

R^1 es H, halógeno o alquilo;

R^2 es alquilo;

R^3 está seleccionado entre el grupo integrado por H, arilo, heteroarilo, heterociclilo, $-(CHR^5)_n$–arilo, – $(CHR^5)_n$–heteroarilo, $-(CHR^5)_n-OR^6$, $-S(O_2)R^6$, $-C(O)R^6$, $-S(O_2)NR^5R^6$, $-C(O)OR^6$, $-C(O)NR^5R^6$, cicloalquilo, $-CH(arilo)_2$, $-(CH_2)_m-NR^8$, $-(CHR^5)_n-CH(arilo)_2$,  y  , en el cual cada uno de dicho arilo, heteroarilo y heterociclilo puede estar sustituido o sustituido en forma opcional con uno o más restos que pueden ser iguales o diferentes, donde cada resto está seleccionado en forma independiente entre el grupo integrado por halógeno, alquilo, arilo, cicloalquilo, CF_3, CN, $-OCF_3$, $-OR^5$, $-NR^5R^6$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^6$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^6$;

R^5 es H o alquilo;

R^6 está seleccionado entre el grupo integrado por H, alquilo, arilo, heteroarilo, arilalquilo y heteroarilalquilo, en el cual cada uno de dicho alquilo, heteroarilalquilo, arilo, heteroarilo y arilalquilo puede estar insustituido o sustituido en forma opcional con uno o más restos que pueden ser iguales o diferentes, donde cada resto está seleccionado en forma independiente entre el grupo integrado por halógeno, alquilo, arilo, cicloalquilo, CF_3, OCF_3, CN, $-OR^5$, $-NR^5R^6$, $-CH_2OR^5$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^6$;

R^7 está seleccionado entre el grupo integrado por alquilo, arilo, heteroarilo, arilalquilo y heteroarilalquilo, en el cual cada uno de dicho alquilo, heteroarilalquilo, arilo, heteroarilo y arilalquilo puede estar insustituido o sustituido en forma opcional con uno o más restos que pueden ser iguales o diferentes, donde cada resto está seleccionado en forma independiente entre el grupo integrado por halógeno, alquilo, arilo, cicloalquilo, CF_3, OCF_3, CN, $-OR^5$, $-NR^5R^6$, $-CH_2OR^5$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^6$;

R^8 está seleccionado entre el grupo integrado por R^6, $-C(O)NR^5R^6$, $-S(O_2)NR^5R^6$, $-C(O)R^7$, $-C(O_2)R^6$, $-S(O_2)R^7$ and $-(CH_2)-$arilo;

R^9 está seleccionado entre el grupo integrado por halógeno, CN, NR^5R^6, $-C(O_2)R^6$, $-C(O)NR^5R^6$, $-OR^6$, $-C(O)R^7$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^6$;

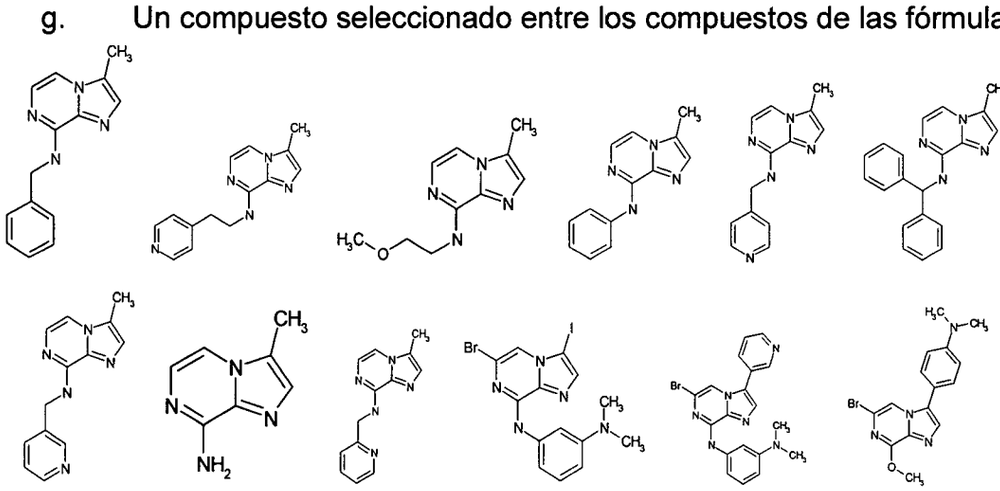
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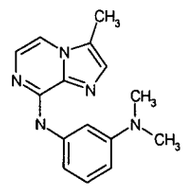
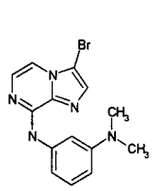
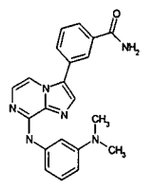
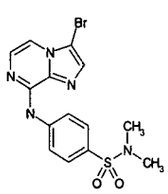
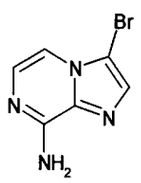
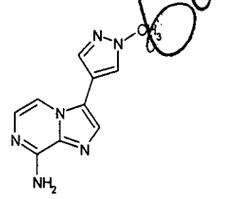
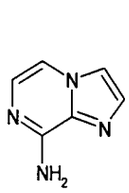
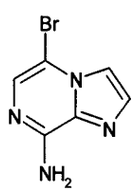
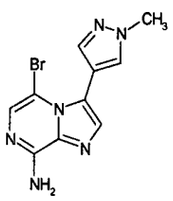
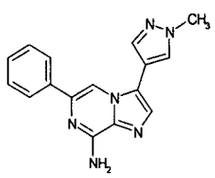
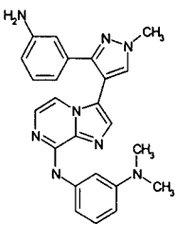
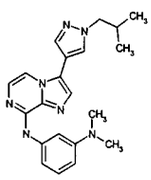
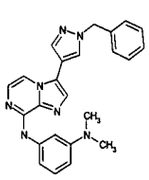
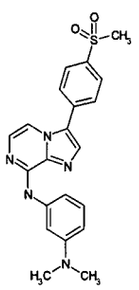
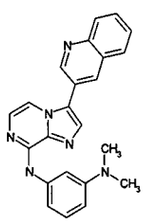
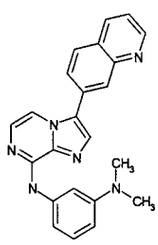
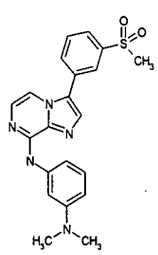
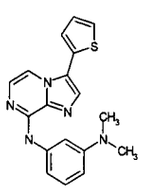
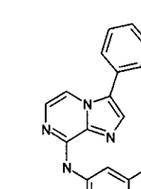
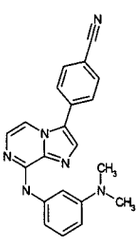
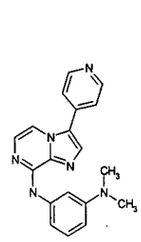
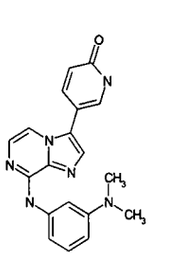
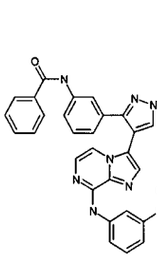
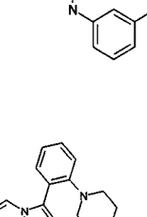
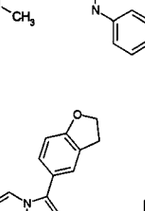
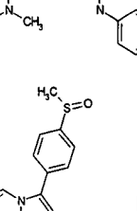
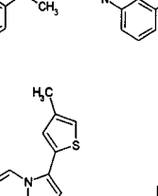
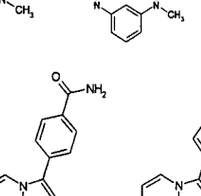
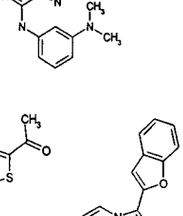
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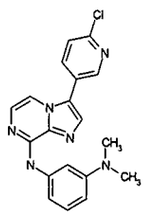
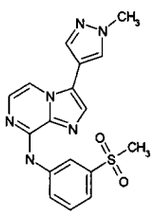
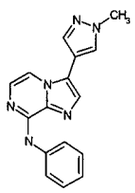
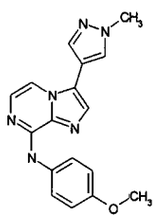
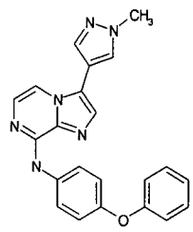
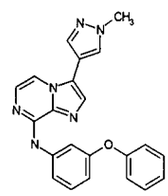
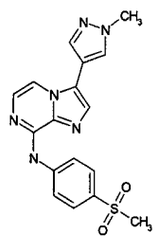
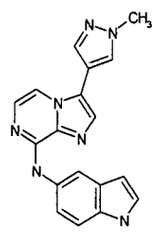
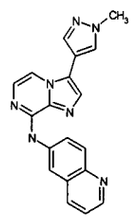
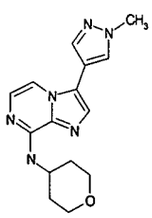
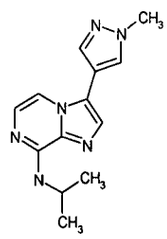
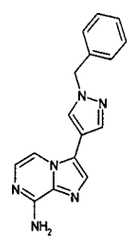
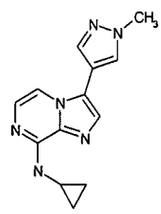
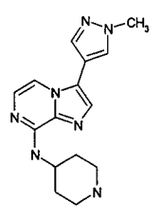
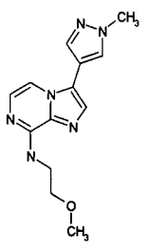
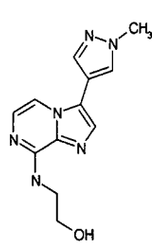
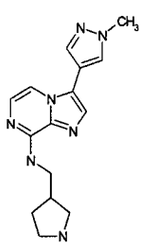
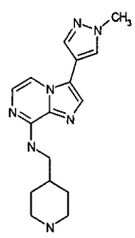
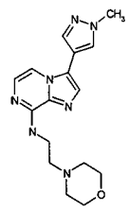
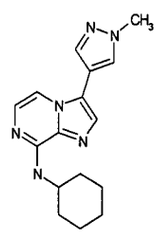
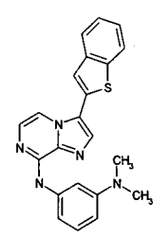
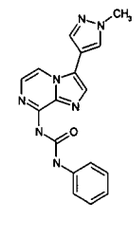
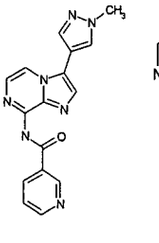
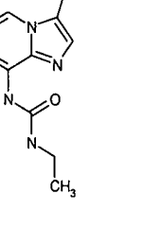
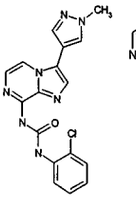
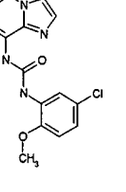
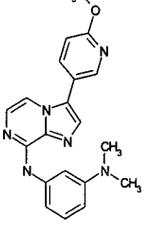
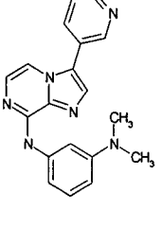
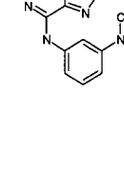
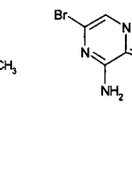
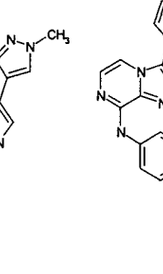
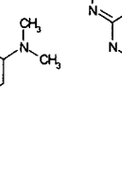
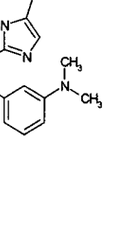
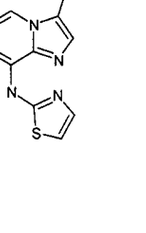
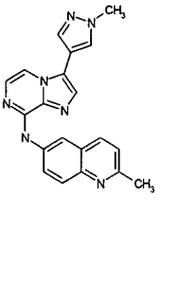
p es 0–3.

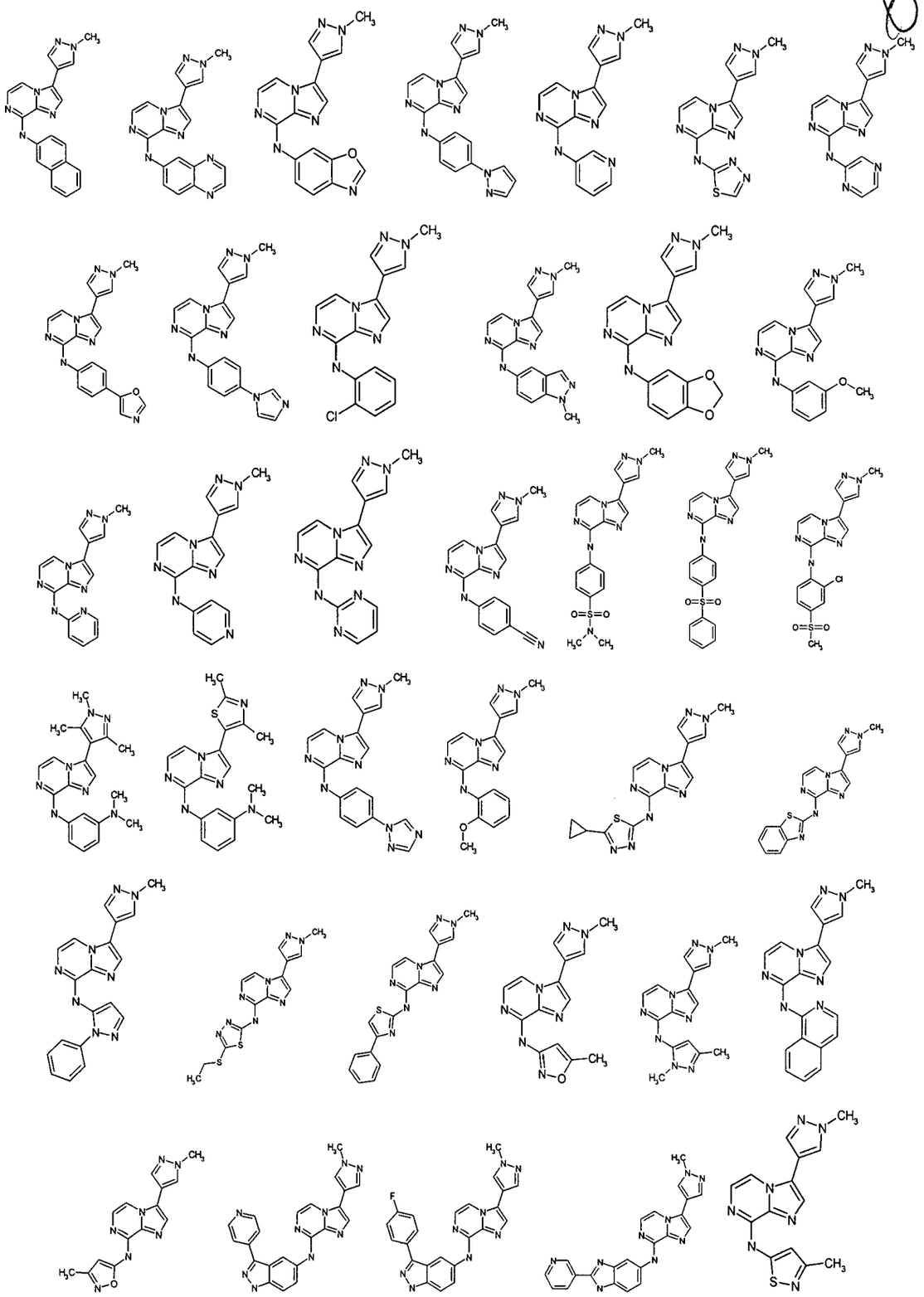
Dichos compuestos de la Fórmula F en (f) se divulgan en WO2004/026877, presentada el 19 de septiembre de 2003, cuyo contenido se incorpora a la presente en su totalidad a modo de referencia;

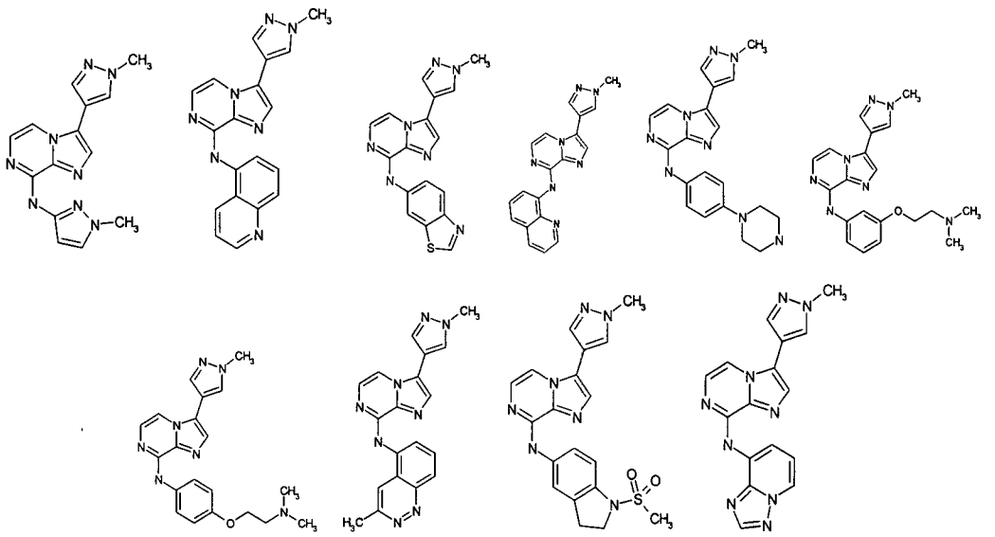
g. Un compuesto seleccionado entre los compuestos de las fórmulas:

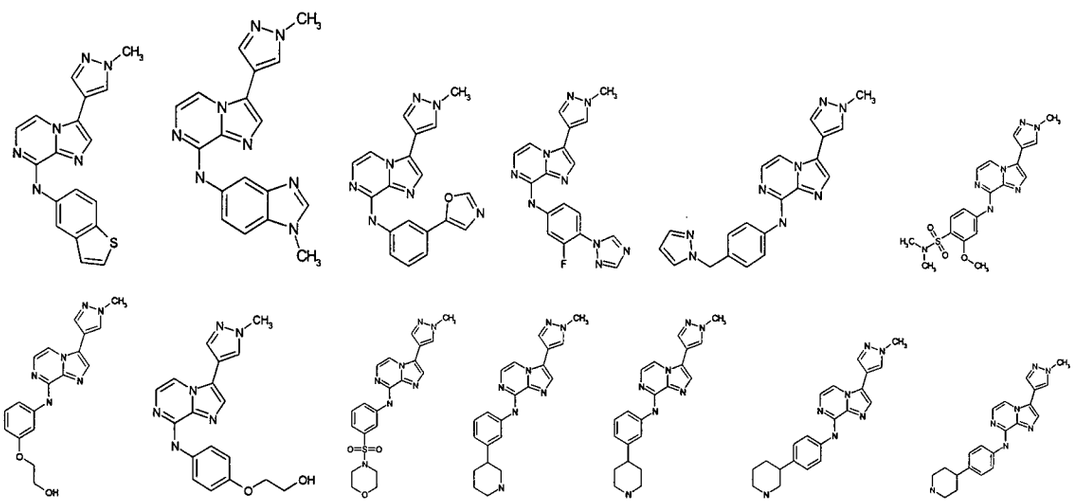


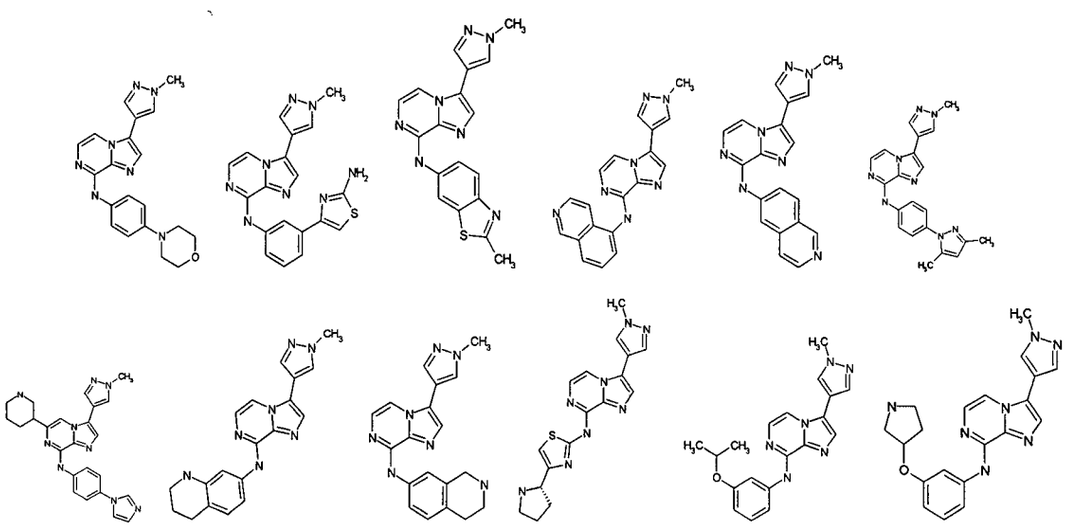






























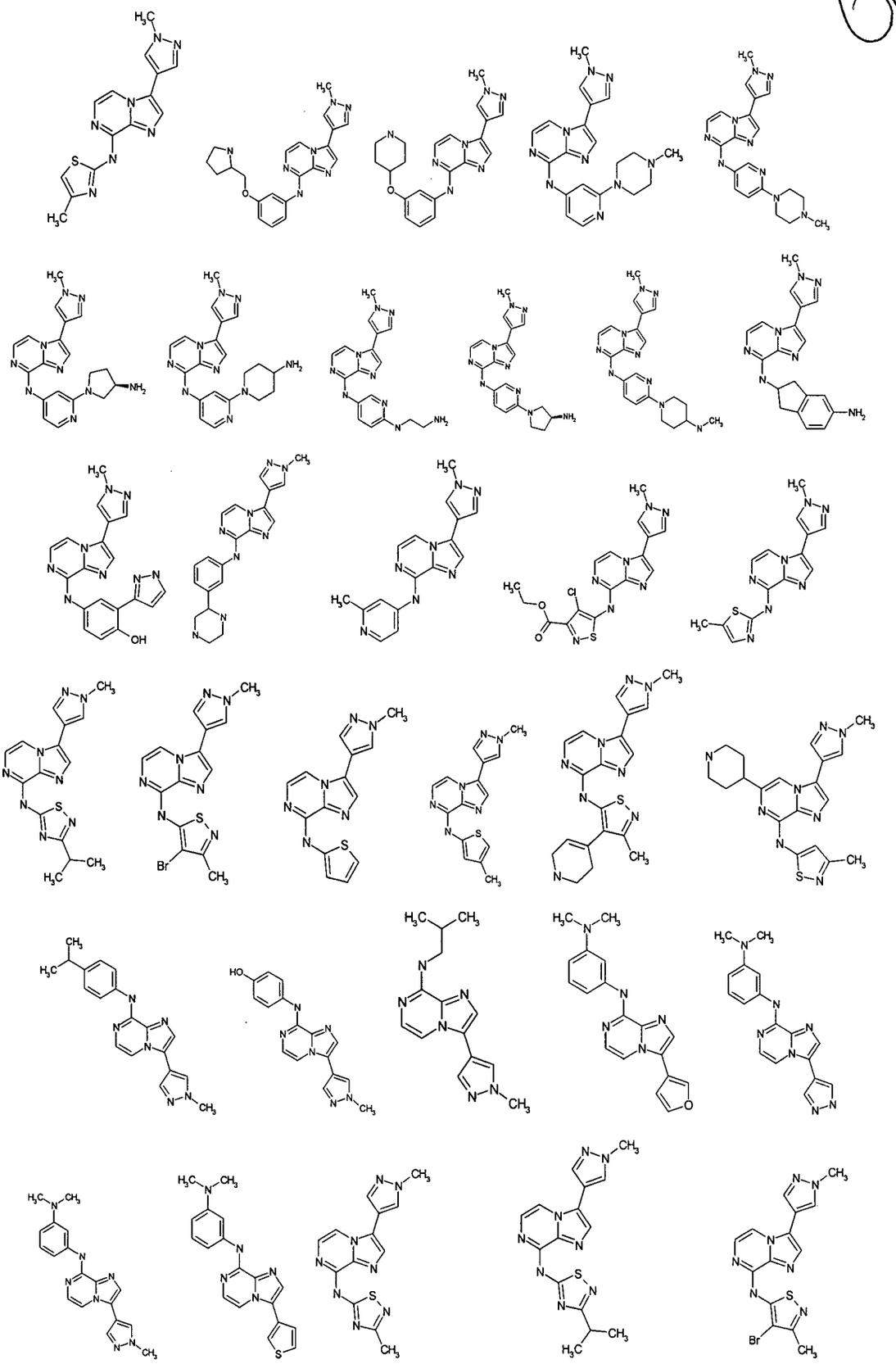


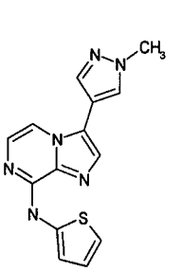
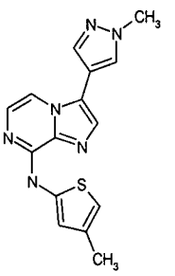
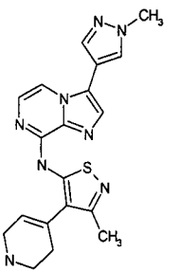
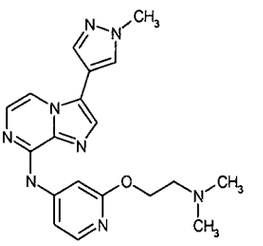
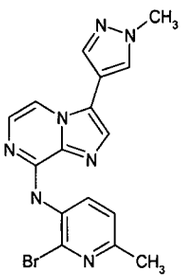
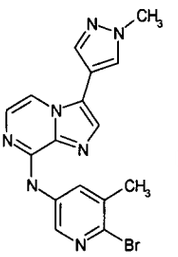
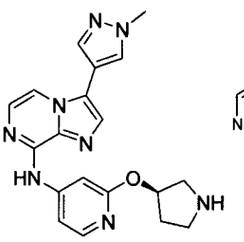
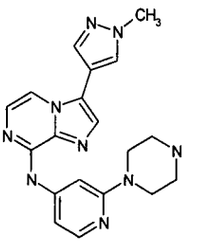
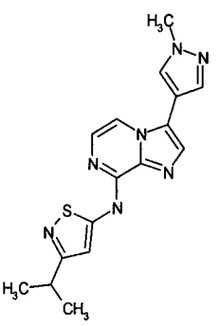
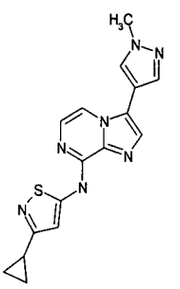
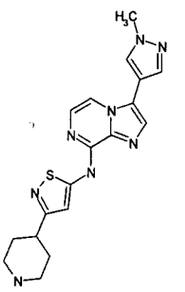
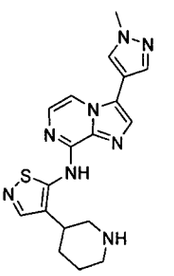
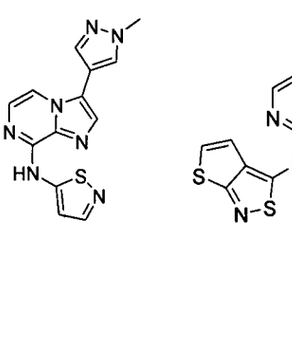
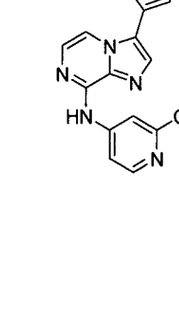
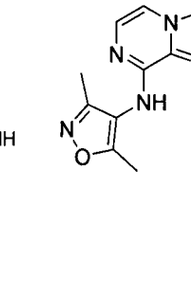
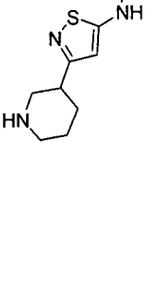


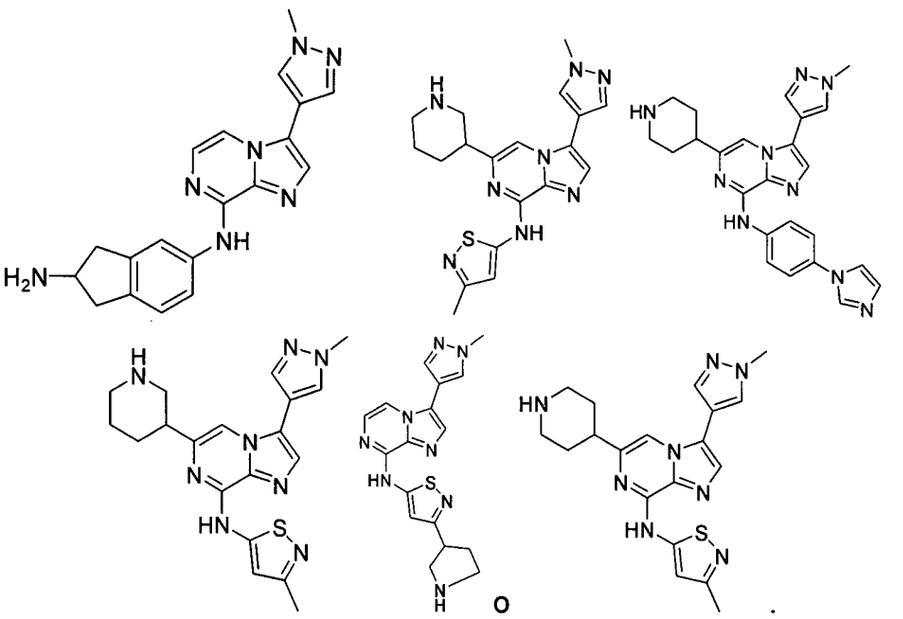








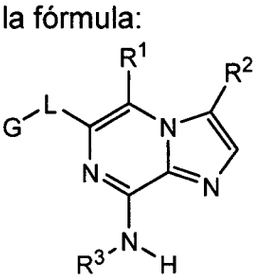



















o una sal, solvato, éster o prodroga del mismo, aceptables para uso farmacéutico.

Dichos compuestos de la Fórmula G en (g) se divulgan en WO2007/058873, presentada el 8 de noviembre de 2006, cuyo contenido se incorpora a la presente en su totalidad a modo de referencia;

h. Un compuesto de la fórmula:



Fórmula H

o una sal, solvato, éster o prodroga del mismo, aceptables para uso farmacéutico, en el cual:

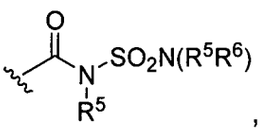
L está seleccionado entre el grupo integrado por S, S(O) y $S(O_2)$;

G es alquilo, alquenilo, cicloalquilo, cicloalquenilo, arilo, heteroarilo, heterociclenilo o heterociclilo, en el cual cada uno de dicho alquilo, alquenilo, cicloalquilo, cicloalquenilo, arilo, heteroarilo, heterociclenilo o heterociclilo puede estar insustituido o sustituido en forma opcional e independiente con uno o más restos que están seleccionados en forma independiente entre el grupo integrado

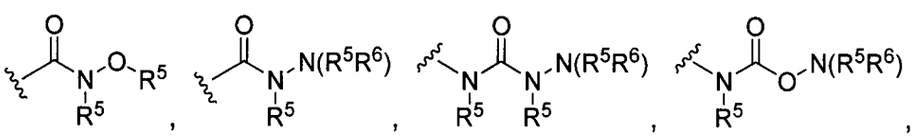
por $-OR^5$, halo, $-CN$, $-C(O)NR^5R^6$, $-N(H)-C(O)R^5$,$-N(H)-C(O)-NR^5R^6$, $-S(O_2)NR^5R^6$, $-NR^5R^6$, $-C(O)R^5$, $-C(O_2)R^5$, $-SR^5$, $-S(O)R^5$, $-S(O_2)R^5$;

R^1 es H, halo, alquilo, arilo o heteroarilo, en el cual cada uno de dicho alquilo, arilo y heteroarilo puede estar insustituido o sustituido con uno o más restos que pueden ser iguales o diferentes donde cada resto está seleccionado en forma independiente entre el grupo integrado por halo, alquilo, alquenilo, alquinilo, cicloalquilo, arilo, heteroarilo, heterociclilo, $-C(O)NR^5R^6$ y $-OR^5$;

R^2 está seleccionado entre el grupo integrado por H, R^9, alquilo, arilo, arilalquilo, heteroarilo, heteroarilalquilo, heterociclilo, alquenilo, alquinilo, cicloalquilo, cicloalquilalquilo, heterociclilalquilo, $-CF_3$, $-C(O)R^7$,

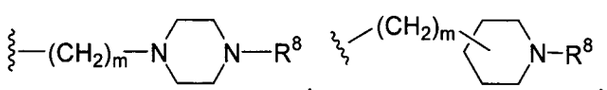


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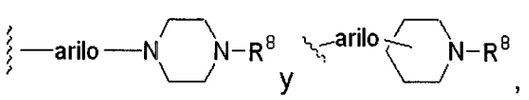


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alquilo sustituido con 1–6 grupos R^9 cuyos grupos pueden ser los mismos o diferentes donde cada R^9 está seleccionado en forma independiente,



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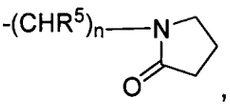
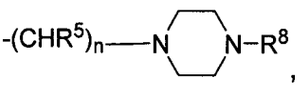
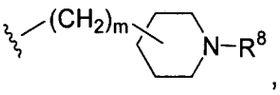


y

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en el cual cada uno de arilo, heteroarilo, cicloalquilo, arilalquilo y heterociclilo mencionados anteriormente puede estar insustituido o sustituido en forma opcional e independiente con uno o más restos que pueden ser iguales o diferentes, donde cada resto está seleccionado en forma independiente entre el grupo integrado por halo, alquilo, alquenilo, alquinilo, cicloalquilo, arilo, heteroarilo, heterociclilo, CF_3, CN, $-OCF_3$, $-OR^6$, $-C(O)R^7$, $-NR^5R^6$, $-C(O_2)R^6$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^6$;

R^3 está seleccionado entre el grupo integrado por H, alquilo, arilo, heteroarilo, heterociclilo, aralquilo, heteroarilalquilo, cicloalquilalquilo, heterociclilalquilo,



$-(CHR^5)_n-OR^6$, $-S(O_2)R^6$, $-C(O)R^6$, $-S(O_2)NR^5R^6$, $-C(O)OR^6$, $-C(O)NR^5R^6$, cicloalquilo, $-CH(arilo)_2$, $-CH(heteroarilo)_2$, $-(CH_2)_m-NR^8$, y  , en el cual cada uno de dicho alquilo, arilo, heteroarilo y heterociclilo puede estar sustituido o sustituido en forma opcional con uno o más restos que pueden ser iguales o diferentes, donde cada resto está seleccionado en forma independiente entre el grupo integrado por halo, alquilo, arilo, cicloalquilo, CF_3, CN, $-OCF_3$, $-OR^5$, $-NR^5R^6$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^6$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^6$;

R^5 es H, alquilo, arilo, heteroarilo, heterociclilo o cicloalquilo; y

R^6 está seleccionado entre el grupo integrado por H, alquilo, arilo, heteroarilo, arilalquilo y heteroarilalquilo, en el cual cada uno de dicho alquilo, heteroarilalquilo, arilo, heteroarilo y arilalquilo puede estar insustituido o sustituido en forma opcional con uno o más restos que pueden ser iguales o diferentes, donde cada resto está seleccionado en forma independiente entre el grupo integrado por halógeno, alquilo, arilo, cicloalquilo, CF_3, OCF_3, CN, $-OR^5$, $-NR^5R^6$, $-CH_2OR^5$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^6$;

R^7 está seleccionado entre el grupo integrado por alquilo, arilo, heteroarilo, arilalquilo y heteroarilalquilo, en el cual cada uno de dicho alquilo, heteroarilalquilo, arilo, heteroarilo y arilalquilo puede estar insustituido o sustituido en forma opcional con uno o más restos que pueden ser iguales o diferentes, donde cada resto está seleccionado en forma independiente entre el grupo integrado por halógeno, alquilo, arilo, cicloalquilo, CF_3, OCF_3, CN, $-OR^5$, $-NR^5R^6$,

$-CH_2OR^5$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^6$;

R^8 está seleccionado entre el grupo integrado por R^6, $-C(O)NR^5R^6$, $-S(O_2)NR^5R^6$, $-C(O)R^7$, $-C(O_2)R^6$, $-S(O_2)R^7$ y $-(CH_2)$–arilo;

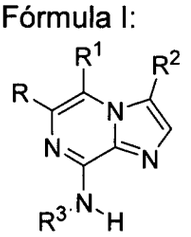
R^9 está seleccionado entre el grupo integrado por halógeno, CN, NR^5R^6, $-C(O_2)R^6$, $-C(O)NR^5R^6$, $-OR^6$, $-C(O)R^7$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$y $-N(R^5)C(O)NR^5R^6$;

m es 0 a 4; y

p es 0–3.

Dichos compuestos de la Fórmula H en (h) se divulgan en WO 2008/054749, presentada el 29 de octubre de 2007, cuyos contenidos se incorporan a la presente en su totalidad a modo de referencia;

i. Un compuesto de la Fórmula I:



Fórmula I

o una sal, solvato, éster o prodroga del mismo, aceptables para uso farmacéutico, en el cual:

R es H, CN, $-NR^5R^6$, cicloalquilo, cicloalquenilo, heterociclenilo, heteroarilo, $-C(O)NR^5R^6$, $-N(R^5)C(O)R^6$, heterociclilo, heteroarilo sustituido con $(CH_2)_{1-3}$ NR^5R^6, alquilo insustituido, o alquilo sustituido con uno o más restos que pueden ser iguales o diferentes donde cada resto está seleccionado en forma independiente entre el grupo integrado por $-OR^5$, heterociclilo, $-N(R^5)C(O)N(R^5R^6)$, $-N(R^5)$–$C(O)OR^6$, $-(CH_2)_{1-3}$–$N(R^5R^6)$ y $-NR^5R^6$;

R^1 es H, Halo, arilo o heteroarilo, en el cual cada uno de dicho arilo y heteroarilo puede estar insustituido o sustituido con uno o más restos que pueden

ser iguales o diferentes donde cada resto está seleccionado en forma independiente entre el grupo integrado por halo, alquilo, alquenilo, alquinilo, cicloalquilo, arilo, heteroarilo, heterociclilo, $-CH_2OR^5$, $-C(O)NR^5R^6$, $-C(O)OH$, $-C(O)NH_2$, $-NR^5R^6$ (en el cual R^5 y R^6, junto con el N de dicho $-NR^5R^6$, forman un anillo heterociclilo), $-S(O)R^5$, $-S(O_2)R^5$, $-CN$, $-CHO$, $-SR^5$, $-C(O)OR^5$, $-C(O)R^5$ y $-OR^5$;

R^2 es H, halo, arilo, arilalquilo o heteroarilo, en el cual cada uno de dicho arilo, arilalquilo y heteroarilo puede estar insustituido o en forma opcional e independiente puede estar sustituido con uno o más restos que pueden ser iguales o diferentes donde cada resto está seleccionado en forma independiente entre el grupo integrado por halo, amida, alquilo, alquenilo, alquinilo, cicloalquilo, arilo, $-C(O)OH$, $-C(O)NH_2$, $-NR^5R^6$ (en el cual R^5 R^6, junto con el N de dicho $-NR^5R^6$, forman un anillo heterociclilo), $-CN$, arilalquilo, $-CH_2OR^5$, $-S(O)R^5$, $-S(O_2)R^5$, $-CN$, $-CHO$, $-SR^5$, $-C(O)OR^5$, $-C(O)R^5$, heteroarilo y heterociclilo;

R^3 es heterociclil–$(CR^7R^8)_n$–X, heterociclenil–$(CR^7R^8)_n$–X, heteroaril–$(CR^7R^8)_n$–X o aril–$(CR^7R^8)_n$–X en el cual cada uno de los restos heterociclil–, heterociclenil–, heteroaril– o aril– de dicho R^3 puede estar insustituido o sustituido con uno o más restos, seleccionados en forma independiente entre el grupo integrado por $-CONR^5R^6$, $-OR^5$ y alquilo,

n es 1–6,

X está seleccionado entre el grupo integrado por $-NR^5R^6$, $-OR^5$, $-SO-R^5$, $-SR^5$, SO_2R^5, heteroarilo, heterociclilo y arilo, en el cual dicho heteroarilo o arilo pueden estar insustituidos o sustituidos con uno o más restos, seleccionados en forma independiente entre el grupo integrado por –O–alquilo, alquilo, halo, o NR^5R^6;

R^7 y R^8 son cada uno en forma independiente hidrógeno, alquilo, heterociclilo, arilo, heteroarilo o cicloalquilo;

R^5 está seleccionado entre el grupo integrado por hidrógeno, alquilo, alquenilo, alcoxialquilo, –alquil–S–alquilo, aminoalquilo, arilo, heteroarilo, heterociclenilo, heterocicloalquilo, cicloalquilo, ciclenilo, heterociclilalcoxilo, –S–alquilheterociclilo, heterociclilo, heterociclenilo, alquilN(alquilo)$_2$, alquilNH(alquilo), alquilN(alquenil)2, –alquilN(alcoxil)2, –alquil–SH, hidroxialquilo, trihaloalquilo, dihaloalquilo, monohaloalquilo, en el cual cada uno de dicho alquilo, alquenilo, alcoxialquilo, –alquil–S–alquilo, aminoalquilo, arilo, heteroarilo, heterociclenilo, heterocicloalquilo, cicloalquilo, ciclenilo, heterociclilalcoxilo, –S–alquilheterociclilo, heterociclilo, heterociclenilo, alquilN(alquilo)$_2$, alquilNH(alquilo), alquilN(alquenil)2, –alquilN(alcoxil)2, –alquil–SH, hidroxialquilo, trihaloalquilo, dihaloalquilo, monohaloalquilo puede estar insustituido o sustituido con uno o más restos seleccionados en forma independiente entre el grupo integrado por alquilo, alquenilo, arilo, ciclenilo, cicloalquilo, arilalquilo, ciclenilalquilo, cicloalquilalquilo, heteroarilo, heterociclenilo, heterociclilo, heteroarilalquilo, heterociclenilalquilo, heterocicloalquilalquilo, alcoxialquilo, –alquil–S–alquilo, –alquilSH, alcoxilo, –S–alquilo, hidroxialquilo, y aminoalquilo;

R^6 está seleccionado entre el grupo integrado por hidrógeno, alquilo, alquenilo, arilo, ciclenilo, cicloalquilo, arilalquilo, ciclenilalquilo, cicloalquilalquilo, heteroarilo, heterociclenilo, heterociclilo, heteroarilalquilo, heterociclenilalquilo, heterocicloalquilalquilo, alcoxialquilo, –alquil–S–alquilo, –alquilSH, alcoxilo, –S–alquilo, hidroxialquilo, aminoalquilo, –alquil–OC(O)alquilo, –alquilOC(O)cicloalquilo, –alquilOC(O)arilo, –alquilOC(O)aralquilo, –alquilOC(O)NR^{5}arilo, –alquilOC(O)NR^{5}alquilo, –alquilOC(O)NR^{5}heterociclilo, –alquilOC(O)NR^{5}heteroaril –alquilOC(O)NR^{5}cicloalquilo, –alquilOC(O)heterociclilo, alquilC(O)OH, alquilC(O)Oalquilo, –alquilC(O)Ocicloalquilo, –alquilC(O)Oarilo, –alquilC(O)Oaralquilo, –alquilC(O)ONR^{5}arilo, –alquilC(O)ONR^{5}alquilo, –alquilC(O)ONR^{5}heterociclilo, –alquilC(O)ONR^{5}heteroaril

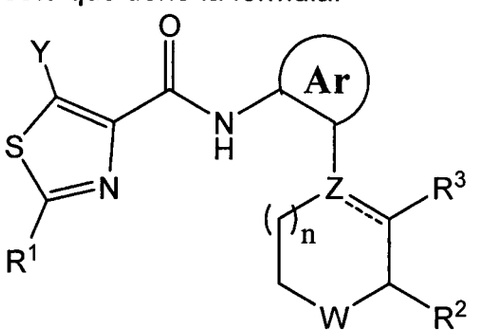
–alquilC(O)ONR^{5}cicloalquilo, –alquilC(O)Oheterociclilo, alquilC(O)OH, y alquilC(O)Oalquilo en el cual cada uno de dicho arilo, ciclenilo, cicloalquilo, arilalquilo, ciclenilalquilo, cicloalquilalquilo, heteroarilo, heterociclenilo, heterociclilo, heteroarilalquilo, heterociclenilalquilo, heterocicloalquilalquilo, –alquil–OC(O)alquilo, –alquilOC(O)cicloalquilo, –alquilOC(O)arilo, –alquilOC(O)aralquilo, –alquilOC(O)NR^{5}arilo, –alquilOC(O)NR^{5}alquilo, –alquilOC(O)NR^{5}heterociclilo, –alquilOC(O)NR^{5}heteroaril –alquilOC(O)NR^{5}cicloalquilo, –alquilOC(O)heterociclilo, alquilC(O)OH, alquilC(O)Oalquilo, –alquilC(O)Ocicloalquilo, –alquilC(O)Oarilo, –alquilC(O)Oaralquilo, –alquilC(O)ONR^{5}arilo, –alquilC(O)ONR^{5}alquilo, –alquilC(O)ONR^{5}heterociclilo, –alquilC(O)ONR^{5}heteroaril –alquilC(O)ONR^{5}cicloalquilo, –alquilC(O)Oheterociclilo, alquilC(O)OH, y alquilC(O)Oalquilo, puede estar insustituido o sustituido con uno o más restos seleccionados en forma independiente entre el grupo integrado por alquilo, alquenilo, arilo, ciclenilo, cicloalquilo, arilalquilo, ciclenilalquilo, cicloalquilalquilo, heteroarilo, heterociclenilo, heterociclilo, heteroarilalquilo, heterociclenilalquilo, heterocicloalquilalquilo, alcoxialquilo, –alquil–S–alquilo, –alquilSH, alcoxilo, –S–alquilo, hidroxialquilo, aminoalquilo, amino, aminodialquilo, aminocicloalquilo, halo, trihaloalquilo, dihaloalquilo, y monohaloalquilo;

en el cual además en cualquier –NR^{5}R^6 en la Fórmula I, dicho R^5 y R^6 pueden estar unidos en forma opcional junto con el N de dicho –NR^{5}R^6 para formar un anillo cíclico o anillo cíclico en puente, en el cual cada uno de dicho anillo cíclico o anillo cíclico en puente, puede estar insustituido o sustituido con uno o más restos, que pueden ser iguales o diferentes, seleccionados en forma independiente entre el grupo integrado por hidroxilo, –SH, alquilo, alquenilo, hidroxialquilo, –alquil–SH, alcoxilo, –S–alquilo, –CO_2–alquilo, –CO_2–alquenilo, arilalquilo, ciclenilalquilo, cicloalquilalquilo, heteroarilalquilo, heterociclenilalquilo,

heterocicloalquilalquilo, heteroarilo, arilo, ciclenilo, cicloalquilo, espiroheterociclilo, espiroheterociclenilo, espiroheteroarilo, espirociclilo, espirociclenilo, espiroarilo, alcoxialquilo, –alquil–S–alquilo, heterociclilo, heterociclenilo, halo, trihaloalquilo, dihaloalquilo, CN y monohaloalquilo.

Dichos compuestos de la Fórmula I en (i) se divulgan en PCT US 2008/007295, presentada el 11 de junio de 2008;

j. Un compuesto que tiene la fórmula:



(J)

o una sal, solvato, éster, prodroga o estereoisómero del mismo, aceptables para uso farmacéutico, en el cual las líneas de guiones indican un enlace opcional y adicional, y en el cual:

R^1 es heteroarilo que contiene nitrógeno, es heterociclilo que contiene nitrógeno, es heteroarilo benzofusionado que contiene nitrógeno o heterociclilo benzofusionado que contiene nitrógeno, en el cual R^1 está unido al resto del compuesto de la fórmula (I) mediante un átomo de nitrógeno en el anillo, y en el cual uno o más átomos de carbono en el anillo de un grupo heteroarilo que contiene nitrógeno, heterociclilo que contiene nitrógeno, heteroarilo benzofusionado que contiene nitrógeno o heterociclilo benzofusionado que contiene nitrógeno puede estar sustituido con hasta 5 sustituyentes, que pueden ser iguales o diferentes, y están seleccionados en forma independiente entre

alquilo, arilo, halo, –OH, –O–alquilo, –O–arilo, $–N(R^8)_2$, $–CF_3$, $–NO_2$, $–C(O)R^8$, $–C(O)OR^8$, $–C(O)N(R^8)_2$, $–OC(O)R^8$ o $–NHC(O)R^8$;

R^2 es –H, –alquilo, $–NH_2$ o $–CH_2NH_2$;

R^3 es –H, –alquilo, $–NH_2$ o $–CH_2NH_2$;

cada vez que aparece R^4 es en forma independiente –H, –alquilo, $–NH_2$, –OH, –alquileno–OH, $–CH_2NH_2$, $–C(O)R^5$, $–C(O)NH_2$, –C(O)NH–alquilo, $–C(O)N(alquilo)_2$, $–NHC(O)R^6$ o $–NHS(O)_2R^6$;

R^5 es –H, –alquilo, –arilo, –heteroarilo, –NHOH;

R^6 es –H, –alquil o $–CF_3$;

R^7 es –H, –OH, alquilo $–C_1–C_6$, –O–(alquilo $C_1–C_6$), o $–CF_3$;

R^8 es –H, alquilo, arilo, heterociclilo, heteroarilo o cicloalquilo;

Ar es –arileno– o –heteroarileno–, en el cual el arileno o heteroarileno está unido mediante 2 de sus átomos de carbono adyacentes en el anillo, y en el cual el –arileno– o –heteroarileno– puede estar sustituido con hasta 4 sustituyentes, que pueden ser iguales o diferentes, y están seleccionados en forma independiente entre –halo, alquilo, alcoxi, ariloxi, $–SR^8$, $–S(O)R^8$, $–S(O)_2R^8$, $–C(O)R^8$, $–C(O)OR^8$, $–C(O)N(R^8)_2$, $–NHC(O)R^8$, $–CF_3$, –CN o NO_2, y de modo que cuando Ar es tetrahidronaftileno, ambos R^1 y R^2 no pueden ser hidrógeno

W es –NH– o $–C(R^4)_2–$, en el cual ambos grupos R^4 y el átomo de carbono al cual están unidos pueden combinarse para formar un grupo heterociclilo o heteroarilo de cinco a siete miembros;

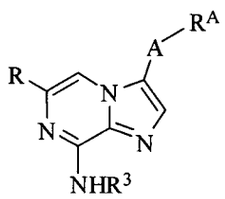
Y es –H, –halo, –alquil o –CN;

Z es $–CR^7–$ o –N–, cuando el enlace adicional opcional está ausente, y –C– cuando el enlace adicional opcional está presente;

n es un número entero cuyo rango es desde 0 a 2;

Dichos compuestos de la Fórmula J en (j) se divulgan en WO 2008/054749, presentada el 29 de octubre de 2007; y

(k) Un compuesto de la Fórmula K:



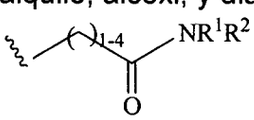
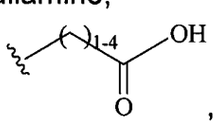
Fórmula K

o una sal, solvato, éster, prodroga o estereoisómero del mismo, aceptables para uso farmacéutico, en el cual:

R es H, halo o alquilo;

R^3 es heteroaril–X, en el cual X es heterociclilalquil– en el cual dicho heterociclilo puede estar insustituido o sustituido en forma opcional con 1–4 restos de alquilo;

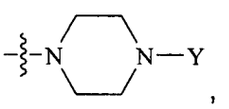
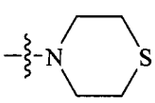
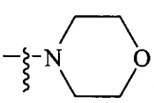
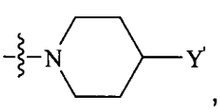
A es –aril– , –heteroaril–, $-N(R^1)$–aril– o $-N(R^1)$–heteroaril– , en el cual cada uno de dicho arilo y heteroarilo puede estar insustituido en forma independiente o puede estar sustituido en forma opcional con uno o más sustituyentes, cuyos sustituyentes pueden ser iguales o diferentes, donde cada sustituyente está seleccionado en forma independiente entre el grupo integrado por alquilo, $-NO_2$, halo, hidroxi, trihaloalquilo, alcoxi, y dialquilamino;

R^A es $-(CH_2)_{1-4}$–heteroarilo,  o  , en el cual dicho heteroarilo puede estar fusionado en forma opcional con un arilo, en el cual cada uno de dicho arilo y heteroarilo en forma independiente puede estar sustituido en forma opcional con uno o más restos, donde cada resto está seleccionado en forma independiente entre el grupo integrado por trihaloalquilo, $-NO_2$, halo, hidroxialquilo, alcoxialquilo y dialquilamino;

R^1 es H o alquilo;

R^2 es H, hidroxialquilo–, arilalquilo–, heteroarilo, arilo, heteroarilalquil–, alquilo, dialquilaminoalquil–, alquilaminoalquil–, cicloalquilalquil–, cicloalquilo, heterociclilalquil– or heterociclilo, en el cual dicho arilo y arilo de arilalquilo pueden

estar insustituidos o sustituidos con uno o más restos seleccionados en forma independiente entre el grupo integrado por trihaloalquilo, $-NO_2$, halo, hidroxialquilo, alcoxialquilo, dialquilamino y heterociclilalquil–, en el cual dicho heterociclilalquilo puede estar insustituido o sustituido con alquilo o $-SO_2NH_2$; dicho heteroarilo y heteroarilo de heteroarilalquilo pueden estar insustituidos o sustituidos con uno o más restos, donde cada resto está seleccionado en forma independiente entre el grupo integrado por hidroxialquilo, alcoxi, alquilo, halo, hidroxilo, y $-NO_2$; y dicho cicloalquilo está insustituido o sustituido con hidroxilo; o

R^1 y R^2 junto con el N al cual cada uno está unido, forman un grupo heterocíclico seleccionado entre el grupo integrado por  ,  ,  y  , en el cual

Y es alcoxialquilo, hidroxialquilo, dialquilaminoalquilo o alquilo, en el cual además

Y' es hidroxilo.

Dichos compuestos de la Fórmula K en el párrafo (k) se divulgan en la Solicitud de Patente Provisional de EEUU, 61/024010, presentada el 28 de enero de 2008.

BREVE DESCRIPCIÓN DE LOS DIBUJOS

La FIG. 1 es un análisis FACS (Análisis por Citometría de Flujo) de células de cáncer de colon HCT–116. Las células se trataron con inhibidor de Aurora quinasa 1000 nM (Compuesto X) (WO 2008/057512, presentada el 6 de noviembre de 2007, Ejemplo 4–3 y la reivindicación 70 y está representado en la Fórmula H y en la Tabla 2, columna 2, fila 16 de la presente solicitud) durante los tiempos indicados, en cuyo tiempo, la droga se removió mediante lavado y se reemplazó con medio nuevo. El análisis FACS se llevó a cabo luego de un total

de 72 horas. La exposición durante menos de 24 horas fue insuficiente para inducir la endoreduplicación (contenido de ADN >4N), en tanto que la exposición de la droga durante 24, 48, o 72 horas produjo la acumulación de células que se sometieron a endoreduplicación.

La FIG. 2 es un análisis FACS de células de cáncer de colon HCT–116 tratadas con inhibidor de Aurora quinasa 1000 nM (Compuesto X) durante los tiempos indicados, en cuyo tiempo, la droga se removió mediante lavado y se reemplazó con medio nuevo. El análisis FACS se llevó a cabo luego de un total de 24 horas. Un tratamiento de veinticuatro horas fue suficiente para inducir la endoreduplicación, sin embargo, un tiempo de exposición menor fue insuficiente para inducir la endoreduplicación.

La FIG. 3 es un análisis FACS de células de cáncer de colon HCT–116 tratadas durante 16 horas con DMSO. Las células luego se expusieron a DMSO o al inhibidor de Aurora quinasa 1000 nM (Compuesto X) durante 4, 8, o 24 horas en cuyo tiempo se cambió el medio. Todas las células se analizaron al cabo de 24–horas.

La FIG. 4 es un análisis FACS de células de cáncer de colon HCT–116 tratadas durante 16 horas con taxotero 5nM. Las células luego se expusieron a DMSO o al inhibidor de Aurora quinasa 1000 nM (Compuesto X) durante 4, 8, y 24 horas en cuyo tiempo se cambió el medio. Todas las células se analizaron al cabo de 24–horas. Taxotero seguido por el inhibidor de Aurora quinasa (Compuesto X) indujo la endoreduplicación. Se observó endoreduplicación incluso cuando la exposición al inhibidor de Aurora quinasa (Compuesto X) fue tan solo de 4 horas.

La FIG. 5 es un análisis FACS de células de cáncer de colon HCT–116 tratadas previamente con nocodazol durante 16 horas. Las células luego se expusieron a DMSO o al inhibidor de Aurora quinasa 1000 nM (Compuesto X)

durante 4, 8, y 24 horas en cuyo tiempo se cambió el medio. Todas las células se analizaron al cabo de 24 horas. Nocodazol seguido por una exposición de 24 horas al inhibidor de Aurora quinasa (Compuesto X) indujo la endoreduplicación, sin embargo, una exposición de 4 u 8 horas al inhibidor de Aurora (Compuesto X) fue insuficiente para inducir la endoreduplicación.

La FIG. 6 es un análisis FACS de células de cáncer de colon HCT–116 tratadas con un inhibidor de Aurora quinasa (Compuesto X) proporcionado al mismo tiempo que taxotero. Una exposición de 4 horas no fue suficiente para inducir la endoreduplicación y se requirió una exposición de 24 horas para inducir la endoreduplicación.

La FIG. 7 es un análisis FACS de células de cáncer de colon HCT–116 tratadas durante 16 horas con Ispinesib 10 nM (Inhibidor de KSP). Las células luego se expusieron a DMSO o al inhibidor de Aurora quinasa 1000 nM (Compuesto X) durante 4, 8, y 24 horas en cuyo tiempo se cambió el medio. Todas las células se analizaron al cabo de 24 horas. Ispinesib seguido por el inhibidor de Aurora quinasa (Compuesto X) indujo la endoreduplicación. Se observó endoreduplicación aun cuando la exposición al inhibidor de Aurora quinasa (Compuesto X) fue tan solo de 4 horas.

La FIG. 8 es un análisis FACS (Análisis por Citometría de Flujo) de células de cáncer de colon HCT–116. Las células se trataron con inhibidor de Aurora quinasa 25nM (Compuesto Z) (PCT US2008/007295, presentada el 11 de junio de 2008, Ejemplo 76–2 y la reivindicación 25, fila 7, columna 4 y está representado en la Tabla 13, compuesto 76–2 de la presente solicitud) durante los tiempos indicados, en cuyo tiempo, la droga se removió mediante lavado y se reemplazó con medio nuevo. El análisis FACS se llevó a cabo luego de un total de 72 horas. La exposición durante menos de 24 horas fue insuficiente para inducir la endoreduplicación (contenido de ADN >4N), en tanto que la exposición de la

droga durante 24, 48, o 72 horas produjo la acumulación de células que se sometieron a endoreduplicación.

La FIG. 9 es un análisis FACS de células de cáncer de colon HCT–116 tratadas con inhibidor de Aurora quinasa 25nM (Compuesto Z) durante los tiempos indicados, en cuyo tiempo, la droga se removió mediante lavado y se reemplazó con medio nuevo. El análisis FACS se llevó a cabo luego de un total de 24 horas. Un tratamiento de veinticuatro horas fue suficiente para inducir la endoreduplicación, sin embargo, un tiempo de exposición menor fue insuficiente para inducir la endoreduplicación.

La FIG. 10 es un análisis FACS de células de cáncer de colon HCT–116 tratadas durante 16 horas con DMSO. Las células luego se expusieron a DMSO o al inhibidor de Aurora quinasa 25nM (Compuesto Z) durante 4, 8, o 24 horas en cuyo tiempo se cambió el medio. Todas las células se analizaron al cabo de 24 horas.

La FIG. 11 es un análisis FACS de células de cáncer de colon HCT–116 tratadas durante 16 horas con taxotero 5nM. Las células luego se expusieron a DMSO o al inhibidor de Aurora quinasa 25nM (Compuesto Z) durante 4, 8, y 24 horas en cuyo tiempo se cambió el medio. Todas las células se analizaron al cabo de 24 horas. Taxotero seguido por el inhibidor de Aurora quinasa (Compuesto Z) indujo la endoreduplicación. Se observó endoreduplicación aun cuando la exposición al inhibidor de Aurora quinasa (Compuesto Z) fue tan solo de 4 horas.

La FIG. 12 es un análisis FACS de células de cáncer de colon HCT–116 tratadas con un inhibidor de Aurora quinasa (Compuesto Z) proporcionado al mismo tiempo que taxotero, una exposición de 4 horas no fue suficiente para inducir la endoreduplicación y se requirió una exposición de 24 horas para inducir la endoreduplicación.

La FIG. 13 es un análisis FACS de células de cáncer de colon HCT–116 tratadas durante 16 horas con Ispinesib 10 nM (Inhibidor de KSP). Las células luego se expusieron a DMSO o al inhibidor de Aurora quinasa 25nM (Compuesto Z) durante 4, 8, y 24 horas en cuyo tiempo se cambió el medio. Todas las células se analizaron al cabo de 24 horas. Ispinesib seguido por el inhibidor de Aurora quinasa (Compuesto Z) indujo la endoreduplicación. Se observó endoreduplicación aun cuando la exposición al inhibidor de Aurora quinasa (Compuesto Z) fue tan solo de 4 horas.

La FIG. 14 es un análisis FACS de células de cáncer de colon HCT–116 tratadas con un inhibidor de Aurora quinasa (Compuesto Z) proporcionado al mismo tiempo que Ispinesib (Inhibidor de KSP) taxotero, una exposición de 4 horas no fue suficiente para inducir la endoreduplicación y se requirió una exposición de 24 horas para inducir la endoreduplicación.

De modo similar a las Figuras descriptas anteriormente (Dibujos) se obtuvieron otros resultados experimentales cuando, por ejemplo, el inhibidor de Aurora quinasa se cambió desde el Compuesto X o Z a otros inhibidores de aurora quinasa divulgados en cualquier otra parte de la presente solicitud.

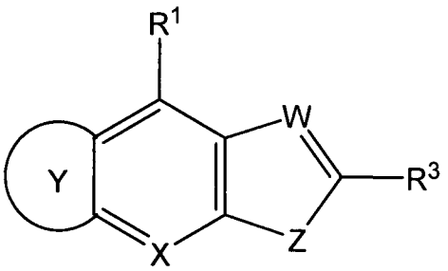
DESCRIPCIÓN DETALLADA

A continuación se ejemplifica el método de tratamiento usando la administración consecutiva de por lo menos un agente antimitótico seguido por al menos un inhibidor de Aurora quinasa descripto en la presente, a un sujeto que lo necesita.

En una forma de realización, la presente invención divulga una composición farmacéutica para tratar o paliar el cáncer que comprende por lo menos un agente antimitótico seleccionado entre el grupo integrado por Taxanos, paclitaxel, docetaxel, Inhibidor de Cenp–E (tal como, por ejemplo GSK–923295 de

Glaxo Smithkline), Abraxano, Epotilona, Monastrol, así como también los inhibidores de KSP tales como, por ejemplo, Ispinesib SB–715992 (de Cytokinetics, South San Francisco, California) y los compuestos de las Fórmulas A–D en los párrafos a–d que aparecen a continuación:

a. Un compuesto representado por la Fórmula estructural A:



Fórmula A

o una sal, solvato o éster del mismo, aceptables para uso farmacéutico, en el cual:

el anillo Y es un arilo de 5 a 6 miembros o un heteroarilo de 5 o 6 miembros fusionado como se indica en la Fórmula A, en el cual en dicho arilo y heteroarilo, cado carbono sustituible del anillo está sustituido en forma independiente con R^2 y cada nitrógeno sustituible del anillo está sustituido en forma independiente con R^6;

W es N o $C(R^{12})$;

X es N o N–óxido;

Z es S, S(=O) o $S(=O)_2$;

R^1 es H, alquilo, alcoxi, hidroxi, halo, –CN, $–S(O)_m–$alquilo, $–C(O)NR^9R^{10}$, $–(CR^9R^{10})_{1–6}OH$, o $–NR^4(CR^9R^{10})_{1–2}OR^9$;

cada R^2 está seleccionado en forma independiente entre el grupo integrado por H, halo, alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo, heteroaralquilo, $–(CR^{10}R^{11})_{0–6}–OR^7$, $–C(O)R^4$, $–C(S)R^4$, $–C(O)OR^7$, $–C(S)OR^7$, $–OC(O)R^7$, $–OC(S)R^7$, $–C(O)NR^4R^5$, $–C(S)NR^4R^5$, $–C(O)NR^4OR^7$, $–C(S)NR^4OR^7$, $–C(O)NR^7NR^4R^5$, $–C(S)NR^7NR^4R^5$, $–C(S)NR^4OR^7$, $–C(O)SR^7$, $–NR^4R^5$, $–NR^4C(O)R^5$, $–NR^4C(S)R^5$, $–NR^4C(O)OR^7$, $–NR^4C(S)OR^7$,

$-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, $-CN$, $-OCF_3$, $-SCF_3$, $-C(=NR^7)NR^4$, $-C(O)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}OR^7$, $-C(S)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(S)NR^7(CH_2)_{1-10}OR^7$, haloalquilo y alquilsililo, en el cual cada uno de dicho alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo o heteroaralquilo está sustituido en forma opcional e independiente con 1–5 restos de R^9;

cada R^3 está seleccionado en forma independiente entre el grupo integrado por H, halo, alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo, heteroaralquilo, $-(CR^{10}R^{11})_{0-6}-OR^7$, $-C(O)R^4$, $-C(S)R^4$, $-C(O)OR^7$, $-C(S)OR^7$, $-OC(O)R^7$, $-OC(S)R^7$, $-C(O)NR^4R^5$, $-C(S)NR^4R^5$, $-C(O)NR^4OR^7$, $-C(S)NR^4OR^7$, $-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, $-CN$, $-OCF_3$, $-SCF_3$, $-C(=NR^7)NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}OR^7$, $-C(S)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(S)NR^7(CH_2)_{1-10}OR^7$, haloalquilo y alquilsililo, en el cual cada uno de dicho alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo o heteroaralquilo está sustituido en forma opcional e independiente con 1–5 restos de R^9;

cada R^4 y R^5 está seleccionado en forma independiente entre el grupo integrado por H, alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo, heteroaralquilo, $-OR^7$, $-C(O)R^7$, y $-C(O)OR^7$, en el cual cada uno de dicho alquilo, cicloalquilo, cicloalquilalquilo,

heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo, o heteroaralquilo está sustituido en forma opcional con 1–4 restos de R^8;

o R^4 y R^5, cuando están unidos al mismo átomo de nitrógeno, se toman en forma opcional junto con el átomo de nitrógeno al cual están unidos para formar un anillo heterocíclico de 3–6 miembros que tiene 0–2 heteroátomos adicionales seleccionados entre N, O o S;

cada R^6 está seleccionado en forma independiente entre el grupo integrado por H, alquilo, arilo, aralquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, heteroarilo, heteroaralquilo, $-(CH_2)_{1-6}CF_3$, $-C(O)R^7$, $-C(O)OR^7$ y $-SO_2R^7$;

cada R^7 está seleccionado en forma independiente entre el grupo integrado por H, alquilo, arilo, aralquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, heteroarilo, y heteroaralquilo, en el cual cada miembro de R^7 excepto H está sustituido en forma opcional con 1–4 restos de R^8;

cada R^8 está seleccionado en forma independiente entre el grupo integrado por halo, alquilo, cicloalquilo, heterociclilo, arilo, heteroarilo, $-NO_2$, $-OR^{10}$, $-$(alquilo C_1–C_6)$-OR^{10}$, $-CN$, $-NR^{10}R^{11}$, $-C(O)R^{10}$, $-C(O)OR^{10}$, $-C(O)NR^{10}R^{11}$, $-CF_3$, $-OCF_3$, $-CF_2CF_3$, $-C(=NOH)R^{10}$, $-N(R^{10})C(O)R^{11}$, $-C(=NR^{10})NR^{10}R^{11}$, y $-NR^{10}C(O)OR^{11}$, en el cual cada uno de dicho alquilo, cicloalquilo, heterociclilo, arilo, y heteroarilo está sustituido en forma opcional e independiente con 1–3 restos seleccionados entre el grupo integrado por halo, alquilo, cicloalquilo, heterociclilo, arilo, heteroarilo, $-NO_2$, $-OR^{10}$, $-(C_1$–C_6 alkyl$)-OR^{10}$, $-CN$, $-NR^{10}R^{11}$, $-C(O)OR^{10}$, $-C(O)NR^{10}R^{11}$, $-CF^3$, $-OCF_3$, $-NR^{10}C(O)OR^{11}$, y $-NR^{10}C(O)R^{40}$;

o dos grupos R^8, cuando están unidos al mismo átomo de carbono, se toman en forma opcional junto con el átomo de carbono al cual están unidos para formar un grupo C=O o un grupo C=S;

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cada R^9 está seleccionado en forma independiente entre el grupo integrado por H, alquilo, alcoxi, OH, CN, halo, $-(CR^{10}R^{11})_{0-4}NR^4R^5$, haloalquilo, hidroxialquilo, alcoxialquilo, $-C(O)NR^4R^5$, $-C(O)OR^7$, $-OC(O)NR^4R^5$, $-NR^4C(O)R^5$, y $-NR^4C(O)NR^4R^5$;

cada R^{10} es en forma independiente H o alquilo; o R^9 y R^{10}, cuando están unidos al mismo átomo de nitrógeno, se toman en forma opcional junto con el átomo de nitrógeno al cual están unidos para formar un anillo heterocíclico de 3–6 miembros que tiene 0–2 heteroátomos adicionales seleccionados entre N, O o S;

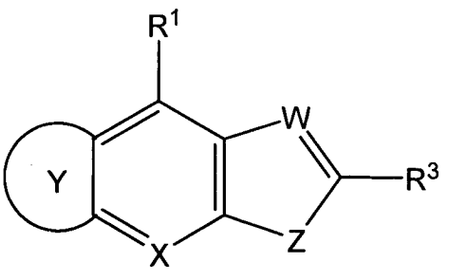
cada R^{11} es en forma independiente H o alquilo; o R^{10} y R^{11}, cuando están unidos al mismo átomo de nitrógeno, se toman en forma opcional junto con el átomo de nitrógeno al cual están unidos para formar un anillo heterocíclico de 3–6 miembros que tiene 0–2 heteroátomos adicionales seleccionados entre N, O o S;

cada R^{12} está seleccionado en forma independiente entre el grupo integrado por H, halo, alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo, heteroaralquilo, $-(CR^{10}R^{11})_{0-6}-OR^7$, $-C(O)R^4$, $-C(S)R^4$, $-C(O)OR^7$, $-C(S)OR^7$, $-OC(O)R^7$, $-OC(S)R^7$, $-C(O)NR^4R^5$, $-C(S)NR^4R^5$, $-C(O)NR^4OR^7$, $-C(S)NR^4OR^7$, $-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, $-CN$, $-OCF_3$, $-SCF_3$, $-C(=NR^7)NR^4$, $-C(O)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}OR^7$, $-C(S)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(S)NR^7(CH_2)_{1-10}OR^7$, haloalquilo y alquilsililo, en el cual cada uno de dicho alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo o heteroaralquilo está sustituido en forma opcional e independiente con 1–5 restos de R^9; y

R^{40} está seleccionado entre el grupo integrado por cicloalquilo, heterociclilo, arilo y heteroarilo, en el cual cada uno de dicho cicloalquilo, heterociclilo, arilo y heteroarilo está sustituido en forma opcional e independiente con 1–3 restos seleccionados en forma independiente entre el grupo integrado por –CN, –OH, halo, alquilo, haloalquilo, alcoxi, y $–NR^{10}R^{11}$;

(ver WO 2006/098962, presentada el 7 de marzo de 2006);

b. Un compuesto representado por la Fórmula estructural B:



Fórmula B

o una sal, solvato o éster del mismo, aceptables para uso farmacéutico, en el cual:

el anillo Y es un anillo de 5 a 7 miembros seleccionados entre el grupo integrado por cicloalquilo, cicloalquenilo, heterociclilo o heterociclenilo fusionado como se indica en la Fórmula B, en el cual en cada uno de dicho anillo de 5 a 7 miembros, cada carbono sustituible en el anillo está sustituido en forma independiente con 1–2 restos de R^2 y cada heteroátomo sustituible en el anillo está sustituido en forma independiente con R^6;

W es N o $C(R^{12})$;

X es N o N–óxido;

Z es S, S(=O) o $S(=O)_2$;

R^1 es H, alquilo, alcoxi, hidroxi, halo, –CN, $–S(O)_m–$alquilo, $–C(O)NR^9R^{10}$, $–(CR^9R^{10})_{1–6}OH$, o $–NR^4(CR^9R^{10})_{1–2}OR^9$; en el cual m es O a 2;

cada R^2 está seleccionado en forma independiente entre el grupo integrado por H, halo, alquilo, cicloalquilo, alquilsililo, cicloalquenilo, heterociclilo,

heterociclenilo, arilo, heteroarilo, $-(CR^{10}R^{11})_{0-6}-OR^7$, $-C(O)R^4$, $-C(S)R^4$, $-C(O)OR^7$, $-C(S)OR^7$, $-OC(O)R^7$, $-OC(S)R^7$, $-C(O)NR^4R^5$, $-C(S)NR^4R^5$, $-C(O)NR^4OR^7$, $-C(S)NR^4OR^7$, $-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, $-CN$, $-OCF_3$, $-SCF_3$, $-C(=NR^7)NR^4$, $-C(O)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}OR^7$, $-C(S)NR^7(CH_2)_{1-10}NR^4R^5$, y $-C(S)NR^7(CH_2)_{1-10}OR^7$, en el cual cada uno de dicho alquilo, cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, arilo, y heteroarilo está sustituido en forma opcional e independiente con 1–5 restos de R^9;

o dos R^2 en el mismo átomo de carbono se toman en forma opcional junto con el átomo de carbono al cual están unidos para formar un grupo C=O, C=S o un grupo etilendioxi;

R^3 está seleccionado en forma independiente entre el grupo integrado por H, halo, alquilo, cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, arilo, heteroarilo, $-(CR^{10}R^{11})_{0-6}-OR^7$, $-C(O)R^4$, $-C(S)R^4$, $-C(O)OR^7$, $-C(S)OR^7$, $-OC(O)R^7$, $-OC(S)R^7$, $-C(O)NR^4R^5$, $-C(S)NR^4R^5$, $-C(O)NR^4OR^7$, $-C(S)NR^4OR^7$, $-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, $-CN$, $-C(=NR^7)NR^4R^5$, $-C(O)N(R^7)-(CR^{40}R^{41})_{1-5}-C(=NR^7)NR^4R^5$, $-C(O)N(R^7)(CR^{40}R^{41})_{1-5}-NR^4R^5$, $-C(O)N(R^7)(CR^{40}R^{41})_{1-5}-C(O)-NR^4R^5$, $-C(O)N(R^7)(CR^{40}R^{41})_{1-5}-OR^7$, $-C(S)NR^7(CH_2)_{1-5}NR^4R^5$, y $-C(S)NR^7(CH_2)_{1-5}OR^7$, en el cual cada uno de dicho alquilo, cicloalquilo,

cicloalquenilo, heterociclilo, heterociclenilo, arilo, y heteroarilo está sustituido en forma opcional e independiente con 1–5 restos de R^9;

cada uno de R^4 y R^5 está seleccionado en forma independiente entre el grupo integrado por H, alquilo, cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, arilo, heteroarilo, $-OR^7$, $-C(O)R^7$, y $-C(O)OR^7$, en el cual cada uno de dicho alquilo, cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, arilo, y heteroarilo, está sustituido en forma opcional con 1–4 restos de R^8;

o R^4 y R^5, cuando están unidos al mismo átomo de nitrógeno, se toman en forma opcional junto con el átomo de nitrógeno al cual están unidos para formar un anillo heterocíclico de 3–6 miembros que tiene 0–2 heteroátomos adicionales seleccionados entre N, O o S;

cada R^6 está seleccionado en forma independiente entre el grupo integrado por H, alquilo, arilo, aralquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, heteroarilo, heteroaralquilo, $-(CH_2)_{1-6}CF_3$, $-C(O)R^7$, $-C(O)OR^7$ y $-SO_2R^7$;

cada R^7 está seleccionado en forma independiente entre el grupo integrado por H, alquilo, arilo, aralquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, heteroarilo, y heteroaralquilo, en el cual cada miembro de R^7 excepto H está sustituido en forma opcional con 1–4 restos de R^8;

cada R^8 está seleccionado en forma independiente entre el grupo integrado por halo, alquilo, cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, arilo, heteroarilo, $-NO_2$, $-OR^{10}$, $-(C_1-C_6$ alkyl$)-OR^{10}$, $-CN$, $-NR^{10}R^{11}$, $-C(O)R^{10}$, $-C(O)OR^{10}$, $-C(O)NR^{10}R^{11}$, $-CF_3$, $-OCF_3$, $-CF_2CF_3$, $-C(=NOH)R^{10}$, $-N(R^{10})C(O)R^{11}$, $-C(=NR^{10})NR^{10}R^{11}$, y $-NR^{10}C(O)OR^{11}$; en el cual cada uno de dicho alquilo, cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, arilo, y heteroarilo está sustituido en forma opcional e independiente con 1–4 restos de R^{42}; en el cual cuando cada uno de dicho cicloalquilo, cicloalquenilo, heterociclilo,

heterociclenilo, arilo, y heteroarilo contiene dos radicales sobre átomos de carbono adyacentes en cualquier parte dentro de dicho cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, arilo, y heteroarilo, y dichos radicales pueden ser tomados en forma opcional e independiente en cada aparición, junto con los átomos de carbono a los cuales están unidos, para formar un anillo carbocíclico o heterocíclico de cinco o seis miembros;

o dos grupos R^8, cuando están unidos al mismo carbono, se toman en forma opcional junto con el átomo de carbono al cual están unidos para formar un grupo C=O o un grupo C=S;

cada R^9 está seleccionado en forma independiente entre el grupo integrado por H, alquilo, alcoxi, OH, CN, halo, $-(CR^{10}R^{11})_{0-4}NR^4R^5$, haloalquilo, hidroxialquilo, alcoxialquilo, $-C(O)NR^4R^5$, $-C(O)OR^7$, $-OC(O)NR^4R^5$, $-NR^4C(O)R^5$, y $-NR^4C(O)NR^4R^5$;

cada R^{10} es en forma independiente H o alquilo; o R^9 y R^{10}, cuando están unidos al mismo átomo de nitrógeno, se toman en forma opcional junto con el átomo de nitrógeno al cual están unidos para formar un anillo heterocíclico de 3–6 miembros que tiene 0–2 heteroátomos adicionales seleccionados entre N, O o S;

cada R^{11} es en forma independiente H, alquilo, cicloalquilo, cicloalquenilo, arilo, heterociclilo, heterociclenilo, o heteroarilo; o R^{10} y R^{11}, cuando están unidos al mismo átomo de nitrógeno, se toman en forma opcional junto con el átomo de nitrógeno al cual están unidos para formar un anillo heterocíclico de 3–6 miembros que tiene 0–2 heteroátomos adicionales seleccionados entre N, O o S; en el cual cada uno de dicho R^{11} alquilo, cicloalquilo, cicloalquenilo, arilo, heterociclilo, heterociclenilo, y heteroarilo está sustituido en forma opcional e independiente con 1–3 restos seleccionados entre el grupo integrado por –CN, –OH, $-NH_2$, –N(H)alquilo, $-N(alquilo)_2$, halo, haloalquilo, CF_3, alquilo, hidroxialquilo, alcoxi, arilo, ariloxi, y heteroarilo;

cada R^{12} está seleccionado en forma independiente entre el grupo integrado por H, halo, alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo, heteroaralquilo, $-(CR^{10}R^{11})_{0-6}-OR^7$, $-C(O)R^4$, $-C(S)R^4$, $-C(O)OR^7$, $-C(S)OR^7$, $-OC(O)R^7$, $-OC(S)R^7$, $-C(O)NR^4R^5$, $-C(S)NR^4R^5$, $-C(O)NR^4OR^7$, $-C(S)NR^4OR^7$, $-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, $-CN$, $-OCF_3$, $-SCF_3$, $-C(=NR^7)NR^4$, $-C(O)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}OR^7$, $-C(S)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(S)NR^7(CH_2)_{1-10}OR^7$, haloalquilo y alquilsililo, en el cual cada uno de dicho alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo o heteroaralquilo está sustituido en forma opcional e independiente con 1–5 restos de R^9;

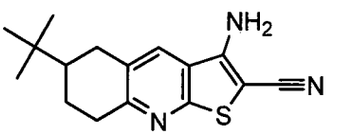
R^{40} y R^{41} pueden ser iguales o diferentes, estando cada uno seleccionado en forma independiente entre el grupo integrado por H, alquilo, arilo, heteroarilo, heterociclilo, heterociclenilo, cicloalquilo y cicloalquenilo;

cada R^{42} está seleccionado en forma independiente entre el grupo integrado por halo, alquilo, cicloalquilo, heterociclilo, arilo, heteroarilo, $-NO_2$, $-OR^{10}$, $-(C_1-C_6$ alkyl$)-OR^{10}$, $-CN$, $-NR^{10}R^{11}$, $-C(O)R^{10}$, $-C(O)OR^{10}$, $-C(O)NR^{10}R^{11}$, $-CF_3$, $-OCF_3$, $-N(R^{10})C(O)R^{11}$, y $-NR^{10}C(O)OR^{11}$;

con la condición de que cuando W es $C(R^{12})$, R^{12} y R^3 se toman en forma opcional junto con los dos átomos de carbono en el anillo a los cuales están unidos para formar un anillo de 6 miembros seleccionados entre el grupo integrado por cicloalquenilo, arilo, heteroarilo, heterociclilo y heterociclenilo, en el cual dicho anillo de 6 miembros está sustituido en forma opcional con 1–3 restos

seleccionados en forma independiente entre oxo, tioxo, $-OR^{11}$, $-NR^{10}R^{11}$, $-C(O)R^{11}$, $-C(O)OR^{11}$, $-C(O)N(R^{10})(R^{11})$, o $-N(R^{10})C(O)R^{11}$;

(ver WO2006/098961, presentada el 7 de marzo de 2006);

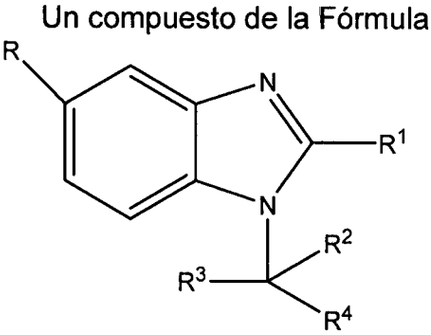
c. 

Fórmula C

o una sal, solvato, o éster del mismo, aceptables para uso farmacéutico;

(ver la Pub. de EEUU Nº 2006/0258699, presentada el 7 de marzo de 2006) y;

d. Un compuesto de la Fórmula D



Fórmula D

o una sal, solvato, o éster del mismo, aceptables para uso farmacéutico, en el cual:

R está seleccionado entre el grupo integrado por H, alquilo, ciano, haloalquilo, halo, —SH, –S–alquilo, –S–haloalquilo, $-S(=O)_2$alquilo, $-S(=O)_2OH$, $-S(=O)_2NH_2$, $-S(=O)_2NH$(alquilo), $S(=O)_2NH$(cicloalquilo), $-S(=O)_2N$(alquilo)$_2$, $-S(=O)_2$heterociclilo, $-S(=O)_2$heteroarilo, cicloalquilo, arilo, heterociclilo, heteroarilo, –NHC(=O)alquilo, $-C(=O)NH_2$, –C(=O)NH(alquilo), –C(=O)NH(cicloalquilo), $-C(=O)N(alquilo)_2$, –C(=O)OH, –C(=O)Oalquilo, –C(=O)heterociclilo, –C(=O)NH(arilo), en el cual cuando cada uno de dicho cicloalquilo, arilo, heterociclilo, heteroarilo, y las porciones "heterociclilo" y "arilo" de dichos grupos R tiene dos sustituyentes sobre átomos de carbono adyacentes, dichos sustituyentes en forma opcional junto con los átomos de carbono a los

cuales están unidos pueden formar un anillo cicloalquilo, arilo, heterociclilo, heterociclenilo, o heteroarilo de cinco a seis miembros; en el cual cada uno de los R alquilo, arilo, cicloalquilo, heterociclilo, y heteroarilo anteriormente mencionados, y las porciones "alquilo", "cicloalquilo", "heterociclilo", y "arilo" de dichos grupos R, en forma opcional con dicho anillo arilo, heterociclilo, heterociclenilo, o heteroarilo de cinco a seis miembros, está sustituido en forma opcional con 1–3 sustituyentes seleccionados en forma independiente entre el grupo integrado por alquilo, alquenilo, alquinilo, hidroxilo, ciano, halo, haloalquilo, haloalcoxi, –C(O)OH, –C(=O)Oalquilo, y $-C(O)NH_2$;

R^1 está seleccionado entre el grupo integrado por alquilo, heterociclilo, –C(=O)arilo, $-NH_2$, –NH(alquilo), –NH(cicloalquilo), –N(alquilo)(cicloalquilo), –NH(heterociclilo),–N(alquil)(heterociclilo), $N(alquilo)_2$, –NH(arilo), –N(alquil)(arilo), $-N(arilo)_2$, –NH(heteroarilo), –N(alquil)(heteroarilo), –NHC(=O)–alquilo, –N(alquil)C(=O)–alquilo, –NHC(=O)Oalquilo, –N(alquil)C(=O)O–alquilo, en el cual cada uno de los alquilo, heterociclilo anteriormente mencionados, y las porciones "alquilo", "cicloalquilo", "arilo", y "heteroarilo" de dichos grupos R^1 está sustituido en forma opcional con 1–3 sustituyentes seleccionados en forma independiente entre el grupo integrado por halo, heterociclilo, arilo, heteroarilo, haloalquilo, haloalcoxi, ariloxi, ciano, –SH, –S–alquilo, –S–haloalquilo, $-S(=O)_2$alquilo, $-S(=O)_2OH$, $-S(=O)_2NH_2$, $-S(=O)_2$NH(alquilo), $S(=O)_2$NH(cicloalquilo), $-S(=O)_2N(alquilo)_2$, $-S(=O)_2$heterociclilo, $-S(=O)_2$heteroarilo, hidroxi, alquilo, alquenilo, alquinilo, $-NH_2$, –NH(alquilo), $-N(alquilo)_2$, alcoxi, –NHC(=O)alquilo, –C(=O)H, –C(=O)alquilo, –C(=O)arilo, , –C(=O)heteroarilo, –C(=O)Oalquilo, $-C(=O)NH_2$, –C(O)NHalquilo, $-C(=O)N(alquilo)_2$; en el cual cuando cada uno de dicho heterociclilo, arilo y heteroarilo tiene dos sustituyentes sobre átomos de carbono adyacentes, dichos sustituyentes en forma opcional junto con los átomos de carbono a los cuales están unidos pueden formar un anillo arilo, heterociclilo, heterociclenilo, o heteroarilo de cinco a seis miembros;

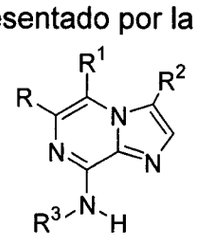
R^2 y R^3 son en forma independiente H o alquilo, o $-C(R^2)(R^3)-$ está ausente;

R^4 está seleccionado entre el grupo integrado por alquilo, cicloalquilo, heterociclilo, arilo y heteroarilo, en el cual cuando cada uno de dicho cicloalquilo, heterociclilo, arilo, y heteroarilo tiene dos sustituyentes sobre átomos de carbono adyacentes, dichos sustituyentes en forma opcional junto con los átomos de carbono a los cuales están unidos pueden formar un anillo arilo, heterociclilo, heterociclenilo, o heteroarilo de cinco a seis miembros; en el cual cada uno de R^4 alquilo, cicloalquilo, heterociclilo, arilo y heteroarilo anteriormente mencionados, en forma opcional con dicho anillo arilo, heterociclilo, heterociclenilo, o heteroarilo de cinco a seis miembros está sustituido en forma opcional con 1–3 sustituyentes seleccionados en forma independiente entre el grupo integrado por ciano, halo, haloalquilo, alquilo, alcoxi, hidroxilo, haloalcoxi, cicloalquilo, heterociclilo, arilo, heteroarilo, $-S(=O)_2$alquilo, $-S(=O)_2NH_2$, $-S(=O)_2NH$(alquilo), $-S(=O)_2N$(alquilo)$_2$, –S–alquilo, –S–haloalquilo, $-C(=O)OH$, $-NH_2$, –NH(alquilo), $-N$(alquilo)$_2$, y $-C(=O)O$alquilo;

Los compuestos representados en la presente solicitud por la Fórmula (d) se divulgan en PCT US2008/006472, presentada el 21 de mayo de 2008;

que además comprenden uno o más de un segundo compuesto, en el cual dicho segundo compuesto es un inhibidor de Aurora quinasa seleccionado entre el grupo integrado por los compuestos representados por las Fórmulas E–K:

e. Un compuesto representado por la Fórmula estructural E:



Fórmula E

o una sal, solvato, éster o prodroga del mismo, aceptables para uso

farmacéutico, en el cual:

R es H, CN, $-NR^5R^6$, cicloalquilo, cicloalquenilo, heterociclenilo, heteroarilo, $-C(O)NR^5R^6$, $-N(R^5)C(O)R^6$, heterociclilo, heteroarilo sustituido con $(CH_2)_{1-3}$ NR^5R^6, alquilo insustituido, o alquilo sustituido con uno o más restos que pueden ser iguales o diferentes donde cada resto está seleccionado en forma independiente entre el grupo integrado por $-OR^5$, heterociclilo, $-N(R^5)C(O)N(R^5R^6)$, $-N(R^5)-C(O)OR^6$, $-(CH_2)_{1-3}-N(R^5R^6)$ y $-NR^5R^6$;

R^1 es H, Halo, arilo o heteroarilo, en el cual cada uno de dicho arilo y heteroarilo puede estar insustituido o sustituido con uno o más restos que pueden ser iguales o diferentes donde cada resto está seleccionado en forma independiente entre el grupo integrado por halo, alquilo, alquenilo, alquinilo, cicloalquilo, arilo, heteroarilo, heterociclilo, $-CH_2OR^5$, $-C(O)NR^5R^6$, $-C(O)OH$, $-C(O)NH_2$, $-NR^5R^6$ (en el cual R^5 y R^6, junto con el N de dicho $-NR^5R^6$, forman un anillo heterociclilo), $-S(O)R^5$, $-S(O_2)R^5$, $-CN$, $-CHO$, $-SR^5$, $-C(O)OR^5$, $-C(O)R^5$ y $-OR^5$;

R^2 es H, halo, arilo, arilalquilo o heteroarilo, en el cual cada uno de dicho arilo, arilalquilo y heteroarilo puede estar insustituido o en forma opcional e independiente puede estar sustituido con uno o más restos que pueden ser iguales o diferentes donde cada resto está seleccionado en forma independiente entre el grupo integrado por halo, amida, alquilo, alquenilo, alquinilo, cicloalquilo, arilo, $-C(O)OH$, $-C(O)NH_2$, $-NR^5R^6$ (en el cual R^5 y R^6, junto con el N de dicho $-NR^5R^6$, forman un anillo heterociclilo), $-CN$, arilalquilo, $-CH_2OR^5$, $-S(O)R^5$, $-S(O_2)R^5$, $-CN$, $-CHO$, $-SR^5$, $-C(O)OR^5$, $-C(O)R^5$, heteroarilo y heterociclilo;

R^3 es H, alquilo, cicloalquilo, heterociclilo, arilo o heteroarilo, en el cual:

– dicho alquilo indicado anteriormente para R^3 puede estar insustituido o sustituido con uno o más restos que pueden ser iguales o diferentes donde cada resto está seleccionado en forma independiente entre el grupo integrado por –

OR^5, alcoxi, heteroarilo, y $-NR^5R^6$;

– dicho arilo indicado anteriormente para R^3 es insustituido, o sustituido en forma opcional, o fusionado en forma opcional, con halo, heteroarilo, heterociclilo, cicloalquilo o heteroarilalquilo, en el cual cada uno de dicho heteroarilo, heterociclilo, cicloalquilo y heteroarilalquilo puede estar insustituido o sustituido en forma opcional e independiente con uno o más restos que pueden ser iguales o diferentes donde cada resto está seleccionado en forma independiente entre alquilo, $-OR^5$, $-N(R^5R^6)$ y $-S(O_2)R^5$; y

– dicho heteroarilo indicado anteriormente para R^3 puede estar insustituido o sustituido en forma opcional, o fusionado en forma opcional, con uno o más restos que pueden ser iguales o diferentes donde cada resto está seleccionado en forma independiente entre el grupo integrado por halo, amino, alcoxicarbonilo, $-OR^5$, alquilo, –CHO, – NR^5R^6, $-S(O_2)N(R^5R^6)$, $-C(O)N(R^5R^6)$, $-SR^5$, alquenilo, alquinilo, cicloalquilo, arilo, heteroarilo, heterociclenilo, y heterociclilo;

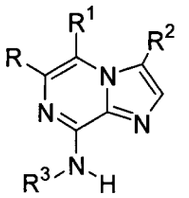
R^5 es H, alquilo, aminoalquilo, arilo, heteroarilo, heterociclilo o cicloalquilo; y

R^6 es H, alquilo, arilo, arilalquilo, heteroarilo, heterociclilo o cicloalquilo;

en el cual además en cualquier $-NR^5R^6$ en la Fórmula I, dicho R^5 y R^6 pueden estar unidos en forma opcional junto con el N de dicho $-NR^5R^6$ para formar un anillo cíclico;

(ver WO07/058942, presentada el 8 de noviembre de 2006);

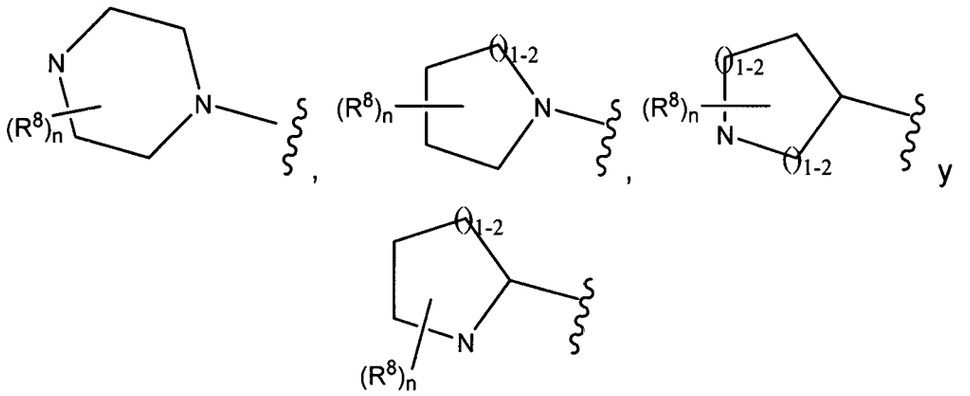
f. Un compuesto representado por la Fórmula estructural:



Fórmula F

o una sal, solvato, éster o prodroga del mismo, aceptables para uso farmacéutico, en el cual:

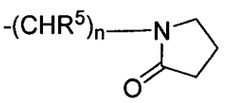
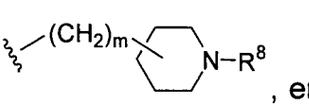
R está seleccionado entre el grupo integrado por H, halógeno, arilo, heteroarilo, cicloalquilo, arilalquilo, heterociclilo, heterociclilalquilo, alquenilo, alquinilo, $-C(O)R^7$,



en el cual cada uno de dicho arilo, heteroarilo, cicloalquilo, arilalquilo, alquenilo, heterociclilo y los restos heterociclilo cuyas estructuras se indican inmediatamente con anterioridad para R pueden estar insustituidos o sustituidos en forma opcional e independiente con uno o más restos que pueden ser iguales o diferentes, donde cada resto está seleccionado en forma independiente entre el grupo integrado por halógeno, alquilo, cicloalquilo, CF_3, CN, $-OCF_3$, $-OR^6$, $-C(O)R^7$, $-NR^5R^6$, $-C(O_2)R^6$, $-C(O)NR^5R^6$, $-(CHR^5)_nOR^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^6$;

R^1 es H, halógeno o alquilo;

R^2 es alquilo;

R^3 está seleccionado entre el grupo integrado por H, arilo, heteroarilo, heterociclilo, $-(CHR^5)_n$–arilo, $-(CHR^5)_n$–heteroarilo, $-(CHR^5)_n-OR^6$, $-S(O_2)R^6$, $-C(O)R^6$, $-S(O_2)NR^5R^6$, $-C(O)OR^6$, $-C(O)NR^5R^6$, cicloalquilo, $-CH(arilo)_2$, $-(CH_2)_m-NR^8$, $-(CHR^5)_n-CH(arilo)_2$,  y  , en el cual cada uno de dicho arilo, heteroarilo y heterociclilo puede estar sustituido o sustituido en forma opcional con uno o más restos que pueden ser iguales o diferentes, donde cada resto está seleccionado en forma independiente entre el

grupo integrado por halógeno, alquilo, arilo, cicloalquilo, CF_3, CN, $-OCF_3$, $-OR^5$, $-NR^5R^6$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^6$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^6$;

R^5 es H o alquilo;

R^6 está seleccionado entre el grupo integrado por H, alquilo, arilo, heteroarilo, arilalquilo y heteroarilalquilo, en el cual cada uno de dicho alquilo, heteroarilalquilo, arilo, heteroarilo y arilalquilo puede estar insustituido o sustituido en forma opcional con uno o más restos que pueden ser iguales o diferentes, donde cada resto está seleccionado en forma independiente entre el grupo integrado por halógeno, alquilo, arilo, cicloalquilo, CF_3, OCF_3, CN, $-OR^5$, $-NR^5R^6$, $-CH_2OR^5$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^6$;

R^7 está seleccionado entre el grupo integrado por alquilo, arilo, heteroarilo, arilalquilo y heteroarilalquilo, en el cual cada uno de dicho alquilo, heteroarilalquilo, arilo, heteroarilo y arilalquilo puede estar insustituido o sustituido en forma opcional con uno o más restos que pueden ser iguales o diferentes, donde cada resto está seleccionado en forma independiente entre el grupo integrado por halógeno, alquilo, arilo, cicloalquilo, CF_3, OCF_3, CN, $-OR^5$, $-NR^5R^6$, $-CH_2OR^5$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ and $-N(R^5)C(O)NR^5R^6$;

R^8 está seleccionado entre el grupo integrado por R^6, $-C(O)NR^5R^6$, $-S(O_2)NR^5R^6$, $-C(O)R^7$, $-C(O_2)R^6$, $-S(O_2)R^7$ y $-(CH_2)$–arilo;

R^9 está seleccionado entre el grupo integrado por halógeno, CN, NR^5R^6, $-C(O_2)R^6$, $-C(O)NR^5R^6$, $-OR^6$, $-C(O)R^7$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^6$;

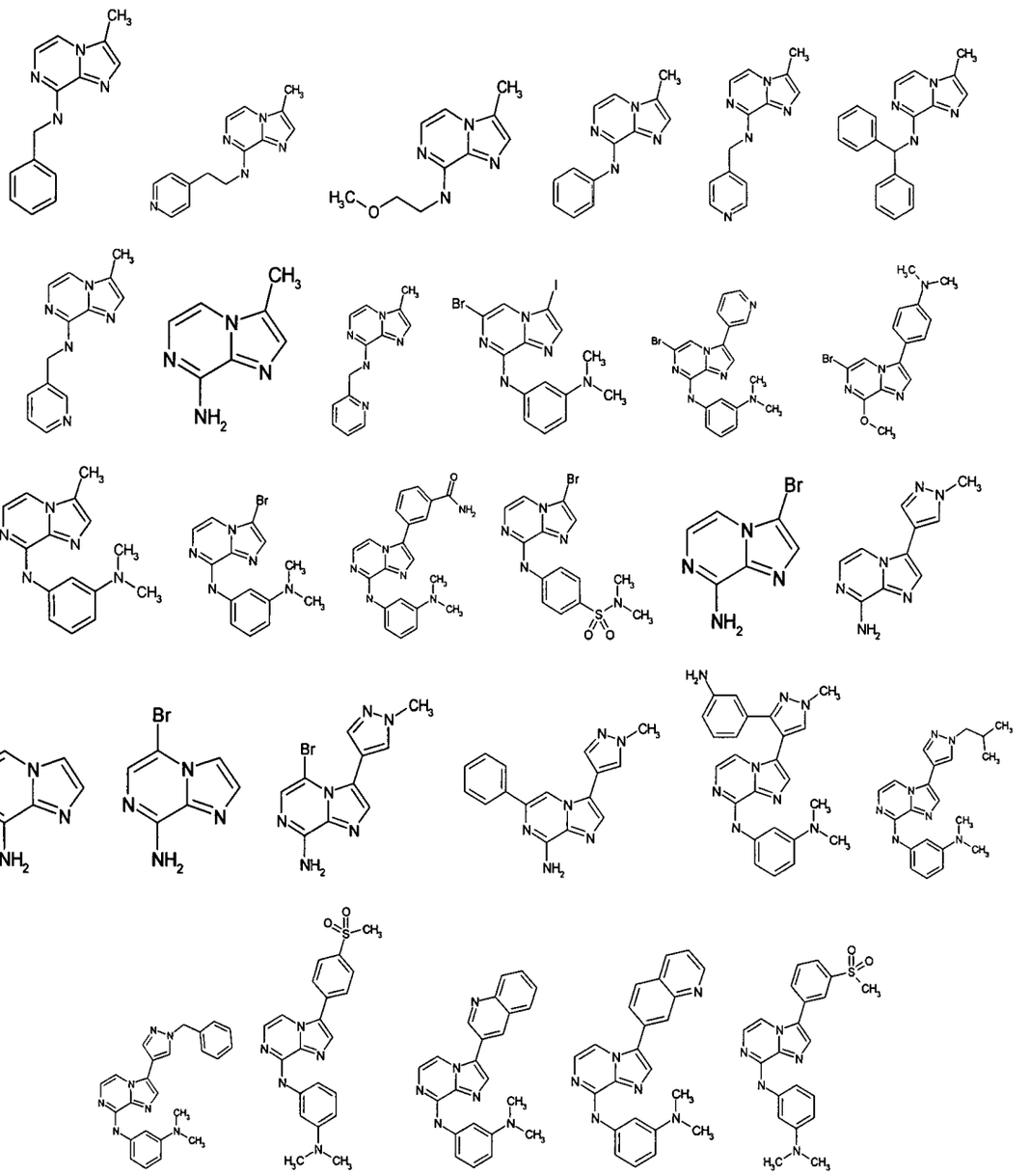
m es 0 a 4;

n es 1–4; y

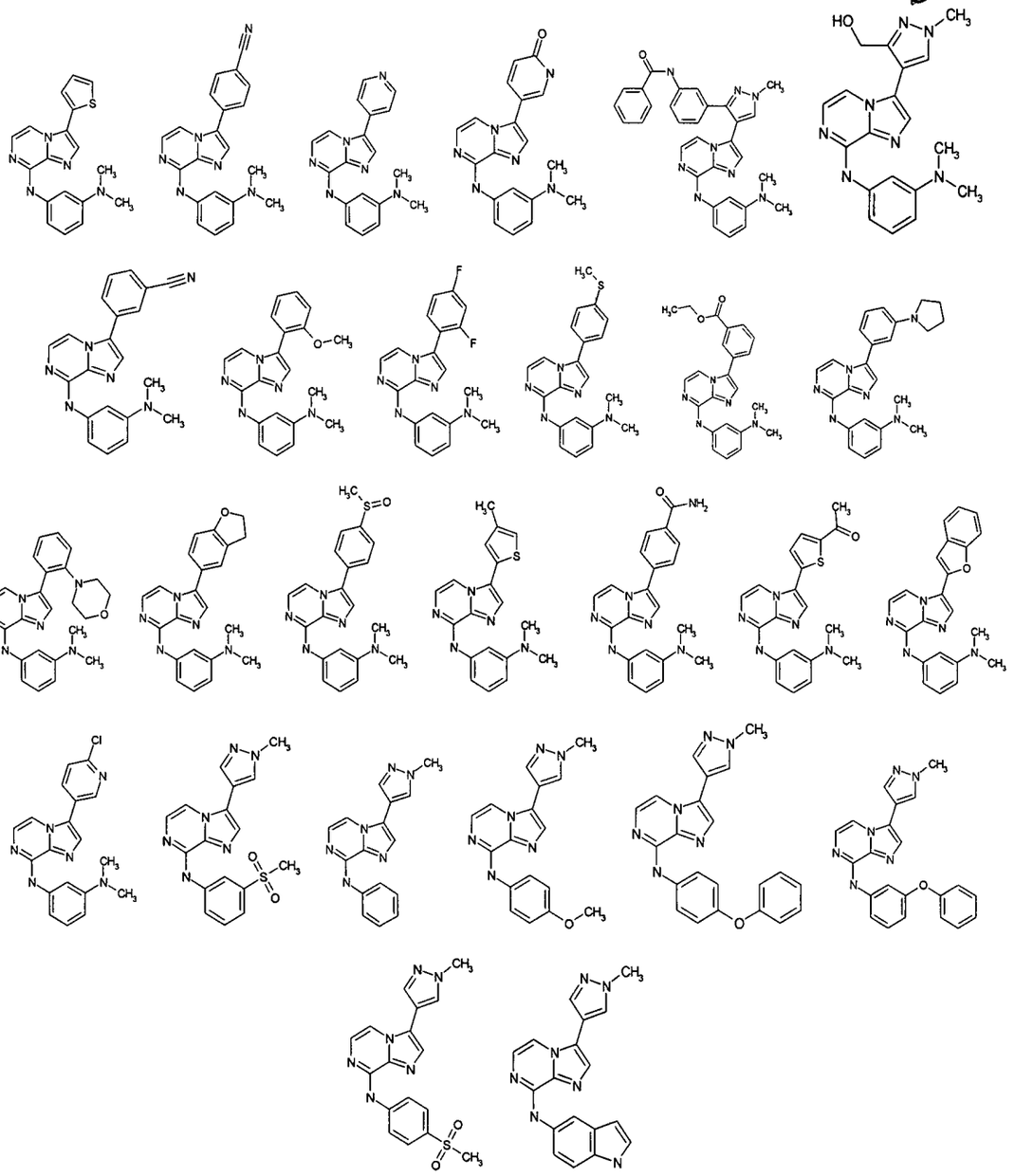
p es 0–3;

(ver WO2004/026877, presentada el 19 de septiembre de 2003);

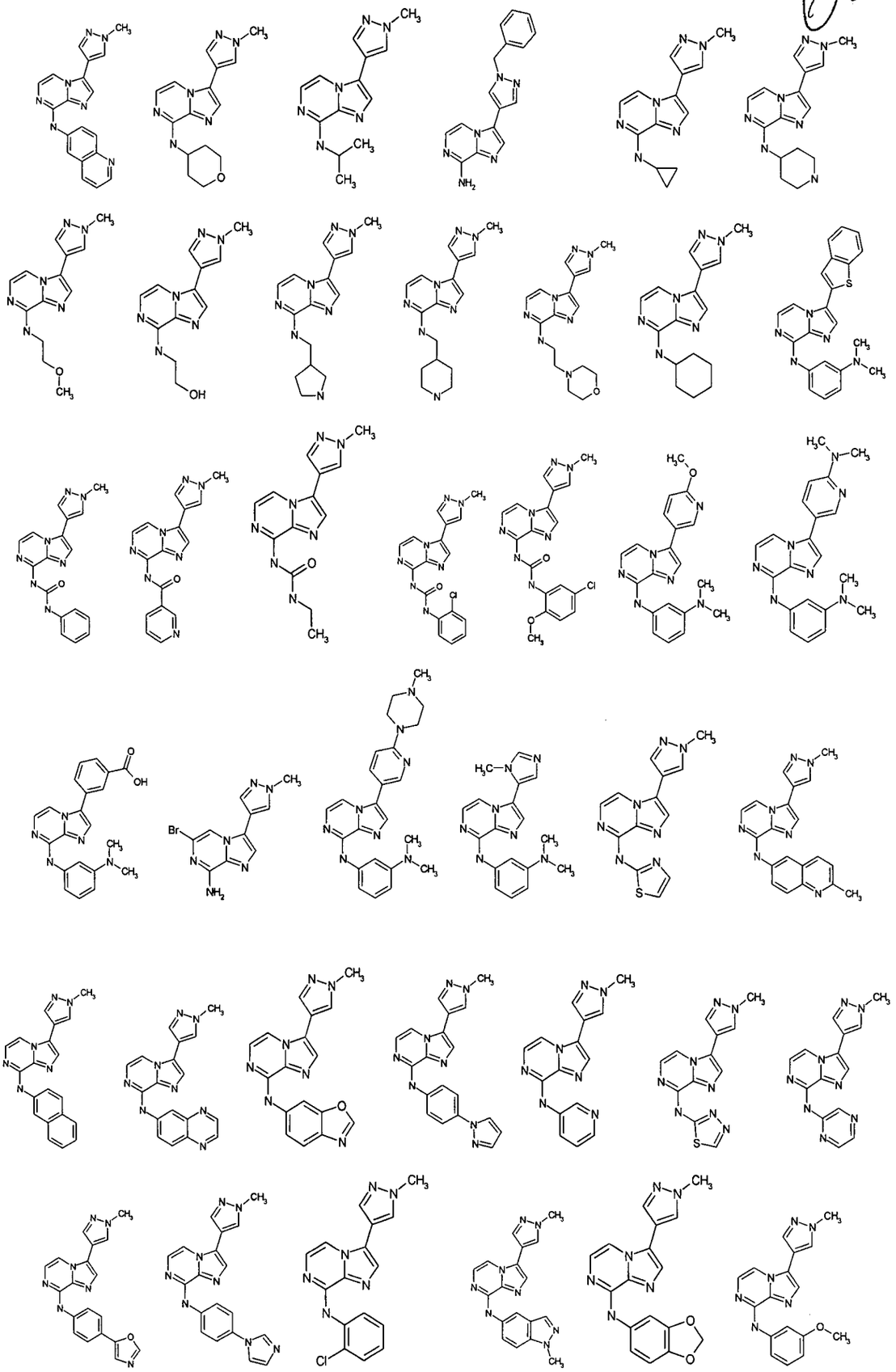
g. Un compuesto seleccionado entre los compuestos de las fórmulas:



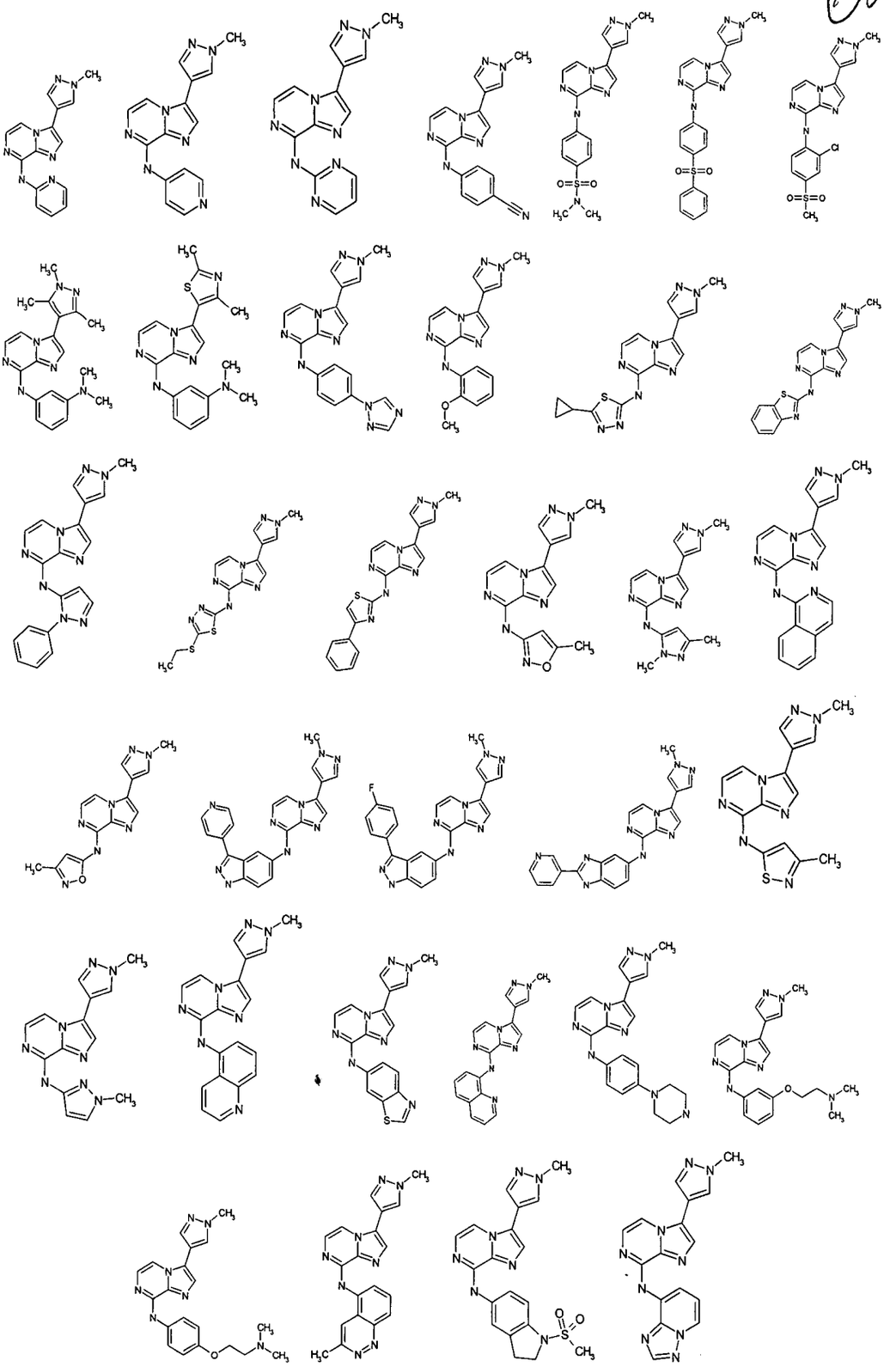
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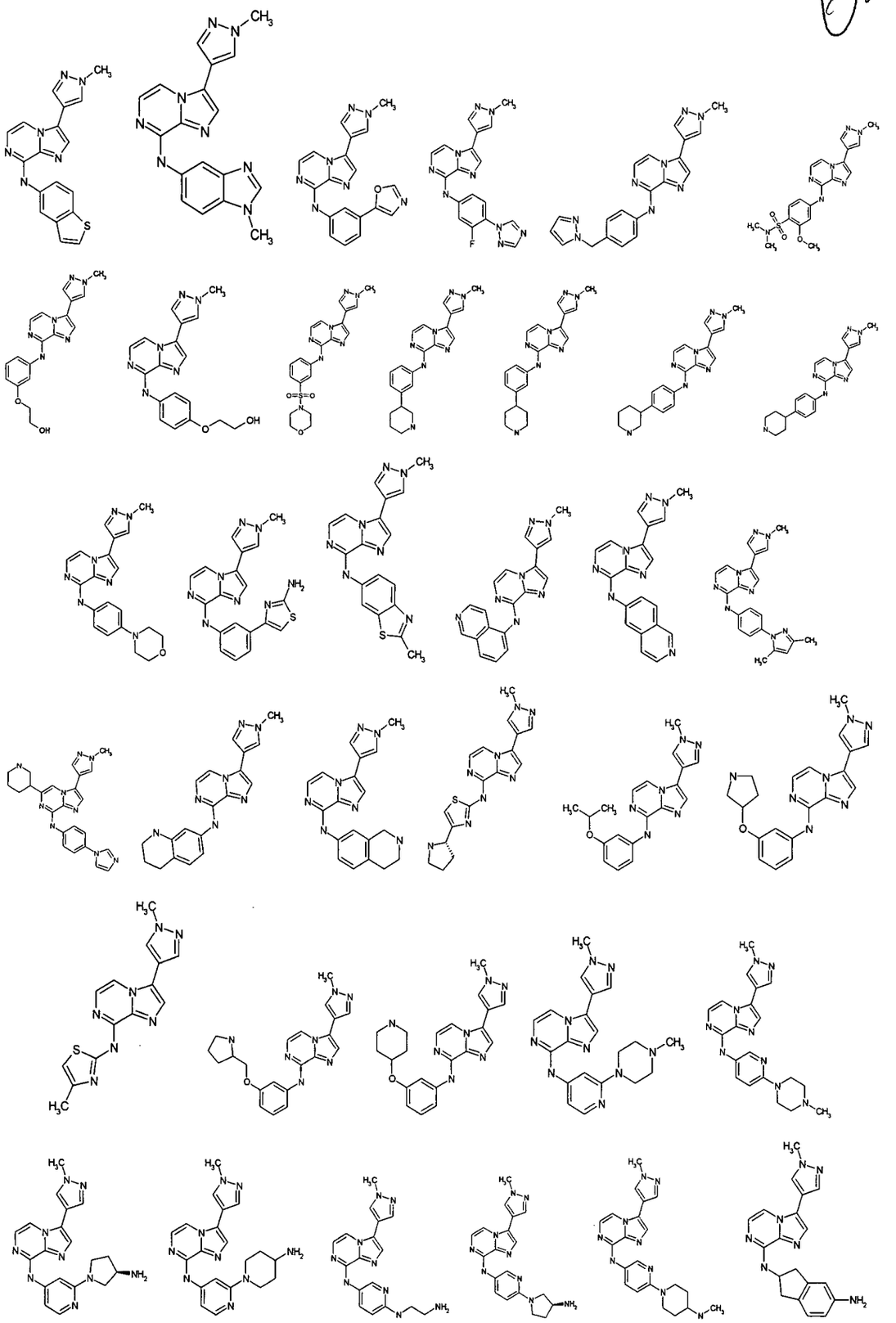


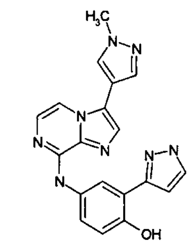
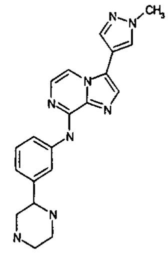
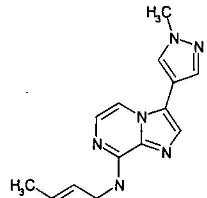
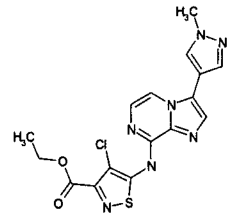
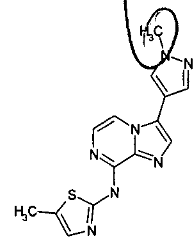
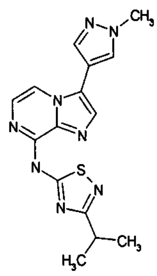
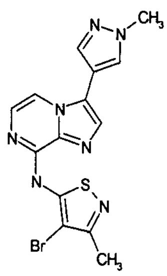
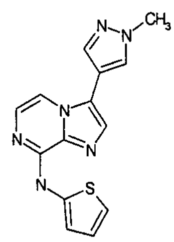
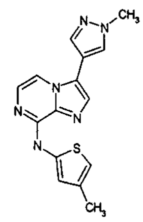
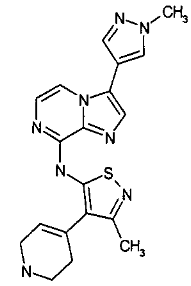
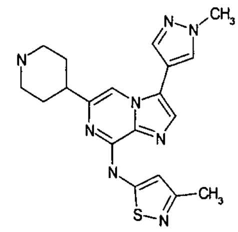
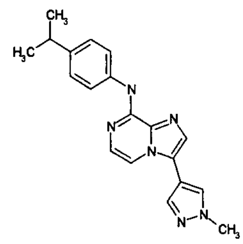
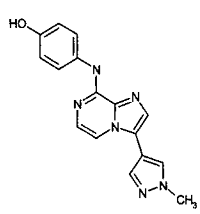
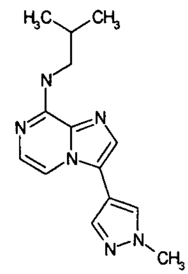
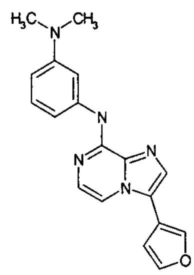
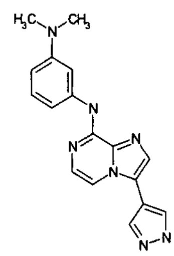
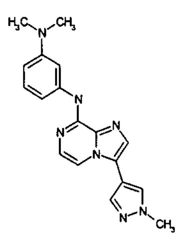
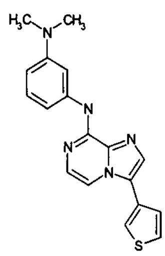
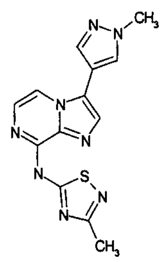
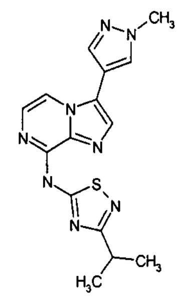
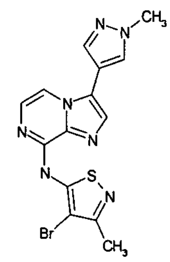
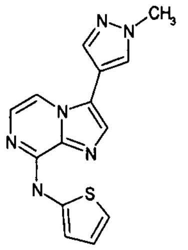
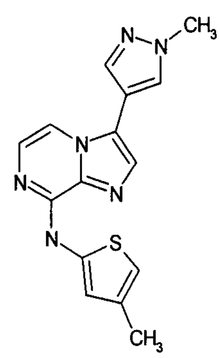
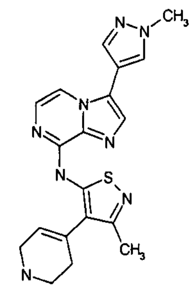
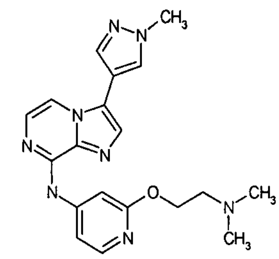
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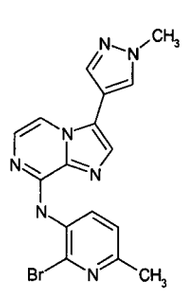
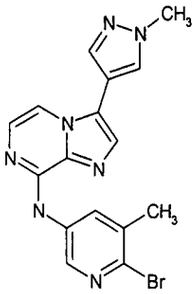
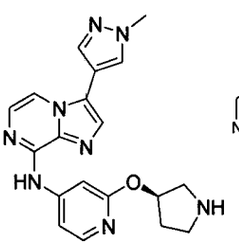
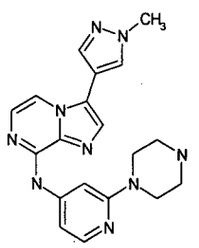
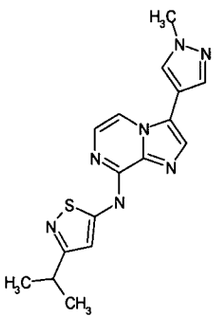
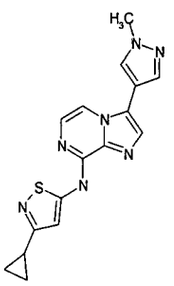
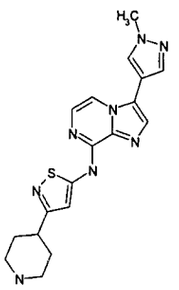
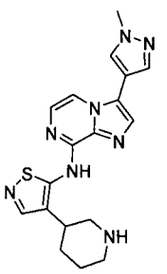
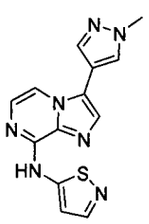
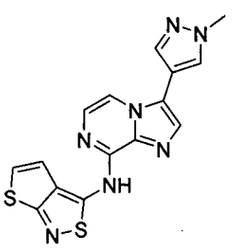
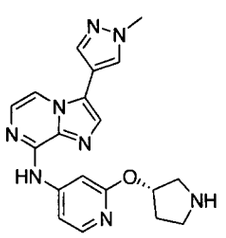
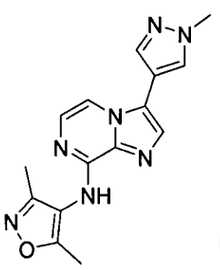
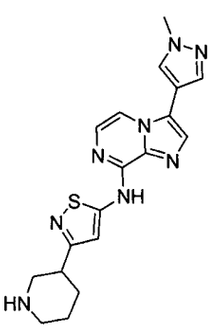
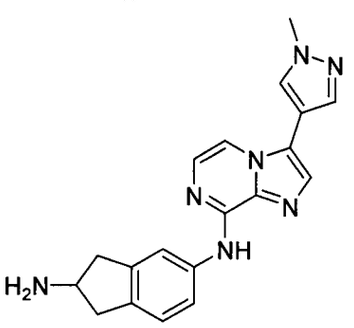
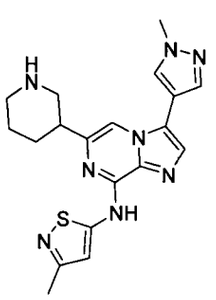
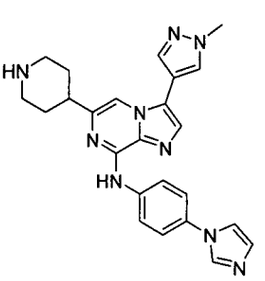
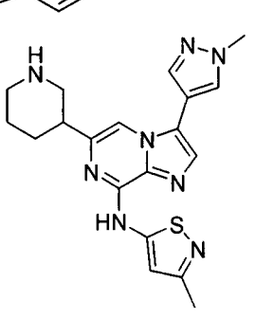
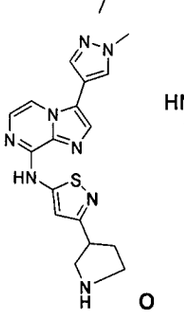
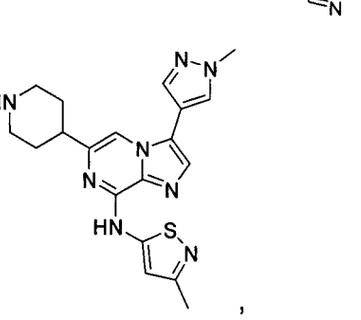
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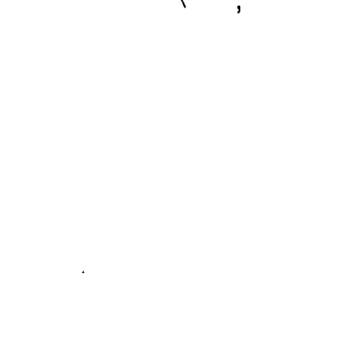




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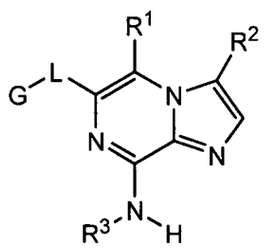






















o una sal, solvato, éster o prodroga del mismo, aceptables para uso farmacéutico,

(ver WO2007/058873, presentada el 8 de noviembre de 2006);

h. Un compuesto de la fórmula:



Fórmula H

o una sal, solvato, éster o prodroga del mismo, aceptables para uso farmacéutico, en el cual:

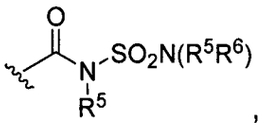
L está seleccionado entre el grupo integrado por S, S(O) y $S(O_2)$;

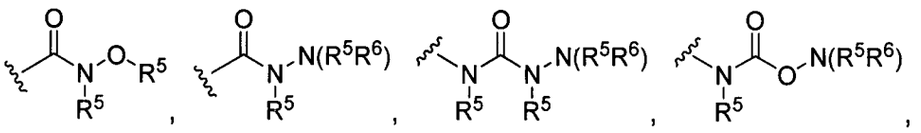
G es alquilo, alquenilo, cicloalquilo, cicloalquenilo, arilo, heteroarilo, heterociclenilo o heterociclilo, en el cual cada uno de dicho alquilo, alquenilo, cicloalquilo, cicloalquenilo, arilo, heteroarilo, heterociclenilo o heterociclilo puede estar insustituido o sustituido en forma opcional e independiente con uno o más restos que están seleccionados en forma independiente entre el grupo integrado por $-OR^5$, halo, $-CN$, $-C(O)NR^5R^6$, $-N(H)-C(O)R^5$,$-N(H)-C(O)-NR^5R^6$, $-S(O_2)NR^5R^6$, $-NR^5R^6$, $-C(O)R^5$, $-C(O_2)R^5$, $-SR^5$, $-S(O)R^5$, $-S(O_2)R^5$;

R^1 es H, halo, alquilo, arilo o heteroarilo, en el cual cada uno de dicho alquilo, arilo y heteroarilo puede estar insustituido o sustituido con uno o más restos que pueden ser iguales o diferentes donde cada resto está seleccionado en forma independiente entre el grupo integrado por halo, alquilo, alquenilo, alquinilo, cicloalquilo, arilo, heteroarilo, heterociclilo, $-C(O)NR^5R^6$ y $-OR^5$;

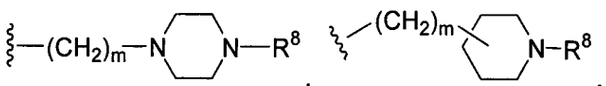
R^2 está seleccionado entre el grupo integrado por H, R^9, alquilo, arilo, arilalquilo, heteroarilo, heteroarilalquilo, heterociclilo, alquenilo, alquinilo, cicloalquilo, cicloalquilalquilo, heterociclilalquilo, $-CF_3$, $-C(O)R^7$,

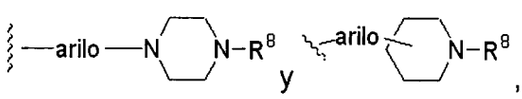
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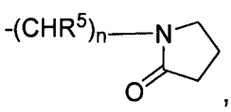
alquilo sustituido con 1–6 grupos de R^9 cuyos grupos pueden ser los mismos o diferentes donde cada R^9 está seleccionado en forma independiente,

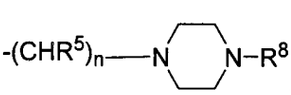




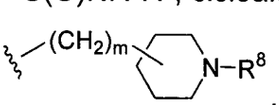
en el cual cada uno de arilo, heteroarilo, cicloalquilo, arilalquilo y heterociclilo mencionados anteriormente puede estar insustituido o sustituido en forma opcional e independiente con uno o más restos que pueden ser iguales o diferentes, donde cada resto está seleccionado en forma independiente entre el grupo integrado por halo, alquilo, alquenilo, alquinilo, cicloalquilo, arilo, heteroarilo, heterociclilo, CF_3, CN, $-OCF_3$, $-OR^6$, $-C(O)R^7$, $-NR^5R^6$, $-C(O_2)R^6$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^6$;

R^3 está seleccionado entre el grupo integrado por H, alquilo, arilo, heteroarilo, heterociclilo, aralquilo, heteroarilalquilo, cicloalquilalquilo, heterociclilalquilo,





$-(CHR^5)_n-OR^6$, $-S(O_2)R^6$, $-C(O)R^6$, $-S(O_2)NR^5R^6$, $-C(O)OR^6$, $-C(O)NR^5R^6$, cicloalquilo, $-CH(arilo)_2$, $-CH(heteroarilo)_2$, $-(CH_2)_m-NR^8$, y



, en el cual cada uno de dicho alquilo, arilo, heteroarilo y heterociclilo puede estar sustituido o sustituido en forma opcional con uno o más restos que pueden ser iguales o diferentes, donde cada resto está seleccionado en forma independiente entre el grupo integrado por halo, alquilo, arilo, cicloalquilo, CF_3, CN, $-OCF_3$, $-OR^5$, $-NR^5R^6$, $-C(O_2)R^5$,

$-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^6$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^6$;

R^5 es H, alquilo, arilo, heteroarilo, heterociclilo o cicloalquilo; y

R^6 está seleccionado entre el grupo integrado por H, alquilo, arilo, heteroarilo, arilalquilo y heteroarilalquilo, en el cual cada uno de dicho alquilo, heteroarilalquilo, arilo, heteroarilo y arilalquilo puede estar insustituido o sustituido en forma opcional con uno o más restos que pueden ser iguales o diferentes, donde cada resto está seleccionado en forma independiente entre el grupo integrado por halógeno, alquilo, arilo, cicloalquilo, CF_3, OCF_3, CN, $-OR^5$, $-NR^5R^6$, $-CH_2OR^5$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^6$;

R^7 está seleccionado entre el grupo integrado por alquilo, arilo, heteroarilo, arilalquilo y heteroarilalquilo, en el cual cada uno de dicho alquilo, heteroarilalquilo, arilo, heteroarilo y arilalquilo puede estar insustituido o sustituido en forma opcional con uno o más restos que pueden ser iguales o diferentes, donde cada resto está seleccionado en forma independiente entre el grupo integrado por halógeno, alquilo, arilo, cicloalquilo, CF_3, OCF_3, CN, $-OR^5$, $-NR^5R^6$, $-CH_2OR^5$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^6$;

R^8 está seleccionado entre el grupo integrado por R^6, $-C(O)NR^5R^6$, $-S(O_2)NR^5R^6$, $-C(O)R^7$, $-C(O_2)R^6$, $-S(O_2)R^7$ y $-(CH_2)$–arilo;

R^9 está seleccionado entre el grupo integrado por halógeno, CN, NR^5R^6, $-C(O_2)R^6$, $-C(O)NR^5R^6$, $-OR^6$, $-C(O)R^7$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^6$;

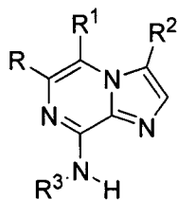
m es 0 a 4; y

p es 0–3;

(ver WO 2008/054749, presentada el 29 de octubre de 2007);

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i. Un compuesto de la Fórmula I:



Fórmula I

o una sal, solvato, éster o prodroga del mismo, aceptables para uso farmacéutico, en el cual:

R es H, CN, $-NR^5R^6$, cicloalquilo, cicloalquenilo, heterociclenilo, heteroarilo, $-C(O)NR^5R^6$, $-N(R^5)C(O)R^6$, heterociclilo, heteroarilo sustituido con $(CH_2)_{1-3}$ NR^5R^6, alquilo insustituido, o alquilo sustituido con uno o más restos que pueden ser iguales o diferentes donde cada resto está seleccionado en forma independiente entre el grupo integrado por $-OR^5$, heterociclilo, $-N(R^5)C(O)N(R^5R^6)$, $-N(R^5)-C(O)OR^6$, $-(CH_2)_{1-3}-N(R^5R^6)$ y $-NR^5R^6$;

R^1 es H, Halo, arilo o heteroarilo, en el cual cada uno de dicho arilo y heteroarilo puede estar insustituido o sustituido con uno o más restos que pueden ser iguales o diferentes donde cada resto está seleccionado en forma independiente entre el grupo integrado por halo, alquilo, alquenilo, alquinilo, cicloalquilo, arilo, heteroarilo, heterociclilo, $-CH_2OR^5$, $-C(O)NR^5R^6$, $-C(O)OH$, $-C(O)NH_2$, $-NR^5R^6$ (en el cual R^5 y R^6, junto con el N de dicho $-NR^5R^6$, forman un anillo heterociclilo), $-S(O)R^5$, $-S(O_2)R^5$, $-CN$, $-CHO$, $-SR^5$, $-C(O)OR^5$, $-C(O)R^5$ y $-OR^5$;

R^2 es H, halo, arilo, arilalquilo o heteroarilo, en el cual cada uno de dicho arilo, arilalquilo y heteroarilo puede estar insustituido o en forma opcional e independiente puede estar sustituido con uno o más restos que pueden ser iguales o diferentes donde cada resto está seleccionado en forma independiente entre el grupo integrado por halo, amida, alquilo, alquenilo, alquinilo, cicloalquilo, arilo, $-C(O)OH$, $-C(O)NH_2$, $-NR^5R^6$ (en el cual R^5 y R^6, junto con el N de dicho

$-NR^5R^6$, forman un anillo heterociclilo), –CN, arilalquilo, $-CH_2OR^5$, $-S(O)R^5$, $-S(O_2)R^5$, –CN, –CHO, $-SR^5$, $-C(O)OR^5$, $-C(O)R^5$, heteroarilo y heterociclilo;

R^3 es heterociclil–$(CR^7R^8)_n$–X, heterociclenil–$(CR^7R^8)_n$–X, heteroaril–$(CR^7R^8)_n$–X o aril–$(CR^7R^8)_n$–X en el cual cada uno de los restos heterociclil–, heterociclenil–, heteroaril– o aril– de dicho R^3 puede estar insustituido o sustituido con uno o más restos, seleccionados en forma independiente entre el grupo integrado por $-CONR^5R^6$, $-OR^5$ y alquilo,

n es 1–6,

X está seleccionado entre el grupo integrado por, $-NR^5R^6$, $-OR^5$, –SO–R^5 y $-SR^5$,

R^7 y R^8 son cada uno en forma independiente hidrógeno o alquilo;

R^5 está seleccionado entre el grupo integrado por hidrógeno, alquilo, alquenilo, alcoxialquilo, –alquil–S–alquilo, aminoalquilo, arilo, heteroarilo, heterociclenilo, heterocicloalquilo, cicloalquilo, cicloalquenilo, heterociclilalcoxilo, –S–alquilheterociclilo, heterociclilo, heterociclenilo, alquilN$(alquilo)_2$, alquilNH(alquilo), alquilN(alquenil)2, –alquilN(alcoxil)2, –alquil–SH e hidroxialquilo, en el cual cada uno de dicho arilo, heteroarilo, heterociclenilo, heterocicloalquilo, cicloalquilo, cicloalquenilo, heterociclilalcoxilo, –S–alquilheterociclilo, heterociclilo, heterociclenilo puede estar insustituido o sustituido con uno o más restos seleccionados en forma independiente entre el grupo integrado por alquilo, alquilo, alquenilo, arilo, cicloalquenilo, cicloalquilo, arilalquilo, cicloalquenilalquilo, cicloalquilalquilo, heteroarilo, heterociclenilo, heterociclilo, heteroarilalquilo, heterociclenilalquilo, heterocicloalquilalquilo, alcoxialquilo, –alquil–S–alquilo, –alquilSH, alcoxilo, –S–alquilo, hidroxialquilo, y aminoalquilo;

R^6 está seleccionado entre el grupo integrado por hidrógeno, alquilo, alquenilo, arilo, cicloalquenilo, cicloalquilo, arilalquilo, cicloalquenilalquilo, cicloalquilalquilo, heteroarilo, heterociclenilo, heterociclilo, heteroarilalquilo,

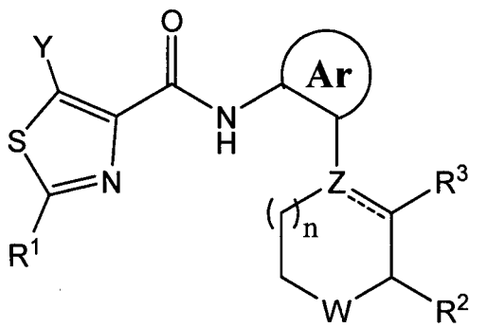
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heterociclenilalquilo, heterocicloalquilalquilo, alcoxialquilo, –alquil–S–alquilo, –alquilSH, alcoxilo, –S–alquilo, hidroxialquilo, y aminoalquilo, en el cual cada uno de dicho arilo, cicloalquenilo, cicloalquilo, arilalquilo, cicloalquenilalquilo, cicloalquilalquilo, heteroarilo, heterociclenilo, heterociclilo, heteroarilalquilo, heterociclenilalquilo, heterocicloalquilalquilo puede estar insustituido o sustituido con uno o más restos seleccionados en forma independiente entre el grupo integrado por alquilo, alquilo, alquenilo, arilo, cicloalquenilo, cicloalquilo, arilalquilo, cicloalquenilalquilo, cicloalquilalquilo, heteroarilo, heterociclenilo, heterociclilo, heteroarilalquilo, heterociclenilalquilo, heterocicloalquilalquilo, alcoxialquilo, –alquil–S–alquilo, –alquilSH, alcoxilo, –S–alquilo, hidroxialquilo, y aminoalquilo;

en el cual además en cualquier $-NR^5R^6$ en la Fórmula I, dicho R^5 y R^6 pueden estar unidos en forma opcional junto con el N de dicho $-NR^5R^6$ para formar un anillo cíclico o anillo cíclico en puente, en el cual cada uno de dicho anillo cíclico o anillo cíclico en puente, puede estar insustituido o sustituido con uno o más restos, que pueden ser iguales o diferentes, seleccionados en forma independiente entre el grupo integrado por hidroxilo, –SH, alquilo, alquenilo, hidroxialquilo, –alquil–SH, alcoxilo, –S–alquilo, $-CO_2$–alquilo, $-CO_2$–alquenilo, arilalquilo, cicloalquenilalquilo, cicloalquilalquilo, heteroarilalquilo, heterociclenilalquilo, heterocicloalquilalquilo, heteroarilo, arilo, cicloalquenilo, cicloalquilo, espiroheterociclilo, espiroheterociclenilo, espiroheteroarilo, espirociclilo, espirociclenilo, espiroarilo, alcoxialquilo, –alquil–S–alquilo, heterociclilo, y heterociclenilo;

(ver WO 2008/057512, presentada el 6 de noviembre de 2007 y PCT Serie Nº US2008/007295, presentada el 11 de junio de 2008);

j. Un compuesto que tiene la fórmula:



(J)

o una sal, solvato, éster, prodroga o estereoisómero del mismo, aceptables para uso farmacéutico, en el cual las líneas de guiones indican un enlace opcional y adicional, y en el cual:

R^1 es heteroarilo que contiene nitrógeno, heterociclilo que contiene nitrógeno, heteroarilo benzofusionado que contiene nitrógeno o heterociclilo benzofusionado que contiene nitrógeno, en el cual R^1 está unido al resto del compuesto de la fórmula (I) mediante un átomo de nitrógeno en el anillo, y en el cual uno o más átomos de carbono en el anillo de un grupo heteroarilo que contiene nitrógeno, heterociclilo que contiene nitrógeno, heteroarilo benzofusionado que contiene nitrógeno o heterociclilo benzofusionado que contiene nitrógeno puede estar sustituido con hasta 5 sustituyentes, que pueden ser iguales o diferentes, y están seleccionados en forma independiente entre alquilo, arilo, halo, –OH, –O–alquilo, –O–arilo, $–N(R^8)_2$, $–CF_3$, $–NO_2$, $–C(O)R^8$, $–C(O)OR^8$, $–C(O)N(R^8)_2$, $–OC(O)R^8$ o $–NHC(O)R^8$;

R^2 es –H, –alquilo, $–NH_2$ o $–CH_2NH_2$;

R^3 es –H, –alquilo, $–NH_2$ o $–CH_2NH_2$;

cada vez que aparece R^4 es en forma independiente –H, –alquilo, $–NH_2$, –OH, –alquileno–OH, $–CH_2NH_2$, $–C(O)R^5$, $–C(O)NH_2$, –C(O)NH–alquilo, $–C(O)N(alquilo)_2$, $–NHC(O)R^6$ o $–NHS(O)_2R^6$;

R^5 es –H, –alquilo, –arilo, –heteroarilo, –NHOH;

R^6 es –H, –alquil o $–CF_3$;

R^7 es –H, –OH, –alquilo C_1–C_6, –O–(alquilo C_1–C_6), o $–CF_3$;

R^8 es –H, alquilo, arilo, heterociclilo, heteroarilo o cicloalquilo;

Ar es –arileno– o –heteroarileno–, en el cual el arileno o heteroarileno está unido mediante 2 de sus átomos de carbono adyacentes en el anillo, y en el cual el –arileno– o –heteroarileno– puede estar sustituido con hasta 4 sustituyentes, que pueden ser iguales o diferentes, y están seleccionados en forma independiente entre –halo, alquilo, alcoxi, ariloxi, $–SR^8$, $–S(O)R^8$, $–S(O)_2R^8$, $–C(O)R^8$, $–C(O)OR^8$, $–C(O)N(R^8)_2$, $–NHC(O)R^8$, $–CF_3$, –CN o NO_2, y de modo que cuando Ar es tetrahidronaftileno, ambos R^1 y R^2 no pueden ser hidrógeno

W es –NH– o $–C(R^4)_2–$, en el cual ambos grupos R^4 y el átomo de carbono al cual están unidos pueden combinarse para formar un grupo heterociclilo o heteroarilo de cinco a siete miembros;

Y es –H, –halo, –alquil o –CN;

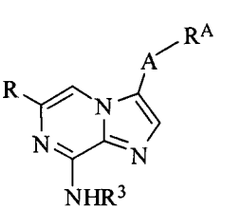
Z es $–CR^7–$ o –N–, cuando el enlace adicional opcional está ausente, y –C– cuando el enlace adicional opcional está presente;

n es un número entero cuyo rango es desde 0 a 2.

Los compuestos representados en la presente solicitud mediante el párrafo (j) se divulgan en WO 2008/054749, presentada el 29 de octubre de 2007.

(ver WO 2008/054749, presentada el 29 de octubre de 2007); y

(k) Un compuesto de la Fórmula K:



Fórmula K

o una sal, solvato, éster, prodroga o estereoisómero del mismo, aceptables

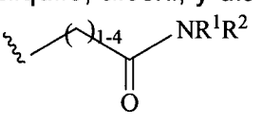
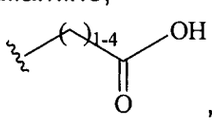
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para uso farmacéutico, en el cual:

R es H, halo o alquilo;

R^3 es heteroaril–X, en el cual X es heterociclilalquil– en el cual dicho heterociclilo puede estar insustituido o sustituido en forma opcional con 1–4 restos de alquilo;

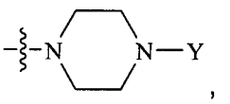
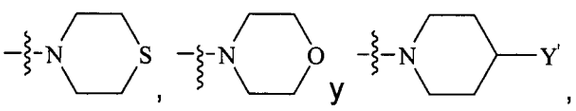
A es –aril– , –heteroaril–, $-N(R^1)$–aril– o $-N(R^1)$–heteroaril– , en el cual cada uno de dicho arilo y heteroarilo puede estar insustituido en forma independiente o puede estar sustituido en forma opcional con uno o más sustituyentes, cuyos sustituyentes pueden ser iguales o diferentes, donde cada sustituyente está seleccionado en forma independiente entre el grupo integrado por alquilo, $-NO_2$, halo, hidroxi, trihaloalquilo, alcoxi, y dialquilamino;

R^A es $-(CH_2)_{1-4}$–heteroarilo,  o  , en el cual dicho heteroarilo puede estar fusionado en forma opcional con un arilo, en el cual cada uno de dicho arilo y heteroarilo en forma independiente puede estar sustituido en forma opcional con uno o más restos donde cada resto está seleccionado en forma independiente entre el grupo integrado por trihaloalquilo, $-NO_2$, halo, hidroxialquilo, alcoxialquilo y dialquilamino;

R^1 es H o alquilo;

R^2 es H, hidroxialquilo–, arilalquilo–, heteroarilo, arilo, heteroarilalquil–, alquilo, dialquilaminoalquil–, alquilaminoalquil–, cicloalquilalquil–, cicloalquilo, heterociclilalquil– or heterociclilo, en el cual dicho arilo y arilo de arilalquilo pueden estar insustituidos o sustituidos con uno o más restos seleccionados en forma independiente entre el grupo integrado por trihaloalquilo, $-NO_2$, halo, hidroxialquilo, alcoxialquilo, dialquilamino y heterociclilalquil–, en el cual dicho heterociclilalquilo puede estar insustituido o sustituido con alquilo o $-SO_2NH_2$; dicho heteroarilo y heteroarilo de heteroarilalquilo pueden estar insustituidos o sustituidos con uno o más restos, donde cada resto está seleccionado en forma

independiente entre el grupo integrado por hidroxialquilo, alcoxi, alquilo, halo, hidroxilo, y $-NO_2$; y dicho cicloalquilo está insustituido o sustituido con hidroxilo; o

R^1 y R^2 junto con el N al cual cada uno está unido, forman un grupo heterocíclico seleccionado entre el grupo integrado por  ,  , en el cual

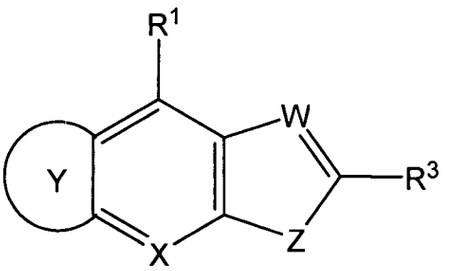
Y es alcoxialquilo, hidroxialquilo, dialquilaminoalquilo o alquilo, en el cual además

Y' es hidroxilo.

Los compuestos representados en la presente solicitud por la Fórmula k se divulgan en la Solicitud de EEUU Nº 61/024010, presentada el 28 de enero de 2008.

En otra forma de realización, el inhibidor de KSP útil en la práctica de la presente invención está representado por la Fórmula AI:

AI. Un compuesto representado por la Fórmula estructural AI:



Fórmula AI

o una sal, solvato o éster del mismo, aceptables para uso farmacéutico, en el cual:

el anillo Y es un arilo de 5 a 6 miembros o un heteroarilo de 5 o 6 miembros fusionado como se indica en la Fórmula A, en el cual en dicho arilo y heteroarilo, cado carbono sustituible del anillo está sustituido en forma independiente con R^2 y cada nitrógeno sustituible del anillo está sustituido en forma independiente con R^6;

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W es N o $C(R^{12})$;

X es N o N–óxido;

Z es S, S(=O) o $S(=O)_2$;

R^1 es H, alquilo, alcoxi, hidroxi, halo, –CN, $–S(O)_m–$alquilo, $–C(O)NR^9R^{10}$, $–(CR^9R^{10})_{1–6}OH$, o $–NR^4(CR^9R^{10})_{1–2}OR^9$;

cada R^2 está seleccionado en forma independiente entre el grupo integrado por H, halo, alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo, heteroaralquilo, $–(CR^{10}R^{11})_{0–6}–OR^7$, $–C(O)R^4$, $–C(S)R^4$, $–C(O)OR^7$, $–C(S)OR^7$, $–OC(O)R^7$, $–OC(S)R^7$, $–C(O)NR^4R^5$, $–C(S)NR^4R^5$, $–C(O)NR^4OR^7$, $–C(S)NR^4OR^7$, $–C(O)NR^7NR^4R^5$, $–C(S)NR^7NR^4R^5$, $–C(S)NR^4OR^7$, $–C(O)SR^7$, $–NR^4R^5$, $–NR^4C(O)R^5$, $–NR^4C(S)R^5$, $–NR^4C(O)OR^7$, $–NR^4C(S)OR^7$, $–OC(ONR^4R^5$, $–OC(S)NR^4R^5$, $–NR^4C(O)NR^4R^5$, $–NR^4C(S)NR^4R^5$, $–NR^4C(O)NR^4OR^7$, $–NR^4C(S)NR^4OR^7$, $–(CR^{10}R^{11})_{0–6}SR^7$, SO_2R^7, $–S(O)_{1–2}NR^4R^5$, $–N(R^7)SO_2R^7$, $–S(O)_{1–2}NR^5OR^7$, –CN, $–OCF_3$, $–SCF_3$, $–C(=NR^7)NR^4$, $–C(O)NR^7(CH_2)_{1–10}NR^4R^5$, $–C(O)NR^7(CH_2)_{1–10}OR^7$, $–C(S)NR^7(CH_2)_{1–10}NR^4R^5$, $–C(S)NR^7(CH_2)_{1–10}OR^7$, haloalquilo y alquilsililo, en el cual cada uno de dicho alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo o heteroaralquilo está sustituido en forma opcional e independiente con 1–5 restos de R^9;

cada R^3 está seleccionado en forma independiente entre el grupo integrado por H, halo, alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo, heteroaralquilo, $–(CR^{10}R^{11})_{0–6}–OR^7$, $–C(O)R^4$, $–C(S)R^4$, $–C(O)OR^7$, $–C(S)OR^7$, $–OC(O)R^7$, $–OC(S)R^7$, $–C(O)NR^4R^5$, $–C(S)NR^4R^5$, $–C(O)NR^4OR^7$, $–C(S)NR^4OR^7$, $–C(O)NR^7NR^4R^5$, $–C(S)NR^7NR^4R^5$, $–C(S)NR^4OR^7$, $–C(O)SR^7$, $–NR^4R^5$, $–NR^4C(O)R^5$, $–NR^4C(S)R^5$, $–NR^4C(O)OR^7$, $–NR^4C(S)OR^7$, $–OC(O)NR^4R^5$, $–OC(S)NR^4R^5$, $–NR^4C(O)NR^4R^5$, $–NR^4C(S)NR^4R^5$, $–NR^4C(O)NR^4OR^7$, $–NR^4C(S)NR^4OR^7$, $–(CR^{10}R^{11})_{0–6}SR^7$, SO_2R^7, $–S(O)_{1–2}NR^4R^5$,

$-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, $-CN$, $-OCF_3$, $-SCF_3$, $-C(=NR^7)NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}OR^7$, $-C(S)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(S)NR^7(CH_2)_{1-10}OR^7$, haloalquilo y alquilsililo, en el cual cada uno de dicho alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo o heteroaralquilo está sustituido en forma opcional e independiente con 1–5 restos de R^9;

cada R^4 y R^5 está seleccionado en forma independiente entre el grupo integrado por H, alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo, heteroaralquilo, $-OR^7$, $-C(O)R^7$, y $-C(O)OR^7$, en el cual cada uno de dicho alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo, o heteroaralquilo está sustituido en forma opcional con 1–4 restos de R^8;

o R^4 y R^5, cuando están unidos al mismo átomo de nitrógeno, se toman en forma opcional junto con el átomo de nitrógeno al cual están unidos para formar un anillo heterocíclico de 3–6 miembros que tiene 0–2 heteroátomos adicionales seleccionados entre N, O o S;

cada R^6 está seleccionado en forma independiente entre el grupo integrado por H, alquilo, arilo, aralquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, heteroarilo, heteroaralquilo, $-(CH_2)_{1-6}CF_3$, $-C(O)R^7$, $-C(O)OR^7$ y $-SO_2R^7$;

cada R^7 está seleccionado en forma independiente entre el grupo integrado por H, alquilo, arilo, aralquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, heteroarilo, y heteroaralquilo, en el cual cada miembro de R^7 excepto H está sustituido en forma opcional con 1–4 restos de R^8;

cada R^8 está seleccionado en forma independiente entre el grupo integrado por halo, alquilo, cicloalquilo, heterociclilo, arilo, heteroarilo, $-NO_2$, $-OR^{10}$, $-$(alquilo C_1–C_6)$-OR^{10}$, $-CN$, $-NR^{10}R^{11}$, $-C(O)R^{10}$, $-C(O)OR^{10}$, $-C(O)NR^{10}R^{11}$,

$-CF_3$, $-OCF_3$, $-CF_2CF_3$, $-C(=NOH)R^{10}$, $-N(R^{10})C(O)R^{11}$, $-C(=NR^{10})NR^{10}R^{11}$, y $-NR^{10}C(O)OR^{11}$, en el cual cada uno de dicho alquilo, cicloalquilo, heterociclilo, arilo, y heteroarilo está sustituido en forma opcional e independiente con 1–3 restos seleccionados entre el grupo integrado por halo, alquilo, cicloalquilo, heterociclilo, arilo, heteroarilo, $-NO_2$, $-OR^{10}$, $-(C_1-C_6$ alkyl$)-OR^{10}$, $-CN$, $-NR^{10}R^{11}$, $-C(O)OR^{10}$, $-C(O)NR^{10}R^{11}$, $-CF^3$, $-OCF_3$, $-NR^{10}C(O)OR^{11}$, y $-NR^{10}C(O)R^{40}$;

o dos grupos R^8, cuando están unidos al mismo átomo de carbono, se toman en forma opcional junto con el átomo de carbono al cual están unidos para formar un grupo C=O o un grupo C=S;

cada R^9 está seleccionado en forma independiente entre el grupo integrado por H, alquilo, alcoxi, OH, CN, halo, $-(CR^{10}R^{11})_{0-4}NR^4R^5$, haloalquilo, hidroxialquilo, alcoxialquilo, $-C(O)NR^4R^5$, $-C(O)OR^7$, $-OC(O)NR^4R^5$, $-NR^4C(O)R^5$, y $-NR^4C(O)NR^4R^5$;

cada R^{10} es en forma independiente H o alquilo; o R^9 y R^{10}, cuando están unidos al mismo átomo de nitrógeno, se toman en forma opcional junto con el átomo de nitrógeno al cual están unidos para formar un anillo heterocíclico de 3–6 miembros que tiene 0–2 heteroátomos adicionales seleccionados entre N, O o S;

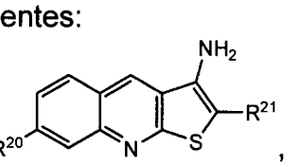
cada R^{11} es en forma independiente H o alquilo; o R^{10} y R^{11}, cuando están unidos al mismo átomo de nitrógeno, se toman en forma opcional junto con el átomo de nitrógeno al cual están unidos para formar un anillo heterocíclico de 3–6 miembros que tiene 0–2 heteroátomos adicionales seleccionados entre N, O o S;

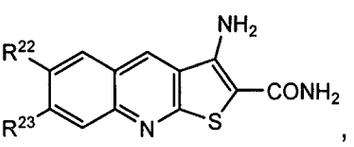
cada R^{12} está seleccionado en forma independiente entre el grupo integrado por H, halo, alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo, heteroaralquilo, $-(CR^{10}R^{11})_{0-6}-OR^7$, $-C(O)R^4$, $-C(S)R^4$, $-C(O)OR^7$, $-C(S)OR^7$, $-OC(O)R^7$, $-OC(S)R^7$, $-C(O)NR^4R^5$, $-C(S)NR^4R^5$, $-C(O)NR^4OR^7$, $-C(S)NR^4OR^7$, $-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$,

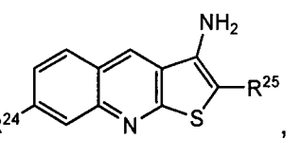
$-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, $-CN$, $-OCF_3$, $-SCF_3$, $-C(=NR^7)NR^4$, $-C(O)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}OR^7$, $-C(S)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(S)NR^7(CH_2)_{1-10}OR^7$, haloalquilo y alquilsililo, en el cual cada uno de dicho alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo o heteroaralquilo está sustituido en forma opcional e independiente con 1–5 restos de R^9; y

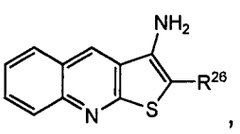
R^{40} está seleccionado entre el grupo integrado por cicloalquilo, heterociclilo, arilo y heteroarilo, en el cual cada uno de dicho cicloalquilo, heterociclilo, arilo y heteroarilo está sustituido en forma opcional e independiente con 1–3 restos seleccionados en forma independiente entre el grupo integrado por –CN, –OH, halo, alquilo, haloalquilo, alcoxi, y $-NR^{10}R^{11}$;

con la condición de que el compuesto de la Fórmula AI excluya cualquiera de los siguientes:

(1) 
, en el cual R^{20} es H, $-CH_3$ o $-OCH_3$ y R^{21} es $-C(O)CH_3$, –C(O)CH=CH–fenilo o –C(O)CH=CH–(4–metoxifenilo);

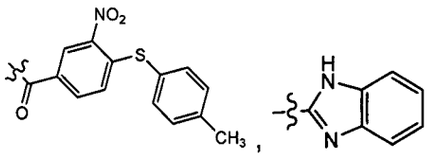
(2) 
, en el cual R^{22} y R^{23} son en forma independiente H o metoxi;

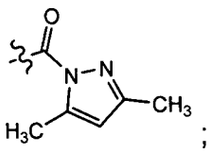
(3) 
, en el cual R^{24} es metilo, metoxi o –Cl y R^{25} es $-CONH_2$ o $-CO_2Et$;

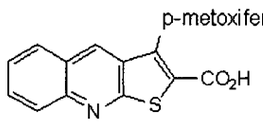
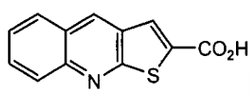
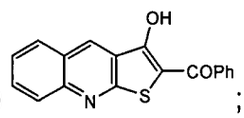
(4) 
, en el cual R^{26} es $-CO_2Me$, $-CO_2Et$, $-CO_2H$, –C(O)–fenilo, –C(O)–p–metilfenilo, –C(O)–p–bromofenilo, $-C(O)CH_3$, –CN,

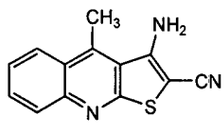
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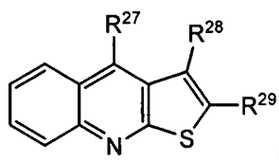
–C(O)NH–fenilo, –C(O)NH–p–metoxifenilo, $-C(O)NHNH_2$, –C(O)NH–p–clorofenilo,




;

(5)  ; (6)  ; (7)  ;

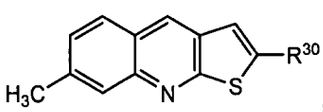
(8)  ;

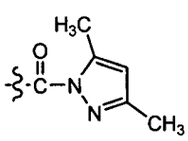
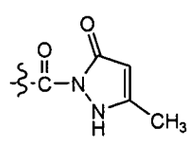
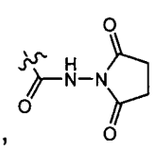
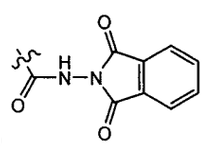
(9)  , en el cual:

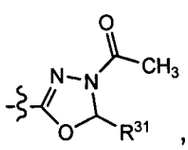
R^{27} es H, –OH, $-OCH_3$ o $-OCH(CH_3)_2$,

R^{28} es –OH, $-OCH_2CN$ o $-OC(O)NH(CH_2)_5CN$, y

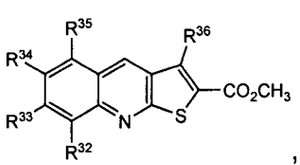
R^{29} es $-C(O)OCH(CH_3)_2$ o –C(O)O–ciclohexilo;

(10)  , en el cual:

R^{30} es 



,


,

$-CO_2CH_3$, $-CO_2C_2H_5$, $-C(O)NH_2$, $-C(O)NHNH_2$, o $-C(O)NHCH_3$ y R^{31} es C_6H_5, p–OHC_6H_4 o p–$CH_3C_6H_4$;

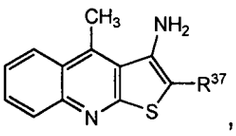
(11)  , en el cual:

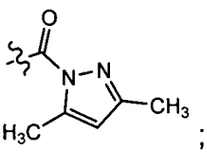
R^{32} es H o NO_2,

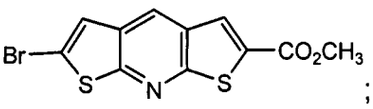
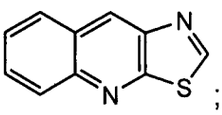
R^{33} y R^{34} son en forma independiente H, $-OCH_3$ o $-OC_2H_5$,

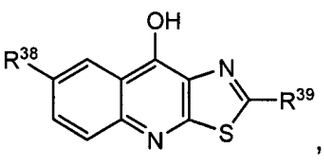
R^{35} es H o $-OCH_3$, y

R^{36} es H, CH_3 o C_6H_5;

(12)  , en el cual:

R^{37} es $-CO_2Me$, $-CO_2Et$, $-CO_2H$, $-C(O)NH_2$, $-C(O)NHNH_2$, $-CN$, $-C(O)NH-p-$metoxifenilo, $-C(O)NH-(2-$piridyl) o  ;

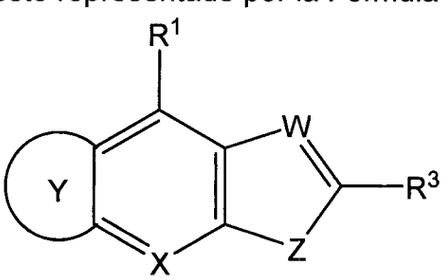
(13)  ; (14)  ; y

(15)  , en el cual R^{38} es H, metilo o CF_3 y R^{39} es SMe, SOMe, SO_2Me, Cl, $NH(CH_2)NEt_2$, o N–(N'–metil)piperazinilo.

Los compuestos representados en la presente solicitud por la Fórmula AI se divulgan en WO 2006/098962, presentada el 7 de marzo de 2006.

En otra forma de realización, el inhibidor de KSP útil en la práctica de la presente invención está representado por la Fórmula BI:

BI. Un compuesto representado por la Fórmula estructural BI:



Fórmula BI

o una sal, solvato o éster del mismo, aceptables para uso farmacéutico, en el cual:

el anillo Y es un anillo de 5 a 7 miembros seleccionado entre el grupo integrado por cicloalquilo, cicloalquenilo, heterociclilo o heterociclenilo fusionado como se indica en la Fórmula B, en el cual en cada uno de dicho anillo de 5 a 7

miembros, cada carbono sustituible en el anillo está sustituido en forma independiente con 1–2 restos de R^2 y cada heteroátomo sustituible en el anillo está sustituido en forma independiente con R^6;

W es N o $C(R^{12})$;

X es N o N–óxido;

Z es S, S(=O) o $S(=O)_2$;

R^1 es H, alquilo, alcoxi, hidroxi, halo, –CN, $–S(O)_m–$alquilo, $–C(O)NR^9R^{10}$, $–(CR^9R^{10})_{1–6}OH$, o $–NR^4(CR^9R^{10})_{1–2}OR^9$; en el cual m es O a 2;

cada R^2 está seleccionado en forma independiente entre el grupo integrado por H, halo, alquilo, cicloalquilo, alquilsililo, cicloalquenilo, heterociclilo, heterociclenilo, arilo, heteroarilo, $–(CR^{10}R^{11})_{0–6}–OR^7$, $–C(O)R^4$, $–C(S)R^4$, $–C(O)OR^7$, $–C(S)OR^7$, $–OC(O)R^7$, $–OC(S)R^7$, $–C(O)NR^4R^5$, $–C(S)NR^4R^5$, $–C(O)NR^4OR^7$, $–C(S)NR^4OR^7$, $–C(O)NR^7NR^4R^5$, $–C(S)NR^7NR^4R^5$, $–C(S)NR^4OR^7$, $–C(O)SR^7$, $–NR^4R^5$, $–NR^4C(O)R^5$, $–NR^4C(S)R^5$, $–NR^4C(O)OR^7$, $–NR^4C(S)OR^7$, $–OC(O)NR^4R^5$, $–OC(S)NR^4R^5$, $–NR^4C(O)NR^4R^5$, $–NR^4C(S)NR^4R^5$, $–NR^4C(O)NR^4OR^7$, $–NR^4C(S)NR^4OR^7$, $–(CR^{10}R^{11})_{0–6}SR^7$, SO_2R^7, $–S(O)_{1–2}NR^4R^5$, $–N(R^7)SO_2R^7$, $–S(O)_{1–2}NR^5OR^7$, –CN, $–OCF_3$, $–SCF_3$, $–C(=NR^7)NR^4$, $–C(O)NR^7(CH_2)_{1–10}NR^4R^5$, $–C(O)NR^7(CH_2)_{1–10}OR^7$, $–C(S)NR^7(CH_2)_{1–10}NR^4R^5$, y $–C(S)NR^7(CH_2)_{1–10}OR^7$, en el cual cada uno de dicho alquilo, cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, arilo, y heteroarilo está sustituido en forma opcional e independiente con 1–5 restos de R^9;

o dos restos de R^2 en el mismo átomo de carbono se toman en forma opcional junto con el átomo de carbono al cual están unidos para formar un grupo C=O, C=S o un grupo etilendioxi;

R^3 está seleccionado en forma independiente entre el grupo integrado por H, halo, alquilo, cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, arilo, heteroarilo, $–(CR^{10}R^{11})_{0–6}–OR^7$, $–C(O)R^4$, $–C(S)R^4$, $–C(O)OR^7$, $–C(S)OR^7$,

$-OC(O)R^7$, $-OC(S)R^7$, $-C(O)NR^4R^5$, $-C(S)NR^4R^5$, $-C(O)NR^4OR^7$, $-C(S)NR^4OR^7$, $-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, $-CN$, $-C(=NR^7)NR^4R^5$, $-C(O)N(R^7)-(CR^{40}R^{41})_{1-5}-C(=NR^7)NR^4R^5$, $-C(O)N(R^7)(CR^{40}R^{41})_{1-5}-NR^4R^5$, $-C(O)N(R^7)(CR^{40}R^{41})_{1-5}-C(O)-NR^4R^5$, $-C(O)N(R^7)(CR^{40}R^{41})_{1-5}-OR^7$, $-C(S)NR^7(CH_2)_{1-5}NR^4R^5$, y $-C(S)NR^7(CH_2)_{1-5}OR^7$, en el cual cada uno de dicho alquilo, cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, arilo, y heteroarilo está sustituido en forma opcional e independiente con 1–5 restos de R^9;

cada uno de R^4 y R^5 está seleccionado en forma independiente entre el grupo integrado por H, alquilo, cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, arilo, heteroarilo, $-OR^7$, $-C(O)R^7$, y $-C(O)OR^7$, en el cual cada uno de dicho alquilo, cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, arilo, y heteroarilo, está sustituido en forma opcional con 1–4 restos de R^8;

o R^4 y R^5, cuando están unidos al mismo átomo de nitrógeno, se toman en forma opcional junto con el átomo de nitrógeno al cual están unidos para formar un anillo heterocíclico de 3–6 miembros que tiene 0–2 heteroátomos adicionales seleccionados entre N, O o S;

cada R^6 está seleccionado en forma independiente entre el grupo integrado por H, alquilo, arilo, aralquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, heteroarilo, heteroaralquilo, $-(CH_2)_{1-6}CF_3$, $-C(O)R^7$, $-C(O)OR^7$ y $-SO_2R^7$;

cada R^7 está seleccionado en forma independiente entre el grupo integrado por H, alquilo, arilo, aralquilo, cicloalquilo, cicloalquilalquilo, heterociclilo,

heterociclilalquilo, heteroarilo, y heteroaralquilo, en el cual cada miembro de R^7 excepto H está sustituido en forma opcional con 1–4 restos de R^8;

cada R^8 está seleccionado en forma independiente entre el grupo integrado por halo, alquilo, cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, arilo, heteroarilo, $-NO_2$, $-OR^{10}$, $-(C_1-C_6$ alkyl$)-OR^{10}$, $-CN$, $-NR^{10}R^{11}$, $-C(O)R^{10}$, $-C(O)OR^{10}$, $-C(O)NR^{10}R^{11}$, $-CF_3$, $-OCF_3$, $-CF_2CF_3$, $-C(=NOH)R^{10}$, $-N(R^{10})C(O)R^{11}$, $-C(=NR^{10})NR^{10}R^{11}$, y $-NR^{10}C(O)OR^{11}$; en el cual cada uno de dicho alquilo, cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, arilo, y heteroarilo está sustituido en forma opcional e independiente con 1–4 restos de R^{42}; en el cual cuando cada uno de dicho cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, arilo, y heteroarilo contiene dos radicales sobre átomos de carbono adyacentes en cualquier parte dentro de dicho cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, arilo, y heteroarilo, y dichos radicales pueden ser tomados en forma opcional e independiente en cada aparición, junto con los átomos de carbono a los cuales están unidos, para formar un anillo carbocíclico o heterocíclico de cinco o seis miembros;

o dos grupos R^8, cuando están unidos al mismo carbono, se toman en forma opcional junto con el átomo de carbono al cual están unidos para formar un grupo C=O o un grupo C=S;

cada R^9 está seleccionado en forma independiente entre el grupo integrado por H, alquilo, alcoxi, OH, CN, halo, $-(CR^{10}R^{11})_{0-4}NR^4R^5$, haloalquilo, hidroxialquilo, alcoxialquilo, $-C(O)NR^4R^5$, $-C(O)OR^7$, $-OC(O)NR^4R^5$, $-NR^4C(O)R^5$, y $-NR^4C(O)NR^4R^5$;

cada R^{10} es en forma independiente H o alquilo; o R^9 y R^{10}, cuando están unidos al mismo átomo de nitrógeno, se toman en forma opcional junto con el átomo de nitrógeno al cual están unidos para formar un anillo heterocíclico de 3–6 miembros que tiene 0–2 heteroátomos adicionales seleccionados entre N, O o S;

cada R^{11} es en forma independiente H, alquilo, cicloalquilo, cicloalquenilo, arilo, heterociclilo, heterociclenilo, o heteroarilo; o R^{10} y R^{11}, cuando están unidos al mismo átomo de nitrógeno, se toman en forma opcional junto con el átomo de nitrógeno al cual están unidos para formar un anillo heterocíclico de 3–6 miembros que tiene 0–2 heteroátomos adicionales seleccionados entre N, O o S; en el cual cada uno de dicho R^{11} alquilo, cicloalquilo, cicloalquenilo, arilo, heterociclilo, heterociclenilo, y heteroarilo está sustituido en forma opcional e independiente con 1–3 restos seleccionados entre el grupo integrado por –CN, –OH, $–NH_2$, –N(H)alquilo, $–N(alquilo)_2$, halo, haloalquilo, CF_3, alquilo, hidroxialquilo, alcoxi, arilo, ariloxi, y heteroarilo;

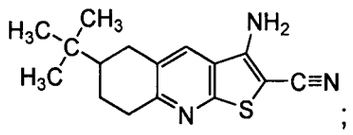
cada R^{12} está seleccionado en forma independiente entre el grupo integrado por H, halo, alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo, heteroaralquilo, $–(CR^{10}R^{11})_{0–6}–OR^7$, $–C(O)R^4$, $–C(S)R^4$, $–C(O)OR^7$, $–C(S)OR^7$, $–OC(O)R^7$, $–OC(S)R^7$, $–C(O)NR^4R^5$, $–C(S)NR^4R^5$, $–C(O)NR^4OR^7$, $–C(S)NR^4OR^7$, $–C(O)NR^7NR^4R^5$, $–C(S)NR^7NR^4R^5$, $–C(S)NR^4OR^7$, $–C(O)SR^7$, $–NR^4R^5$, $–NR^4C(O)R^5$, $–NR^4C(S)R^5$, $–NR^4C(O)OR^7$, $–NR^4C(S)OR^7$, $–OC(O)NR^4R^5$, $–OC(S)NR^4R^5$, $–NR^4C(O)NR^4R^5$, $–NR^4C(S)NR^4R^5$, $–NR^4C(O)NR^4OR^7$, $–NR^4C(S)NR^4OR^7$, $–(CR^{10}R^{11})_{0–6}SR^7$, SO_2R^7, $–S(O)_{1–2}NR^4R^5$, $–N(R^7)SO_2R^7$, $–S(O)_{1–2}NR^5OR^7$, –CN, $–OCF_3$, $–SCF_3$, $–C(=NR^7)NR^4$, $–C(O)NR^7(CH_2)_{1–10}NR^4R^5$, $–C(O)NR^7(CH_2)_{1–10}OR^7$, $–C(S)NR^7(CH_2)_{1–10}NR^4R^5$, $–C(S)NR^7(CH_2)_{1–10}OR^7$, haloalquilo y alquilsililo, en el cual cada uno de dicho alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo o heteroaralquilo está sustituido en forma opcional e independiente con 1–5 restos de R^9;

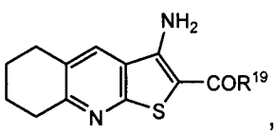
R^{40} y R^{41} pueden ser iguales o diferentes, estando cada uno seleccionado en forma independiente entre el grupo integrado por H, alquilo, arilo, heteroarilo, heterociclilo, heterociclenilo, cicloalquilo y cicloalquenilo;

cada R^{42} está seleccionado en forma independiente entre el grupo integrado por halo, alquilo, cicloalquilo, heterociclilo, arilo, heteroarilo, $-NO_2$, $-OR^{10}$, $-(C_1-C_6$ alkyl$)-OR^{10}$, $-CN$, $-NR^{10}R^{11}$, $-C(O)R^{10}$, $-C(O)OR^{10}$, $-C(O)NR^{10}R^{11}$, $-CF_3$, $-OCF_3$, $-N(R^{10})C(O)R^{11}$, y $-NR^{10}C(O)OR^{11}$;

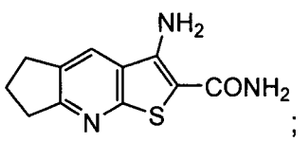
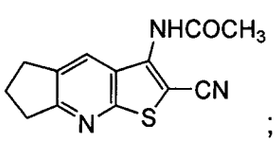
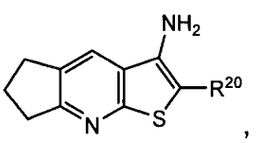
con la condición de que cuando W es $C(R^{12})$, R^{12} y R^3 se toman en forma opcional junto, con los dos átomos de carbono en el anillo a los cuales están unidos para formar un anillo de 6 miembros seleccionado entre el grupo integrado por cicloalquenilo, arilo, heteroarilo, heterociclilo y heterociclenilo, en el cual dicho anillo de 6 miembros está sustituido en forma opcional con 1–3 restos seleccionados en forma independiente entre oxo, tioxo, $-OR^{11}$, $-NR^{10}R^{11}$, $-C(O)R^{11}$, $-C(O)OR^{11}$, $-C(O)N(R^{10})(R^{11})$, o $-N(R^{10})C(O)R^{11}$;

con la condicional adicional de que el compuesto de la Fórmula (BI) es distinto de cualquiera de los siguientes compuestos (1)–(9) que se ilustran inmediatamente a continuación:

(1)  ;

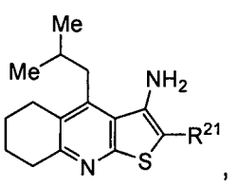
(2)  , en el cual:

R^{19} es –NHOH, –OMe, –OEt, –O–n–propilo, u –O–i–propilo;

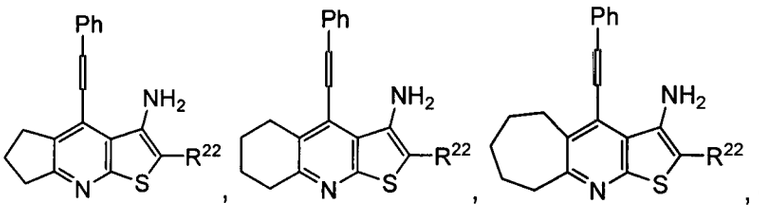
(3)  ; (4)  ; (5)  ,

en el cual:

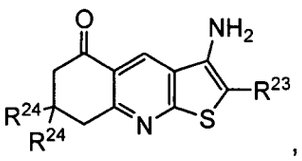
R^{20} es $-CN$, $-C(O)C_6H_5$, $-CO_2C_2H_5$, $-CO_2H$, o $-C(O)NH_2$;

(6)  , en el cual:

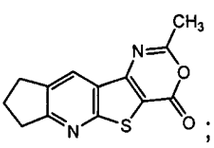
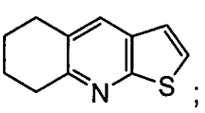
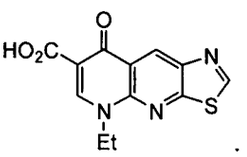
R^{21} es 4–$ClC_6H_4C(O)$– o 4–$PhC_6H_4C(O)$–;

(7)  , en el cual:

R^{22} es –CN, –C(O)CH_3 o –$CO_2C_2H_5$;

(8)  , en el cual:

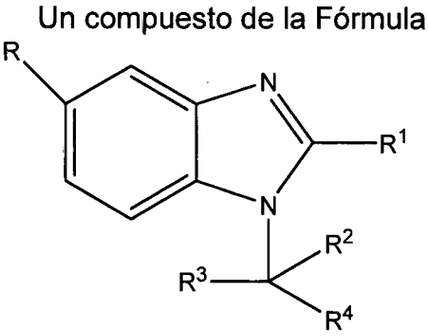
R^{23} es –C(O)NH_2, –C(O)NHPh, o benzoílo y R^{24} es H o metilo;

(9)  ; (10)  ; y (11)  .

Los compuestos representados en la presente solicitud por la Fórmula BI se divulgan en WO2006/098961, presentada el 7 de marzo de 2006.

En otra forma de realización, el inhibidor de KSP útil en la práctica de la presente invención está representado por la Fórmula DI:

D1: Un compuesto de la Fórmula DI



Fórmula DI

o una sal, solvato, o éster del mismo, aceptables para uso farmacéutico, en el cual:

R está seleccionado entre el grupo integrado por H, alquilo, ciano, haloalquilo, halo, —SH, –S–alquilo, –S–haloalquilo, –S(=O)$_2$alquilo, –S(=O)$_2$OH, –S(=O)$_2$$NH_2$, –S(=O)$_2$NH(alquilo), S(=O)$_2$NH(cicloalquilo), –S(=O)$_2$N(alquilo)$_2$, –S(=O)$_2$heterociclilo, –S(=O)$_2$heteroarilo, cicloalquilo, arilo, heterociclilo,

heteroarilo, –NHC(=O)alquilo, –C(=O)NH_2, –C(=O)NH(alquilo), –C(=O)NH(cicloalquilo), –C(=O)N(alquilo)$_2$, –C(=O)OH, –C(=O)Oalquilo, –C(=O)heterociclilo, –C(=O)NH(arilo), en el cual cuando cada uno de dicho cicloalquilo, arilo, heterociclilo, heteroarilo, y las porciones "heterociclilo" y "arilo" de dichos grupos R tiene dos sustituyentes sobre átomos de carbono adyacentes, dichos sustituyentes en forma opcional junto con los átomos de carbono a los cuales están unidos pueden formar un anillo cicloalquilo, arilo, heterociclilo, heterociclenilo, o heteroarilo de cinco a seis miembros; en el cual cada uno de los R alquilo, arilo, cicloalquilo, heterociclilo, y heteroarilo anteriormente mencionados, y las porciones "alquilo", "cicloalquilo", "heterociclilo", y "arilo" de dichos grupos R, en forma opcional con dicho anillo arilo, heterociclilo, heterociclenilo, o heteroarilo de cinco a seis miembros, está sustituido en forma opcional con 1–3 sustituyentes seleccionados en forma independiente entre el grupo integrado por alquilo, alquenilo, alquinilo, hidroxilo, ciano, halo, haloalquilo, haloalcoxi, –C(O)OH, –C(=O)Oalquilo, y –C(O)NH_2;

R^1 está seleccionado entre el grupo integrado por alquilo, heterociclilo, –C(=O)arilo, –NH_2, –NH(alquilo), –NH(cicloalquilo), –N(alquilo)(cicloalquilo), –NH(heterociclilo),–N(alquil)(heterociclilo), N(alquilo)$_2$, –NH(arilo), –N(alquil)(arilo), –N(arilo)$_2$, –NH(heteroarilo), –N(alquil)(heteroarilo), –NHC(=O)–alquilo, –N(alquil)C(=O)–alquilo, –NHC(=O)Oalquilo, –N(alquil)C(=O)O–alquilo, en el cual cada uno de los alquilo, heterociclilo anteriormente mencionados, y las porciones "alquilo", "cicloalquilo", "arilo", y "heteroarilo" de dichos grupos R^1 está sustituido en forma opcional con 1–3 sustituyentes seleccionados en forma independiente entre el grupo integrado por halo, heterociclilo, arilo, heteroarilo, haloalquilo, haloalcoxi, ariloxi, ciano, –SH, –S–alquilo, –S–haloalquilo, –S(=O)$_2$alquilo, –S(=O)$_2$OH, –S(=O)$_2$$NH_2$, –S(=O)$_2$NH(alquilo), S(=O)$_2$NH(cicloalquilo), –S(=O)$_2$N(alquilo)$_2$, –S(=O)$_2$heterociclilo, –S(=O)$_2$heteroarilo, hidroxi, alquilo,

alquenilo, alquinilo, $-NH_2$, –NH(alquilo), $-N(alquilo)_2$, alcoxi, –NHC(=O)alquilo, –C(=O)H, –C(=O)alquilo, –C(=O)arilo, , –C(=O)heteroarilo, –C(=O)Oalquilo, $-C(=O)NH_2$, –C(O)NHalquilo, $-C(=O)N(alquilo)_2$; en el cual cuando cada uno de dicho heterociclilo, arilo y heteroarilo tiene dos sustituyentes sobre átomos de carbono adyacentes, dichos sustituyentes en forma opcional junto con los átomos de carbono a los cuales están unidos pueden formar un anillo arilo, heterociclilo, heterociclenilo, o heteroarilo de cinco a seis miembros;

R^2 y R^3 son en forma independiente H o alquilo, o $-C(R^2)(R^3)-$ está ausente;

R^4 está seleccionado entre el grupo integrado por alquilo, cicloalquilo, heterociclilo, arilo y heteroarilo, en el cual cuando cada uno de dicho cicloalquilo, heterociclilo, arilo, y heteroarilo tiene dos sustituyentes sobre átomos de carbono adyacentes, dichos sustituyentes en forma opcional junto con los átomos de carbono a los cuales están unidos pueden formar un anillo arilo, heterociclilo, heterociclenilo, o heteroarilo de cinco a seis miembros; en el cual cada uno de dichos R^4 alquilo, cicloalquilo, heterociclilo, arilo y heteroarilo anteriormente mencionados, en forma opcional con dicho anillo arilo, heterociclilo, heterociclenilo, o heteroarilo de cinco a seis miembros está sustituido en forma opcional con 1–3 sustituyentes seleccionados en forma independiente entre el grupo integrado por ciano, halo, haloalquilo, alquilo, alcoxi, hidroxilo, haloalcoxi, cicloalquilo, heterociclilo, arilo, heteroarilo, $-S(=O)_2$alquilo, $-S(=O)_2NH_2$, $-S(=O)_2NH$(alquilo), $-S(=O)_2N(alquilo)_2$, –S–alquilo, –S–haloalquilo, –C(=O)OH, $-NH_2$, –NH(alquilo), $-N(alquilo)_2$, y –C(=O)Oalquilo;

con la condición de que:

(1) cuando R es –C(=O)Oalquilo, R^1 es NH(arilo) en el cual dicho arilo está sustituido en forma opcional, ambos R^2 y R^3 son H, y R^4 es fenilo, entonces dicho R^4 fenilo es sustituido con por lo menos un grupo haloalquilo;

(2) cuando R es –C(=O)Oalquilo, R^1 es NH(arilo) o NH(alquilo), en el cual las porciones "alquilo" y "arilo" de dicho R^1 están sustituidas en forma opcional e independiente, ambos R^2 y R^3 son H, y R^4 es heteroarilo sustituido en forma opcional, entonces dicho R^4 heteroarilo es distinto de tiofenilo y furanilo;

(3) cuando R es –C(=O)Oalquilo en el cual dicho alquilo es sustituido en forma opcional, y R^1 es NH(arilo) en el cual dicho arilo es insustituido o sustituido con por lo menos un sustituyente seleccionado entre el grupo integrado por halo, nitro, y alquilo, entonces R^4 es distinto de cicloalquilo insustituido;

(4) cuando R es –C(=O)Oalquilo en el cual dicho alquilo es sustituido en forma opcional, R^1 es $–NH_2$, y $–CR^2R^3$ está ausente, entonces R^4 es distinto de cicloalquilo sustituido en forma opcional;

(5) cuando R es $–C(=O)NH_2$, entonces R^1 es –NH(alquilo) o –N(alquil)(arilo), en el cual cada uno de dicho alquilo y arilo está sustituido en forma opcional e independiente;

(6) cuando R es –COOH o –C(=O)Oalquilo, en el cual dicho alquilo es sustituido en forma opcional, R^1 es –NH(alquilo), o $–N(alquilo)_2$ en el cual la porción "alquilo" de cada uno de dicho R^1 está sustituido en forma opcional, y $–CR^2R^3$ está ausente, entonces R^4 es distinto de cicloalquilo insustituido;

(7) cuando R es –C(=O)Oalquilo en el cual dicho alquilo es sustituido en forma opcional, R^1 es $–NH_2$, NH(alquilo), o NH(arilo), en el cual la porción "alquilo" y "arilo" de cada uno de dicho R^1 está sustituido en forma opcional e independiente, entonces R^4 es distinto de alquilo insustituido o alquilo sustituido con por lo menos un resto seleccionado entre el grupo integrado por alcoxi, $–N(alquilo)_2$, heterociclilo, y heteroarilo;

(8) cuando R es –C(=O)Oalquilo en el cual dicho alquilo es sustituido en forma opcional, R^1 es $–NH_2$, y $–C(R^2)(R^3)–$ está ausente, entonces R^4 es distinto

de cicloalquilo, cicloalquenilo, heterociclenilo, o heteroarilo sustituido en forma opcional;

(9) cuando R es –C(=O)Oalquilo, en el cual dicho alquilo es sustituido en forma opcional, R^1 es –NH(heterociclil) en el cual dicho heterociclil está sustituido en forma opcional, ambos R^2 y R^3 son H, entonces R^4 es distinto de heteroarilo sustituido en forma opcional;

(10) cuando R es –C(=O)Oalquilo, en el cual dicho alquilo es sustituido en forma opcional, ambos R^2 y R^3 son H, y R^4 es arilo o heteroarilo sustituido en forma opcional, entonces R^1 es distinto de $–NH_2$ o –NH(alquilo) en el cual dicho alquilo es sustituido en forma opcional;

(11) cuando R es –C(=O)OH, $–C(R^2)(R^3)–$ está ausente, y R^4 es cicloalquilo sustituido en forma opcional, entonces R^1 es distinto de –NHC(=O)alquilo, –NH(arilo), o –N(alquil)(arilo) en el cual las porciones "alquilo" y "arilo" de dicho R^1 están sustituidas en forma opcional e independiente;

(12) cuando R es –C(=O)OH, R^1 es $–NH_2$, y ambos R^2 y R^3 son H, entonces R^4 es distinto de arilo sustituido en forma opcional;

(13) cuando R es –C(=O)Oalquilo en el cual dicho alquilo es sustituido en forma opcional, R^1 es heterociclilo o heteroarilo sustituido en forma opcional, ambos R^2 y R^3 son H, y R^4 es arilo, entonces dicho R^4 arilo es sustituido con por lo menos un grupo haloalquilo;

(14) cuando R es –C(=O)OH, R^1 heterociclilo sustituido en forma opcional, ambos R^2 y R^3 son H, y R^4 es arilo, entonces dicho R^4 arilo es sustituido con por lo menos un grupo haloalquilo; o

(15) cuando R es H o halo, y R^4 es arilo, entonces dicho R^4 arilo es sustituido con por lo menos un grupo haloalquilo,

(16) cuando R es H, ambos R^2 y R^3 son H, R^1 es –NH(arilo), y R^4 es arilo sustituido con por lo menos un grupo haloalquilo, entonces dicho "arilo" de R^1 es sustituido con uno o más grupos distintos de halo o haloalquilo;

(17) cuando R es –C(=O)NH(arilo) o –C(=O)N(alquil)(arilo), entonces R^1 es distinto de heterociclilo sustituido en forma opcional; o

(18) cuando R es H, R^1 es distinto de $–NH_2$ o –NH(heterociclil).

Los compuestos representados en la presente solicitud por la Fórmula DI se divulgan en PCT US2008/007295, presentada el 11 de junio de 2008.

En otra forma de realización, la presente invención divulga un método para tratar o paliar el cáncer que comprende administrar, en forma consecutiva a un mamífero que necesita dicho tratamiento, una cantidad de por lo menos un primer compuesto, en el cual dicho primer compuesto es un agente antimitótico seleccionado entre el grupo integrado por Taxanos, paclitaxel, docetaxel, Inhibidor de Cenp–E (tal como, por ejemplo GSK–923295), Abraxano, Epotilona, Monastrol, e inhibidores de KSP tales como, por ejemplo, Ispinesib SB–715992 (Cytokinetics), y los compuestos de las Fórmulas A–D tal como se describieron anteriormente; seguido por la administración de por lo menos un segundo compuesto, en el cual dicho segundo compuesto es un inhibidor de Aurora quinasa seleccionado entre el grupo integrado por los compuestos representados por las Fórmulas E–K tal como se describieron anteriormente.

En otra forma de realización, la presente invención divulga un método para inducir la endoreduplicación en células cancerígenas que comprende el tratamiento previo de las células cancerígenas con por lo menos un agente antimitótico, en el cual dicho agente antimitótico está seleccionado entre el grupo integrado por Taxanos, paclitaxel, docetaxel, Inhibidor de Cenp–E (tales como, por ejemplo GSK–923295), Abraxano, Epotilona, Monastrol, e inhibidores de KSP tales como, por ejemplo, Ispinesib SB–715992 (Cytokinetics) y los compuestos

representados por las Fórmulas A–D tal como se describieron anteriormente; con la subsiguiente exposición al inhibidor de Aurora quinasa durante alrededor de 1–12 horas, por ejemplo alrededor de 4 horas, en el cual dicho inhibidor de Aurora quinasa está seleccionado entre el grupo de compuestos representados por las Fórmulas E–K tal como se describieron anteriormente.

En otra forma de realización, la presente invención tiene como resultado la endoreduplicación de las células cancerígenas, que produce la muerte de las células cancerígenas, que incluyen (pero no se limitan a) los siguientes: tumor de vejiga, mama (que incluye cáncer de mama por mutación de BRCA), colorectal, colon, riñón, hígado, pulmón (que incluye cáncer de pulmón de células pequeñas y cáncer de pulmón de células no pequeñas), cabeza y cuello, esófago, vejiga, vesícula biliar, ovario, páncreas, estómago, cuello de útero, glándula tiroides, próstata, y piel, incluyendo carcinoma celular escamoso;

leucemia, leucemia linfocítica aguda, leucemia linfoblástica aguda, linfoma de células B, linfoma de células T, linfoma de Hodgkins, linfoma de no Hodgkins, linfoma de células vellosas, linfoma celular de corteza, mieloma y linfoma de Burkett;

leucemia linfocítica crónica ("CLL, según sus siglas en inglés"),

leucemia mielogenosa aguda y crónica, síndrome mielodisplásico y leucemia promielocítica;

fibrosarcoma, rabdomiosarcoma;

linfoma celular de corteza, mieloma;

astrocitoma, neuroblastoma, glioblastoma, tumores gliales malignos, carcinoma hepatocelular, tumores estromales gastrointestinales ("GIST, según sus siglas en inglés") y schwannomas;

melanoma, mieloma múltiple, seminoma, teratocarcinoma, osteosarcoma, xenoderma pigmentoso, queratoacantoma, cáncer folicular de tiroides y sarcoma de Kaposi.

Asimismo, la presente invención produce la endoreduplicación de las células cancerígenas, que incluye más preferentemente, células de cáncer de colon, células de cáncer de mama, células de cáncer de pulmón, células de cáncer de próstata y células de cáncer de ovario.

En otra forma de realización, la administración del tratamiento combinado de por lo menos un agente antimitótico seguido por al menos uno de los inhibidores de aurora quinasa de la presente invención puede ser útil en la quimioprevención del cáncer. La quimioprevención se define como la inhibición del desarrollo del cáncer invasivo ya sea bloqueando el evento mutagénico que se inicia o bloqueando la progresión de células pre–malignas que ya han sufrido una agresión o inhibiendo la recaída del tumor.

El tratamiento combinado de la presente invención también puede ser útil para inhibir la angiogénesis and metástasis del tumor.

En otra forma de realización, las células cancerígenas se tratan previamente con por lo menos un agente antimitótico preferentemente durante alrededor de 1 a 72 horas.

En otra forma de realización, las células cancerígenas se tratan previamente con por lo menos un agente antimitótico preferentemente durante alrededor de 12 a 72 horas.

En otra forma de realización, las células cancerígenas se tratan previamente con por lo menos un agente antimitótico, más preferentemente durante alrededor de 12 a 24 horas.

En otra forma de realización, las células cancerígenas se tratan previamente con por lo menos un agente antimitótico, muy preferentemente durante alrededor de 16 horas.

En otra forma de realización, las células cancerígenas se tratan previamente con por lo menos un agente antimitótico, muy preferentemente durante alrededor de 4 horas.

En otra forma de realización, las células cancerígenas se tratan previamente con por lo menos un agente antimitótico, muy preferentemente durante alrededor de 2 horas.

En otra forma de realización, las células cancerígenas se tratan previamente con por lo menos un agente antimitótico muy preferentemente durante alrededor de 1 hora.

En otra forma de realización, las células cancerígenas se exponen a dicho inhibidor de Aurora quinasa durante alrededor de 1–72 horas luego de la administración del agente antimitótico.

En otra forma de realización, las células cancerígenas se exponen a dicho inhibidor de Aurora quinasa durante alrededor de 2–24 horas luego de la administración del agente antimitótico.

En otra forma de realización, las células cancerígenas se exponen a dicho inhibidor de Aurora quinasa preferentemente durante alrededor de 1–12 horas luego de la administración del agente antimitótico.

En otra forma de realización, las células cancerígenas se exponen a dicho inhibidor de Aurora quinasa más preferentemente durante alrededor de 1–6 horas luego de la administración del agente antimitótico.

En otra forma de realización, las células cancerígenas se exponen a dicho inhibidor de Aurora quinasa más preferentemente durante alrededor de 1–4 horas luego de la administración del agente antimitótico.

En otra forma de realización, las células cancerígenas se exponen a dicho inhibidor de Aurora quinasa más preferentemente durante alrededor de 2–4 horas luego de la administración del agente antimitótico.

En otra forma de realización, las células cancerígenas se exponen a dicho inhibidor de Aurora quinasa muy preferentemente durante alrededor de 2 horas luego de la administración del agente antimitótico.

En otra forma de realización, las células cancerígenas se exponen a dicho inhibidor de Aurora quinasa muy preferentemente durante alrededor de 4 horas luego de la administración del agente antimitótico.

En otra forma de realización, las células cancerígenas se exponen a dicho inhibidor de Aurora quinasa durante alrededor de 1–4 horas luego de la administración del agente antimitótico a dichas células cancerígenas durante alrededor de 1–16 horas.

En otra forma de realización, las células cancerígenas se exponen a dicho inhibidor de Aurora quinasa durante alrededor de 1–4 horas luego de la administración del agente antimitótico a dichas células cancerígenas durante alrededor de 2–16 horas.

En otra forma de realización, las células cancerígenas se exponen a dicho inhibidor de Aurora quinasa durante alrededor de 1–4 horas luego de la administración del agente antimitótico a dichas células cancerígenas durante alrededor de 2 horas.

En otra forma de realización, las células cancerígenas se exponen a dicho inhibidor de Aurora quinasa durante alrededor de 1–4 horas luego de la administración del agente antimitótico a dichas células cancerígenas durante alrededor de 4 horas.

En otra forma de realización, las células cancerígenas se exponen a dicho inhibidor de Aurora quinasa durante alrededor de 1 hora luego de la

administración del agente antimitótico a dichas células cancerígenas durante alrededor de 1 horas.

En otra forma de realización, las células cancerígenas se exponen a dicho inhibidor de Aurora quinasa durante alrededor de 2 horas luego de la administración del agente antimitótico a dichas células cancerígenas durante alrededor de 2 horas.

En otra forma de realización, las células cancerígenas se exponen a dicho inhibidor de Aurora quinasa durante alrededor de 4 horas luego de la administración del agente antimitótico a dichas células cancerígenas durante alrededor de 4 horas.

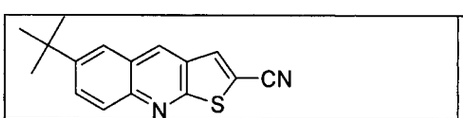
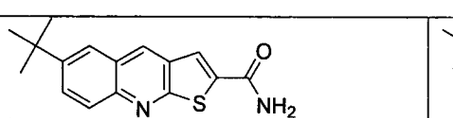
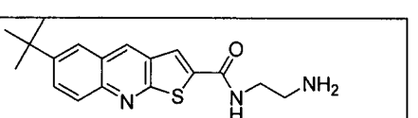
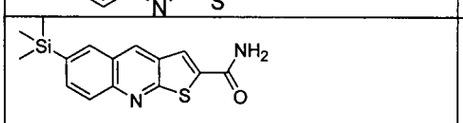
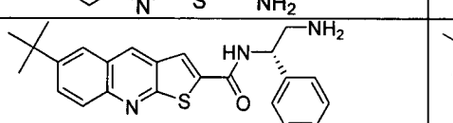
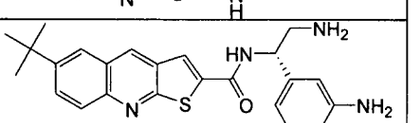
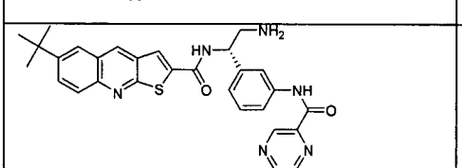
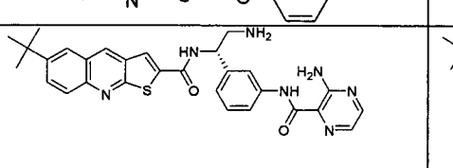
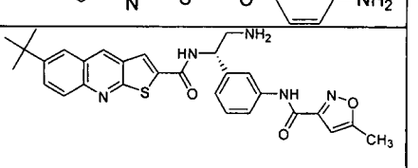
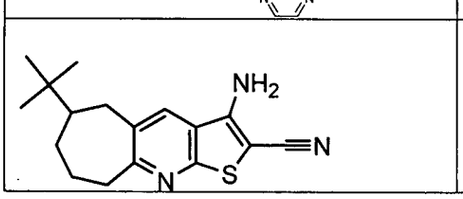
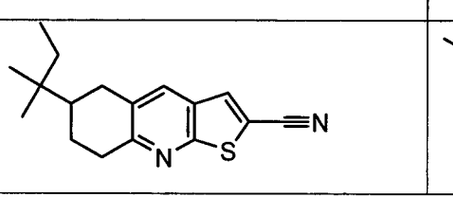
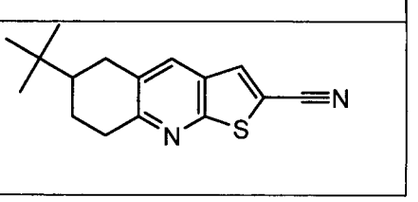
En otra forma de realización, los agentes antimitóticos usados en la presente invención incluyen Taxanos, paclitaxel, docetaxel, Inhibidor de Cenp–E (tal como, por ejemplo GSK–923295), Abraxano, Epotilona, Monastrol, e inhibidores de KSP tales como, por ejemplo, Ispinesib SB–715992 (Cytokinetics), y los compuestos de las Fórmulas A–D tal como se describieron anteriormente.

Incluso en otra forma de realización, un método para retrasar el desarrollo de un tumor in vivo comprende los pasos de (a) primero administrar al tumor in vivo por lo menos un agente antimitótico seleccionado entre el grupo integrado por Taxanos, paclitaxel, docetaxel, Inhibidor de Cenp–E (tal como, por ejemplo GSK–923295), Abraxano, Epotilona, Monastrol, e inhibidores de KSP tales como, por ejemplo, Ispinesib SB–715992 (Cytokinetics), y los compuestos representados por las Fórmulas A–D tal como se describieron anteriormente y (b) luego administrar a dicho tumor por lo menos un inhibidor de Aurora quinasa, en el cual dicho inhibidor de Aurora quinasa está seleccionado entre el grupo integrado por un compuesto representado por las Fórmulas E–K tal como se describieron anteriormente.

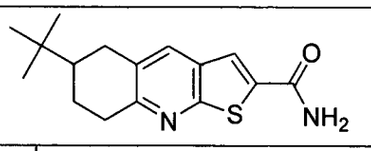
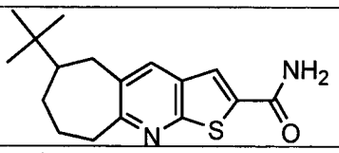
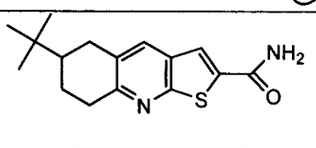
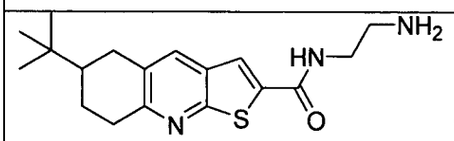
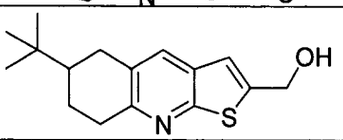
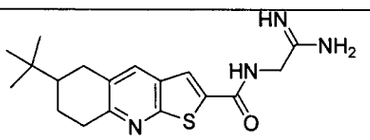
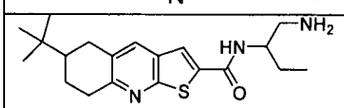
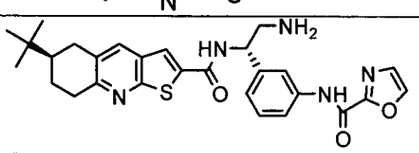
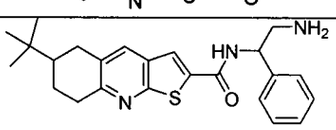
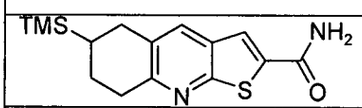
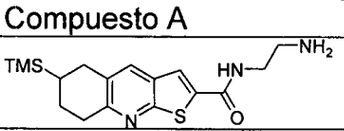
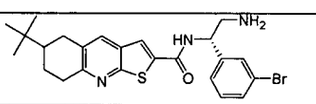
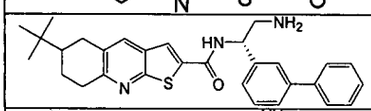
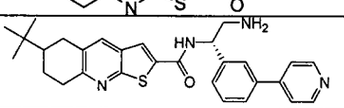
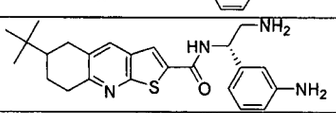
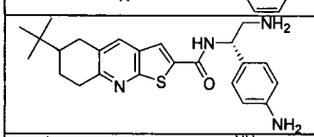
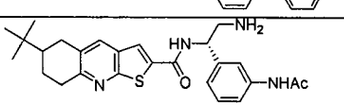
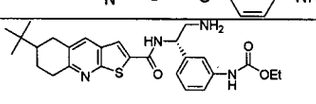
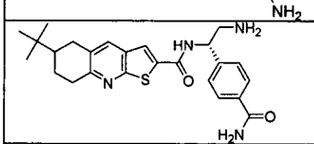
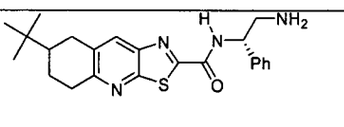
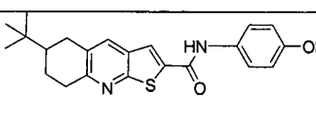
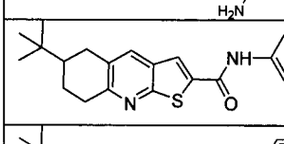
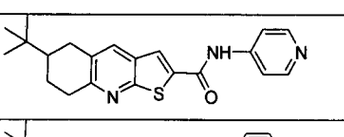
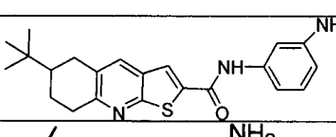
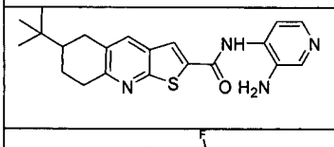
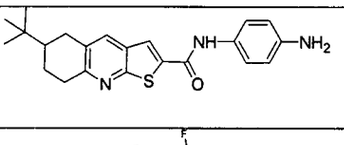
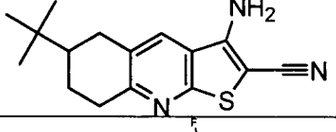
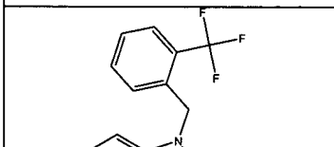
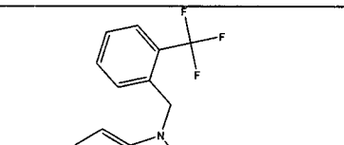
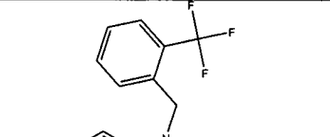
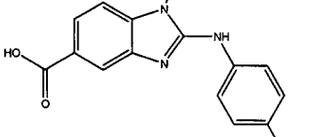
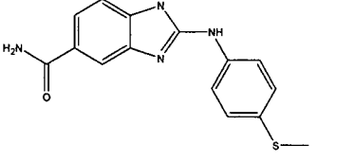
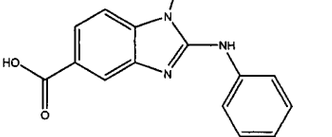
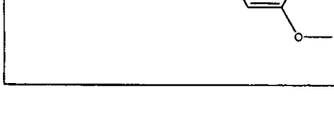
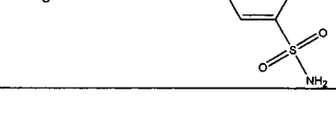
En otra forma de realización, la presente invención provee un método para inducir poliploidía en células cancerígenas que comprende los pasos de (a) primero administrar a células cancerígenas in vivo por lo menos un agente antimitótico seleccionado entre el grupo integrado por Taxanos, paclitaxel, docetaxel, Inhibidor de Cenp–E (tal como, por ejemplo GSK–923295), Abraxano, Epotilona, Monastrol, e inhibidores de KSP tales como, por ejemplo, Ispinesib SB–715992 (Cytokinetics), y los compuestos representados por las Fórmulas A–D tal como se describieron anteriormente y (b) luego administrar a dichas células cancerígenas por lo menos un inhibidor de Aurora quinasa, en el cual dicho inhibidor de Aurora quinasa está seleccionado entre el grupo integrado por un compuesto representado por las Fórmulas E–K tal como se describieron anteriormente.

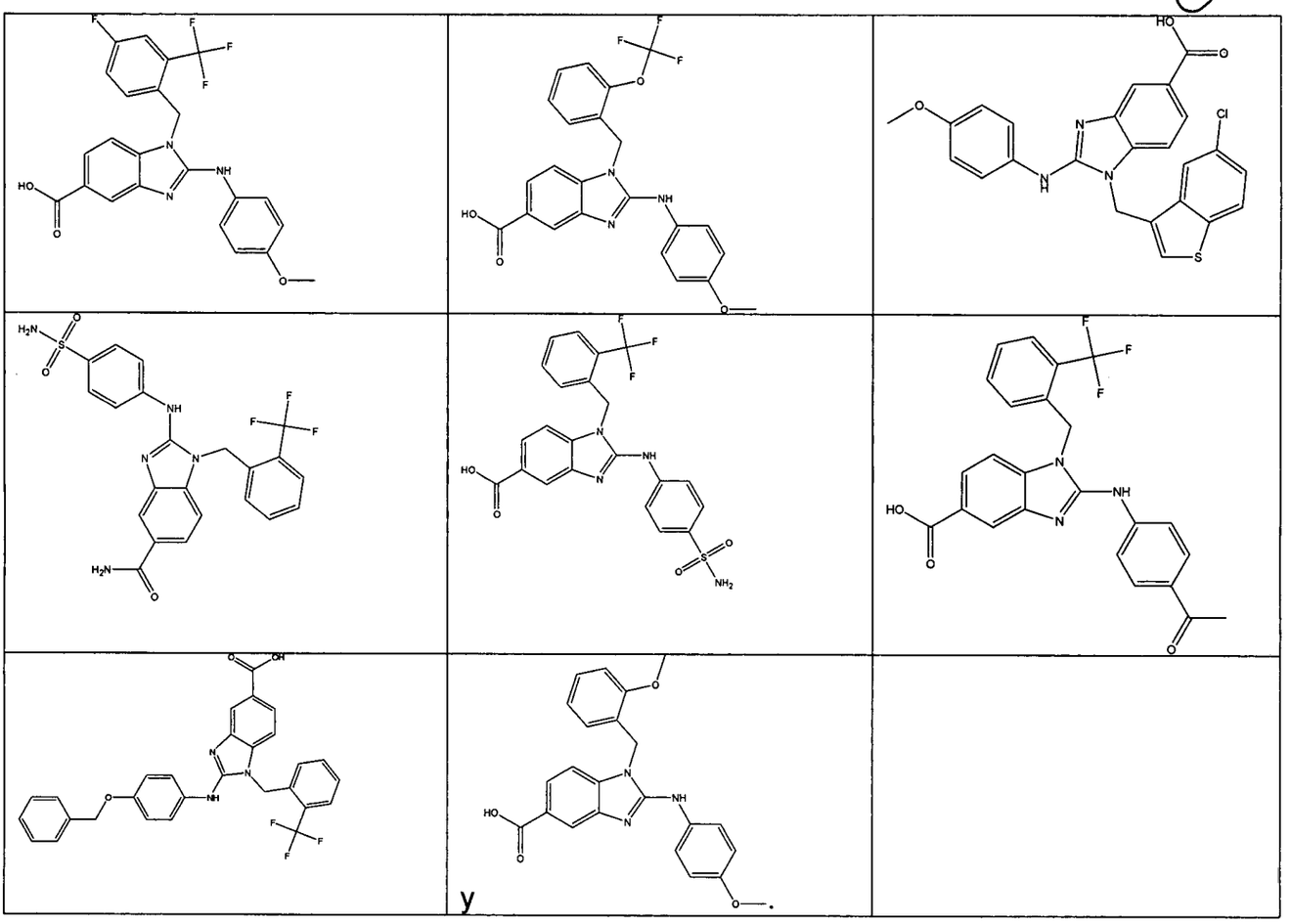
Otra forma de realización de la presente invención provee una composición farmacéutica y un método de tratamiento en el cual los compuestos comprendidos en las Fórmulas A–D están seleccionados entre el grupo integrado por los compuestos incluidos en la Tabla 1 que se ilustran inmediatamente a continuación:

Tabla 1

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	 Compuesto A	
		
		
		
		
		
		
		
		
		

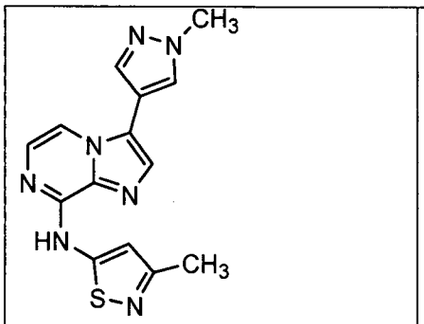
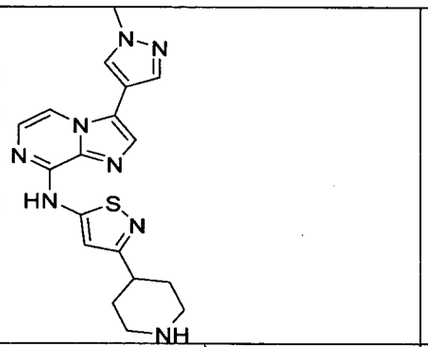
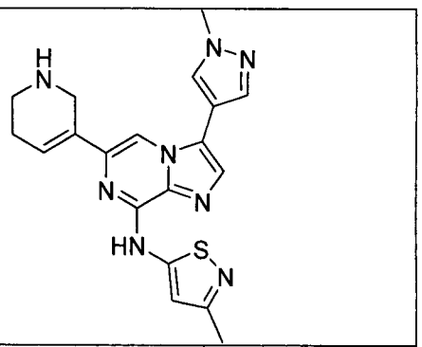
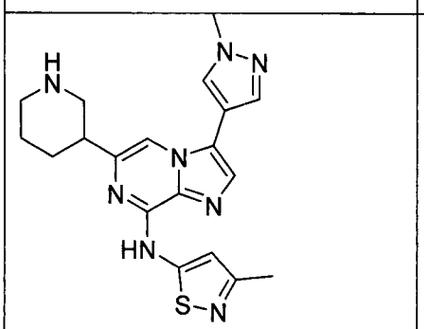
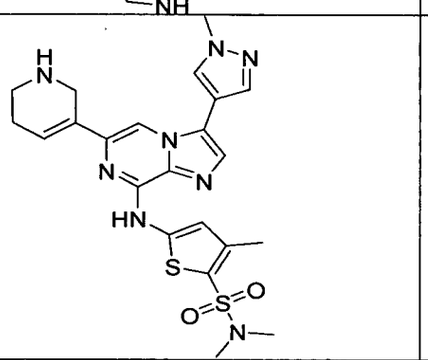
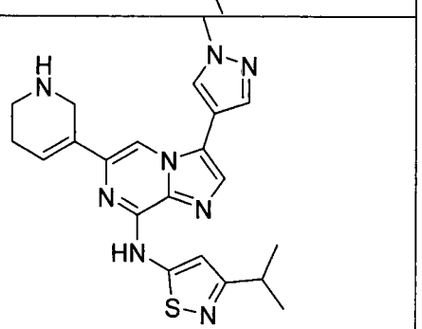
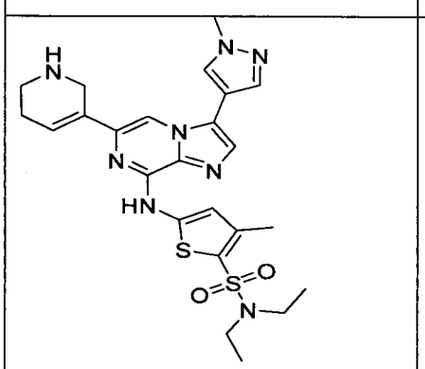
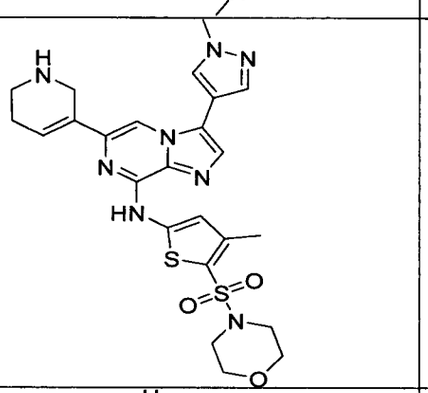
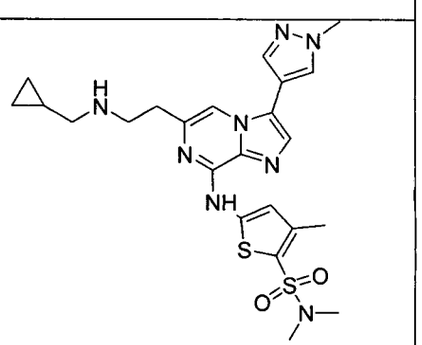
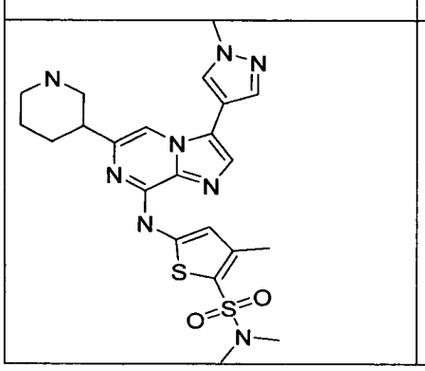
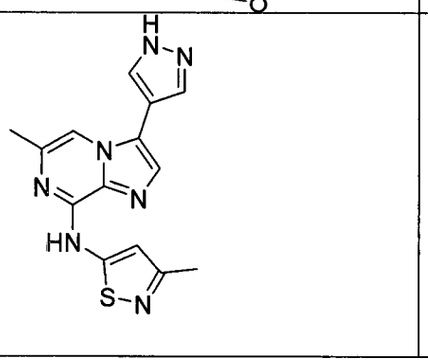


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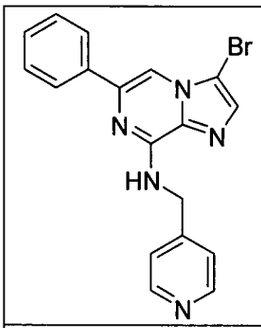
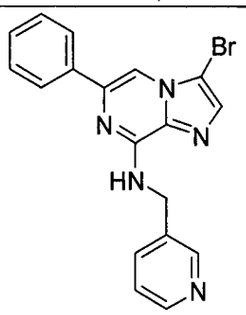
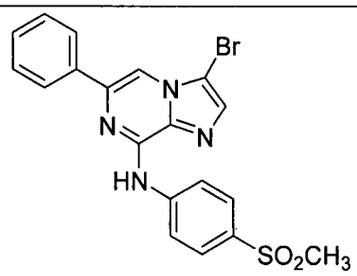
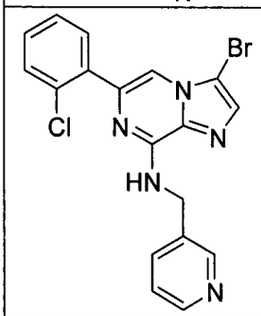
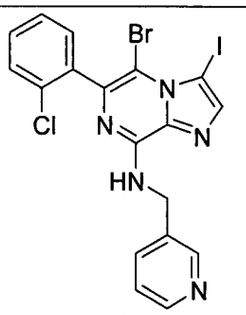
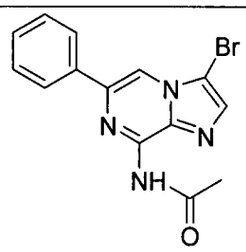
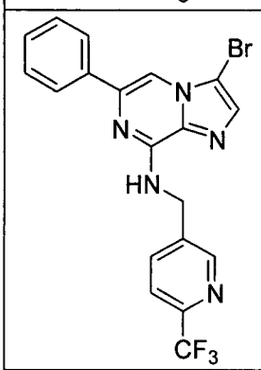
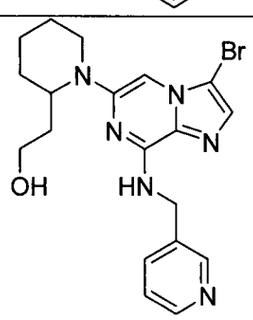
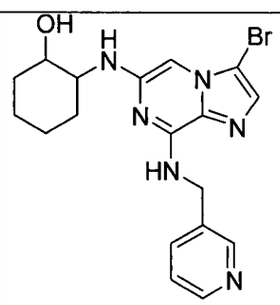
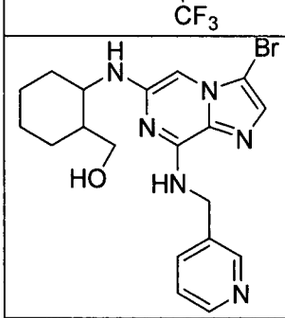
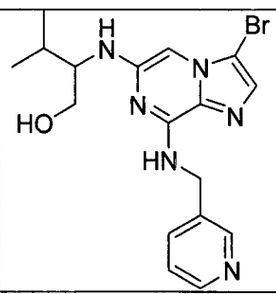
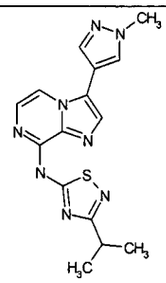
o una sal o solvato de los mismos, aceptable para uso farmacéutico. Los compuestos de la Tabla 1 anterior se divulgan en las siguientes referencias: WO 2006/098962, presentada el 7 de marzo de 2006, WO2006/098961, presentada el 7 de marzo de 2006, Pub. de EEUU Nº 2006/0258699, presentada el 7 de marzo de 2006, y la Solicitud de EEUU Nº 60/939963, presentada el 24 de mayo de 2007.

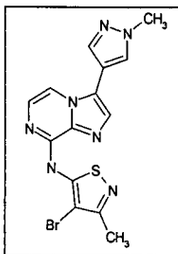
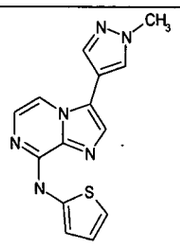
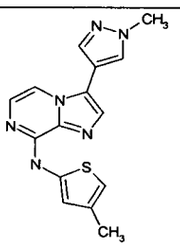
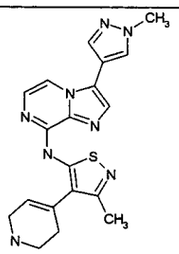
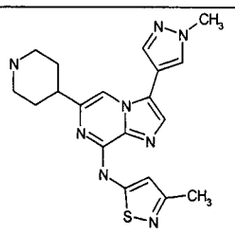
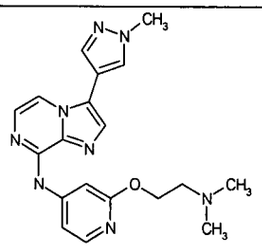
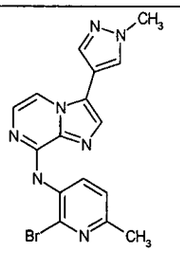
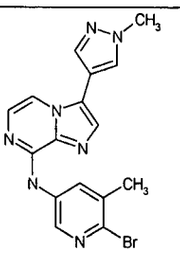
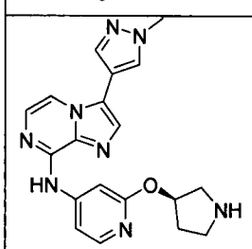
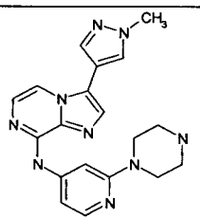
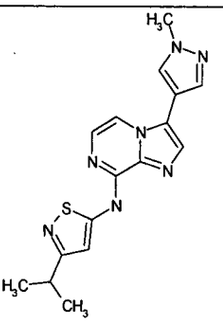
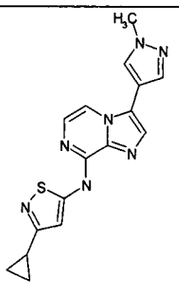
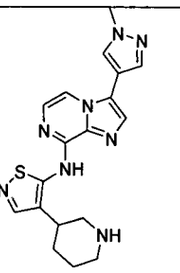
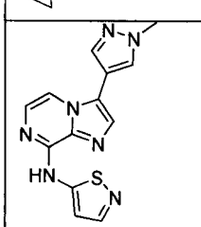
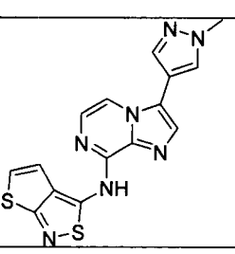
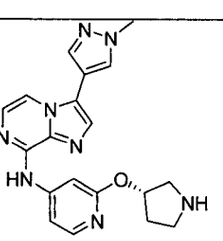
Incluso en otra forma de realización, la presente invención provee una composición farmacéutica y un método de tratamiento tal como se describió anteriormente en el cual los compuestos comprendidos en las Fórmulas E–K están seleccionados entre el grupo de compuestos incluidos en la Tabla **2** que se ilustran inmediatamente a continuación:

Tabla 2

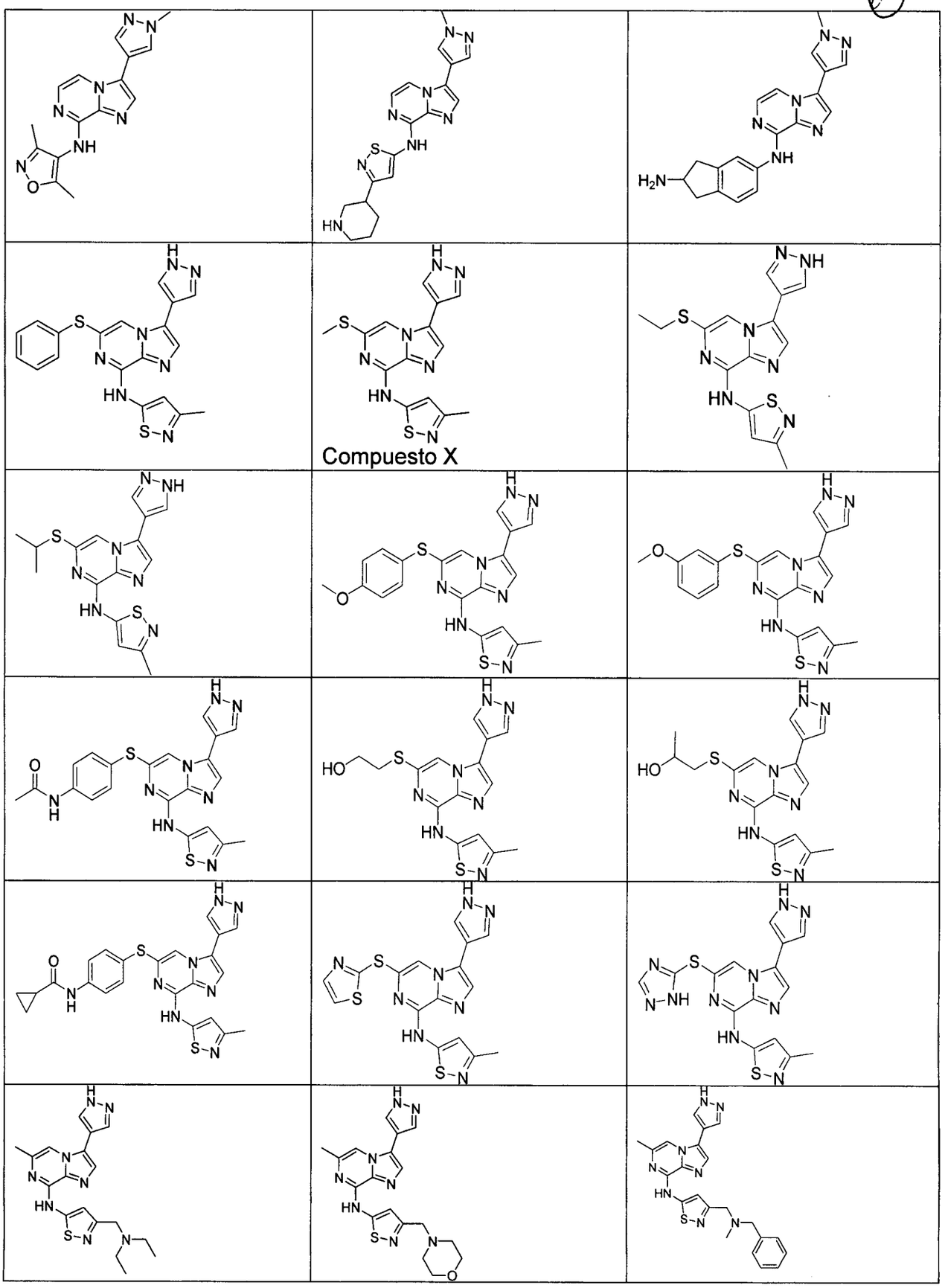
		
		
		
		

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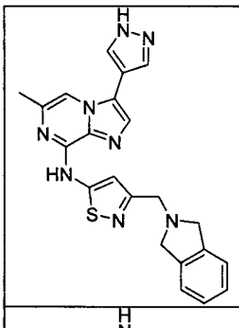
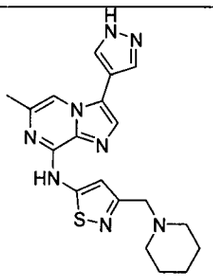
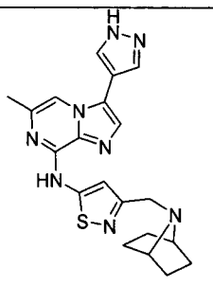
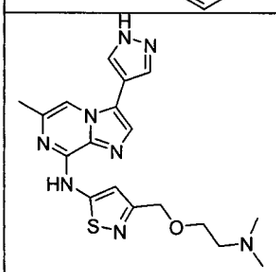
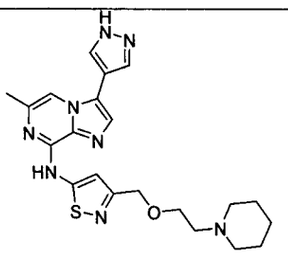
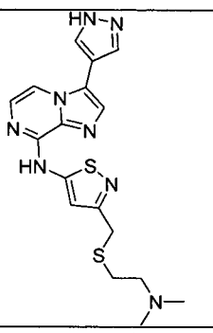
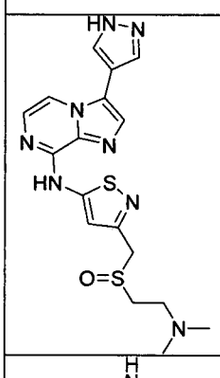
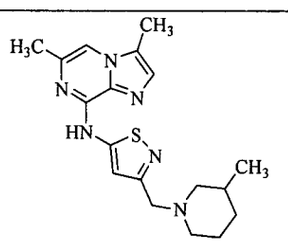
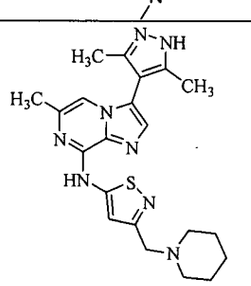
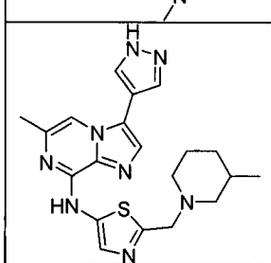
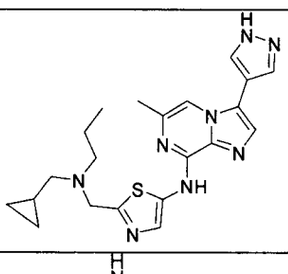
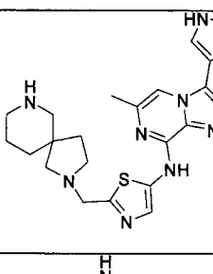
		
		
		
		
		
		

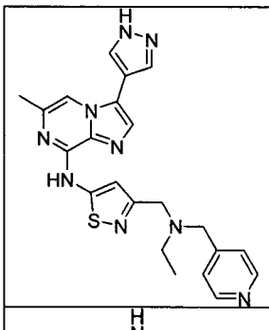
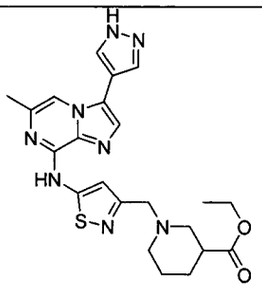
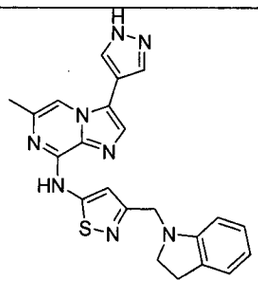
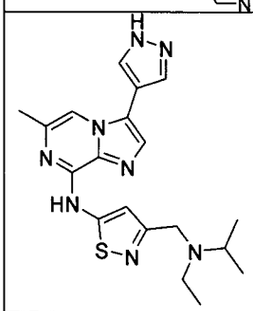
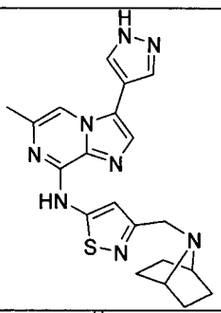
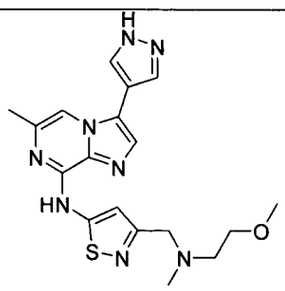
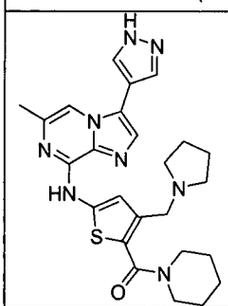
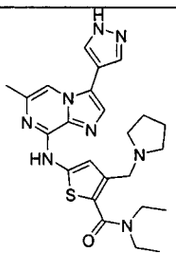
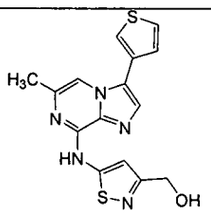
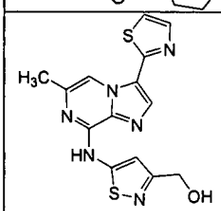
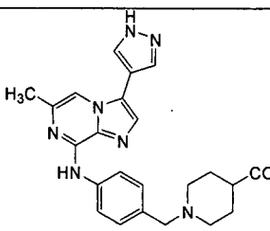
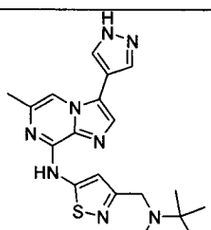
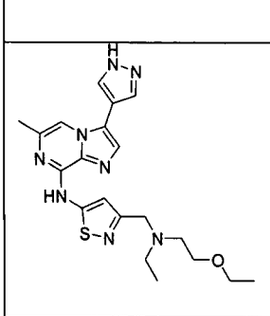
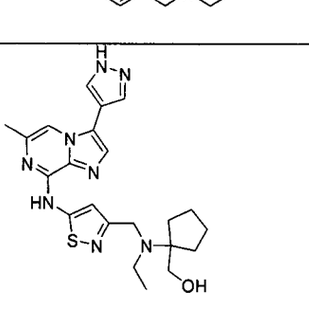
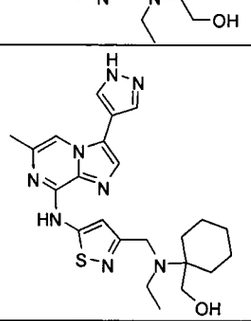
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Compuesto X

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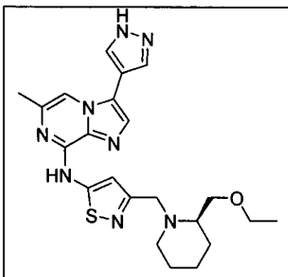
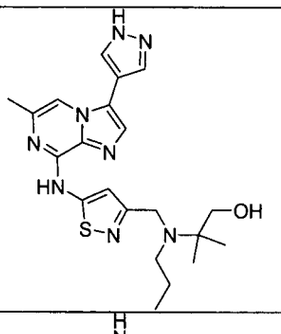
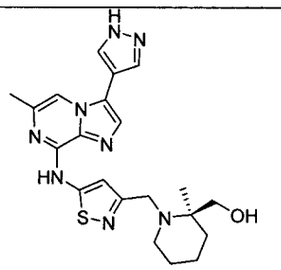
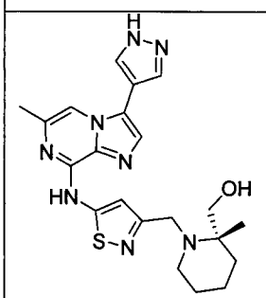
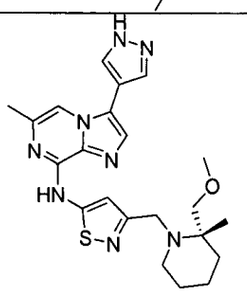
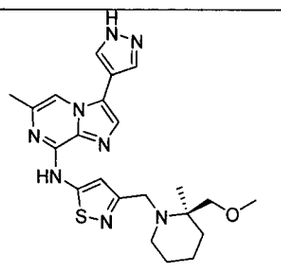
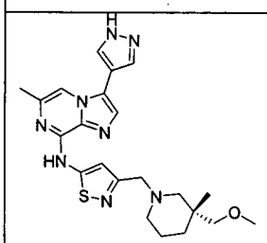
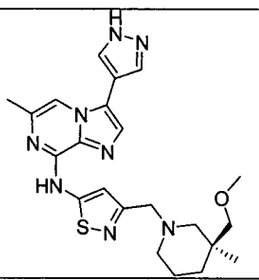
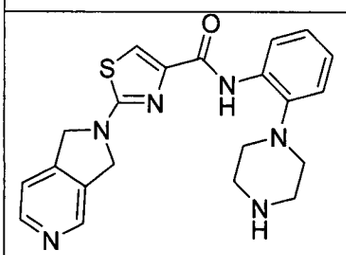
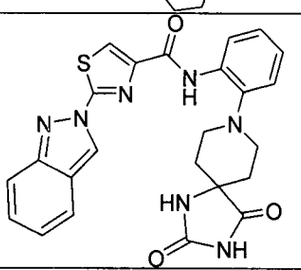
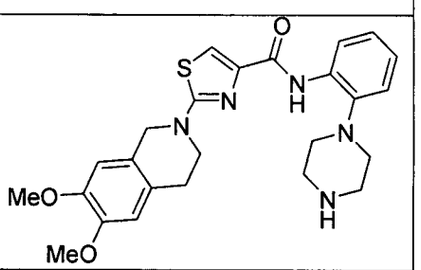
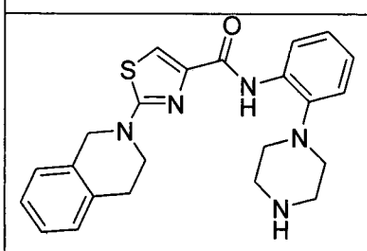
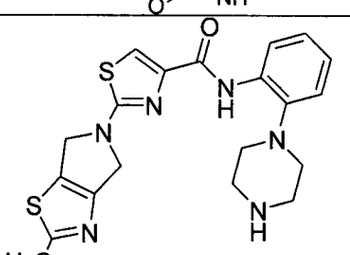
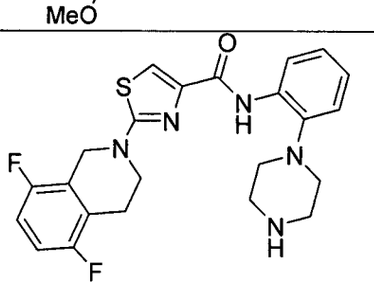
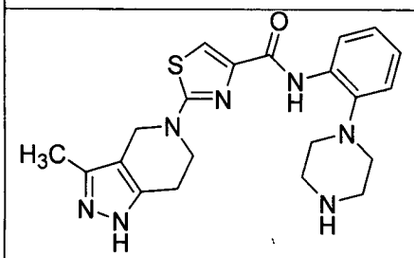
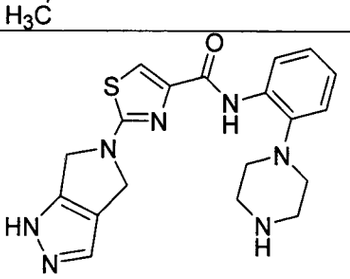
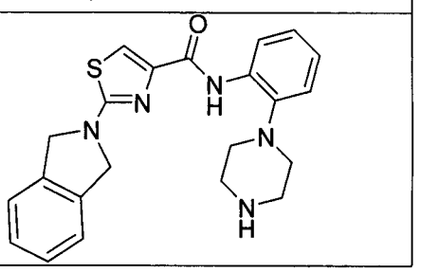
		
		
		
		
		

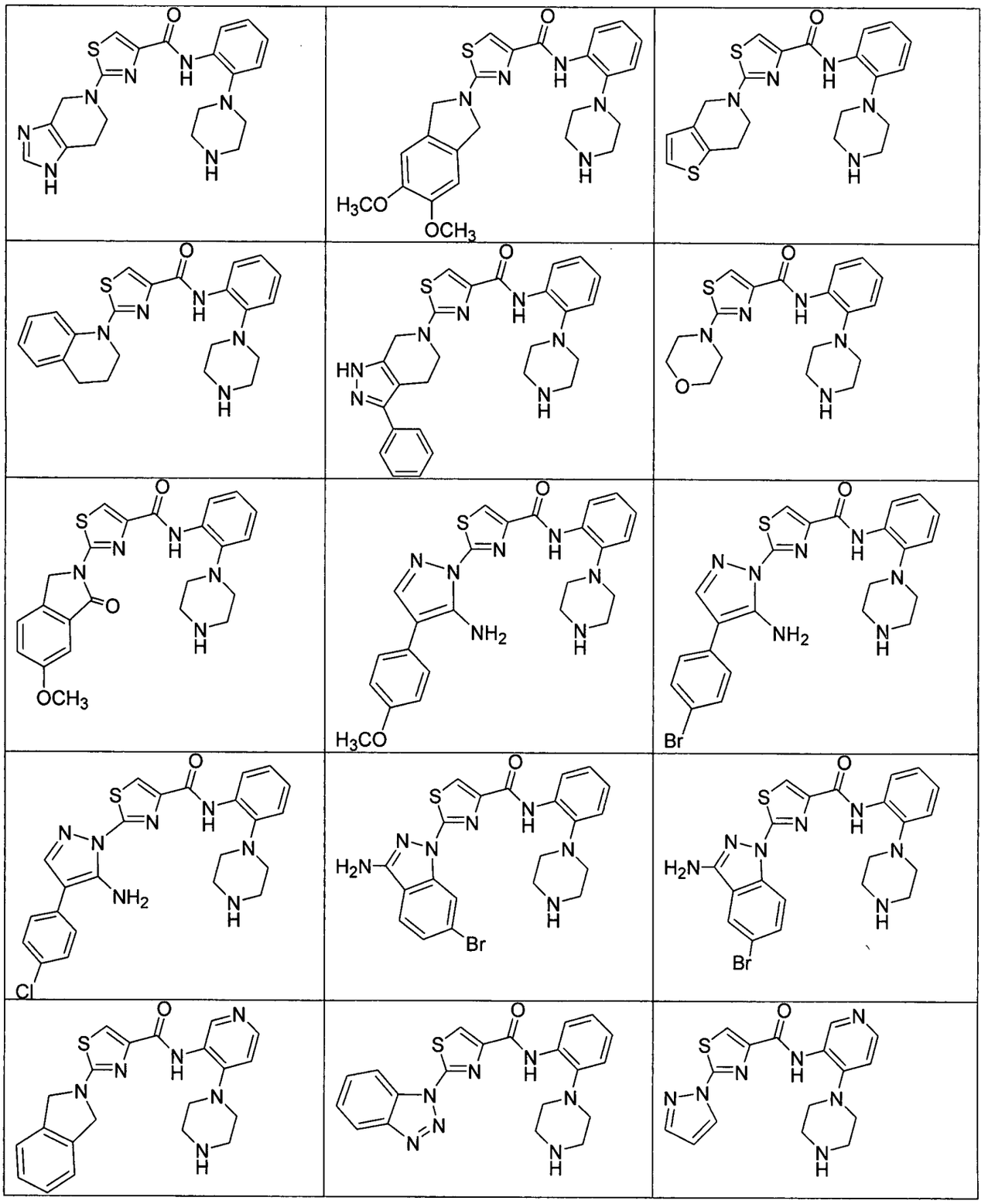




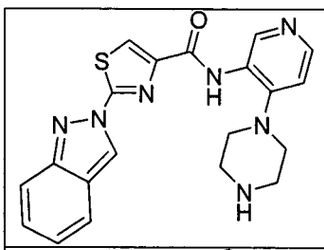
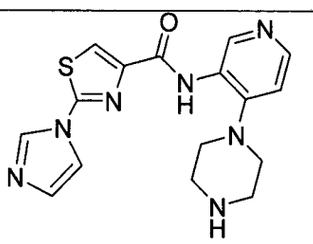
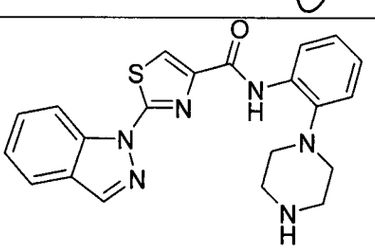
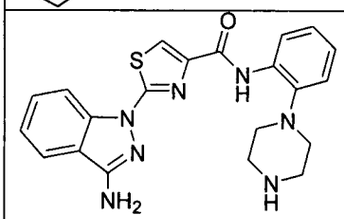
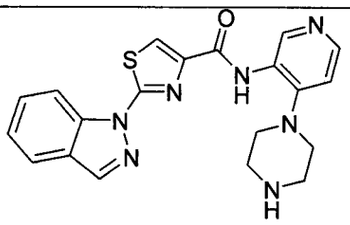
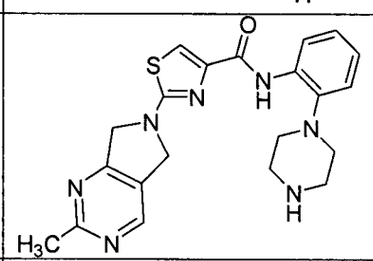
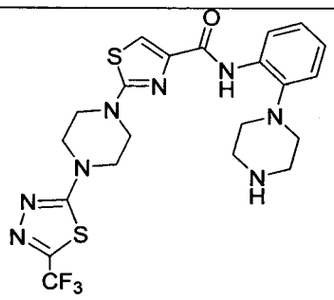
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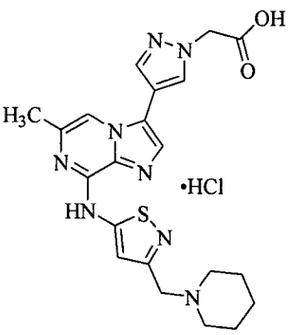
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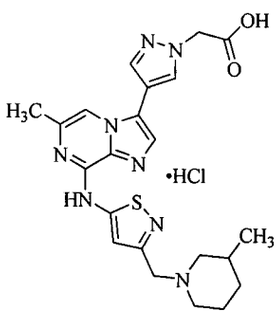


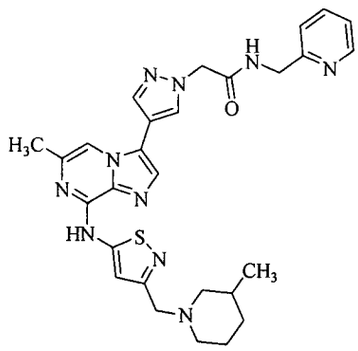
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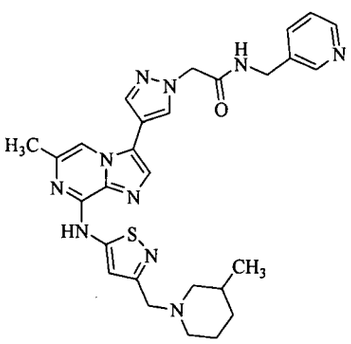
		
		
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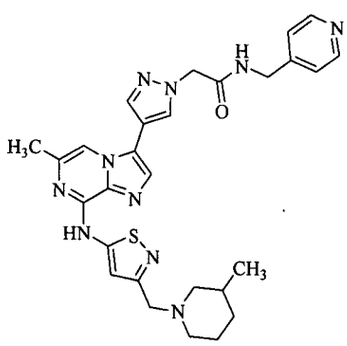
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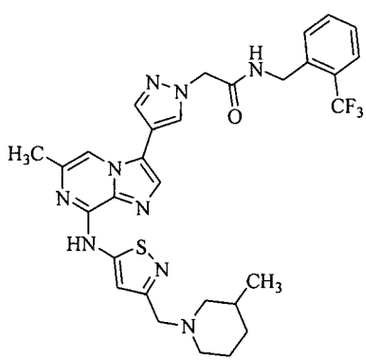


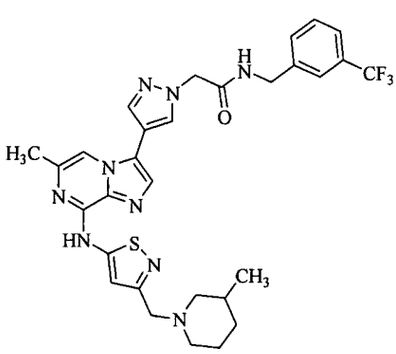


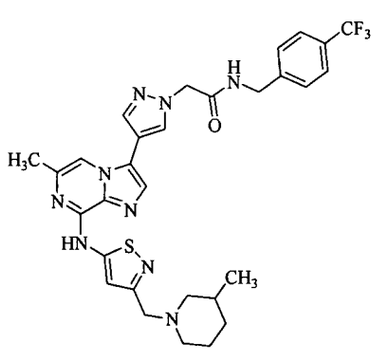


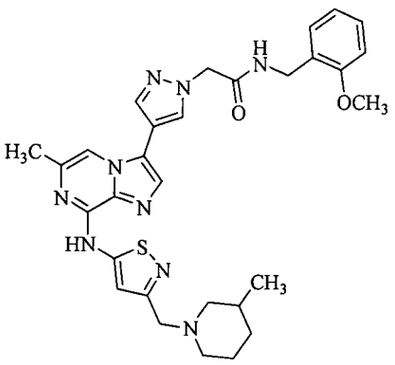


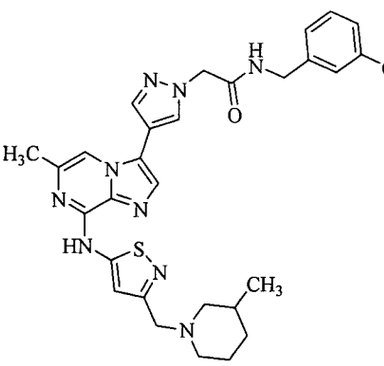


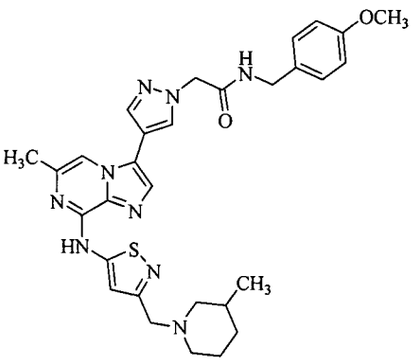


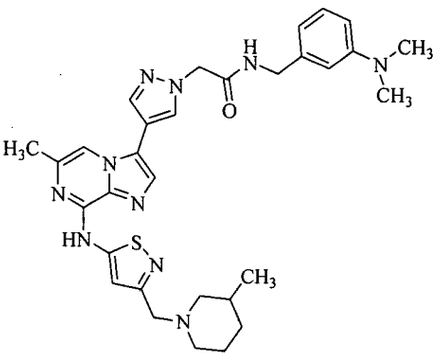


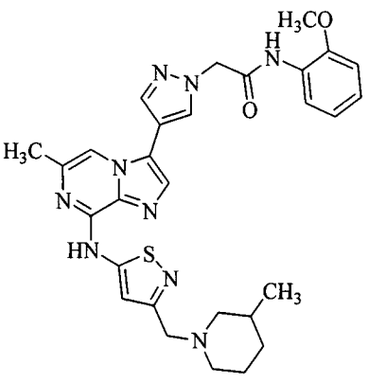


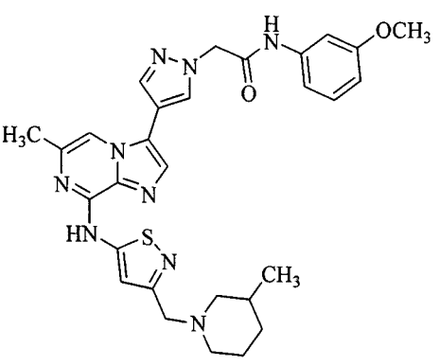


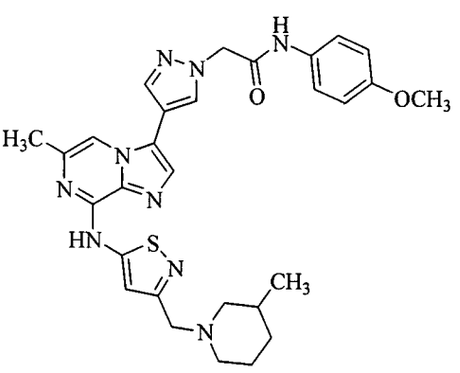


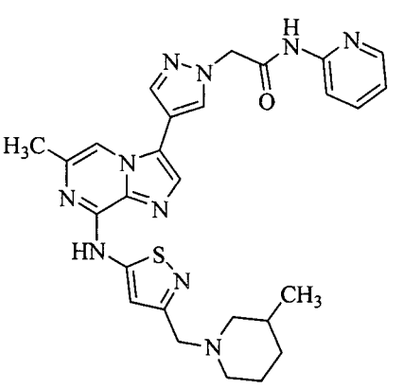


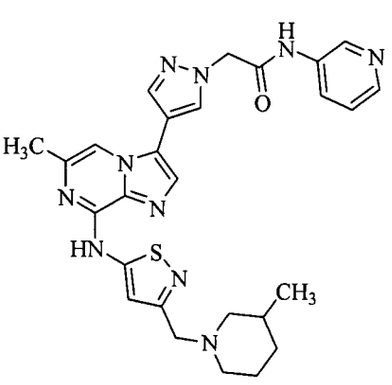


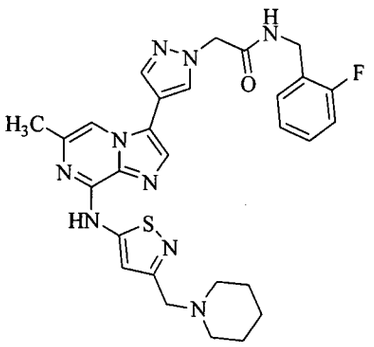


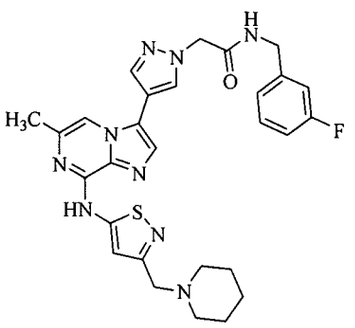


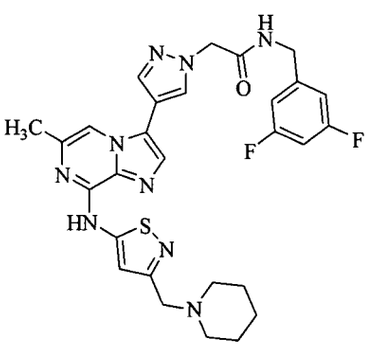


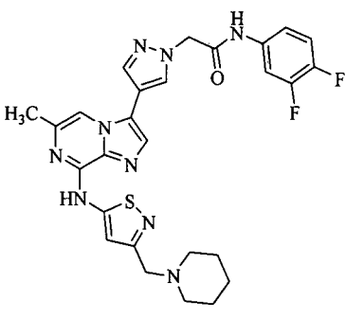


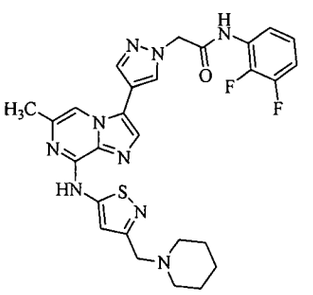


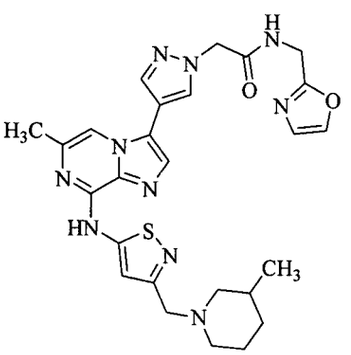


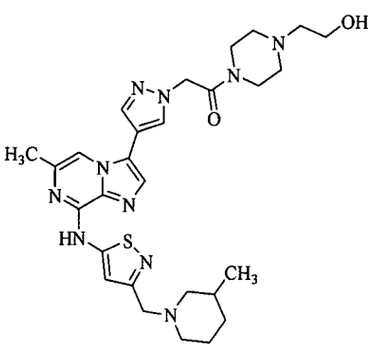


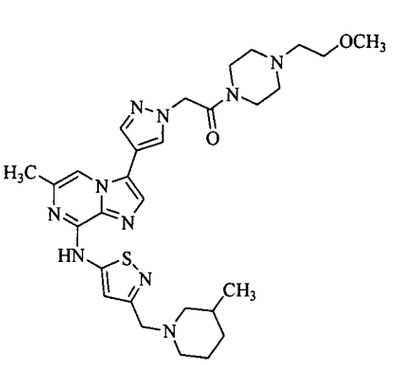


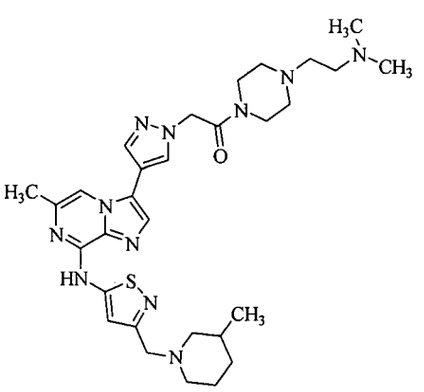




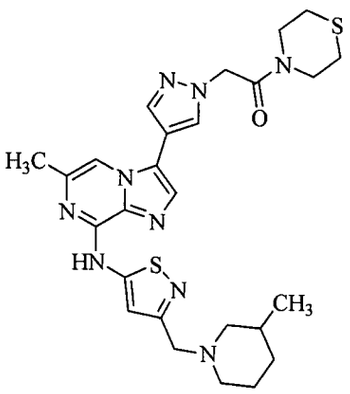


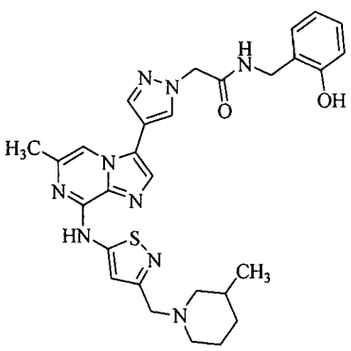


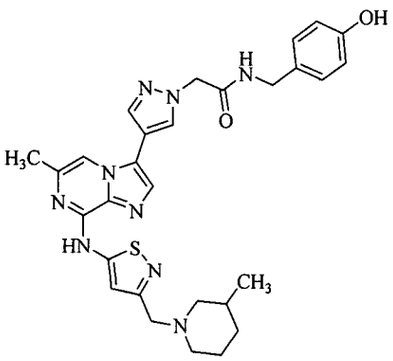


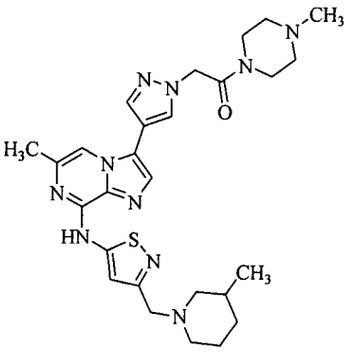


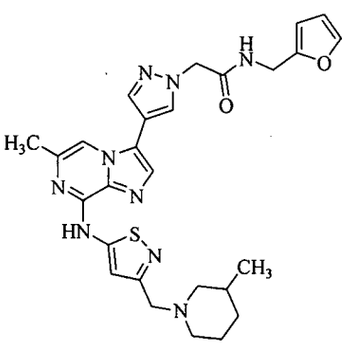
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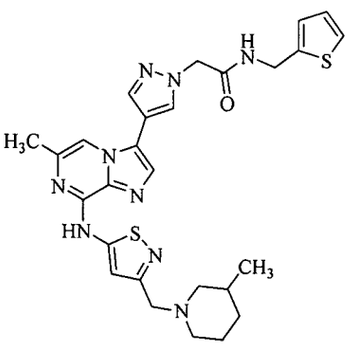


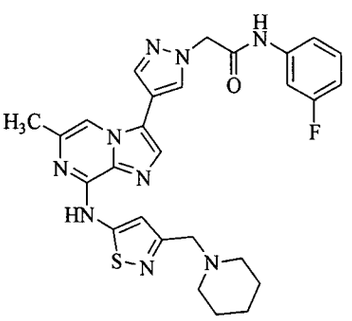


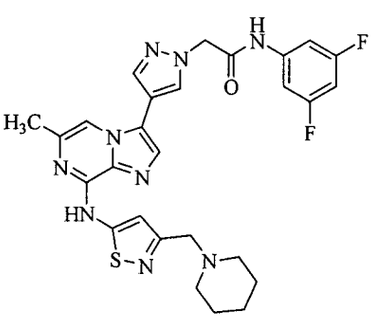


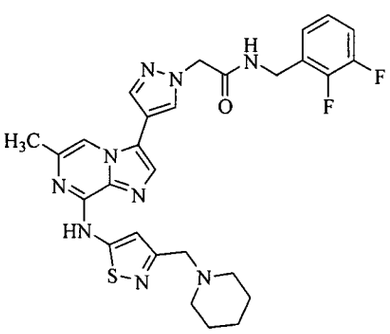


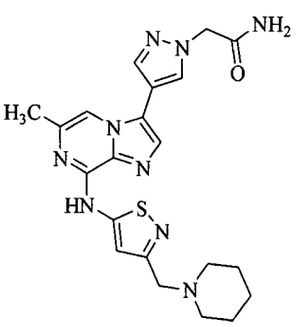


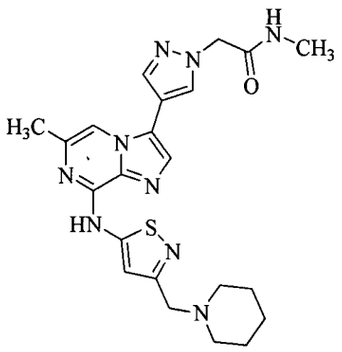


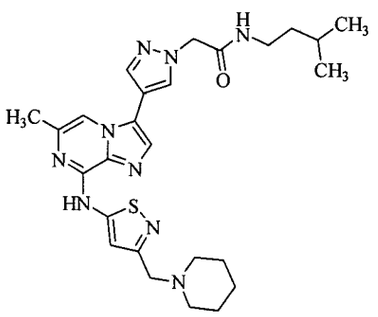


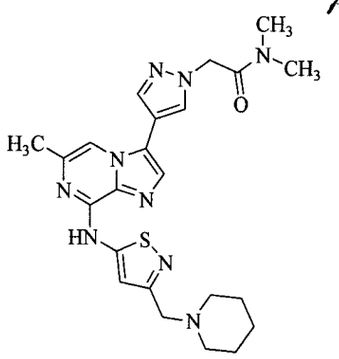


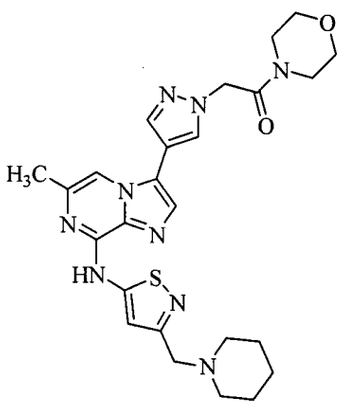


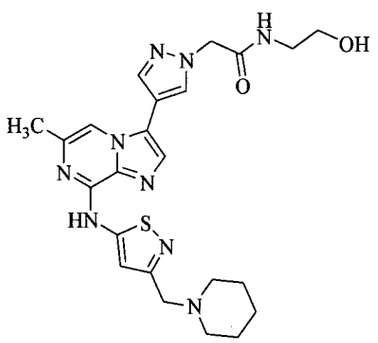


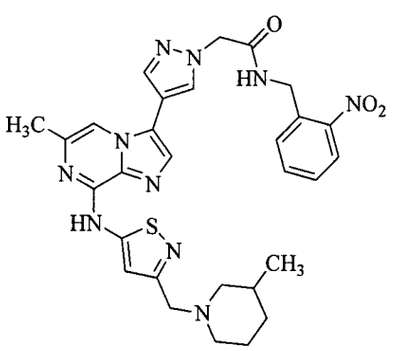


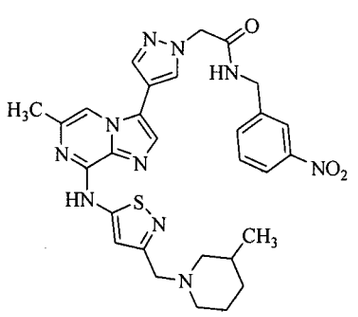


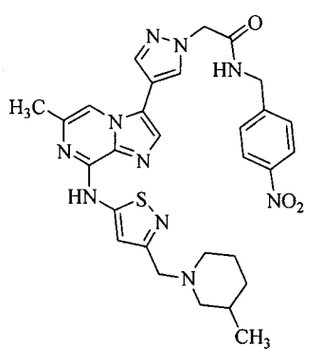


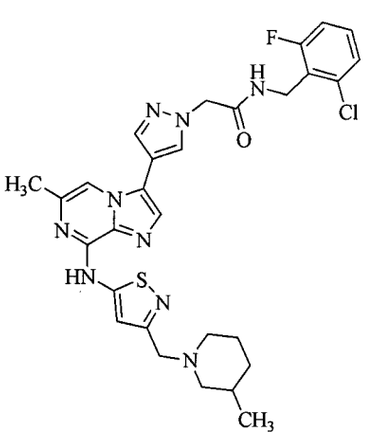


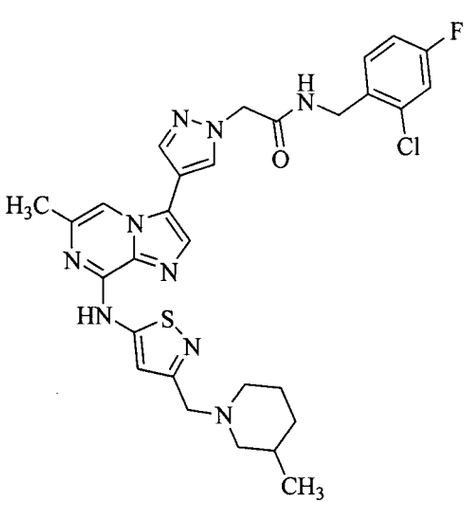


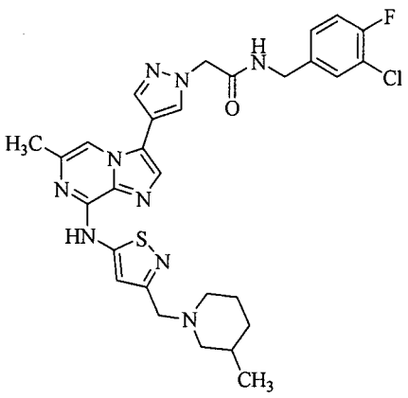


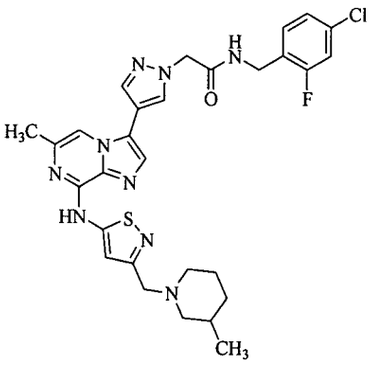


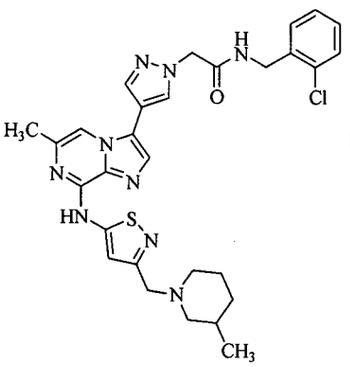


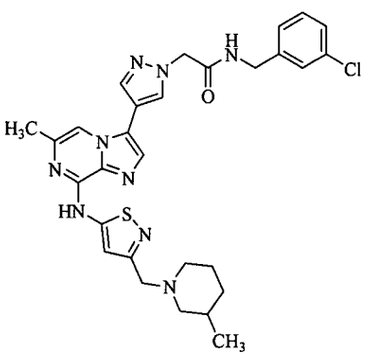


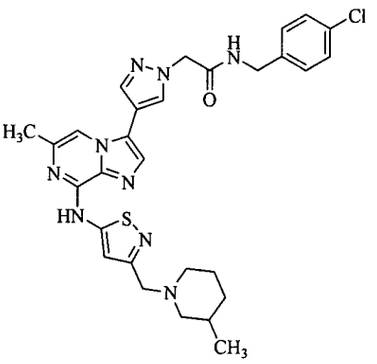


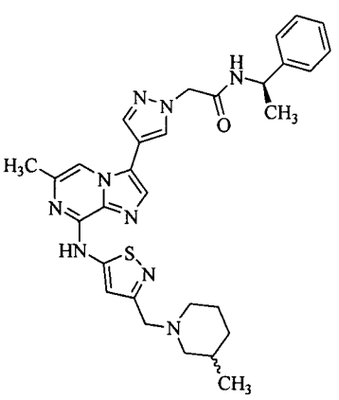


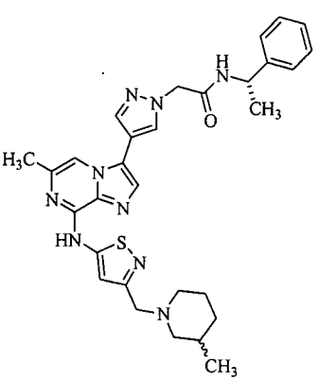


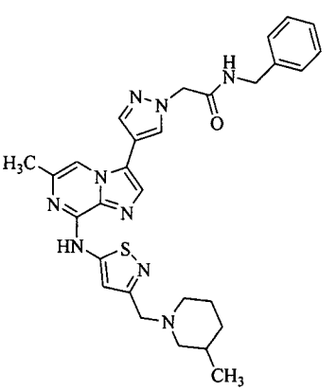


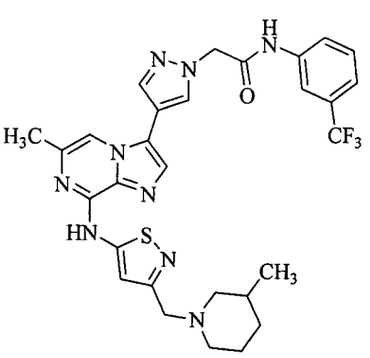


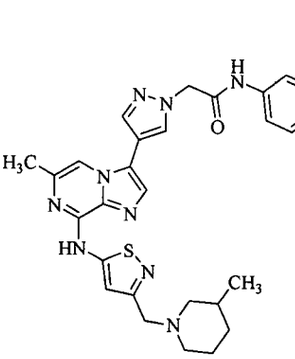


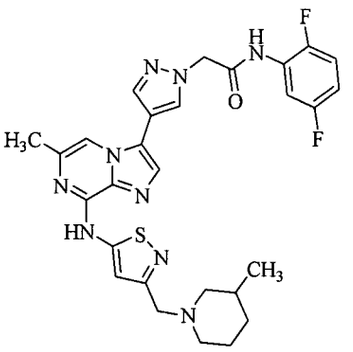


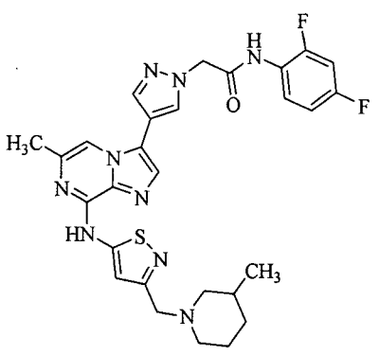


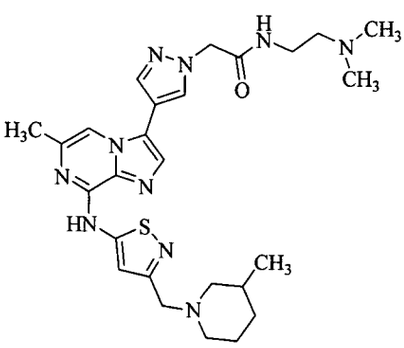


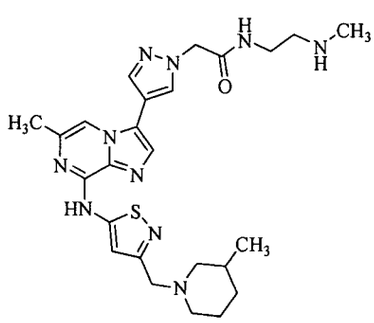


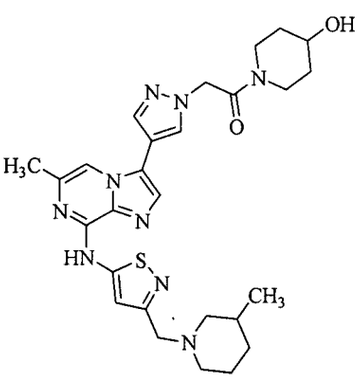


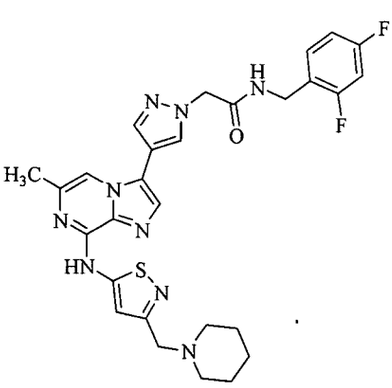


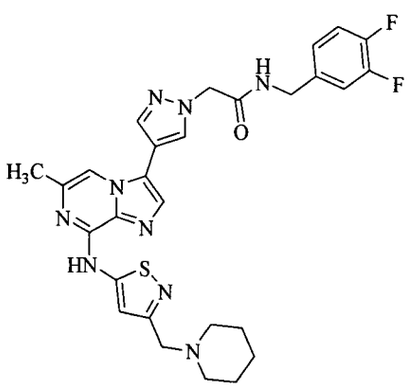


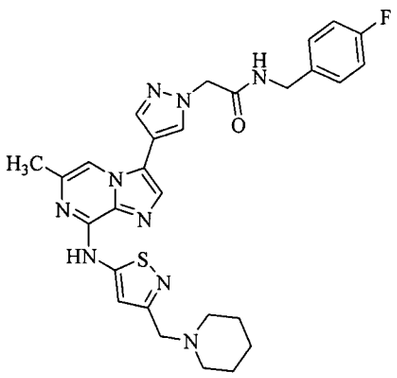


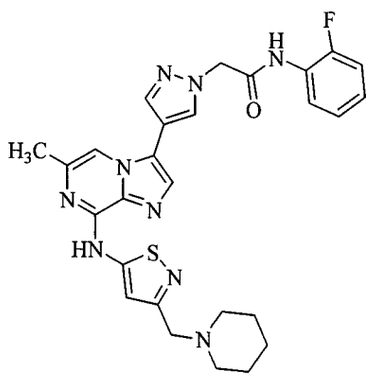


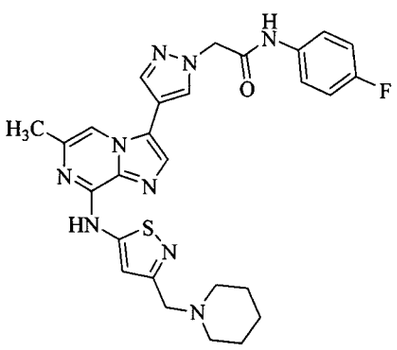


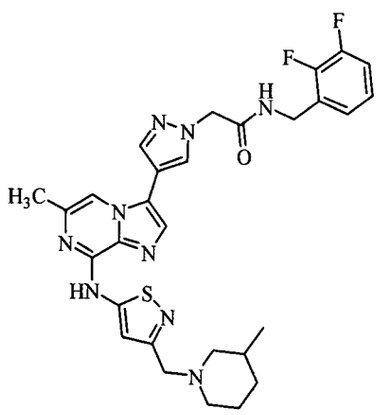


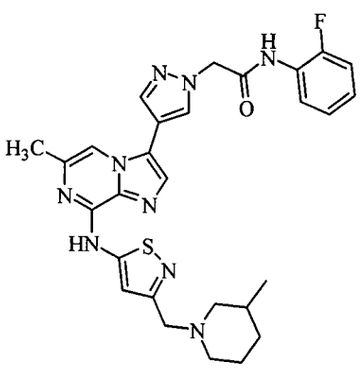


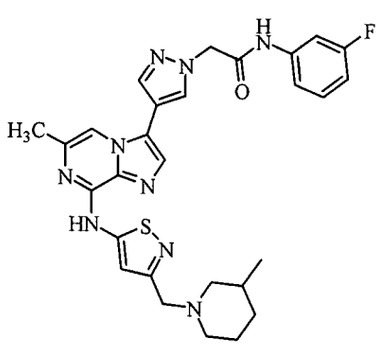


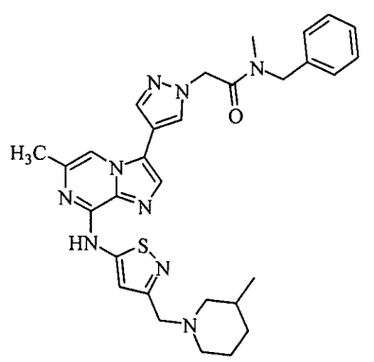


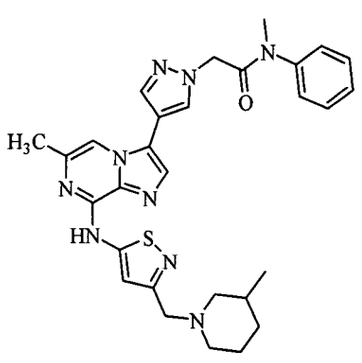


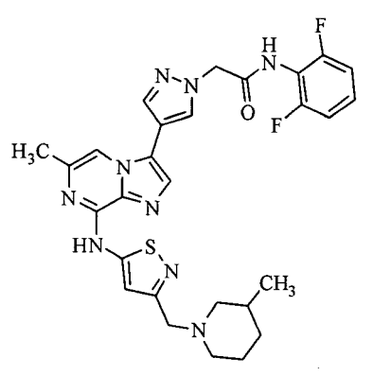


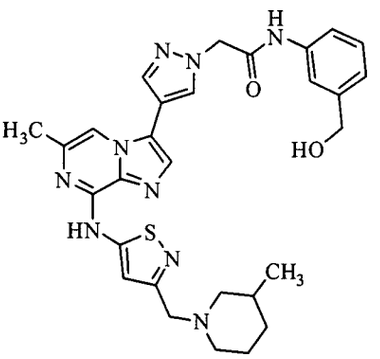


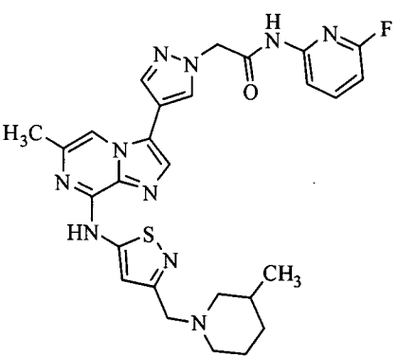


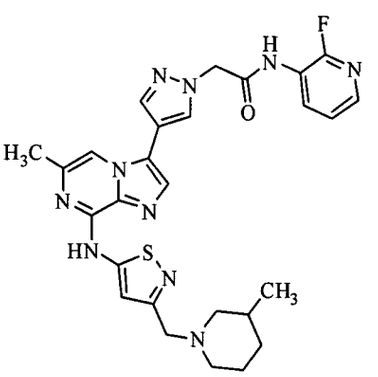


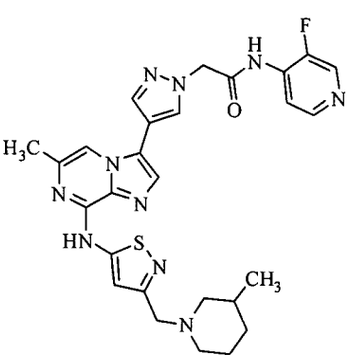


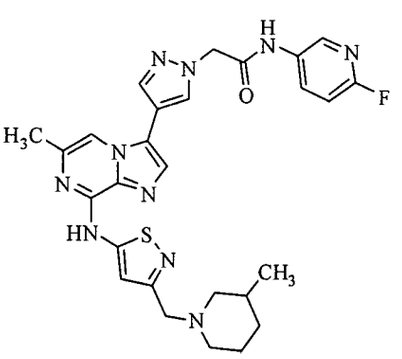


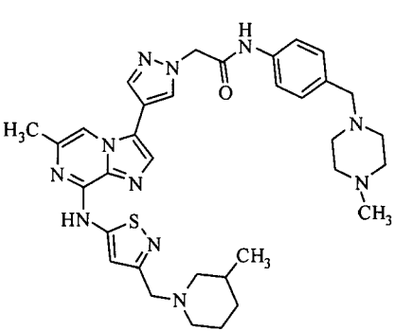


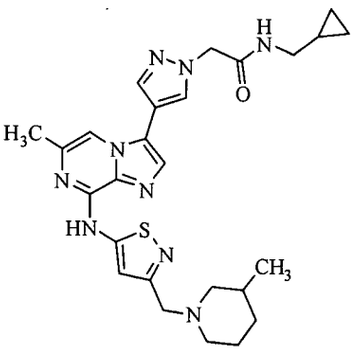


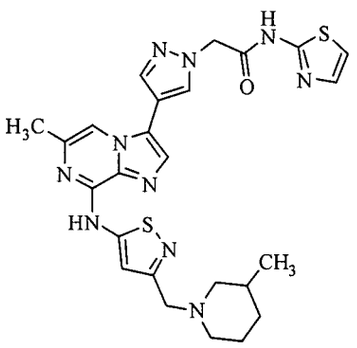


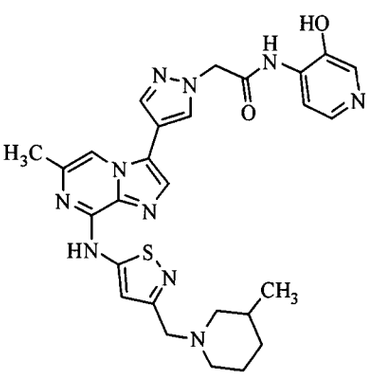


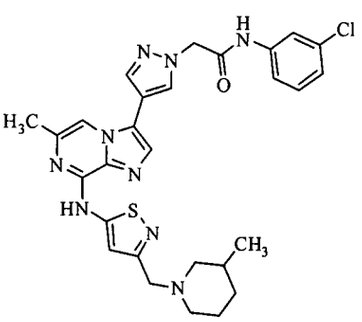


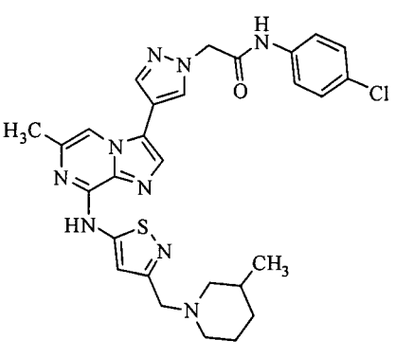


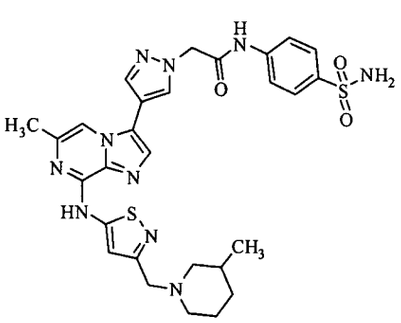


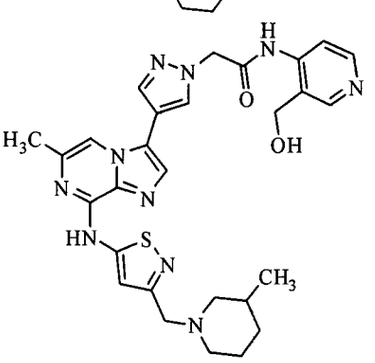


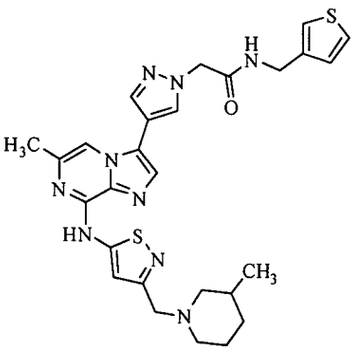


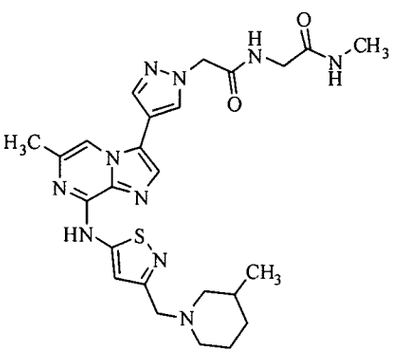


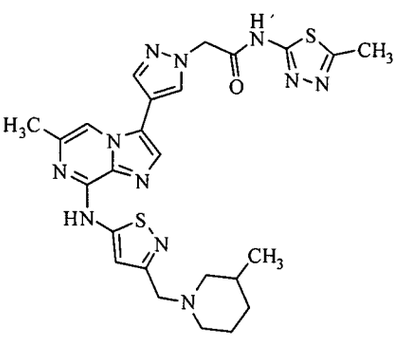


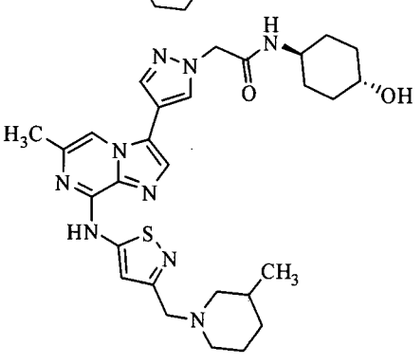


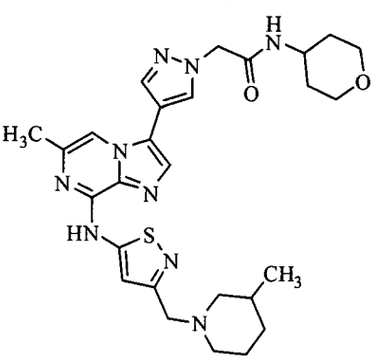


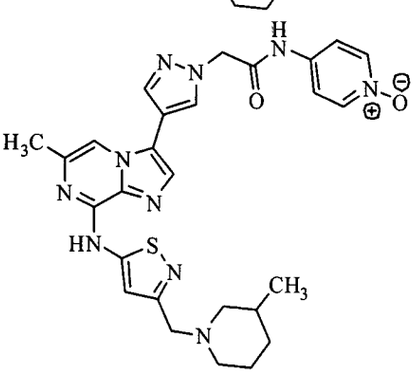


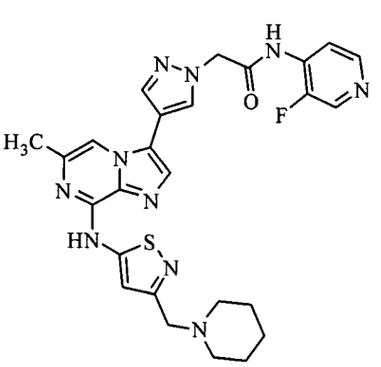


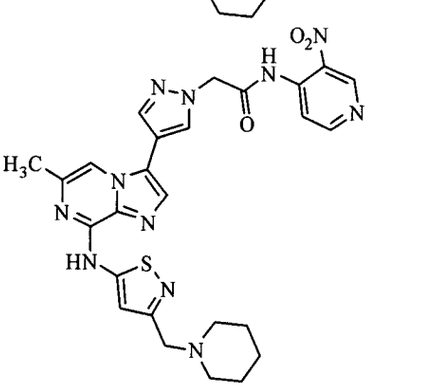


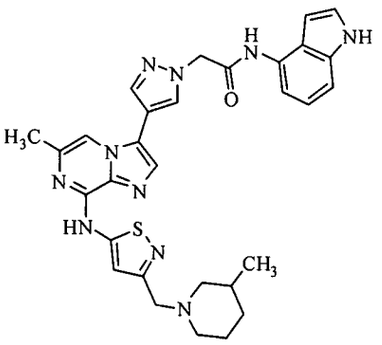


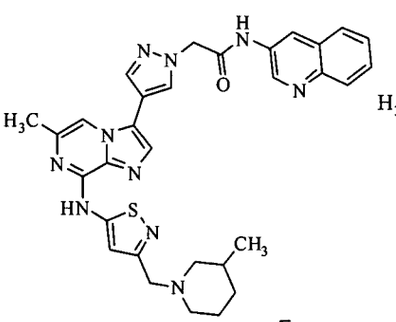


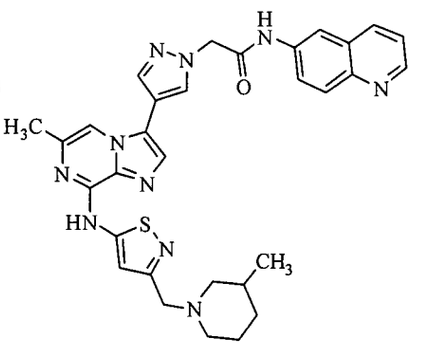


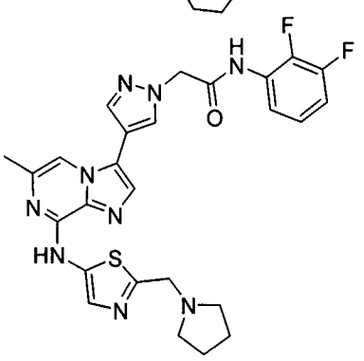


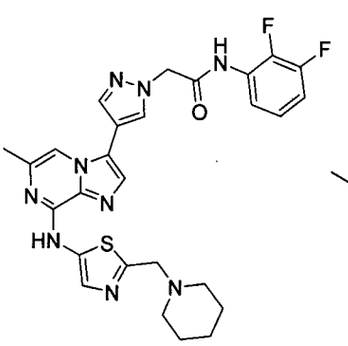


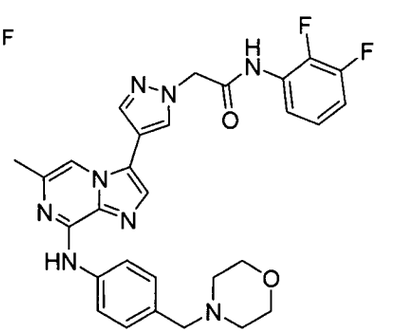


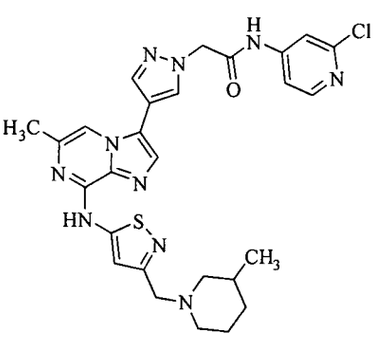


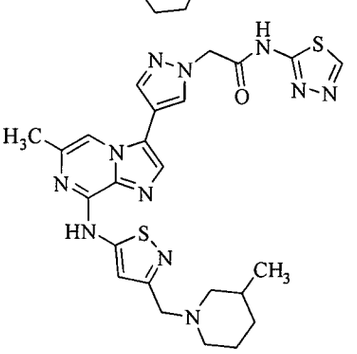


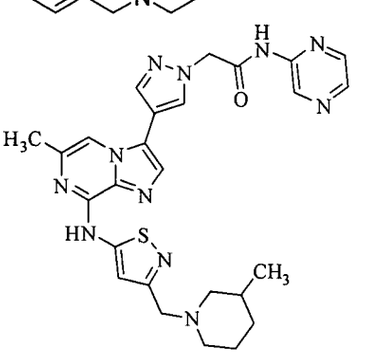


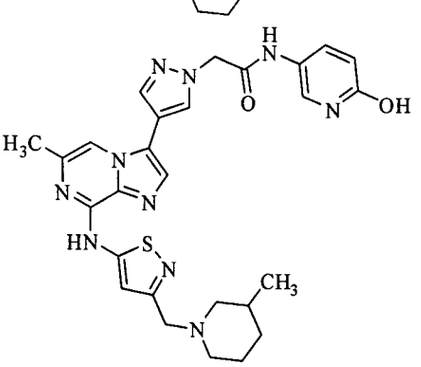


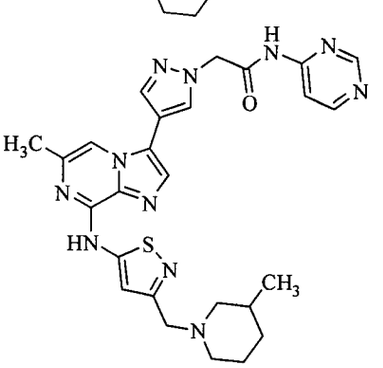


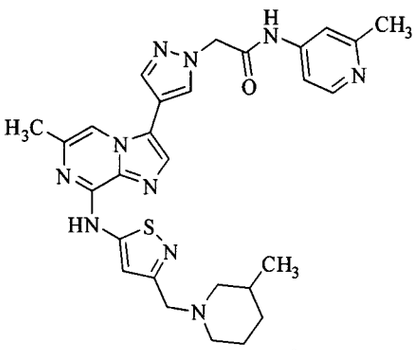


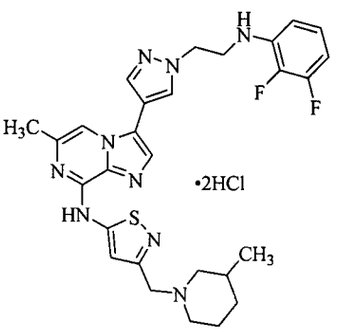


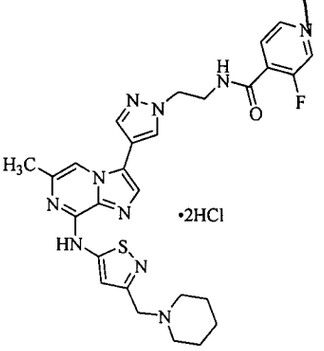


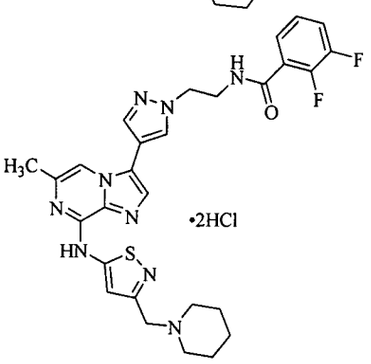


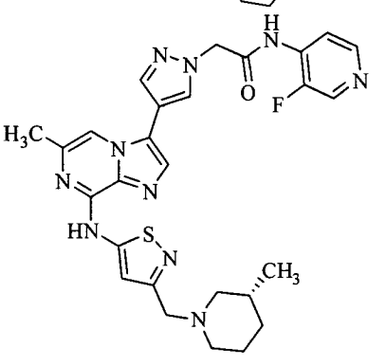


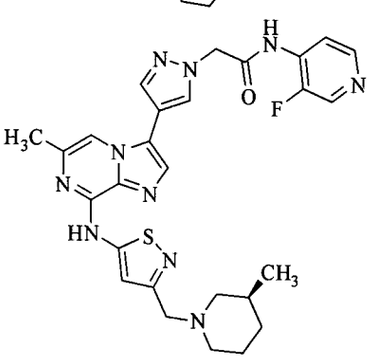


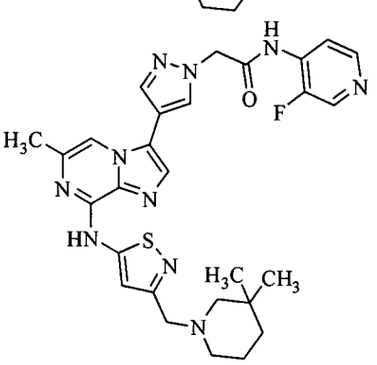


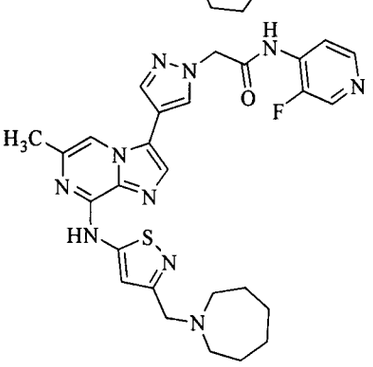


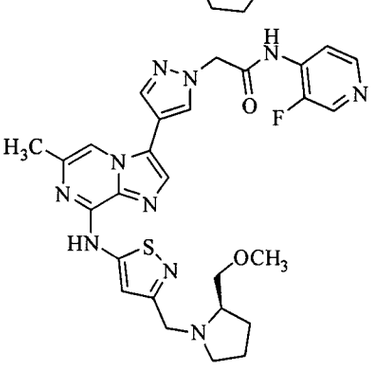


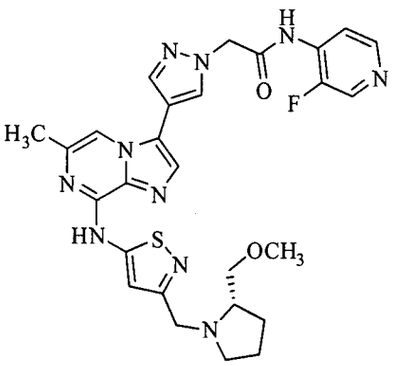


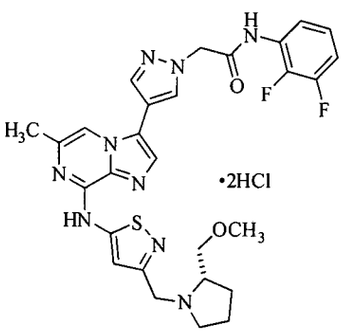


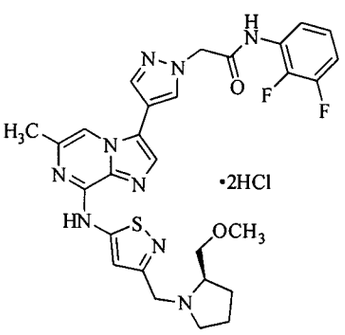


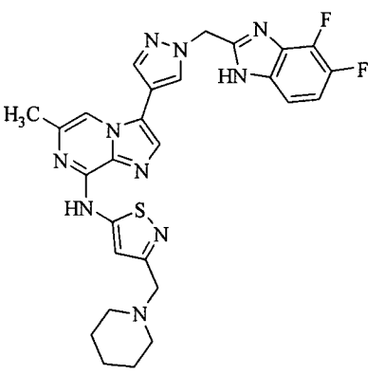


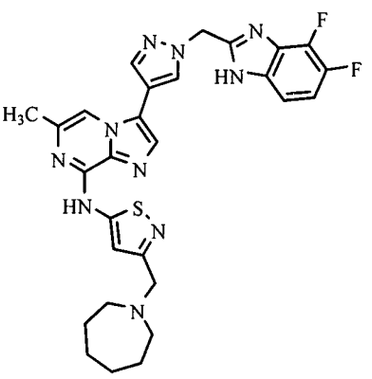


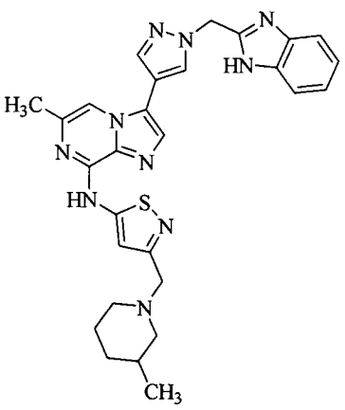


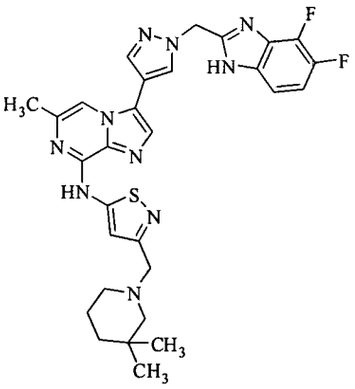


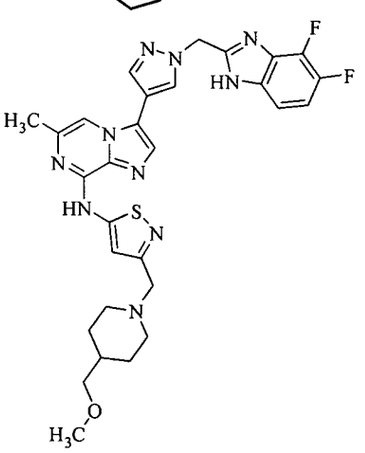


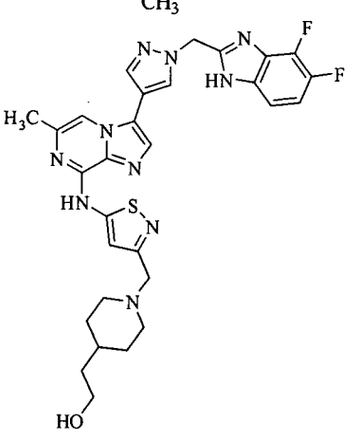


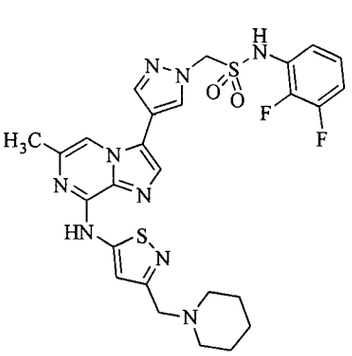




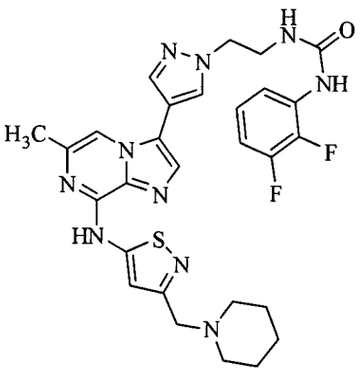


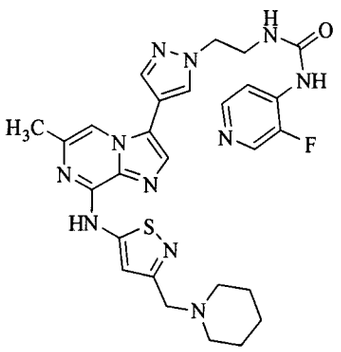


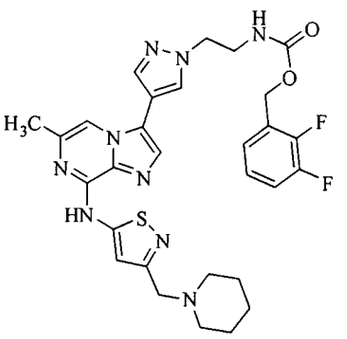


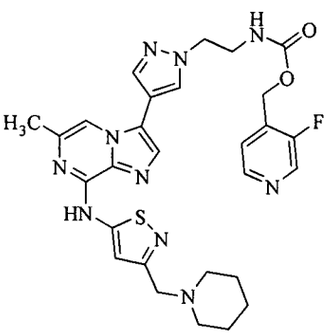


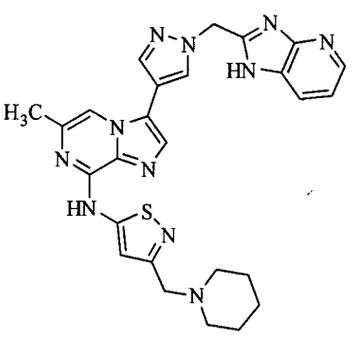
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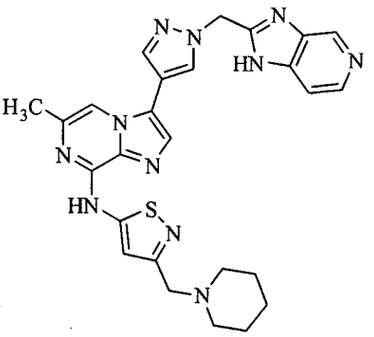


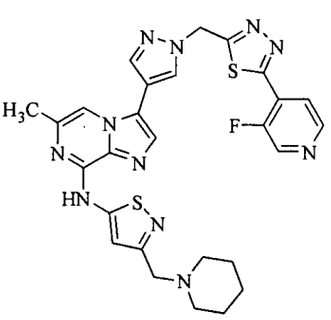


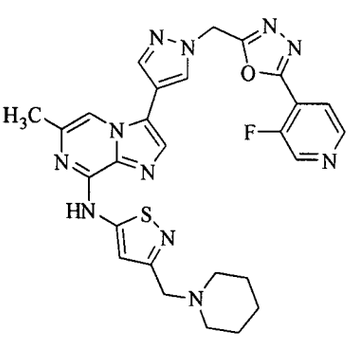


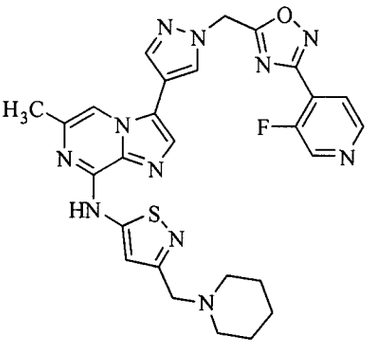


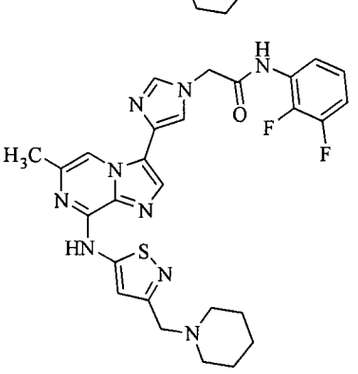


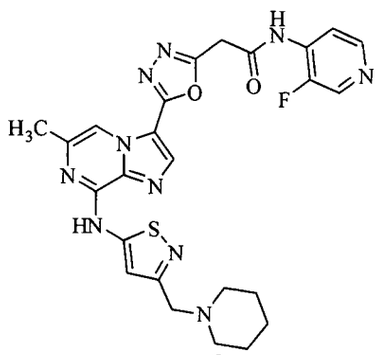


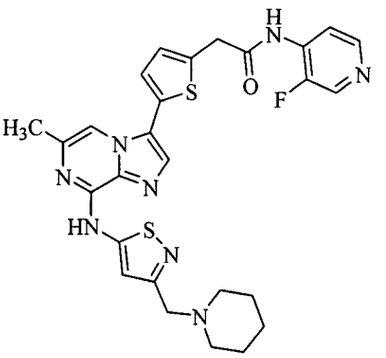


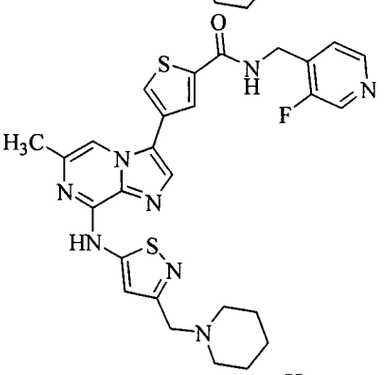


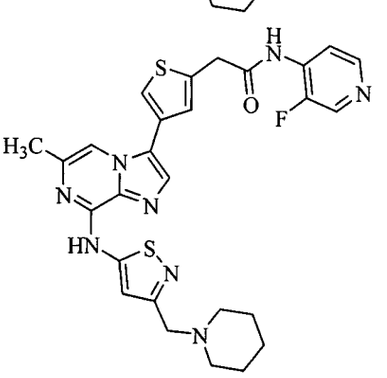


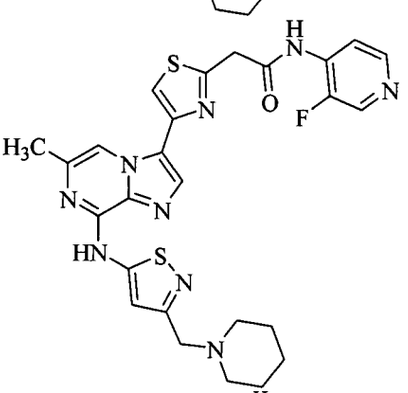


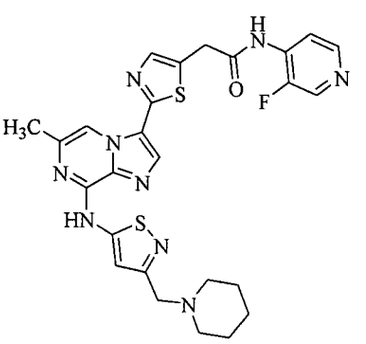


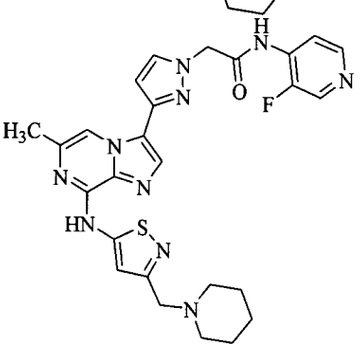


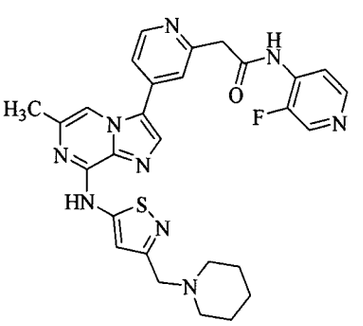


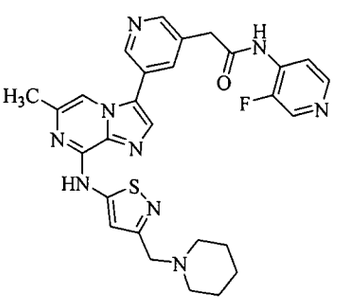


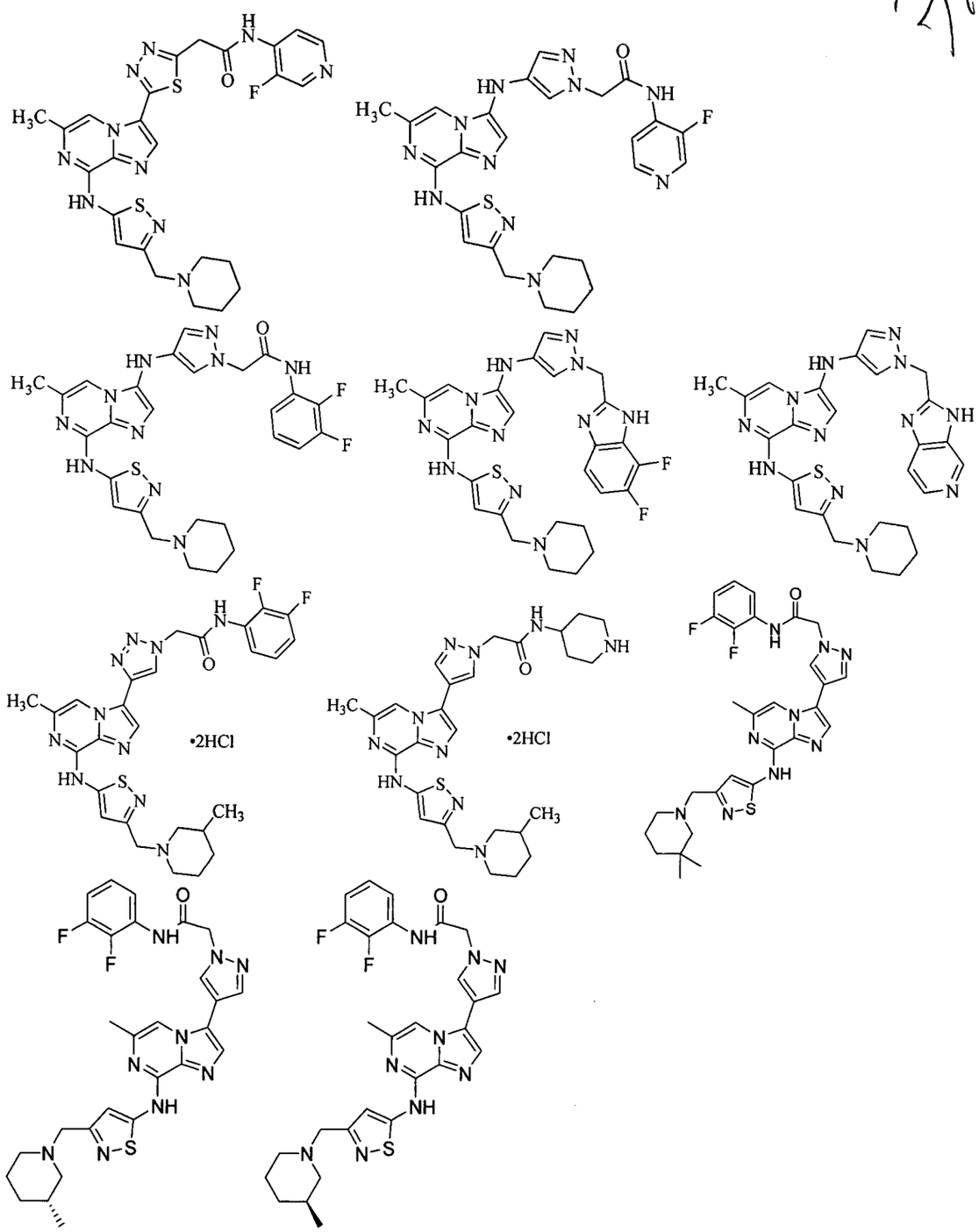












o sales, solvatos, ésteres o prodrogas de los mismos, aceptables para uso farmacéutico. Los compuestos incluidos en la Tabla **2** anterior se divulgan en las siguientes referencias: WO2007/058942 presentada el 8 de noviembre de 2006, WO2004/026877 presentada el 19 de septiembre de 2003, WO2007/058873

presentada el 8 de noviembre de 2006, Solicitud de EEUU Nº 60/943999 presentada el 14 de junio de 2007, Solicitud de EEUU Serie Nº 60/987932 presentada el 4 de noviembre de 2007 y Solicitud de EEUU Nº 60/855421 presentada el 31 de octubre de 2006, así como también en la Solicitud de Patente Provisional de EEUU Serie Nº ——— (Registro de Representante Legal Nº OC06760L01), presentada de la misma fecha adjunta.

Según se usó anteriormente, y en toda la presente divulgación, los siguientes términos, a menos que se indique lo contrario, se interpretarán de acuerdo con los siguientes significados, incluyendo cualquier sustitución posible de los grupos o restos indicados:

"Agente antimitótico" es un compuesto que inhibe el desarrollo celular interrumpiendo la división celular. Dichos compuestos inhiben específicamente una célula en mitosis. Esto incluye compuestos que seleccionan como blanco los microtúbulos, centrosoma o husos de la célula.

"Endoreduplicación" es el proceso en una célula donde hay una acumulación de ADN poliploide o aneuploide como resultado de rondas de ciclos celulares en ausencia de citocinesis (división celular física).

"Polyploidía" es una célula que posee más ADN que dos conjuntos completos de cromosomas.

"Aneuploidía" es una célula que contiene un contenido anormal de cromosomas.

"Paciente" incluye tanto seres humanos como animales.

"Mamífero" se refiere a seres humanos y otros animales mamíferos.

"Alquilo" se refiere a un grupo hidrocarburo alifático que puede ser recto o ramificado y comprende desde alrededor de 1 hasta alrededor de 20 átomos de carbono en la cadena. Los grupos alquilo preferidos contienen desde alrededor de 1 hasta alrededor de 12 átomos de carbono en la cadena. Los grupos alquilo más

preferidos contienen desde alrededor de 1 hasta alrededor de 6 átomos de carbono en la cadena. Ramificado se refiere a que uno o más grupos alquilo inferiores tales como, por ejemplo, metilo, etilo o propilo, están unidos a una cadena lineal de alquilo. "Alquilo inferior" se refiere a un grupo que tiene desde alrededor de 1 hasta alrededor de 6 átomos de carbono en la cadena que puede ser recta o ramificada. "Alquilo" puede estar insustituido o sustituido en forma opcional por uno o más sustituyentes que pueden ser iguales o diferentes, donde cada sustituyente está seleccionado en forma independiente entre el grupo integrado por halo, alquilo, arilo, cicloalquilo, ciano, hidroxi, alcoxi, alquiltio, amino, oxima (por ejemplo, =N–OH), –NH(alquilo), –NH(cicloalquilo), $–N(alquilo)_2$, –O–C(O)–alquilo, –O–C(O)–arilo, –O–C(O)–cicloalquilo, carboxi y –C(O)O–alquilo. Algunos ejemplos no restrictivos de grupos alquilo apropiados incluyen metilo, etilo, n–propilo, isopropilo y t–butilo.

"Alquenilo" se refiere a un grupo hidrocarburo alifático que contiene por lo menos un enlace doble carbono–carbono y que puede ser recto o ramificado y que comprende desde alrededor de 2 hasta alrededor de 15 átomos de carbono en la cadena. Los grupos alquenilo preferidos tienen desde alrededor de 2 hasta alrededor de 12 átomos de carbono en la cadena; y más preferentemente desde alrededor de 2 hasta alrededor de 6 átomos de carbono en la cadena. Ramificado se refiere a que uno o más grupos alquilo inferiores tales como, por ejemplo, metilo, etilo o propilo, están unidos a una cadena lineal de alquenilo. "Alquenilo inferior" se refiere desde alrededor de 2 hasta alrededor de 6 átomos de carbono en la cadena que puede ser recta o ramificada. "Alquenilo" puede estar insustituido o sustituido en forma opcional por uno o más sustituyentes que pueden ser iguales o diferentes, donde cada sustituyente está seleccionado en forma independiente entre el grupo integrado por halo, alquilo, arilo, cicloalquilo, ciano, alcoxi y –S(alquilo). Algunos ejemplos no restrictivos de grupos alquenilo

apropiados incluyen etenilo, propenilo, n–butenilo, 3–metilbut–2–enilo, n–pentenilo, octenilo y decenilo.

"Alquileno" se refiere a un grupo disfuncional obtenido por la remoción de un átomo de hidrógeno de un grupo alquilo que se definió anteriormente. Algunos ejemplos no restrictivos de alquileno incluyen metileno, etileno y propileno.

"Alquinilo" se refiere a un grupo hidrocarburo alifático que contiene por lo menos un enlace triple carbono–carbono y que puede ser recto o ramificado y que comprende desde alrededor de 2 hasta alrededor de 15 átomos de carbono en la cadena. Los grupos alquinilo preferidos tienen desde alrededor de 2 hasta alrededor de 12 átomos de carbono en la cadena; y más preferentemente desde alrededor de 2 hasta alrededor de 4 átomos de carbono en la cadena. Ramificado se refiere a que uno o más grupos alquilo inferiores tales como, por ejemplo, metilo, etilo o propilo, están unidos a una cadena lineal de alquinilo. "Alquinilo inferior" se refiere desde alrededor de 2 hasta alrededor de 6 átomos de carbono en la cadena que puede ser recta o ramificada. Algunos ejemplos no restrictivos de grupos alquinilo apropiados incluyen etinilo, propinilo, 2–butinilo y 3–metilbutinilo. "Alquinilo" puede estar insustituido o sustituido en forma opcional por uno o más sustituyentes que pueden ser iguales o diferentes, donde cada sustituyente está seleccionado en forma independiente entre el grupo integrado por alquilo, arilo y cicloalquilo.

"Arilo" se refiere a un sistema de anillo aromático, monocíclico o multicíclico que comprende desde alrededor de 6 hasta alrededor de 14 átomos de carbono, preferentemente desde alrededor de 6 hasta alrededor de 10 átomos de carbono. El grupo arilo puede estar sustituido en forma opcional con uno o más "sustituyentes del sistema de anillo" que pueden ser iguales o diferentes, y que son tal como se definieron en la presente. Algunos ejemplos no restrictivos de grupos arilo apropiados incluyen fenilo y naftilo.

"Anillo cíclico en puente" es un anillo hidrocarburo tal como, por ejemplo, anillo cicloalquilo, cicloalquenilo, o arilo o que contiene heteroátomos tales como, por ejemplo, heterociclilo, heterociclenilo, o heteroarilo tal como se describieron en la presente, que contiene un puente, que es un enlace de valencia o un átomo o una cadena sin ramificar de átomos que conecta dos partes diferentes del anillo. Los dos átomos de carbono terciarios conectados a través del puente se denominan "cabezas de puente".

"Heteroarilo" se refiere a un sistema de anillo aromático, monocíclico o multicíclico que comprende desde alrededor de 5 hasta alrededor de 14 átomos del anillo, preferentemente desde alrededor de 5 hasta alrededor de 10 átomos del anillo, en el cual uno o más de los átomos del anillo es un elemento distinto de carbono, por ejemplo nitrógeno, oxígeno o azufre, solos o combinados. Los heteroarilos preferidos contienen desde alrededor de 5 hasta alrededor de 6 átomos del anillo. El "heteroarilo" puede estar sustituido en forma opcional por uno o más "sustituyentes del sistema de anillo" que pueden ser iguales o diferentes, y que son tal como se definieron en la presente. El prefijo aza, oxa o tia antes del nombre radical heteroarilo se refiere a que por lo menos un atomo de nitrógeno, oxígeno o azufre, respectivamente, está presente como átomo del anillo. Un átomo de nitrógeno de un heteroarilo puede oxidarse en forma opcional en el N–óxido correspondiente. "Heteroarilo" también puede incluir un heteroarilo, tal como se definió anteriormente, fusionado a un arilo tal como se definió anteriormente. Algunos ejemplos no restrictivos de heteroarilos apropiados incluyen piridilo, pirazinilo, furanilo, tienilo, pirimidinilo, piridona (incluyendo piridonas N–sustituidas), isoxazolilo, isotiazolilo, oxazolilo, tiazolilo, pirazolilo, furazanilo, pirrolilo, pirazolilo, triazolilo, 1,2,4–tiadiazolilo, pirazinilo, piridazinilo, quinoxalinilo, ftalazinilo, oxindolilo, 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 y similares. El término "heteroarilo" también se refiere a restos heteroarilo parcialmente saturados tales como, por ejemplo, tetrahidroisoquinolilo, tetrahidroquinolilo y similares.

"Aralquilo" o "arilalquilo" se refiere a un grupo aril–alquil– en el cual el arilo y el alquilo son tal como se describieron previamente. Los aralquilos preferidos comprenden un grupo alquilo inferior. Algunos ejemplos no restrictivos de grupos aralquilo apropiados incluyen bencilo, 2–fenetilo y naftalenilmetilo. El enlace al resto principal es a través de alquilo.

"Alquilarilo" se refiere a un grupo alquil–aril– en el cual el alquilo y el arilo son tal como se describieron previamente. Los alquilarilos preferidos comprenden un grupo alquilo inferior. Un ejemplo no restrictivo de un grupo alquilarilo apropiado es tolilo. El enlace al resto principal es a través de arilo.

"Cicloalquilo" se refiere a un sistema de anillo no aromático, mono o multicíclico, que comprende desde alrededor de 3 hasta alrededor de 10 átomos de carbono, preferentemente desde alrededor de 5 hasta alrededor de 10 átomos de carbono. Los anillo cicloalquilo preferidos contienen desde alrededor de 5 hasta alrededor de 7 átomos del anillo. El cicloalquilo puede estar sustituido en forma opcional con uno o más "sustituyentes del sistema de anillo" que pueden ser iguales o diferentes, y que son tal como se definieron anteriormente. Algunos ejemplos no restrictivos de cicloalquilos monocíclicos apropiados incluyen ciclopropilo, ciclopentilo, ciclohexilo, cicloheptilo y similares. Algunos ejemplos no restrictivos de cicloalquilos multicíclicos apropiados incluyen 1–decalinilo, norbornilo, adamantilo y similares.

"Cicloalquilalquilo" se refiere a un resto cicloalquilo tal como se definió anteriormente unido mediante un resto alquilo (definido anteriormente) a un

núcleo principal. Algunos ejemplos no restrictivos de cicloalquilalquilos apropiados incluyen ciclohexilmetilo, adamantilmetilo y similares.

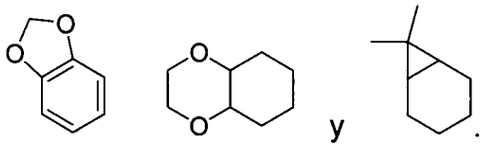
"Cicloalquenilo" se refiere a un sistema de anillo no aromático, mono o multicíclico, que comprende desde alrededor de 3 hasta alrededor de 10 átomos de carbono, preferentemente desde alrededor de 5 hasta alrededor de 10 átomos de carbono, que contiene por lo menos un enlace doble carbono–carbono. Los anillos cicloalquenilo preferidos contienen desde alrededor de 5 hasta alrededor de 7 átomos del anillo. El cicloalquenilo puede estar sustituido en forma opcional con uno o más "sustituyentes del sistema de anillo" que pueden ser iguales o diferentes, y que son tal como se definieron anteriormente. Algunos ejemplos no restrictivos de cicloalquenilos monocíclicos apropiados incluyen ciclopentenilo, ciclohexenilo, ciclohepta–1,3–dienilo, y similares. Un ejemplo no restrictivo de un cicloalquenilo multicíclico apropiado es norbornilenilo.

"Cicloalquenilalquilo" se refiere a un resto cicloalquenilo, tal como se definió anteriormente, unido mediante un resto alquilo (definido anteriormente) a un núcleo principal. Algunos ejemplos no restrictivos de cicloalquenilalquilos apropiados incluyen ciclopentenilmetilo, ciclohexenilmetilo y similares.

"Halógeno" se refiere a flúor, cloro, bromo, o yodo. Se prefieren flúor, cloro y bromo.

"Sustituyente del sistema de anillo" se refiere a un sustituyente unido a un sistema de anillo aromático o no aromático que, por ejemplo, reemplaza un hidrógeno disponible en el sistema de anillo. Los sustituyentes del sistema de anillo pueden ser iguales o diferentes, estando cada uno seleccionado en forma independiente entre el grupo integrado por alquilo, alquenilo, alquinilo, arilo, heteroarilo, aralquilo, alquilarilo, heteroaralquilo, heteroarilalquenilo, heteroarilalquinilo, alquilheteroarilo, hidroxi, hidroxialquilo, alcoxi, ariloxi, aralcoxi, acilo, aroilo, halo, nitro, ciano, carboxi, alcoxicarbonilo, ariloxicarbonilo,

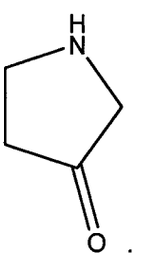
aralcoxicarbonilo, alquilsulfonilo, arilsulfonilo, heteroarilsulfonilo, alquiltio, ariltio, heteroariltio, aralquiltio, heteroaralquiltio, cicloalquilo, heterociclilo, amida, –CHO, –O–C(O)–alquilo, –O–C(O)–arilo, –O–C(O)–cicloalquilo, $–C(=N–CN)–NH_2$, $–C(=NH)–NH_2$, –C(=NH)–NH(alquilo), oxima (por ejemplo, =N–OH), $Y_1Y_2N–$, $Y_1Y_2N–$alquil–, $Y_1Y_2NC(O)–$, $Y_1Y_2NSO_2–$ y $–SO_2NY_1Y_2$, en el cual Y_1 e Y_2 pueden ser iguales o diferentes y están seleccionados en forma independiente entre el grupo integrado por hidrógeno, alquilo, arilo, cicloalquilo, y aralquilo. "Sustituyente del sistema de anillo" también puede referirse a un solo resto que reemplaza simultáneamente dos hidrógenos disponibles sobre dos átomos de carbono adyacentes (un H sobre cada carbono) en un sistema de anillo. Algunos ejemplos de dicho resto incluyen metilendioxi, etilendioxi, $–C(CH_3)_2–$ y similares que forman restos tales como, por ejemplo:



"Heteroarilalquilo" se refiere a un resto heteroarilo, tal como se definió anteriormente, unido mediante un resto alquilo (definido anteriormente) a un núcleo principal. Algunos ejemplos no restrictivos de heteroarilos apropiados incluyen 2–piridinilmetilo, quinolinilmetilo y similares.

"Heterociclilo" se refiere a un sistema de anillo no aromático, saturado, monocíclico o multicíclico, que comprende desde alrededor de 3 hasta alrededor de 10 átomos del anillo, preferentemente desde alrededor de 5 hasta alrededor de 10 átomos del anillo, en el cual uno o más de los átomos en el sistema de anillo es un elemento distinto de carbono, por ejemplo nitrógeno, oxígeno o azufre, solos o combinados. No hay átomos de oxígeno y/o azufre adyacentes presentes en el sistema de anillo. Los heterociclilos preferidos contienen desde alrededor de 5 hasta alrededor de 6 átomos del anillo. El prefijo aza, oxa o tia antes del nombre radical heterociclilo se refiere a que por lo menos un atomo de nitrógeno, oxígeno

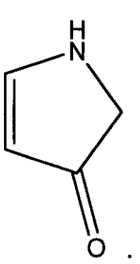
o azufre, respectivamente, está presente como átomo del anillo. En el anillo heterociclilo puede existir cualquier –NH protegido tal como, por ejemplo, como un grupo –N(Boc), –N(CBz), –N(Tos) y similares; dichas protecciones también forman parte de la presente invención. El heterociclilo puede estar sustituido en forma opcional por uno o más "sustituyentes del sistema de anillo" que pueden ser iguales o diferentes, y que son tal como se definieron en la presente. El átomo de nitrógeno o azufre del heterociclilo puede oxidarse en forma opcional en el N–óxido, S–óxido o S,S–dióxido correspondiente. Algunos ejemplos no restrictivos de anillos heterociclilo monocíclicos apropiados incluyen piperidilo, pirrolidinilo, piperazinilo, morfolinilo, tiomorfolinilo, tiazolidinilo, 1,4–dioxanilo, tetrahidrofuranilo, tetrahidrotiofenilo, lactama, lactona, y similares. "Heterociclilo" también puede referirse a un solo resto (por ejemplo, carbonilo) que reemplaza simultáneamente dos hidrógenos disponibles en el mismo átomo de carbono en un sistema de anillo. Un ejemplo de dicho resto es pirrolidona:



"Heterociclilalquilo" se refiere a un resto heterociclilo, tal como se definió anteriormente, unido mediante un resto alquilo (definido anteriormente) a un núcleo principal. Algunos ejemplos no restrictivos de heterociclilalquilos apropiados incluyen piperidinilmetilo, piperazinilmetilo y similares.

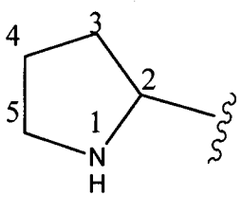
"Heterociclenilo" se refiere a un sistema de anillo no aromático, monocíclico o multicíclico, que comprende desde alrededor de 3 hasta alrededor de 10 átomos del anillo, preferentemente desde alrededor de 5 hasta alrededor de 10 átomos del anillo, en el cual uno o más de los átomos en el sistema de anillo es un

elemento distinto de carbono, por ejemplo un átomo de nitrógeno, oxígeno o azufre, solos o combinados, y que contiene por lo menos un enlace doble carbono–carbono o un enlace doble carbono–nitrógeno. No hay átomos de oxígeno y/o azufre adyacentes presentes en el sistema de anillo. Los anillos heterociclenilo preferidos contienen desde alrededor de 5 hasta alrededor de 6 átomos del anillo. El prefijo aza, oxa o tia antes del nombre radical heterociclenilo se refiere a que por lo menos un atomo de nitrógeno, oxígeno o azufre, respectivamente, está presente como átomo del anillo. El heterociclenilo puede estar sustituido en forma opcional por uno o más sustituyentes del sistema de anillo, en el cual "sustituyente del sistema de anillo" es tal como se definió anteriormente. El átomo de nitrógeno o azufre del heterociclenilo puede oxidarse en forma opcional en el N–óxido, S–óxido o S,S–dióxido correspondiente. Algunos ejemplos no restrictivos de grupos heterociclenilo apropiados incluyen 1,2,3,4–tetrahidropiridinilo, 1,2–dihidropiridinilo, 1,4–dihidropiridinilo, 1,2,3,6–tetrahidropiridinilo, 1,4,5,6–tetrahidropirimidinilo, 2–pirrolinilo, 3–pirrolinilo, 2–imidazolinilo, 2–pirazolinilo, dihidroimidazolilo, dihidrooxazolilo, dihidrooxadiazolilo, dihidrotiazolilo, 3,4–dihidro–2H–piranilo, dihidrofuranilo, fluorodihidrofuranilo, 7–oxabiciclo[2.2.1]heptenilo, dihidrotiofenilo, dihidrotiopiranilo, y similares. “Heterociclenilo” también puede referirse a un solo resto (por ejemplo, carbonilo) que reemplaza simultáneamente dos hidrógenos disponibles en el mismo átomo de carbono en un sistema de anillo. Un ejemplo de dicho resto es pirrolidinona:



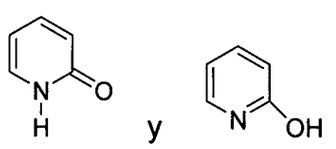
"Heterociclenilalquilo" se refiere a un resto heterociclenilo, tal como se definió anteriormente, unido mediante un resto alquilo (definido anteriormente) a un núcleo principal.

Cabe destacar que en los sistemas de anillo que contienen heteroátomos de la presente invención, no hay grupos hidroxilo sobre átomos de carbono adyacentes a un N, O o S, así como también no hay grupos N o S sobre el carbono adyacente a otro heteroátomo. Por lo tanto, por ejemplo, en el anillo:



no hay –OH unido directamente a los carbonos 2 y 5 marcados.

Además, cabe destacar que las formas tautoméricas tales como, por ejemplo, los restos:



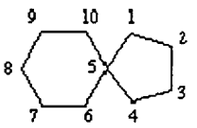
se consideran equivalentes en determinadas formas de realización de la presente invención.

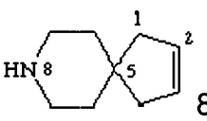
"Alquinilalquilo" se refiere a un grupo alquinil–alquilo– en el cual el alquinilo y el alquilo son tal como se describieron previamente. Los alquinilalquilos preferidos contienen un alquinilo inferior y un grupo alquilo inferior. El enlace al resto principal es a través de alquilo. Algunos ejemplos no restrictivos de grupos alquinilalquilo apropiados incluyen propargilmetilo.

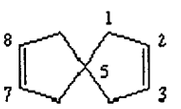
"Heteroaralquilo" se refiere a un grupo heteroaril–alquil– en el cual el heteroarilo y el alquilo son tal como se describieron previamente. Los heteroaralquilos preferidos contienen un grupo alquilo inferior. Algunos ejemplos no restrictivos de grupos aralquilo apropiados incluyen piridilmetilo, y quinolin–3–ilmetilo. El enlace al resto principal es a través de alquilo.

"Los sistemas de anillo espiro" tienen dos o más anillos unidos por un átomo en común. Los sistemas de anillo espiro preferidos incluyen

espiroheteroarilo, espiroheterociclenilo, espiroheterociclilo, espirocicloalquilo, espirociclenilo, y espiroarilo. Los sistemas de anillo espiro pueden estar sustituidos en forma opcional por uno o más sustituyentes del sistema de anillo, cuyo "sustituyente del sistema de anillo" es tal como se definió anteriormente. Algunos ejemplos no restrictivos de sistemas de anillo espiro apropiados incluyen



espiro[4.5]decano, 

8–azaspiro[4.5]dec–2–eno, y 

espiro[4.4]nona–2,7–dieno.

"Hidroxialquilo" se refiere a un grupo HO–alquil– en el cual alquilo es tal como se definió anteriormente. Los hidroxialquilos preferidos contienen alquilo inferior. Algunos ejemplos no restrictivos de grupos hidroxialquilo apropiados incluyen hidroximetilo y 2–hidroxietilo.

"Acilo" se refiere a un grupo H–C(O)–, alquil–C(O)– o cicloalquil–C(O)–, en el cual los diversos grupos son tal como se describieron previamente. El enlace al resto principal es a través de carbonilo. Los acilos preferidos contienen un alquilo inferior. Algunos ejemplos no restrictivos de grupos acilo apropiados incluyen formilo, acetilo y propanoilo.

"Aroilo" se refiere a un grupo aril–C(O)– en el cual el grupo arilo es tal como se describió anteriormente. El enlace al resto principal es a través de carbonilo. Algunos ejemplos no restrictivos de grupos apropiados incluyen benzoilo y 1– naftoilo.

"Alcoxi" se refiere a un grupo alquil–O– en el cual el grupo alquilo es tal como se describió anteriormente. Algunos ejemplos no restrictivos de grupos alcoxi apropiados incluyen metoxi, etoxi, n–propoxi, isopropoxi y n–butoxi. El enlace al resto principal es a través de oxígeno de éter.

"Ariloxi" se refiere a un grupo aril–O– en el cual el grupo arilo es tal como se describió anteriormente. Algunos ejemplos no restrictivos de grupos ariloxi apropiados incluyen fenoxi y naftoxi. El enlace al resto principal es a través de oxígeno de éter.

"Aralquiloxi" se refiere a un grupo aralquil–O– en el cual el grupo aralquilo es tal como se describió anteriormente. Algunos ejemplos no restrictivos de grupos aralquiloxi apropiados incluyen benciloxi y 1– o 2–naftalenmetoxi. El enlace al resto principal es a través de oxígeno de éter.

"Alquiltio" se refiere a un grupo alquil–S– en el cual el grupo alquilo es tal como se describió anteriormente. Algunos ejemplos no restrictivos de grupos alquiltio apropiados incluyen metiltio y etiltio. El enlace al resto principal es a través de azufre.

"Ariltio" se refiere a un grupo aril–S– en el cual el grupo arilo es tal como se describió anteriormente. Algunos ejemplos no restrictivos de grupos ariltio apropiados incluyen feniltio y naftiltio. El enlace al resto principal es a través de azufre.

"Aralquiltio" se refiere a un grupo aralquil–S– en el cual el grupo aralquilo es tal como se describió anteriormente. Un ejemplo no restrictivo de un grupo aralquiltio apropiado es benciltio. El enlace al resto principal es a través de azufre.

"Alcoxicarbonilo" se refiere a un grupo alquil–O–CO–. Algunos ejemplos no restrictivos de grupos alcoxicarbonilo apropiados incluyen metoxicarbonilo y etoxicarbonilo. El enlace al resto principal es a través de carbonilo.

"Ariloxicarbonilo" se refiere a un grupo aril–O–C(O)–. Algunos ejemplos no restrictivos de grupos ariloxicarbonilo apropiados incluyen fenoxicarbonilo y naftoxicarbonilo. El enlace al resto principal es a través de carbonilo.

"Aralcoxicarbonilo" se refiere a un grupo aralquil–O–C(O)–. Un ejemplo no restrictivo de un grupo aralcoxicarbonilo apropiado es benciloxicarbonilo. El enlace al resto principal es a través de carbonilo.

"Alquilosulfonilo" se refiere a un grupo alquil–S(O_2)–. Los grupos preferidos son aquellos en los cuales el grupo alquilo es alquilo inferior. El enlace al resto principal es a través de sulfonilo.

"Arilsulfonilo" se refiere a un grupo aril–S(O_2)–. El enlace al resto principal es a través de sulfonilo.

El término "sustituido" se refiere a que uno o más hidrógenos sobre el átomo designado es reemplazado con una selección del grupo indicado, siempre que la valencia normal del átomo designado en las condiciones existentes no esté excedida, y que la sustitución proporcione un compuesto estable. Las combinaciones de sustituyentes y/o variables están permitidas sólo si dichas combinaciones proporcionan compuestos estables. "Compuesto estable" o "estructura estable" se refieren a un compuesto que es suficientemente robusto para sobrevivir al aislamiento, a un grado útil de pureza, desde una mezcla de reacción, y que permite su formulación en un agente terapéutico eficaz.

El término "sustituido en forma opcional" se refiere a la sustitución opcional con los grupos, radicales o restos especificados.

Los términos "purificado", "en forma purificada" o "en forma aislada y purificada", aplicados a un compuesto, se refieren al estado físico de dicho compuesto luego de su aislamiento desde un proceso de síntesis (por ejemplo, a partir de una mezcla de reacción), o fuente natural o combinación de los mismos. Por lo tanto, los términos "purificado", "en forma purificada" o "en forma aislada y purificada", aplicados a un compuesto, se refieren al estado físico de dicho compuesto luego de su obtención desde un proceso o procesos de purificación

descriptos en la presente o bien conocidos por el experto en la técnica (por ejemplo, cromatografía, recristalización y similares), con un grado de pureza suficiente que puede ser calificado por técnicas analíticas estándares descriptas en la presente o bien conocidas por el experto en la técnica.

Además, cabe destacar que cualquier carbono así como también cualquier heteroátomo con valencias no satisfechas en el texto, esquemas, ejemplos y en la Tablas de la presente se presume que tiene la cantidad suficiente de átomos de hidrógeno para satisfacer las valencias.

Cuando un grupo funcional en un compuesto se denomina "protegido", se refiere a que el grupo está en forma modificada para excluir reacciones secundarias indeseadas en el sitio protegido cuando el compuesto es sometido a una reacción. Los grupos protectores apropiados serán reconocidos por los expertos en la técnica como así también mediante referencia a la bibliografía estándar tal como, por ejemplo, T. W. Greene *y col., Protective Groups in organic Synthesis* (1991), Wiley, New York.

Cuando una variable (por ejemplo, arilo, heterociclo, R^2, etcétera) aparece más de una vez en cualquier constituyente o en cualquiera de las Fórmulas A–J, su definición en cada caso es independiente de su definición en cada otra aparición.

Según se usa en la presente, el término "composición" tiene como objeto abarcar un producto que comprende los ingredientes especificados en las cantidades especificadas, así como también cualquier producto que resulta, directamente o indirectamente, de la combinación de los ingredientes especificados en las cantidades especificadas.

Las prodrogas y solvatos de los compuestos de la invención también están contemplados en la presente invención. Una descripción sobre prodrogas es

divulgada por T. Higuchi y V. Stella, *Pro–drugs as Novel Delivery Systems* (1987) 14 de A.C.S. Symposium Series, y en *Bioreversible Carriers in Drug Design,* (1987) Edward B. Roche, ed., American Pharmaceutical Association and Pergamon Press. El término "prodroga" se refiere a un compuesto (por ejemplo, un precursor de droga) que se transforma *in vivo* para producir un compuesto de cualquiera de las Fórmulas A–J o una sal, hidrato o solvato del compuesto, aceptables para uso farmacéutico. La transformación puede ocurrir por varios mecanismos (por ejemplo, por procesos metabólicos o químicos) tales como, por ejemplo, a través de hidrólisis en sangre. El uso de prodrogas es descripto por T. Higuchi y W. Stella, "Pro–drugs as Novel Delivery Systems," Vol. 14 de A.C.S. Symposium Series, y en Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

Por ejemplo, si un compuesto de cualquiera de las Fórmulas A–J o una sal, hidrato o solvato del compuesto, aceptables para uso farmacéutico, 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), alcanoiloximetil (C_2–C_{12}), 1–(alcanoiloxi)etil que tiene desde 4 hasta 9 átomos de carbono, 1–metil–1–(alcanoiloxi)–etil que tiene desde 5 hasta 10 átomos de carbono, alcoxicarboniloximetilo que tiene desde 3 hasta 6 átomos de carbono, 1–(alcoxicarboniloxi)etilo que tiene desde 4 hasta 7 átomos de carbono, 1–metil–1–(alcoxicarboniloxi)etilo que tiene desde 5 hasta 8 átomos de carbono, N–(alcoxicarbonil)aminometilo que tiene desde 3 hasta 9 átomos de carbono, 1–(N–(alcoxicarbonil)amino)etilo que tiene desde 4 hasta 10 átomos de carbono, 3–ftalidilo, 4–crotonolactonilo, gama–butirolacton–4–ilo, di–N,N alquilamino–(C_1–C_2)alquilo(C_2–C_3) (tal como, por ejemplo, β–

dimetilaminoetilo), carbamoil–alquilo(C_1–C_2), N,N–dialquilcarbamoil(C_1–C_2)–alquilo(C1–C2) y piperidin–, pirrolidin– o morfolinalquilo (C_2–C_3), y similares.

Del mismo modo, si un compuesto de cualquiera de las Fórmulas A–J contiene un grupo alcohol funcional, se puede formar 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–(alcanoiloxi(C_1–C_6))etilo, 1–metil–1–(alcanoiloxi(C_1–C_6))etilo, alcoxicarboniloximetilo (C_1–C_6), N–alcoxicarbonilaminometilo(C_1–C_6), succinoilo, alcanoilo(C_1–C_6), α–amino(C_1–C_4)alcanilo, arilacilo y α–aminoacilo, o α–aminoacil–α–aminoacilo, donde cada grupo α–aminoacilo está seleccionado en forma independiente entre los L–aminoácidos naturales, $P(O)(OH)_2$, $–P(O)(Oalquilo(C_1–C_6))_2$ o glicosilo (el radical proviene de la remoción de un grupo hidroxilo de la forma hemiacetal de un carbohidrato), y similares.

Si un compuesto de cualquiera de las Fórmulas A–J incorpora un grupo funcional 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–carbonilo, RO–carbonilo, NRR'–carbonilo, donde R y R' son cada uno en forma independiente alquilo(C_1–C_{10}), cicloalquilo(C_3–C_7), bencilo, o R–carbonilo es un □–aminoacilo natural o □–aminoacilo natural, —C(OH)C(O)OY^1 en el cual Y^1 es H, alquilo(C_1–C_6) o bencilo, —C(OY^2)Y^3 en el cual Y^2 es alquilo(C_1–C_4) e Y^3 es alquilo(C_1–C_6), carboxialquilo(C_1–C_6), aminoalquilo(C_1–C_4) o mono–N—o di–N,N–alquilaminoalquilo(C_1–C_6), —C(Y^4)Y^5 en el cual Y^4 es H o metilo e Y^5 es mono–N— o di–N,N–alquilamino(C_1–C_6)morfolino, piperidin–1–ilo o pirrolidin–1–ilo, y similares.

Uno o más compuestos de la invención pueden existir en formas no solvatadas así como también en formas solvatadas con disolventes aceptables

para uso farmacéutico tales como, por ejemplo, agua, etanol, y similares, y la presente invención abarca ambas formas no solvatada y solvatada. "Solvato" se refiere a una asociación física de un compuesto de la presente invención con una o más moléculas de disolvente. Dicha asociación física implica diversos grados de enlace iónico y covalente, incluyendo el enlace de hidrógeno. En determinados casos, el solvato podrá aislarse, por ejemplo cuando una o más moléculas de disolvente se incorporan a la estructura reticular del sólido cristalino. "Solvato" abarca solvatos de fase en solución y solvatos aislables. Algunos ejemplos no restrictivos de solvatos apropiados incluyen etanolatos, metanolatos, y similares. "Hidrato" es un solvato en el cual la molécula de disolvente es H_2O.

Uno o más compuestos de la invención pueden convertirse en forma opcional en un solvato. La preparación de solvatos es generalmente conocida. De este modo, por ejemplo, M. Caira *y col., J. Pharmaceutical Sci.*, 93(3), 601–611 (2004) describe la preparación de los solvatos del fluconazol antifúngico en acetato de etilo así como también desde agua. Preparaciones similares de solvatos, hemisolvatos, hidratos y similares se describen en E. C. van Tonder *et al, AAPS PharmSciTech.*, 5(1), artículo 12 (2004); y A. L. Bingham *et al*, *Chem. Commun.*, 603–604 (2001). Un proceso no restrictivo típico, incluye disolver el compuesto de la invención en cantidades deseadas del disolvente deseado (orgánico o agua o mezclas de los mismos) a una temperatura superior a la ambiente, y enfriar la solución a un rango suficiente para formar cristales que luego se aíslan mediante métodos estándares. Técnicas analíticas tales como, por ejemplo Espectroscopía I. R., muestran la presencia del disolvente (o agua) en los cristales como un solvato (o hidrato).

El término "cantidad efectiva" o "cantidad efectiva para uso terapéutico" se utiliza para describir una cantidad de compuesto o una composición de la

presente invención, efectiva para inhibir las enfermedades indicadas anteriormente y por lo tanto producir el efecto terapéutico, paliativo, inhibidor o preventivo deseado.

Los compuestos de cualquiera de las Fórmulas A–J pueden formar sales que también están dentro del alcance de esta invención. La referencia a un compuesto de cualquiera de las Fórmulas A–J debe comprenderse incluyendo referencia a las sales del mismo, a menos que se indique lo contrario. El término "sal(es)", como se emplea en la presente, indica sales ácidas formadas con ácidos inorgánicos y/u orgánicos, así como también sales básicas formadas con bases inorgánicas y/u orgánicas. Además, cuando un compuesto de cualquiera de las Fórmulas A–J contiene un resto básico tal como, pero sin limitarse a, una piridina o imidazol, y un resto ácido tal como, pero sin limitarse a, un ácido carboxílico, pueden formarse zwitteriones ("sales internas") y se incluyen dentro del término "sal(es)" como se utiliza en la presente. Se prefieren sales aceptables para uso farmacéutico (es decir, no tóxicas, aceptables para uso fisiológico), aunque también son útiles otras sales. Pueden formarse sales de los compuestos de cualquiera de las Fórmulas A–J, por ejemplo, haciendo reaccionar un compuesto de cualquiera de las Fórmulas A–J 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.

Las sales de adición ácida representativas incluyen acetatos, ascorbatos, benzoatos, bencensulfonatos, bisulfatos, boratos, butiratos, citratos, canforatos, canforsulfonatos, fumaratos, clorhidratos, bromhidratos, yodhidratos, lactatos, maleatos, metansulfonatos, naftalensulfonatos, nitratos, oxalatos, fosfatos, propionatos, salicilatos, succinatos, sulfatos, tartaratos, tiocianatos, toluensulfonatos (también conocidos como tosilatos) y similares. Además, los ácidos que se consideran en general apropiados para la formación de sales útiles

para uso farmacéutico a partir de compuestos farmacéuticos básicos se describen, por ejemplo, en P. Stahl *y col.,* Camille G. (eds.) *Handbook of Pharmaceutical Salts. Properties, Selection and Use.* (2002) Zurich: Wiley–VCH; S. Berge *y col., Journal of Pharmaceutical Sciences* (1977) 66(1) 1–19; P. Gould, *International J. of Pharmaceutics* (1986) 33 201–217; Anderson *y col., The Practice of Medicinal Chemistry* (1996), Academic Press, New York; y en *The Orange Book* (Food & Drug Administration, Washington, D.C. en su sitio Web). Estas descripciones se incorporan a la presente a modo de referencia.

Las sales básicas representativas incluyen sales de amonio, sales de metal alcalino tales como sales de sodio, litio, y potasio, sales de metal alcalino–térreo tales como sales de calcio y magnesio, sales con bases orgánicas (por ejemplo, aminas orgánicas) tales como diciclohexilaminas, t–butil aminas, y sales con aminoácidos tales como arginina, lisina y similares. Los grupos básicos que contienen nitrógeno pueden cuaternizarse con agentes tales como haluros de alquilo inferior (por ejemplo, cloruros de metilo, etilo, y butilo, bromuros y yoduros), sulfatos de dialquilo (por ejemplo, sulfatos de dimetilo, dietilo y dibutilo), haluros de cadena larga (por ejemplo, cloruros, bromuros y yoduros de decilo, laurilo y estearilo), haluros de aralquilo (por ejemplo, bromuros de bencilo y fenetilo), y otros.

Como tales, se desea que dichas sales ácidas y básicas sean sales aceptables para uso farmacéutico dentro del alcance de esta invención y todas las sales ácidas y básicas se consideran equivalentes a las formas libres de los compuestos correspondientes para los propósitos de la invención.

Los ésteres aceptables para uso farmacéutico de los presentes compuestos de la presente incluyen los siguientes grupos: (1) ésteres del ácido carboxílico obtenidos por esterificación de los grupos hidroxi, donde el resto no carbonilo de la porción del ácido carboxílico de la agrupación de éster se

selecciona de alquilo de cadena recta o ramificada (por ejemplo, acetilo, n–propilo, t–butilo, o n–butilo), alcoxialquilo (por ejemplo, metoximetilo), aralquilo (por ejemplo, bencilo), ariloxialquilo (por ejemplo, fenoximetilo), arilo (por ejemplo, fenilo sustituido en forma opcional con, por ejemplo, halógeno, alquilo C_{1-4}, o alcoxi C_{1-4} o amino); (2) ésteres de sulfonato, tales como alquil o aralquilsulfonilo (por ejemplo, metansulfonilo); (3) ésteres de aminoácido (por ejemplo, L–valilo o L–isoleucilo); (4) ésteres de fosfonato y (5) ésteres de mono, di o trifosfato. Los ésteres de fosfato pueden además esterificarse, por ejemplo, mediante un alcohol C_{1-20} o derivado reactivo del mismo, o mediante un 2,3–diacil(C_{6-24}) glicerol.

Los compuestos de cualquiera de las Fórmulas A–J y sus sales, solvatos, hidratos, ésteres y prodrogas, pueden existir en su forma tautomérica (por ejemplo, como una amida o imino éter). Todas dichas formas tautoméricas están contempladas en la presente invención como parte de la misma.

Los compuestos de cualquiera de las Fórmulas A–J pueden contener centros quirales o asimétricos, y por lo tanto existen en diferentes formas estereoisoméricas. Se pretende que todas las formas estereoisoméricas de los compuestos de cualquiera de las Fórmulas A–J, así como también las mezclas de las mismas, que incluyen mezclas racémicas, formen parte de la presente invención. Además, la presente invención abarca todos los isómeros geométricos y posicionales. Por ejemplo, si un compuesto de cualquiera de las Fórmulas A–J incorpora un enlace doble o un anillo fusionado, las formas cis y trans, así como también las mezclas, se consideran dentro del alcance de la invención.

Pueden separarse mezclas diastereoméricas en sus diastereómeros individuales en base a sus diferencias físico–químicas mediante métodos bien conocidos por aquellos con experiencia en la técnica, tales como, por ejemplo, mediante cromatografía y/o cristalización fraccionada. Pueden separarse enantiómeros convirtiendo la mezcla enantiomérica en una mezcla

diastereomérica mediante reacción con un compuesto ópticamente activo apropiado (por ejemplo, auxiliares quirales tales como un alcohol quiral o cloruro de ácido de Mosher), separando los diastereómeros y convirtiendo (por ejemplo, hidrolizando) los diastereómeros individuales en los enantiómeros puros correspondientes. Además, algunos de los compuestos de cualquiera de las Fórmulas A–J pueden ser atropisómeros (por ejemplo, biarilos sustituidos) y se consideran parte de esta invención. Pueden también separarse enantiómeros mediante el uso de una columna de HPLC quiral.

También es posible que los compuestos de cualquiera de las Fórmulas A–J existan en diferentes formas tautoméricas, y todas dichas formas están comprendidas dentro del alcance de la invención. Asimismo, por ejemplo, todas las formas ceto–enol e imina–enamina de los compuestos están incluidas en la invención.

Todos los estereoisómeros (por ejemplo, isómeros geométricos, isómeros ópticos y similares) de los presentes compuestos (que incluyen aquellos de las sales, solvatos, ésteres y prodrogas de los compuestos así como también las sales, solvatos y ésteres de las prodrogas), tales como aquellos que pueden existir a causa 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, se contemplan dentro del alcance de esta invención, como isómeros posicionales (tales como, por ejemplo, 4–piridilo y 3–piridilo). (Por ejemplo, si un compuesto de cualquiera de las Fórmulas A–J incorpora un enlace doble o un anillo fusionado, las formas cis y trans, así como también las mezclas, se consideran dentro del alcance de la invención. Asimismo, por ejemplo, la presente invención incluye todas las formas ceto–enol e imina–enamina de los compuestos). Los estereoisómeros individuales de los compuestos de la presente invención pueden,

por ejemplo, estar sustancialmente libres de otros isómeros, o pueden mezclarse, por ejemplo, como racematos o con otros estereoisómeros seleccionados. Los centros quirales de la presente invención pueden tener la configuración S o R de acuerdo a lo definido por las Recomendaciones *IUPAC* 1974. El uso de los términos "sal", "solvato", "éster", "prodroga" y similares, pretende aplicarse igualmente a la sal, solvato, éster y prodroga de enantiómeros, estereoisómeros, rotámeros, tautómeros, isómeros posicionales, racematos o prodrogas de los compuestos de la invención.

La presente invención también abarca compuestos isotópicamente marcados de la invención que son idénticos a los indicados en la presente, excepto por el hecho de que uno o más átomos se reemplazan mediante un átomo que tiene una masa atómica o un número de masa diferente de la masa atómica o número de masa usualmente hallados en la naturaleza. Los ejemplos de isótopos que pueden incorporarse en compuestos de la invención incluyen isótopos de hidrógeno, carbono, nitrógeno, oxígeno, fósforo, flúor y cloro, tales como ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, y ^{36}Cl, respectivamente.

Ciertos compuestos isotópicamente marcados de cualquiera de las Fórmulas A–J (por ejemplo, aquellos marcados con ^{3}H y ^{14}C) son útiles en el compuesto y/o ensayos de distribución del tejido del substrato. En particular se prefieren los isótopos titulados (es decir, ^{3}H) y carbono–14 (es decir, ^{14}C) por su facilidad de preparación y detectabilidad. Además, la sustitución con isótopos más pesados tales como deuterio (es decir, ^{2}H) puede aportar ciertas ventajas terapéuticas que resultan de una mayor estabilidad metabólica (por ejemplo, aumento de la vida media *in vivo* o reducción de los requerimientos de dosis) y por lo tanto pueden preferirse en algunas circunstancias. Los compuestos isotópicamente marcados de cualquiera de las Fórmulas A–J pueden en general prepararse mediante procedimientos análogos a aquellos divulgados en los

Esquemas y/o en los Ejemplos a continuación, utilizando un reactivo apropiado isotópicamente marcado en lugar de un reactivo no isotópicamente marcado.

Se pretende incluir en la presente invención formas polimórficas de los compuestos de cualquiera de las Fórmulas A–J, y de las sales, solvatos, ésteres y prodrogas de los compuestos de cualquiera de las Fórmulas A–J.

Más específicamente, el tratamiento combinado de la presente invención que comprende primero la administración del agente antimitótico descripto anteriormente, seguido por la administración de los compuestos de cualquiera de las Fórmulas E–K puede ser útil en el tratamiento de una variedad de cánceres, que incluye (pero sin limitarse a) los siguientes: tumor de vejiga, mama (que incluye cáncer de mama por mutación de BRCA), colorectal, colon, riñón, hígado, pulmón (que incluye cáncer de pulmón de células pequeñas y cáncer de pulmón de células no pequeñas), cabeza y cuello, esófago, vejiga, vesícula biliar, ovario, páncreas, estómago, cuello de útero, glándula tiroides, próstata, y piel, incluyendo carcinoma celular escamoso;

leucemia, leucemia linfocítica aguda, leucemia linfoblástica aguda, linfoma de células B, linfoma de células T, linfoma de Hodgkins, linfoma de no Hodgkins, linfoma de células vellosas, linfoma celular de corteza, mieloma y linfoma de Burkett;

leucemia linfocítica crónica ("CLL"),

leucemia mielogenosa aguda y crónica, síndrome mielodisplásico y leucemia promielocítica;

fibrosarcoma, rabdomiosarcoma;

linfoma celular de corteza, mieloma;

astrocitoma, neuroblastoma, glioblastoma, tumores gliales malignos, carcinoma hepatocelular, tumores estromales gastrointestinales ("GIST") y schwannomas;

melanoma, mieloma múltiple, seminoma, teratocarcinoma, osteosarcoma, xenoderma pigmentoso, queratoacantoma, cáncer folicular de tiroides y sarcoma de Kaposi.

El tratamiento combinado de la presente invención puede ser útil en la quimioprevención del cáncer. La quimioprevención se define como la inhibición del desarrollo del cáncer invasivo ya sea bloqueando el evento mutagénico que se inicia o bloqueando la progresión de células pre–malignas que ya han sufrido una agresión o inhibiendo la recaída del tumor.

El tratamiento combinado de la presente invención también puede ser útil para inhibir la angiogénesis y metástasis del tumor.

Algunos ejemplos no restrictivos de agente antimitótico adecuado se seleccionan entre el grupo integrado por taxotero (docetaxel) , taxol (paclitaxel), inhibidores de KSP (tales como, por ejemplo, aquellos de las Fórmulas A–D descriptos en la presente o Ispinesib SB–715992 (Cytokinetics), y el inhibidor de la proteína E asociada al centrosoma ("CENP–E") (por ejemplo, GSK–923295), ABRAXANE® (Abraxis BioScience Inc y AstraZeneca Pharmaceuticals), y epotilona que incluye epotilona A, B o D.

Debería administrarse por lo menos un inhibidor de aurora quinasa de cualquiera de las Fórmulas E–K a continuación de la administración de por lo menos un agente antimitótico o cuando se administra una formulación combinada de por lo menos un agente antimitótico y por lo menos un inhibidor de aurora quinasa, el inhibidor de aurora quinasa se liberaría en el tiempo luego de la liberación del agente antimitótico. Dichas técnicas son conocidas por el experto en la materia como así también por los médicos intervinientes.

Por consiguiente, en un aspecto, la presente invención incluye combinaciones que comprenden una cantidad de uno o más agentes antimitóticos indicados anteriormente y una cantidad de por lo menos un compuesto de

cualquiera de las Fórmulas E–K, o una sal, solvato, éster o prodroga del mismo, aceptables para uso farmacéutico, cuya combinación también incluye un agente de liberación en el tiempo que libera el inhibidor de aurora quinasa luego del agente antimitótico, en cantidades y en un tiempo que produce un efecto terapéutico deseado.

Otro aspecto de la presente invención es un método para inhibir una o más Aurora quinasas en un paciente que lo necesita, que comprende administrar al paciente, una cantidad terapéuticamente efectiva de por lo menos un compuesto de cualquiera de las Fórmulas E–K o una sal, solvato, éster o prodroga del mismo, aceptables para uso farmacéutico, luego de la administración de uno o más agentes antimitóticos descriptos anteriormente.

Otro aspecto de la presente invención es un método para tratar, o demorar el avance de, una enfermedad asociada con una o más Aurora quinasas en un paciente que lo necesita, que comprende administrar una cantidad terapéuticamente efectiva de por lo menos un compuesto de cualquiera de las Fórmulas E–K o una sal, solvato, éster o prodroga del mismo, aceptables para uso farmacéutico luego de la administración de un agente antimitótico descripto anteriormente.

Incluso otro aspecto de la presente invención es un método para tratar una o más enfermedades asociadas con Aurora quinasa, que comprende administrar a un mamífero que necesita dicho tratamiento una cantidad de un primer compuesto, que es un agente antimitótico o una sal, solvato, éster o prodroga del mismo, aceptables para uso farmacéutico; y una cantidad de por lo menos un segundo compuesto, cuyo segundo compuesto es un compuesto de cualquiera de las Fórmulas E–K, en el cual las cantidades del primer compuesto y del segundo compuesto producen un efecto terapéutico.

Otro aspecto de la presente invención es un método para tratar, o demorar

el avance de, una enfermedad asociada con una o más Aurora quinasas en un paciente que lo necesita, que comprende administrar un agente antimitótico y a continuación una cantidad terapéuticamente efectiva de una composición farmacéutica que comprende en combinación por lo menos un portador aceptable para uso farmacéutico y por lo menos un compuesto de acuerdo con cualquiera de las Fórmulas E–K, o una sal, solvato, éster o prodroga del mismo, aceptables para uso farmacéutico.

En los métodos anteriores, la Aurora quinasa que ha de inhibirse puede ser Aurora B y/o Aurora A/B, A/B/C, o B/C.

Las propiedades farmacológicas de las composiciones farmacéuticas que comprenden por separado por lo menos un agente antimitótico y por lo menos un compuesto de cualquiera de las Fórmulas E–K, o una sal, solvato, éster o prodroga, aceptables para uso farmacéutico, de dicho compuesto y por lo menos un portador aceptable para uso farmacéutico pueden confirmarse a través de una variedad de ensayos farmacológicos. Los ensayos farmacológicos representativos que se describen en la presente a continuación se han llevado a cabo con composiciones farmacéuticas de acuerdo con la invención.

La presente invención se refiere además a composiciones farmacéuticas que comprenden por separado por lo menos un agente antimitótico y por lo menos un compuesto de cualquiera de las Fórmulas E–K, o una sal, solvato, éster o prodroga, aceptables para uso farmacéutico, de dicho compuesto y por lo menos un portador aceptable para uso farmacéutico.

Para preparar las composiciones farmacéuticas a partir de los compuestos descriptos por la presente invención, los portadores 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 desde alrededor de 5

hasta alrededor de 95 por ciento del principio activo. Los portadores sólidos adecuados son conocidos en la técnica e incluyen, por ejemplo, carbonato de magnesio, estearato de magnesio, talco, azúcar o lactosa. Los comprimidos, polvos, sellos y cápsulas pueden utilizarse como formas de dosificación sólidas apropiadas para administración oral. Algunos ejemplos de portadores aceptables para uso farmacéutico y métodos de elaboración de diversas composiciones se pueden hallar en A. Gennaro (ed.), *Remington's Pharmaceutical Sciences,* 18th Edition, (1990), Mack Publishing Co., Easton, Pennsylvania.

Las preparaciones en forma líquida incluyen soluciones, suspensiones y emulsiones. A modo de ejemplo se pueden mencionar soluciones en agua o agua–propilenglicol para inyección parenteral o el agregado de edulcorantes y opacadores para soluciones, suspensiones y emulsiones orales. Las preparaciones en forma líquida también pueden incluir soluciones para administración intranasal.

Las preparaciones en aerosol apropiadas para inhalación pueden incluir soluciones y sólidos en forma de polvo, que pueden estar en combinación con un portador aceptable para uso farmacéutico tal como un gas comprimido inerte, por ejemplo nitrógeno.

También se incluyen preparaciones en forma sólida que se pretende convertir, poco antes del uso, a preparaciones en forma líquida para administración oral o parenteral. Tales formas líquidas incluyen soluciones, suspensiones y emulsiones.

Los compuestos de la invención pueden también administrarse en forma transdérmica. Las composiciones transdérmicas pueden adoptar la forma de cremas, lociones, aerosoles y/o emulsiones y pueden incluirse en un parche transdérmico de tipo matriz o reservorio como es convencional en la técnica para este propósito.

Los compuestos de la presente invención también pueden administrarse por vía subcutánea.

Preferentemente, el compuesto se administra por vía oral o intravenosa.

También se contemplan métodos de administración que son combinaciones de los métodos de administración mencionados anteriormente. Dichos métodos son típicamente definidos por los expertos en la técnica.

Preferentemente, la preparación farmacéutica se encuentra en forma de dosis unitaria. En dicha forma, la preparación se subdivide en dosis unitarias de tamaño adecuado que contienen cantidades apropiadas de los componentes activos, por ejemplo, una cantidad efectiva de agente antimitótico y una cantidad efectiva de inhibidor de Aurora quinasa de la Fórmula E – J, para lograr el efecto deseado.

Otro aspecto of la presente invención es un kit que comprende, por separado, una cantidad terapéuticamente efectiva de por lo menos un agente antimitótico y por lo menos un compuesto de cualquiera de las Fórmulas E–K, o una sal, solvato, éster o prodroga, aceptables para uso farmacéutico, de dicho compuesto y un portador, vehículo o diluyente aceptable para uso farmacéutico.

EJEMPLOS DE SÍNTESIS

La síntesis de los compuestos de los párrafos (d), (h), (i), (j) y (k), que no han sido publicados desde la fecha de presentación de la presente solicitud de patente, se incluye a continuación, tal como se declaró respectivamente en la Solicitud de Patente Provisional de EEUU, Serie Nº 60/939963, 60/858244, 60/987932 (y 60/943999), 60/855421 y Registro del Representante Legal Nº OC06760L01 (presentado de la misma fecha adjunta).

La síntesis de los compuestos del párrafo (d) tal como se describe en la Solicitud de EEUU, Serie Nº 60/939963 se indica a continuación.

Método A

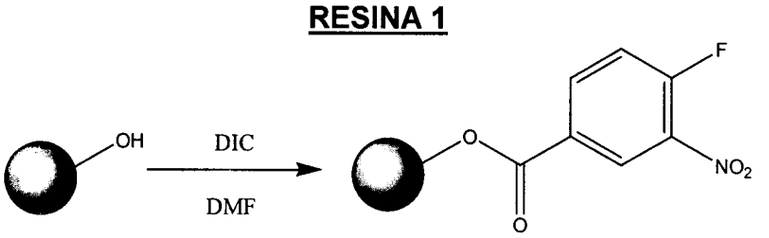
Procedimiento operativo estándar (SOP, según sus siglas en inglés) Para la Síntesis en Fase Sólida de Bencimidazoles

cloruro de 4–Fluoro–3–nitrobenzoílo



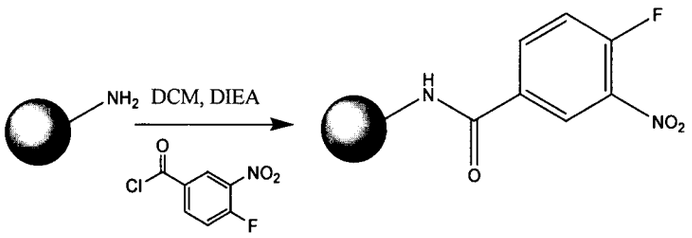
Se disolvió ácido 4–Fluoro–4–nitrobenzoico (277 mg, 1,5 mmol) en DCM (5mL) y se agregó cloruro de oxalilo (630μL, 5 eq.) seguido por 2 μL de DMF. La solución se agitó durante 1 h a temperatura ambiente luego se concentró para proporcionar 1,5 mmol de cloruro de ácido que se almacenó bajo argón y debe usarse fresco en el siguiente paso.

RESINA 1



A resina Wang (3,0 mmol) se agregó DMF (30mL) y ácido 4–fluoro–3–nitrobenzoico (1,66g, 9,0 mmol), DIC (1,4mL, 9,0 mmol) y DMAP (80 mg). La mezcla se agitó hasta la mañana siguiente a temperatura ambiente y se filtró. La resina se lavó con DMF (4x), i–PrOH, DCM (3x cada una), Et_2O y se secó al vacío.

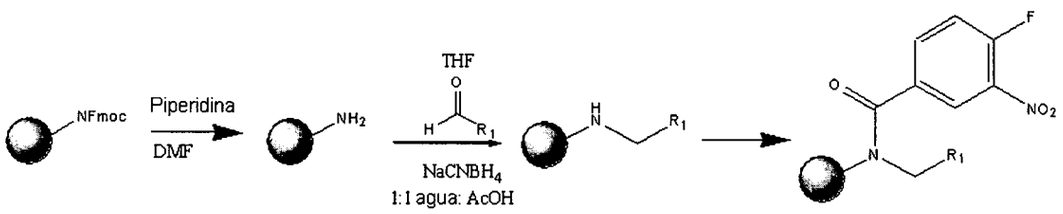
RESINA 2



A resina Rink AM (Novabiochem, 0,4 mmol) se agregó una mezcla de piperidina y DMF (6mL, 50%) y la mezcla se agitó durante 45 min y se filtró. La resina se lavó meticulosamente con DMF, i–PrOH, DCM (3x cada una), Et_2O y se secó.

A la resina se agregó DCM (5mL), DIEA (315μL, 1,8 mmol) y cloruro de 4–Fluoro–3–nitrobenzoílo (1,5 mmol) recién preparado en 3mL de DCM. La mezcla se agitó hasta la mañana siguiente a temperatura ambiente y luego se filtró. La resina se lavó con DCM, i–PrOH, DCM (3x cada una), Et_2O y se secó.

RESINA 3



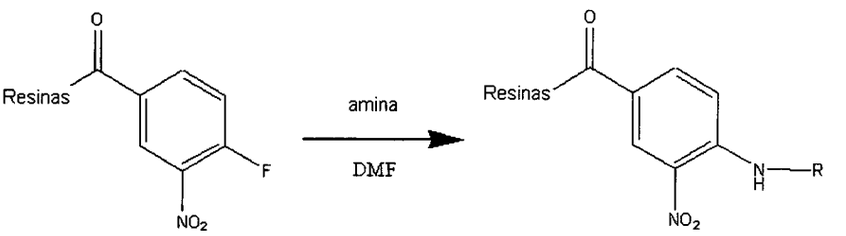
A resina Rink AM (Novabiochem, 0,4 mmol) se agregó una mezcla de piperidina y DMF (6mL, 50%) y la mezcla se agitó durante 45 min y se filtró. La resina se lavó meticulosamente con DMF, i–PrOH, DCM (3x cada una), Et_2O y se secó.

A la resina se agregó THF (8mL), una mezcla de aldehídos (0,4 mmol total) seguido por una mezcla de ácido acético y agua desionizada (50%, 800 μL). La mezcla se agitó durante 5 min y luego se agregó $NaCNBH_3$ en THF (1M, 400 μL). La mezcla se agitó durante 3 horas a temperatura ambiente y se filtró

(manipulando el desperdicio por separado debido a cianoborohidruro). La resina se lavó con THF, H_2O, MeOH, THF, DCM (3x cada una), Et_2O y se secó.

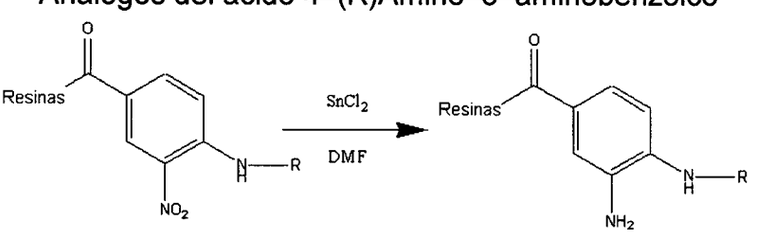
A la resina se agregó DCM (5mL), DIEA (315µL, 1,8 mmol) y cloruro de 4–Fluoro–3–nitrobenzoílo (1,5mmol) recién preparado en 3mL de DCM. La mezcla se agitó hasta la mañana siguiente a temperatura ambiente y luego se filtró. La resina se lavó con DCM, i–PrOH, DCM (3x cada una), Et_2O y se secó.

Análogos del ácido 4–(R)Amino–3–nitrobenzoico



A la resina (0,1 mmol) se agregó DIEA 5% en DMF (1mL) y la amina (2,3 eq.) y la mezcla se agitó hasta la mañana siguiente a temperatura ambiente. A recipientes que contenían componentes básicos de reacción lenta o impedidos, se agregó un componente básico de reacción rápida del mismo conjunto de componentes básicos (5 eq.) y la mezcla se agitó durante 3 h a temperatura ambiente (cubierta). La resina se separó por filtración, se lavó con DMF, i–PrOH, DCM (3x cada una), Et_2O y se secó.

Análogos del ácido 4–(R)Amino–3–aminobenzoico

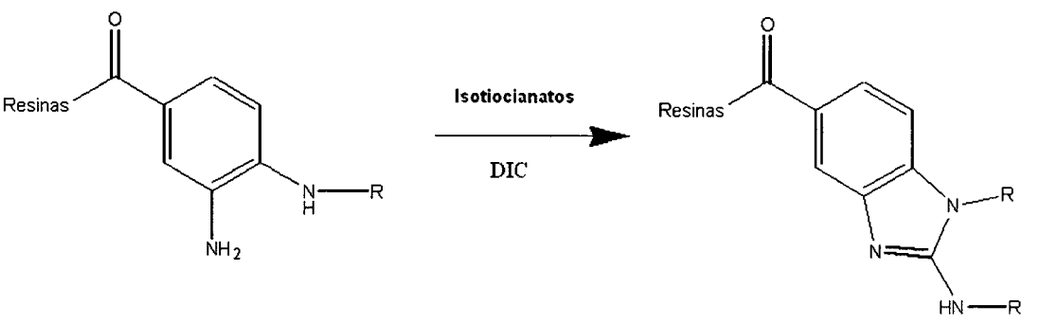


(Para este paso se usaron cloruro de estaño (II) anhidro fresco y DMF)

A la resina (0,1 mmol) se agregó una solución 2M de cloruro de estaño (II) (fresco, anhidro) en DMF (anhidro, 1mL) y la mezcla se agitó hasta la mañana

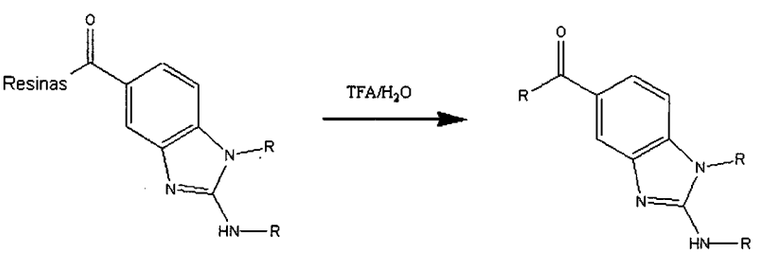
siguiente a temperatura ambiente La resina se separó por filtración, se lavó con DMF, i–PrOH, DCM (3x cada una), Et_2O y se secó.

Análogos de Bencimidazol



A la resina (0,1 mmol) se agregó DMF (0,8 mL) e isotiocianato (0,5 mmol) y la mezcla se agitó durante 1 día a temperatura ambiente. Se inyectó DIC (79μL, 0,5 mmol) y la mezcla se agitó hasta la mañana siguiente a temperatura ambiente. La resina se separó por filtración, se lavó con DMF, i–PrOH, DCM (3x cada una), Et_2O y se secó.

Clivaje



A la resina (0,1–0,2 mmol) se agregó TFA/H_2O (95:5, 1mL) y la mezcla se agitó durante 1 h a temperatura ambiente. La resina se filtró y se lavó con acetonitrilo (2x2mL). El filtrado se concentró al vacío para proporcionar el producto.

Método B

Secuencia de reacción y condiciones similares al protocolo anterior, sin embargo la reacción se llevó a cabo en solución.

Método C

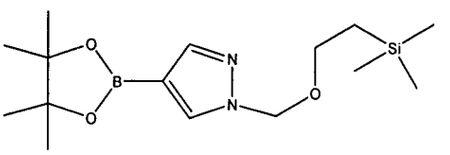
Los compuestos se modificaron adicionalmente luego del paso de clivaje en el Método A.

La síntesis de los compuestos del párrafo (h) tal como se describe en la Solicitud de EEUU, Serie Nº 60/858244 se indica a continuación.

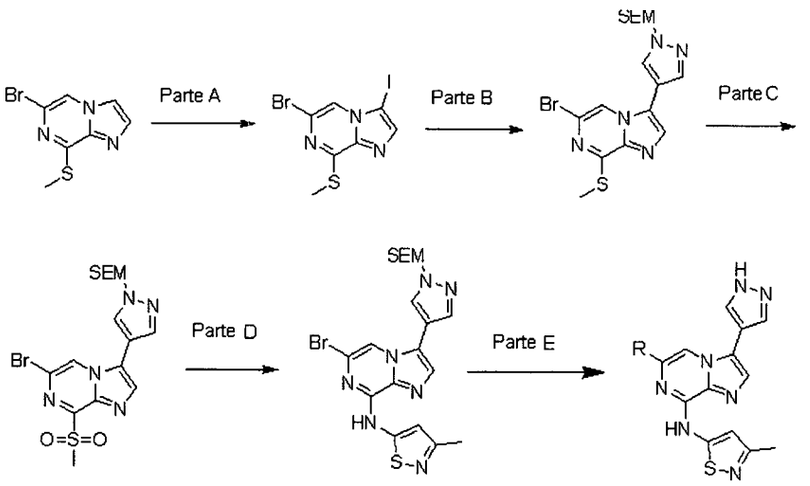
SÍNTESIS DE LOS COMPUESTOS (h):

Ejemplo de preparación 1:

A una suspensión de carbonato de potasio (5,85 g, 1,5 equiv.) y 4–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)–1h–pirazol (5,48 g, 1,0 equiv.) en NMP (50 mL) a temperatura ambiente se agregó SEMCl (5,2 mL, 1,05 equiv.) por goteo (ligeramente exotérmica). La mezcla resultante se dejó agitar durante 45 min adicionales a temperatura ambiente. La reacción se diluyó con acetato de etilo, se enjuagó con agua (2x), salmuera y se secó (sulfato de sodio). La filtración y concentración proporcionó el compuesto del título que se usó sin purificación. MH^+ = 325.



Ejemplo de preparación 2



Parte A

A una solución de bromuro (US2006/0106023) (2,00 g, 8,19 mmol) en DMF (50 mL) se agregó N–yodosuccinimida (1,84 g, 8,19 mmol). La mezcla de reacción se agitó a 60°C durante 16 h. La mezcla se enfrió a temperatura ambiente y se concentró. La purificación por cromatografía en columna (SiO_2, 40% acetato de etilo/hexanos) proporcionó el compuesto 4 en forma de un sólido de color blanco 2,30 g (76%). ^{1}H–RMN(400 MHz, DMSO–d_6) δ 8,3 (s, 1H), 7,8 (s, 1H), 2,6 (s, 3H). MH^+ = 371.

Parte B

Un frasco se cargó con yoduro de la Parte A (1,83 g, 1,00 equiv.), boronato del Ejemplo de preparación 1 (2,08 g, 1,3 equiv.), $PdCl_2$(dppf) (0,4 g, 0,1 equiv.) y fosfato de potasio monohidrato (3,4 g, 3,0 equiv.). Luego de purgar el frasco con argón, se agregaron 1,4–dioxano (50 mL) y agua (5 mL) y la mezcla resultante se calentó a 40°C hasta la mañana siguiente (23 h). La reacción se enfrió hasta temperatura ambiente. Se agregó EtOAc a la mezcla de reacción y se filtró a través de Celite. Luego de la concentración, el residuo se purificó mediante cromatografía en columna (gel de sílice, 25% EtOAc/hexano) para proporcionar el compuesto del título (46%).

Parte C

A una solución del compuesto de la Parte B (1,02 g, 1,0 equiv.) en DCM (10 mL) se agregó *m*–CPBA (1,1 g, 77%, 2,05 equiv.) en una porción. La mezcla de reacción se agitó a temperatura ambiente durante 30 min. La mezcla se concentró y luego se dividió entre EtOAc y agua. La capa orgánica se lavó con $NaHCO_3$ (ac. sat., dos veces), salmuera y se secó (Na_2SO_4). Luego de la concentración, el compuesto del producto en bruto 6 se usó en el siguiente paso directamente sin purificación posterior.

Parte D

A una solución de clorhidrato de 5–amino–3–metilisotiazol (0,135 g, 1,4 equiv.) en DMSO (9 mL) a temperatura ambiente se agregó NaH (0,11 g de 60% dispersión en aceite, 3,0 equiv.) en una porción. Luego de aproximadamente 10 min, el compuesto de la Parte C (0,30 g, 1,00 equiv.) se agregó en una porción. Luego de 15 min a temperatura ambiente, la reacción se templó con cloruro de amonio ac. sat. y luego se extrajo con acetato de etilo (x2). Las capas orgánicas combinadas se lavaron con agua (x2), salmuera y se secaron (sulfato de sodio). El residuo en bruto se purificó mediante cromatografía proporcionando el compuesto del título (0,18 g. 56%). MH^+ = 506.

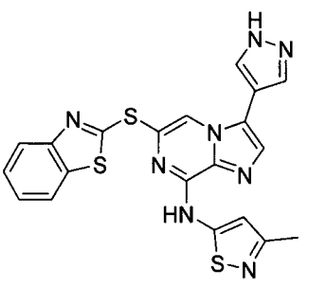
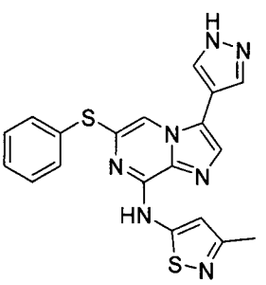
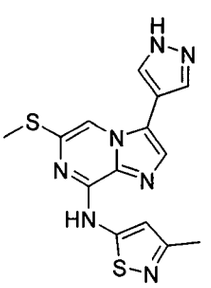
Parte E

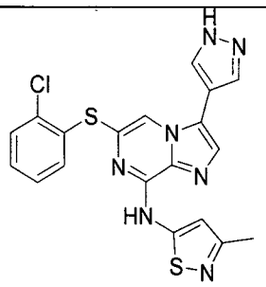
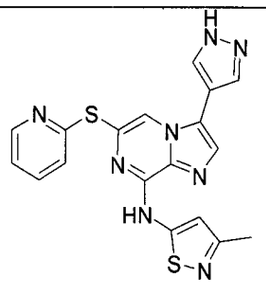
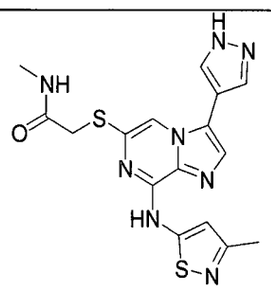
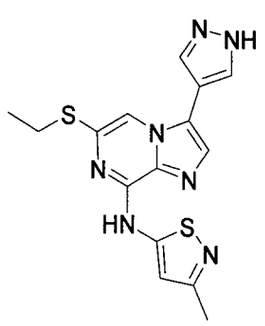
Una mezcla de bromuro del ejemplo de preparación 3, Parte D (30 mg, 0,059 mmol, 1 equiv.), metantiolato de sodio (1,4 equiv.), $PdCl_2$(dppf) (0,07 equiv.), t–butóxido de sodio (1,1 equiv.) en 1,2–dimetoxietano (1mL) se agitó a 85°C bajo Ar durante 16 horas. La mezcla de reacción se enfrió hasta temperatura ambiente, se filtró a través de Celite y el filtrado se concentró. El residuo se retornó en acetato de etilo y se lavó con agua, salmuera, se secó sobre sulfato de sodio anhidro y se concentró para proporcionar el residuo en bruto. MH^+ = 488. Una solución del compuesto en bruto en THF (1 mL) se trató con HCL 4N en

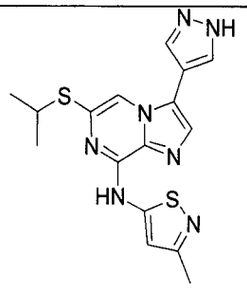
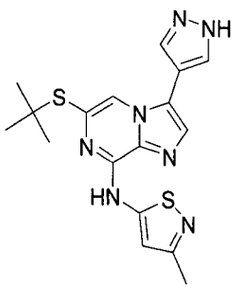
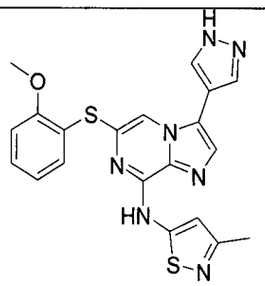
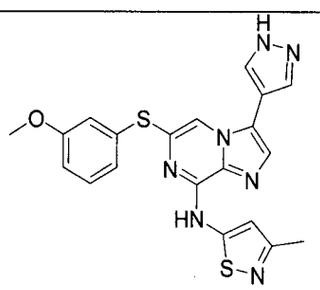
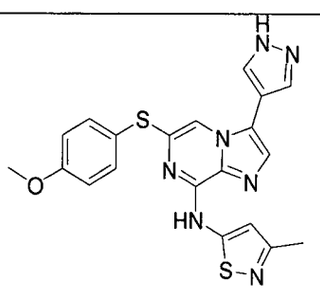
solución de dioxano (1 mL) a 60°C durante 10 min. El disolvente se removió y el residuo se purificó mediante CL–Prep. La conversión a una sal clorhidrica proporcionó el compuesto del título.

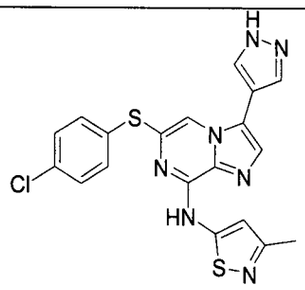
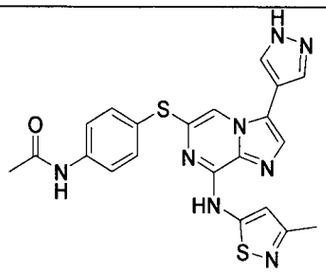
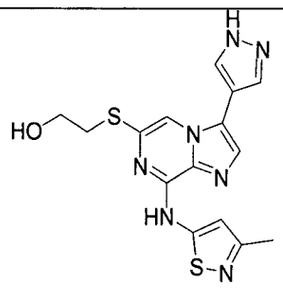
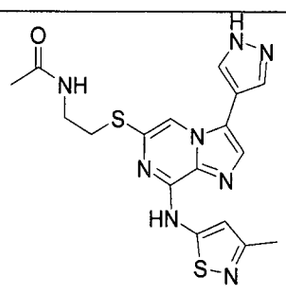
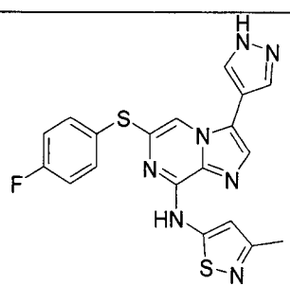
Los compuestos que se ilustrados a continuación en la Tabla A se prepararon realizando básicamente el mismo procedimiento que en el ejemplo de preparación 4.

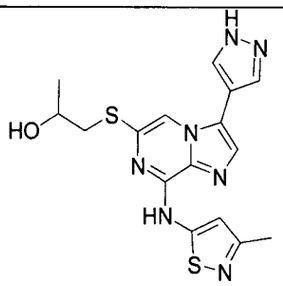
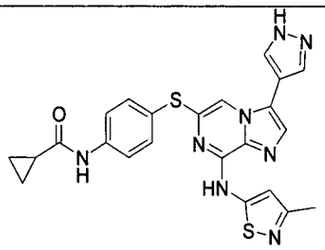
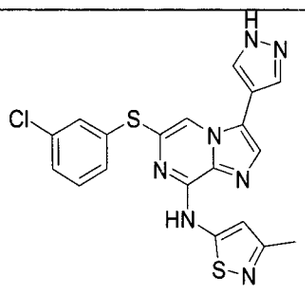
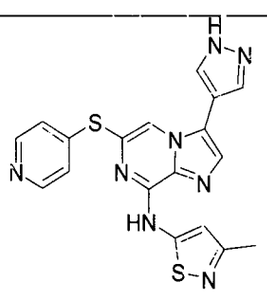
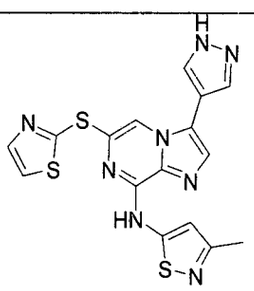
Tabla A

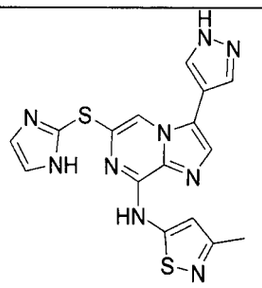
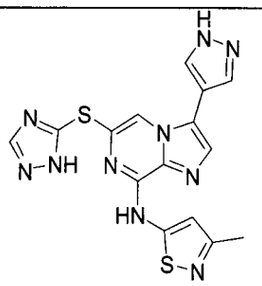
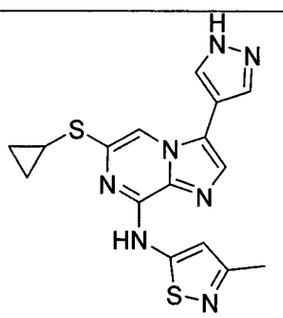
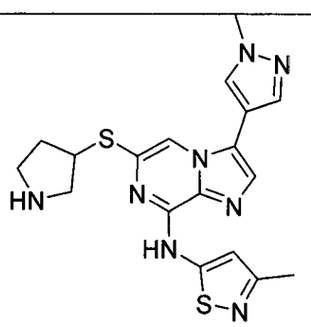
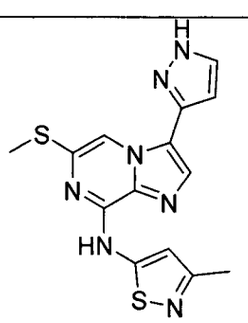
Ejemplo	*Compuesto*	*Masa exacta*	*MS m/z (MH)+*	*HPLC MS t_R*
4–1		462	463	1,45
4–2		405	406	1,38
4–3		343	344	1,12

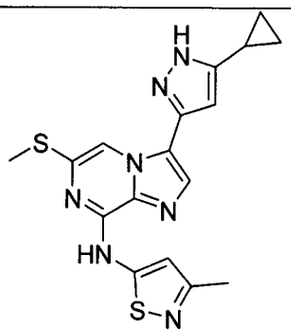
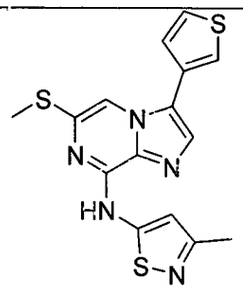
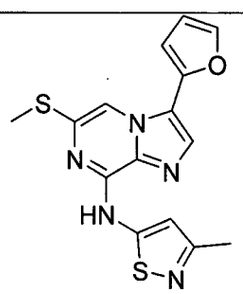
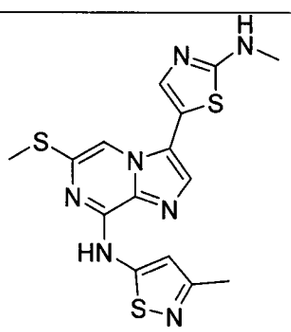
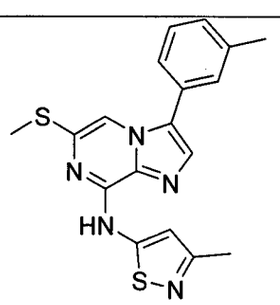
4–4		439,04	440,0	3,75
4–5		406,08	407,0	2,78
4–6		400,09	401,0	2,43
4–7		357,08	358,1	3,17
4–8		371,1	372,1	3,41

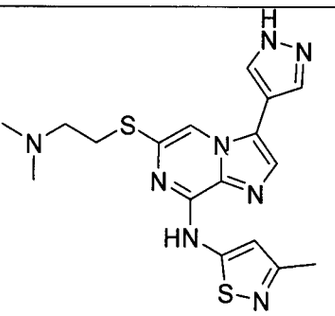
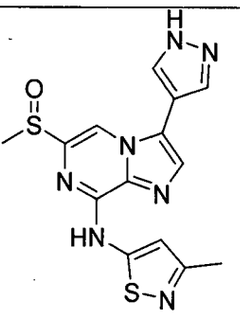
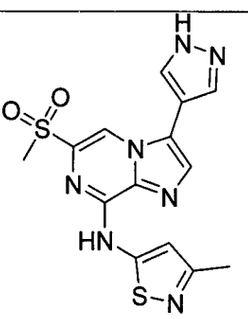
				
4–9		385,1	386,1	3,48
4–10		435,09	436,1	3,40
4–11		435,09	436,1	3,54
4–12		435,09	436,1	3,61

4–13		439,04	440,0	3,91
4–14		462,1	463,1	3,07
4–15		373,08	374,0	2,44
4–16		414,1	415,1	2,53
4–17		423,07	424,1	3,63

4–18		387,09	388,1	2,64
4–19		488,12	489,1	3,44
4–20		439,04	440,0	3,88
4–21		406,08	407,0	2,36
4–22		412,03	413,0	2,89

4–23		395,07	396,1	2,07
4–24		396,07	397,1	2,28
4–25		369,1	370,1	
4–26		412,1	413,1	2,5
4–27		343,1	344,1	1,38

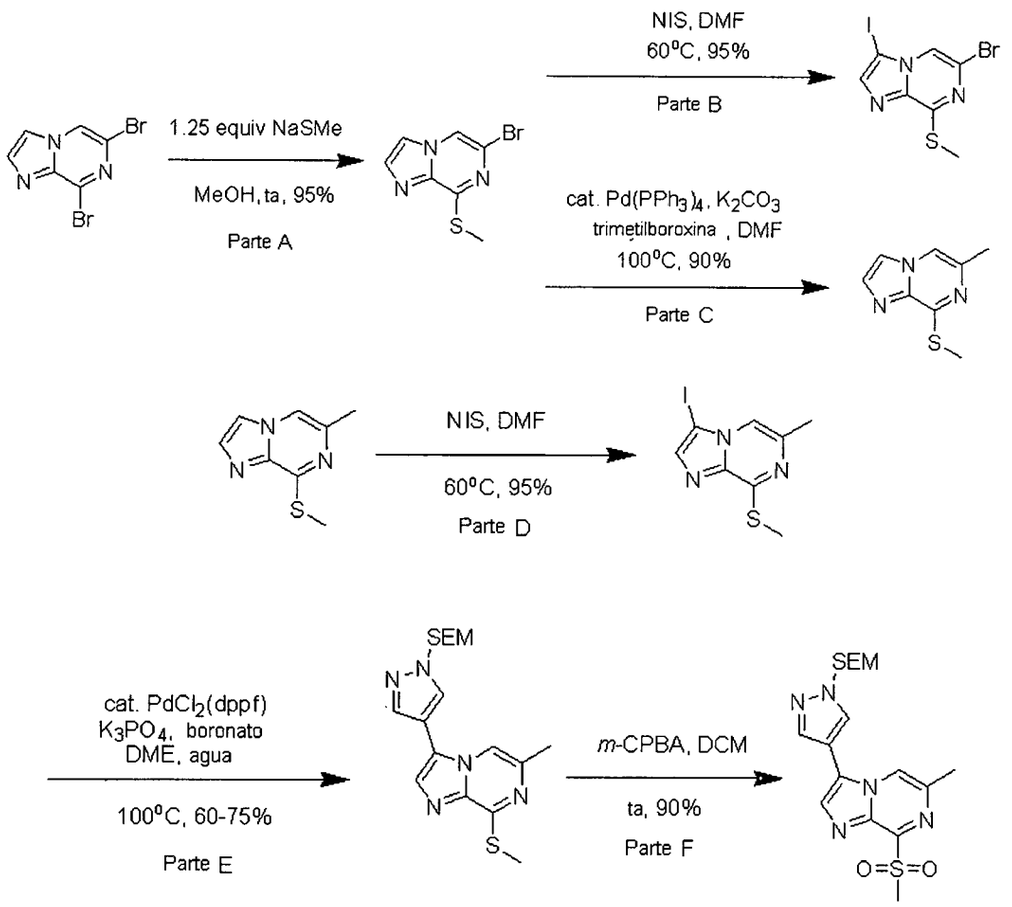
4–28		383,1	384,1	1,48
4–29		395,0	396,0	5,63
4–30		343,1	344,1	5,5
4–31		389,1	390,1	3,8
4–32		367,1	367,1	6,2

4–33		400,1	401,1	0,85
4–34		359,1	360,1	2,6
4–35		375,1	376,1	2,6

SÍNTESIS DE LOS COMPUESTOS DE (i):

La síntesis de los compuestos del párrafo (i) tal como se describe en las Solicitudes de EEUU, Serie Nº 60/943999 presentada el 14 de junio de 2007 y Serie Nº 60/987932, presentada el 14 de noviembre de 2007, se ilustra a continuación.

EJEMPLO 1



Parte A: Preparada de acuerdo con US20060106023 (A1).

Parte B: A una solución del compuesto del Ejemplo 1, Parte A (2,00 g, 8,19 mmol) en DMF (50 mL) se agregó N–yodosuccinimida (1,84 g, 8,19 mmol). La mezcla de reacción se agitó a 60C durante 16 horas. La mezcla se enfrió hasta 25C y se concentró. El residuo se disolvió en DCM con una pequeña cantidad de metanol y luego se cargó sobre la columna. La purificación por cromatografía en columna (SiO_2, 40% acetato de etilo/hexanos) proporcionó el compuesto 4 en forma de un sólido de color blanco 2,30 g (76%). ^{1}H–RMN(400 MHz, DMSO–d_6) δ 8,3 (s, 1H), 7,8 (s, 1H), 2,6 (s, 3H). HPLC–MS t_R = 1,87 Min (UV $_{254nm}$). La masa se calculó para la fórmula $C_7H_5BrIN3S$ 370,01; se observó LC/MS m/z 370,9 (M+H).

Parte C: Una suspensión de bromuro de la Parte B (45,6 g), Pd(PPh3)4 (10,8 g), carbonato de potasio (77,4 g), trimetilboroxina (46,9 g) y carbonato de potasio (77,4 g) en DMF (410 mL) se calentó hasta la mañana siguiente bajo nitrógeno a 105C. Luego de enfriarse, la mezcla se diluyó con acetato de etilo (1 L), se lavó con salmuera (2 x 500 mL), se secó (sulfato de magnesio), se filtró, se concentró y purificó mediante cromatografía en. El compuesto del título se obtuvo en forma de un sólido de color amarillo pálido (21,4 g, 64%).

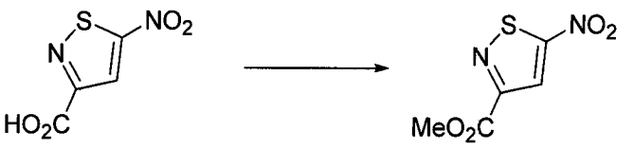
Parte D: A una solución de DMF (400 mL) del compuesto del Ejemplo 1, Parte C (21,8 g) se agregó N–yodosuccinimida (26,9 g) y la mezcla de reacción se calentó hasta la mañana siguiente a 60C. La mezcla se concentró y se agregó agua (400 mL). Luego de agitar durante 1 hora a temperatura ambiente, se agregó carbonato de sodio saturado (250 mL) y posteriormente se agitó durante otros 30 min a temperatura ambiente. La mezcla se filtró, se lavó con agua, metanol (100 mL) y la torta de filtración se secó hasta la mañana siguiente al vacío. Se obtuvo un sólido de color marrón (31,4 g, 87%).

Parte E: Un frasco se cargó con yoduro de la Parte D (1,00 equiv.), Bpin–compuesto 5a (1,3 equiv.), PdCl2(dppf) (0,1 equiv.) y fosfato de potasio monohidrato (3,0 equiv.). Luego de purgar el frasco con argón, se agregaron 1,4–dioxano (50 mL) y agua (5) y la mezcla resultante se calentó a 80C hasta la mañana siguiente (23 h). La reacción se enfrió hasta temperatura ambiente. Se agregó EtOAc a la mezcla de reacción y se filtró a través de Celite. Luego de la concentración, el residuo se purificó mediante cromatografía en columna (gel de sílice, 25% EtOAc/hexano) para proporcionar el compuesto del título.

Parte F: A una solución del compuesto del Ejemplo 1, Parte E (1,0 equiv.) en DCM (10 mL) se agregó *m*–CPBA (2,05 equiv.) en una porción. La mezcla de reacción se agitó a temperatura ambiente durante 30 min. La mezcla se concentró y luego se dividió entre EtOAc y agua. La capa orgánica se lavó con $NaHCO_3$ (ac.

sat., dos veces), salmuera y se secó (Na_2SO_4). Luego de la concentración se obtuvo el compuesto del título y se usó en el siguiente paso directamente sin purificación posterior.

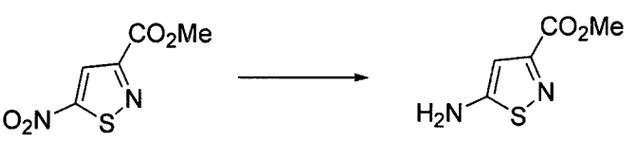
EJEMPLO 2



1 **2**

A una solución de 1[1] (1,04 g, 5,98 mmol) en 20 mL de DMF, se agregó K_2CO_3 (2,48 g, 17,9 mmol) y MeI (1,27 g, 8,96 mmol). La reacción se agitó a temperatura ambiente hasta la mañana siguiente. Se diluyó con 200 mL de 50% EtOAc/hexanos y se lavó con agua (200 mL) y salmuera (100 mL). La capa orgánica se concentró. Al residuo se agregó 20 mL de hexanos. El sólido se recolectó mediante filtración para proporcionar 2. El filtrado se concentró y se purificó mediante cromatografía en columna eluyendo con 25% EtOAc/hexanos para proporcionar una cantidad adicional de 2. El rendimiento combinado de 2 es 1,05 g. ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,37 (s, 1H), 4,05 (s, 3H).

EJEMPLO 3

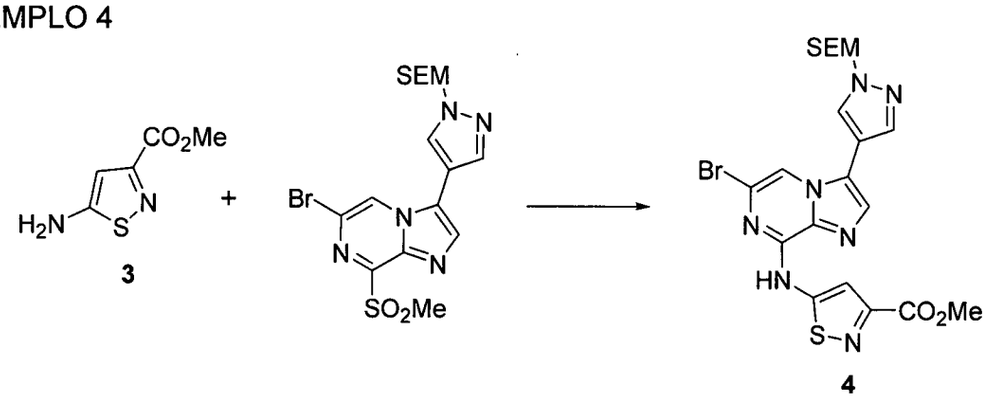


2 **3**

A una solución de 2 (260 mg, 1,38 mmol) en 6 mL de AcOH se agregó polvo de hierro (774 mg, 13,8 mmol). La mezcla de reacción se calentó a 70–75 °C durante 12 min. La mezcla se enfrió hasta temperatura ambiente y luego se agregó 20 mL de MeOH. La mezcla de reacción se filtró a través de Celite (el celite se enjuagó con una cantidad adicional de MeOH). El filtrado se concentró

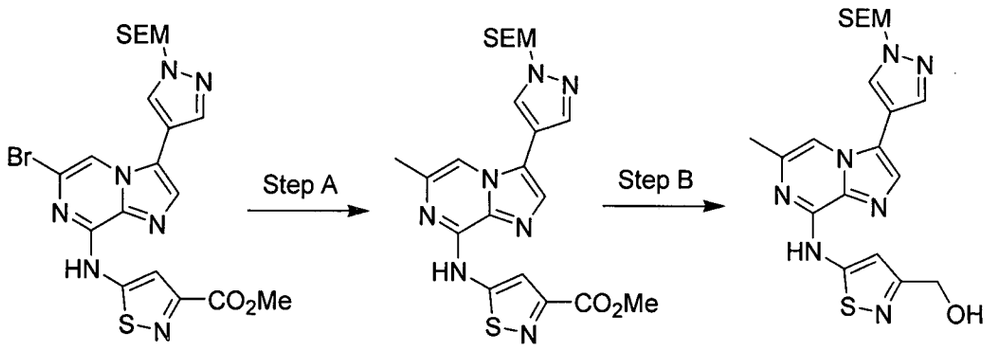
para remover la mayor cantidad de AcOH. Al residuo se agregaron 15 mL de 20% MeOH/CH_2Cl_2 seguido por 20 mL de $NaHCO_3$ acuosa saturada. La mezcla se agitó hasta que dejó de formar burbujas. La mezcla se extrajo por EtOAc (60 mL x 2), se secó sobre Na_2SO_4, y luego se concentró. Al residuo se agregaron 5 mL de éter seguido por 5 mL de hexanos. El sólido se recolectó mediante filtración para proporcionar 160 mg del compuesto en bruto 3 que contiene un poco de amina acilada pero suficientemente pura para la reacción de desplazamiento de sulfonas. El filtrado se purificó mediante cromatografía en columna con 20% de AcOEt/ CH_2Cl_2 para proporcionar una cantidad adicional de 30 mg de 3. ^{1}H RMN (400 MHz, $CDCl_3$) δ 6,85 (s, 1H), 4,61 (s ancho, 2H), 3,92 (s, 3H).

EJEMPLO 4



A una solución del compuesto 3 (89 mg, 0,56 mmol) y 6–bromo–8–metansulfonil–3–[1–(2–trimetilsilanil–etoximetil)–1H–pirazol–4–il]–imidazo[1,2–a]pirazina (258 mg, 0,55 mmol) en 2 mL de DMF, se agregó NaH (60% dispersión en aceite, 44 mg, 1,1 mmol). La reacción se agitó a temperatura ambiente durante 15 min. Se templó con 5 mL de NH_4Cl acuosa saturada y se diluyó con 30 mL de agua. El sólido se recolectó mediante filtración, se lavó con agua y MeOH. Se secó al vacío para proporcionar 255 mg del compuesto 4. ^{1}H RMN (400 MHz, DMSO–d_6) δ 8,85 (s, 1H), 8,22 (s, 1H), 8,15 (s, 1H), 7,96 (s, 1H), 7,62 (s, 1H), 5,50 (s, 2H), 3,85 (s, 3H), 3,60 (t, 2H), 1,83 (t, 2H), 0,00 (s, 9H).

EJEMPLO 5

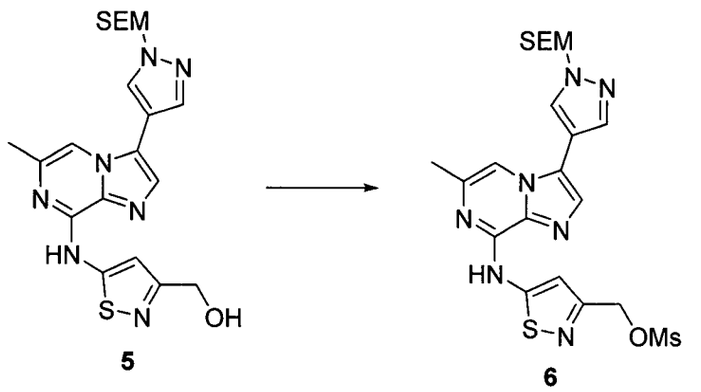


4 5

Paso A: A una solución de 4 (76 mg, 0,14 mmol) en 6 mL de THF se agregó $Pd(PPh_3)_4$ (16 mg, 0,014 mmol) y 0,35 mL de MeZnCl (solución 2 M en THF, 0,69 mmol). La reacción se agitó a 80 °C durante 20 min. Se enfrió hasta temperatura ambiente y se templó agregando 0,5 mL de MeOH. Se diluyó con 30 mL de CH_2Cl_2 y se lavó con 20 mL de solución acuosa de HCL 0,5 N. El disolvente se removió al vacío. El residuo se purificó mediante cromatografía instantánea eluyendo con 5% MeOH/CH_2Cl_2 para proporcionar 50 mg de metil éster del ácido 5–{6–metil–3–[1–(2–trimetilsilanil–etoximetil)–1H–pirazol–4–il]–imidazo[1,2–a]pirazin–8–ilamino}–isotiazol–3–carboxílico contaminado por una pequeña cantidad de óxido de trifenilfosfina.

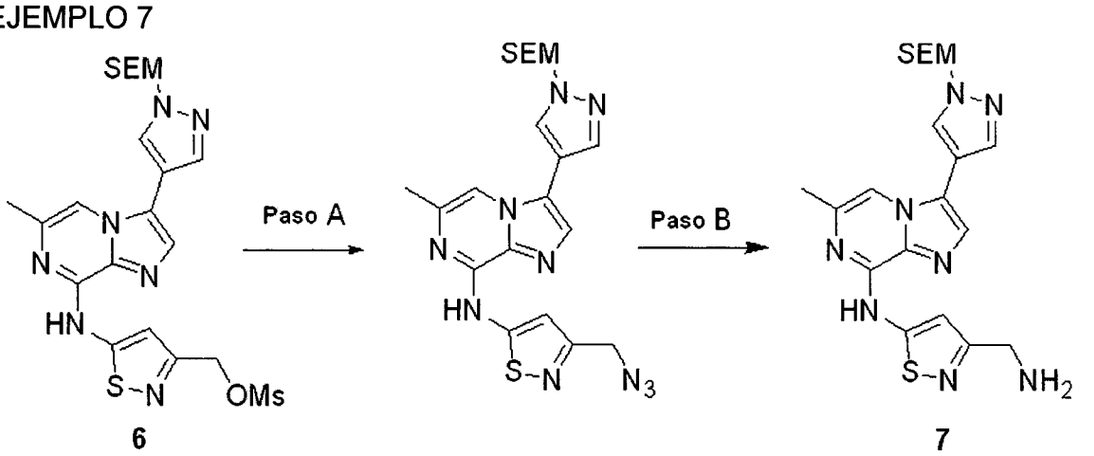
Paso B: El material en bruto anterior se disolvió en 5 mL de THF. A la solución se agregó 0,5 mL de $LiBHEt_3$ (solución 1 M en THF). La reacción se agitó a temperatura ambiente durante 30 min. Se templó agregando 5 mL de solución de acuosa saturada de NH_4Cl. La mezcla se extrajo por 30 mL de CH_2Cl_2. La capa orgánica se concentró y purificó mediante cromatografía instantánea eluyendo con 5% MeOH/CH_2Cl_2 para proporcionar 25 mg del compuesto 5. RMN (400 MHz, $CDCl_3$) δ 7,90 (s, 1H), 7,82 (s, 1H), 7,60 (s, 1H), 7,48 (s, 1H), 6,90 (s, 1H), 5,55 (s, 2H), 4,75 (s ancho, 2H), 3,65 (t, 2H), 2,50 (s, 3H), 1,00 (t, 2H), 0,00 (s, 9H).

EJEMPLO 6



A una solución del compuesto 5 (200 mg, 0,438 mmol) en 20 mL de THF, se agregó trietilamina (0,21 mL, 1,5 mmol) y cloruro de metansulfonilo (0,10 mL, 1,3 mmol). La reacción se agitó a temperatura ambiente durante 30 min. Se templó agregando 1 mL de MeOH. La solución se diluyó por 30 mL de CH_2Cl_2, se lavó consecutivamente con 15 mL de HCl 2 N acuoso, agua, y salmuera. El disolvente se removió al vacío para proporcionar 230 mg del compuesto en bruto 6 que se usó en otras transformaciones sin purificación posterior.

EJEMPLO 7

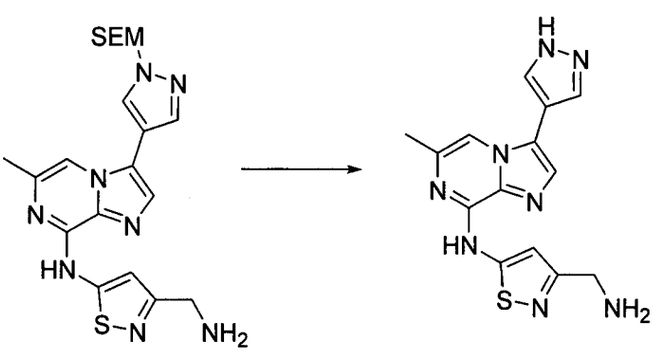


Paso A: La mezcla del compuesto 6 (17 mg, 0,032 mmol) y azida de sodio (15 mg, 0,23 mmol) en 1 mL de DMF se calentó a 70 °C durante 3 h. Se enfrió hasta temperatura ambiente y se agregó 10 mL de agua. El sólido resultante se recolectó mediante filtración y purificó mediante cromatografía instantánea eluyendo con 5% MeOH/CH_2Cl_2 para proporcionar 12 mg de (3–azidometil–

isotiazol–5–il)–{6–metil–3–[1–(2–trimetilsilanil–etoximetil)–1H–pirazol–4–il]–imidazo[1,2–a]pirazin–8–il}–amina.

Paso B: El material anterior se disolvió in 3 mL de MeOH. A la solución se agregó 15 mg de 10% en peso Pd/C. La mezcla se agitó bajo H_2 (1 atm) durante 1 h. Se filtró a través de Celite. El filtrado se concentró al vacío para proporcionar 12 mg del compuesto 7. RMN (400 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.80 (s, 1H), 7.60 (s, 1H), 7.47 (s, 1H), 6.86 (s, 1H), 5.55 (s, 2H), 4.00 (s ancho, 2H), 3.65 (t, 2H), 2.50 (s, 3H), 1.00 (t, 2H), 0,00 (s, 9H).

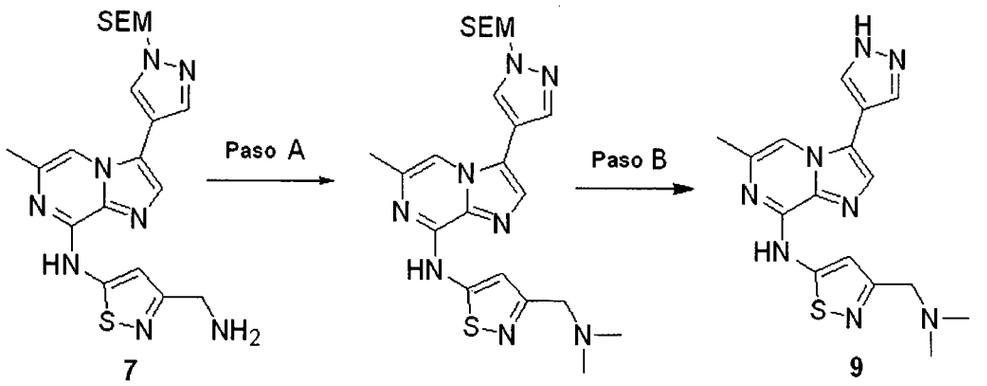
EJEMPLO 8



7 **8**

A una solución del compuesto 7 (12 mg, 0,026 mmol) en 2 mL de THF calentada a 70 °C, se agregó 0,5 mL de HCl 4 N en dioxano. A la mezcla de reacción se agregó MeOH hasta que la misma resultó homogénea. La reacción se agitó a 70 °C durante 1 h y luego se enfrió hasta temperatura ambiente. El sólido se recolectó mediante filtración y se lavó con éter para proporcionar 9 mg del compuesto 8 como su sal HCl. RMN (400 MHz, CD_3OD) δ 8,23 (s, 1H), 8,20 (s, 2H), 8,03 (s, 1H), 7,20 (s, 1H), 4,22 (s, 2H), 2,59 (s, 3H). HPLC–MS t_R = 1,82 min (UV $_{254nm}$). La masa se calculó para la fórmula $C_{14}H_{14}N_8S$ 326,1; se observó MH^+ (LCMS) 327,2 (m/z).

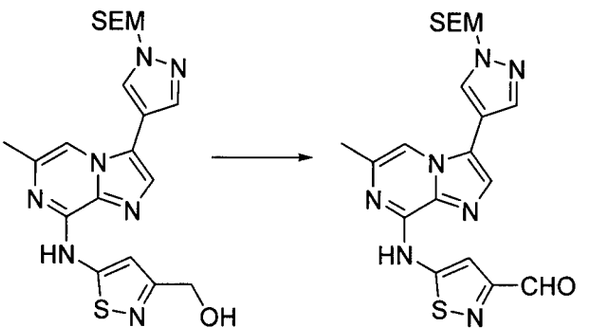
EJEMPLO 9



Paso A: A una solución del compuesto 7 (9 mg, 0,02 mmol) en 1 mL de $MeOH/CH_2Cl_2$ (1:1), se agregó formaldehido (40% en peso en agua, 6 mg, 0,2 mmol). Se agitó a temperatura ambiente durante 15 min, en cuyo tiempo se agregó $NaBH_4$ (16 mg, 0,4 mmol) en dos porciones. La mezcla se purificó mediante cromatografía instantánea eluyendo con NH4Cl (ac.)/$MeOH/CH_2Cl_2$ (1:5:190) para proporcionar 5 mg de (3–dimetilaminometil–isotiazol–5–il)–{6–metil–3–[1–(2–trimetilsilanil–etoximetil)–1H–pirazol–4–il]–imidazo[1,2–a]pirazin–8–il}–amina.

Paso B: El material anterior luego se disolvió en 2 mL de THF. La solución resultante se calentó a 70 °C en cuyo tiempo se agregó 0,5 mL de HCl 4 N en dioxano. A la mezcla de reacción se agregó 1 mL de MeOH. La reacción se agitó a 70 °C durante 1 h y luego se enfrió hasta temperatura ambiente. La mayor parte del disolvente se removió al vacío. Al residuo se agregó 5 mL de éter. El sólido se recolectó mediante filtración y se lavó con éter para proporcionar 5 mg del compuesto 9 como su sal HCl. RMN (400 MHz, CD_3OD) δ 8,21 (s, 1H), 8,18 (s, 2H), 8,08 (s, 1H), 7,30 (s, 1H), 4,42 (s, 2H), 2,95 (s, 6H), 2,59 (s, 3H). HPLC–MS t_R = 2,04 min (UV_{254nm}). La masa se calculó para la fórmula $C_{16}H_{18}N_8S$ 354,1; se observó MH^+ (LCMS) 355,2 (m/z).

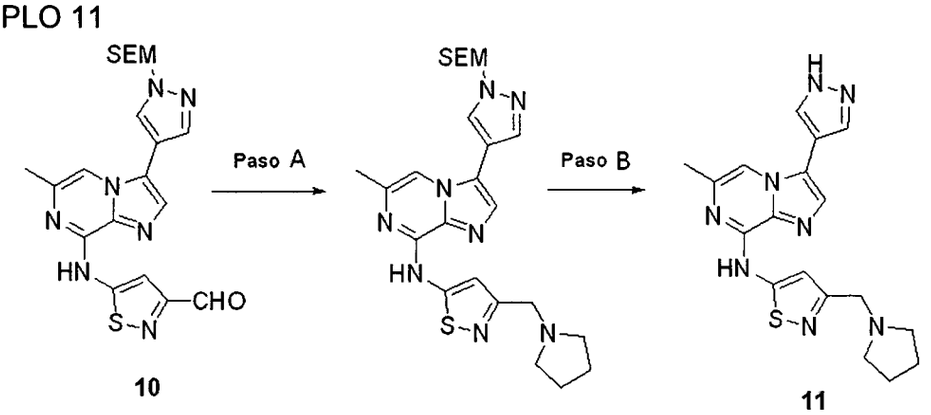
EJEMPLO 10



5 **10**

A una solución del compuesto 5 (2,50 g, 5.47 mmol) en 100 mL de THF, se agregó 0,3 mL de agua seguido por periodinano Dess–Martin (6,96 g, 16,4 mmol). La reacción se agitó a temperatura ambiente durante 30 min. El sólido se separó por filtración. El filtrado se diluyó con 200 mL de CH_2Cl_2, y se lavó con 100 mL de solución acuosa saturada de NH_4Cl. La capa orgánica se secó sobre Na_2SO_4 anhidro y luego se concentró. Al residuo se agregó 30 mL de acetonitrilo. El sólido se recolectó mediante filtración para proporcionar 2,05 g del compuesto 10. RMN (400 MHz, DMSO–d_6) δ 12,38 (s, 1H), 9,84 (s, 1H), 8,60 (s, 1H), 8,11 (s, 1H), 7,96 (s, 1H), 7,91 (s, 1H), 7,55 (s, 1H), 5,50 (s, 2H), 3,60 (t, 2H), 2,45 (s, 3H), 1,83 (t, 2H), 0,00 (s, 9H).

EJEMPLO 11



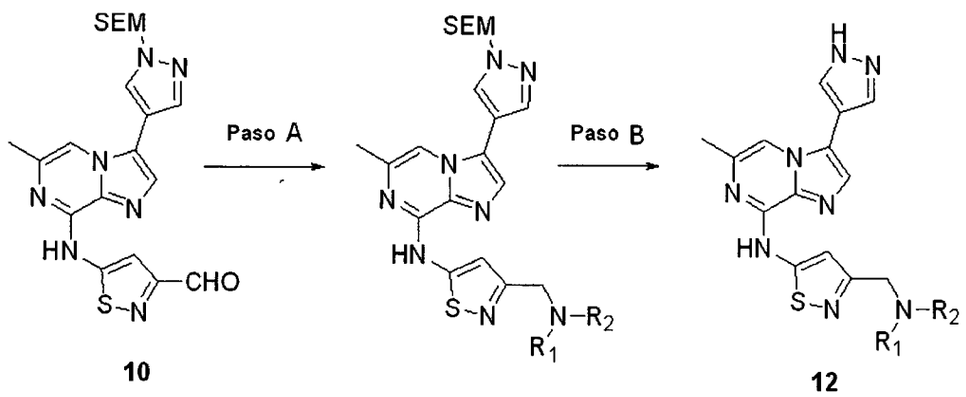
10 **11**

Paso A: Una solución del compuesto 10 (100 mg, 0,220 mmol) y pirrolidina (156 mg, 2,20 mmol) en 14 mL de CH_2Cl_2 se agitó a temperatura ambiente durante 20 min. A la solución se agregó dos gotas de ácido acético, seguido por $NaBH_4$ (67 mg, 1,8 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 5 min en cuyo tiempo se agregó 3 mL de MeOH. La agitación se continuó durante otros 20 min. La reacción se templó agregando 15 mL de solución acuosa saturada de $NaHCO_3$. Luego se diluyó con 20 mL de CH_2Cl_2, la capa orgánica se aisló. El disolvente se removió al vacío. El residuo se purificó mediante cromatografía instantánea eluyendo con NH_4Cl (ac.)/MeOH/CH_2Cl_2 (1:10:190) para proporcionar 98 mg de {6–metil–3–[1–(2–trimetilsilanil–etoximetil)–1H–pirazol–4–il]–imidazo[1,2–a]pirazin–8–il}–(3–pirrolidin–1–ilmetil–isotiazol–5–il)–amina. RMN (400 MHz, $CDCl_3$) δ 7,88 (s, 1H), 7,81 (s, 1H), 7,60 (s, 1H), 7,48 (s, 1H), 6,96 (s, 1H), 5,55 (s, 2H), 3,80 (s, 2H), 3,65 (t, 2H), 2,70 (s ancho, 4H), 2,50 (s, 3H), 1,85 (s ancho, 4H), 0,96 (t, 2H), 0,00 (s, 9H).

Paso B: A una solución de {6–metil–3–[1–(2–trimetilsilanil–etoximetil)–1H–pirazol–4–il]–imidazo[1,2–a]pirazin–8–il}–(3–pirrolidin–1–ilmetil–isotiazol–5–il)–amina (98 mg, 0,19 mmol) en 8 mL de THF calentada a 70 °C, se agregó 2 mL de HCl 4 N en dioxano. A la mezcla de reacción se agregó MeOH hasta que la misma resultó homogénea. La reacción se agitó a 70 °C durante 1 h y luego se enfrió hasta temperatura ambiente. A la mezcla se agregó 3 mL de éter. El sólido se recolectó mediante filtración y se lavó con éter para proporcionar 79 mg del compuesto 11 como su sal HCl. RMN (400 MHz, CD_3OD) δ 8,18 (s, 2H), 8,13 (s, 1H), 8,00 (s, 1H), 7,22 (s, 1H), 4,50 (s, 2H), 3,62–3,68 (m, 2H), 3,06–3,15 (m, 2H), 2,58 (s, 3H), 1,95–2,22 (m, 4H). HPLC–MS t_R = 2,03 min (UV $_{254nm}$). La masa se calculó para la fórmula $C_{18}H_{20}N_8S$ 380,2; se observó MH^+ (LCMS) 381,2 (m/z).

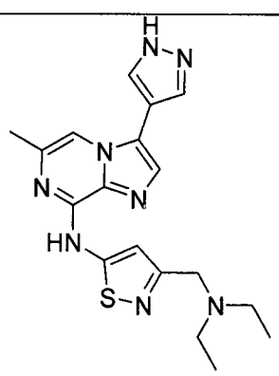
EJEMPLO 12

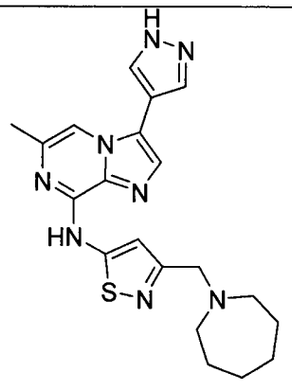
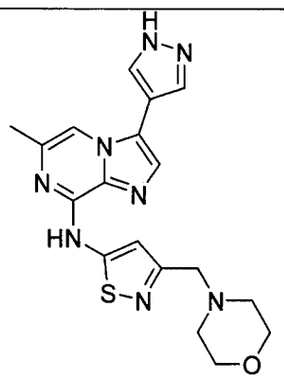
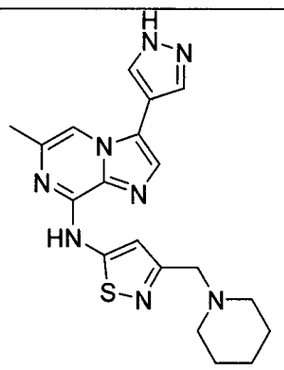
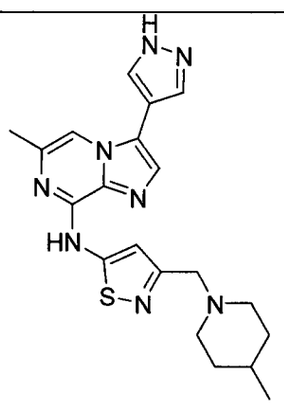
Siguiendo básicamente el mismo procedimiento indicado en el Ejemplo 11, sólo reemplazando pirrolidina con otras aminas alifáticas respectivas en el paso A, se prepararon los compuestos ilustrados en la columna 2 de la Tabla 1 que aparece inmediatamente a continuación.

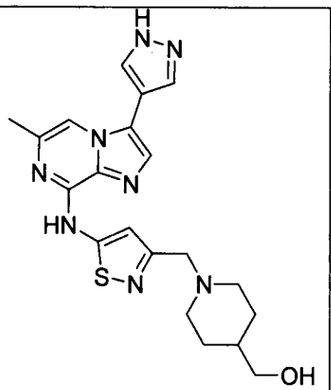
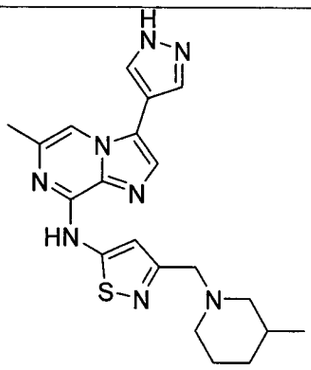
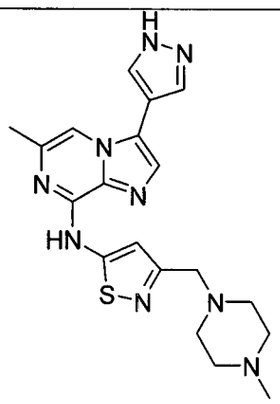
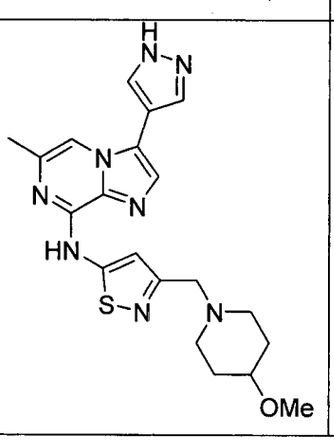


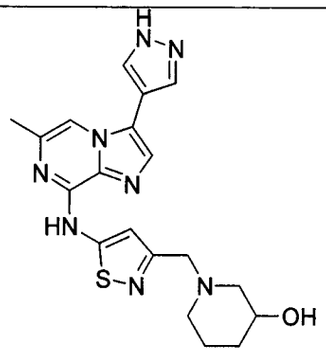
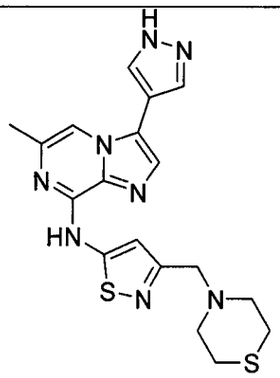
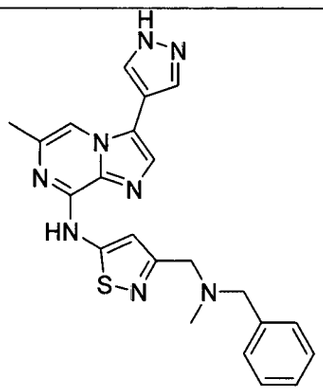
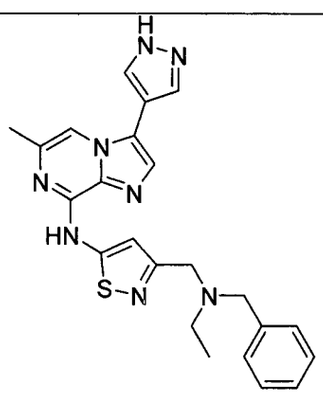
10 **12**

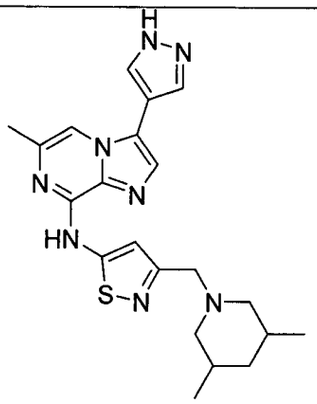
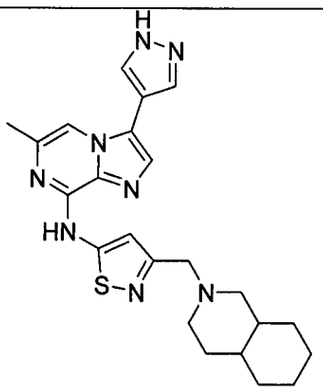
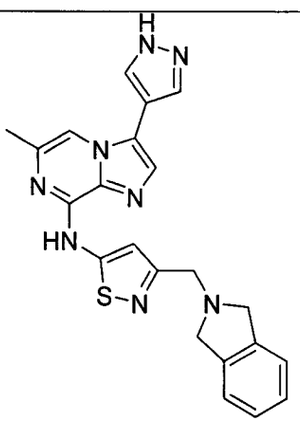
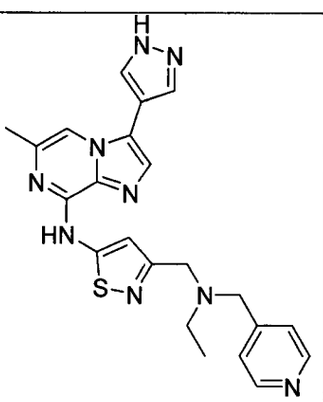
TABLA 1

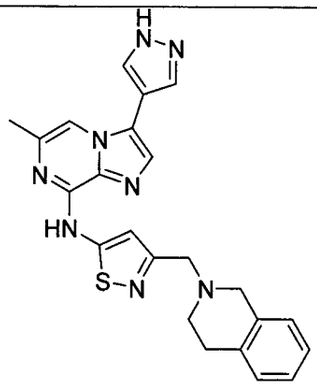
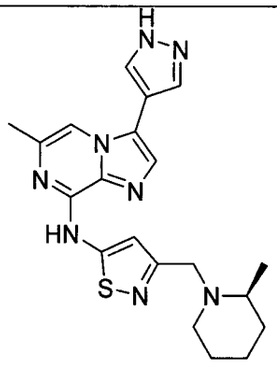
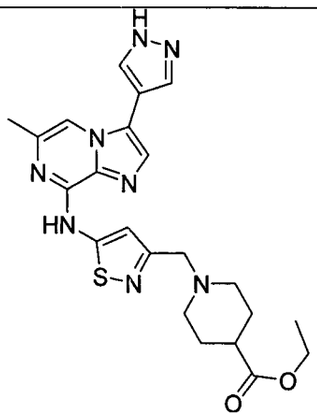
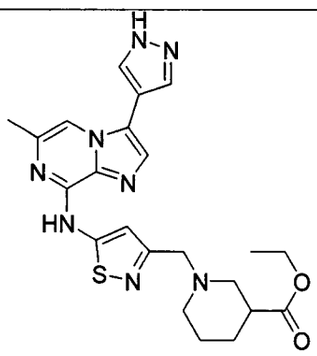
Ejemplo	Columna 2	PM	LCMS MH^+ m/z	HPLC MS t_R
12–1		382,5	383,2	2,15

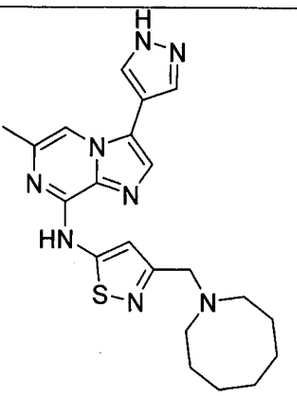
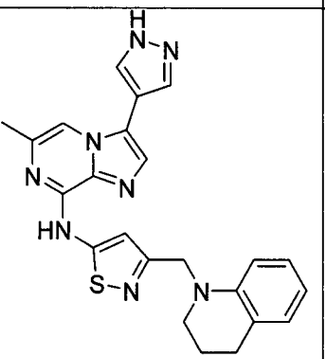
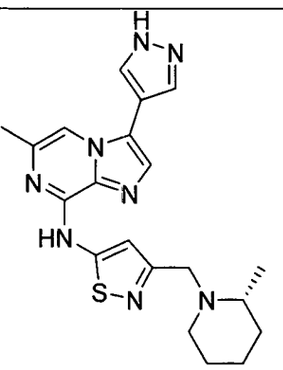
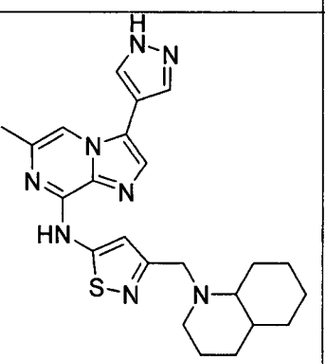
12–2		408,5	409,2	2,31
12–3		396,5	229,2	1,49
12–4		394,5	395,2	2,18
12–5		408,5	409,2	2,26

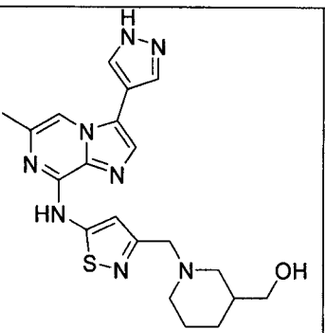
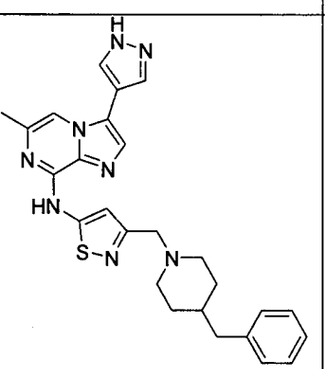
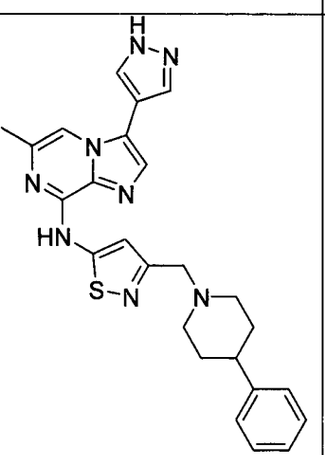
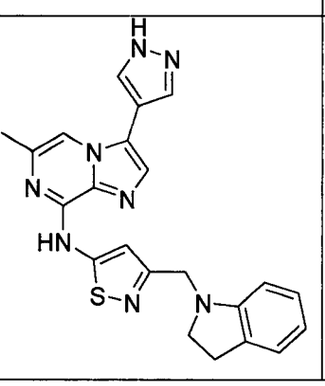
12–6		424,5	425,2	1,95
12–7		408,5	409,2	2,35
12–8		409,5	410,2	1,76
12–9		424,5	425,2	2,18

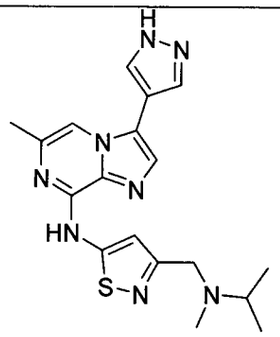
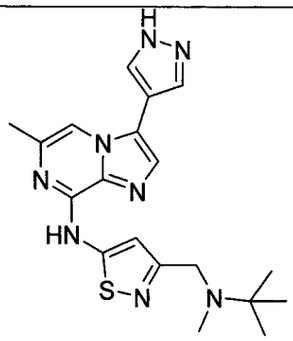
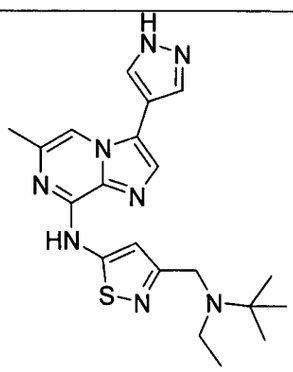
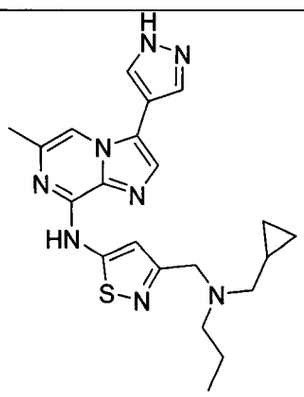
12–10		410,5	411,2	2,04
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12–12		430,5	431,2	2,35
12–13		444,6	445,2	2,40

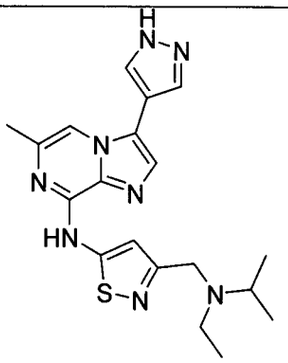
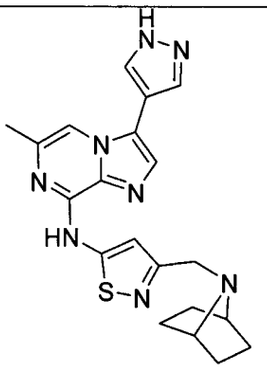
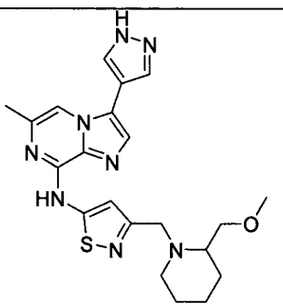
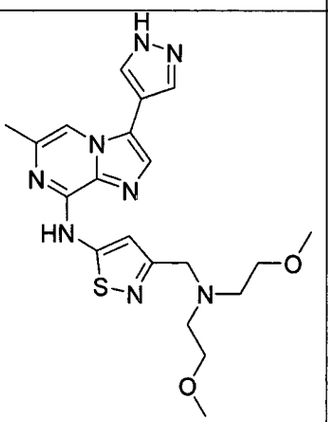
12–14		422,5	423,2	2,50
12–15		448,6	449,2	2,69
12–16		428,5	429,2	2,34
12–17		445,5	446,2	1,76

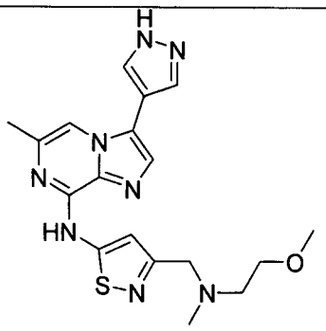
12–18		442,5	443,2	2,39
12–19		408,5	409,2	2,15
12–20		466,6	467,3	2,23
12–21		466,6	467,3	2,24

12–22		422,5	423,2	2,41
12–23		442,5	443,2	3,51
12–24		408,5	409,2	2,32
12–25		448,5	449,2	2,65

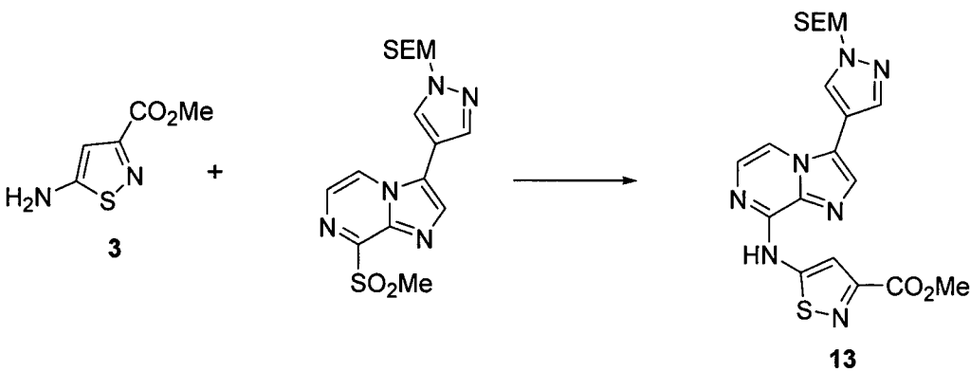
12–26		424,5	425,2	2,07
12–27		484,6	485,3	2,79
12–28		470,6	471,3	2,60
12–29		428,5	429,2	3,27

12–30		382,17	393,17	1,97
12–31		396,18	397,18	2,01
12–32		410,20	411,20	2,04
12–33		422,20	423,20	2,52

12–34		396,18	397,18	2,25
12–35		406,17	407,17	2,24
12–36		438,20	439,20	2,36
12–37		442,19	443,19	2,30

12–38		398,16	399,16	2,12

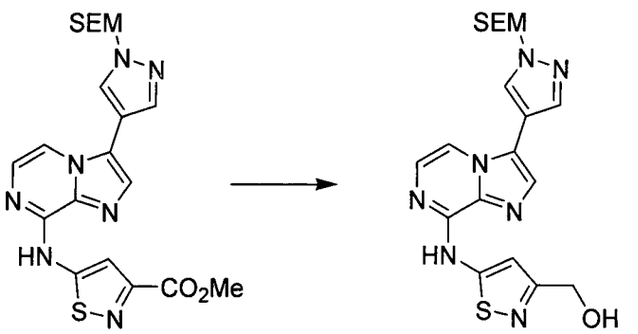
EJEMPLO 13



3 **13**

Se preparó el compuesto 13 siguiendo básicamente el mismo procedimiento indicado en el Ejemplo 4, sólo reemplazando 6–bromo–8–metansulfonil–3–[1–(2–trimetilsilanil–etoximetil)–1H–pirazol–4–il]–imidazo[1,2–a]pirazina con 8–metansulfonil–3–[1–(2–trimetilsilanil–etoximetil)–1H–pirazol–4–il]–imidazo[1,2–a]pirazina. RMN (400 MHz, DMSO–d_6) δ 8,66 (s, 1H), 8,22 (d, 1H), 8,21 (s, 1H), 8,03 (s, 1H), 7,82 (d, 1H), 5,58 (s, 2H), 3,96 (s, 3H), 3,69 (t, 2H), 3,40 (s, 1H), 0,95 (t, 2H), 0,02 (s, 9H).

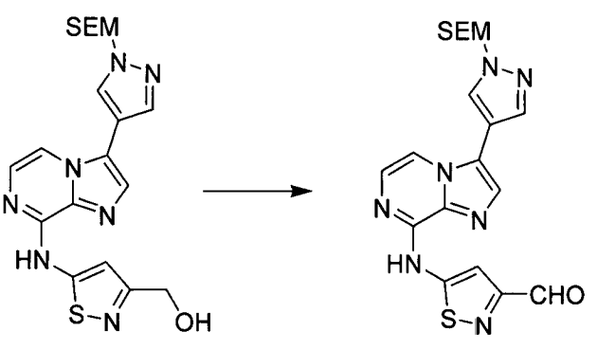
EJEMPLO 14



13 14

A una solución del compuesto 13 (830 mg, 1,76 mmol) en 50 mL de CH_2Cl_2 agitada a 0 °C, se agregó 7,05 mL de $LiBHEt_3$ (solución 1 M en THF). La reacción se agitó a temperatura ambiente durante 10 min. Se templó agregando solución acuosa saturada de NH_4Cl. La capa orgánica se separó y se lavó con solución acuosa saturada de $NaHCO_3$. El disolvente se removió al vacío. Al residuo se agregó 10 mL de MeOH. El sólido se recolectó mediante filtración para proporcionar 530 mg del compuesto 14. RMN (400 MHz, CD_3OD) δ 8,38 (s, 1H), 7,98 (s, 1H), 7,97 (d, 2H), 7,78 (s, 1H), 7,69 (d, 2H), 7,15 (s, 1H), 5,55 (s, 2H), 4,62 (s, 2H), 3,66 (t, 2H), 0,92 (t, 2H), 0,00 (s, 9H).

EJEMPLO 15

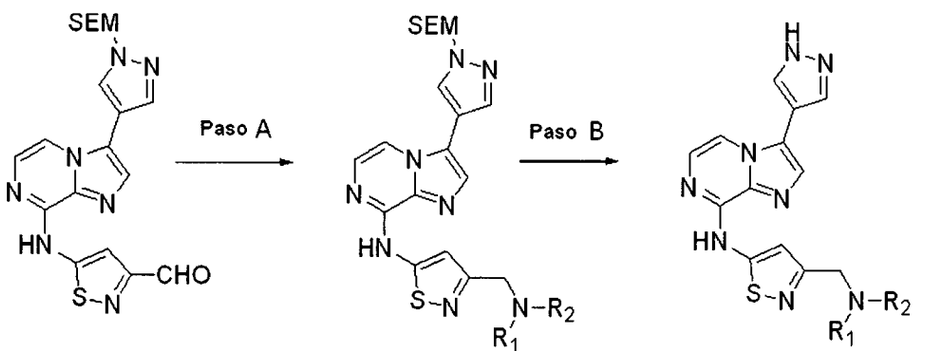


14 15

A una solución del compuesto 14 (258 mg, 0,582 mmol) en 20 mL de THF, se agregó 0,05 mL de agua seguido por periodinano Dess–Martin (740 mg, 1,75 mmol). La reacción se agitó a temperatura ambiente durante 1,5 h. El sólido se

separó por filtración. El filtrado se diluyó con 100 mL de CH_2Cl_2, y se lavó con agua y salmuera. El disolvente se removió al vacío, el residuo se purificó mediante cromatografía instantánea eluyendo con 5% de $MeOH/CH_2Cl_2$ para proporcionar 230 mg del compuesto 15.

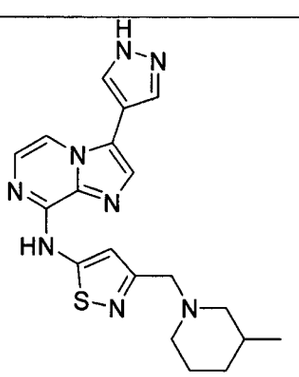
EJEMPLO 16

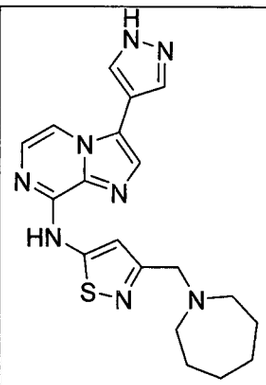
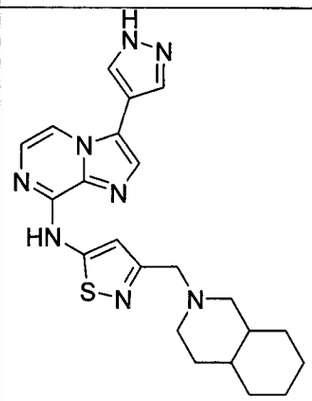
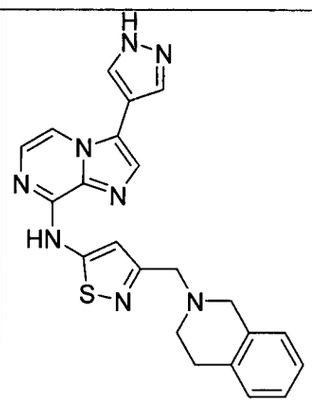
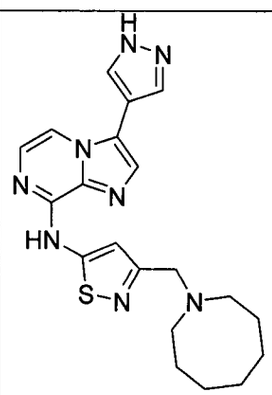


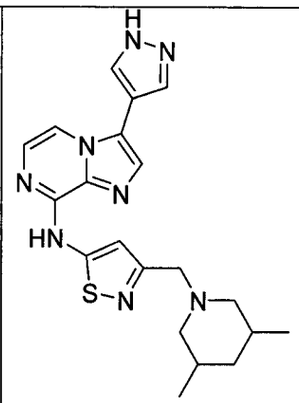
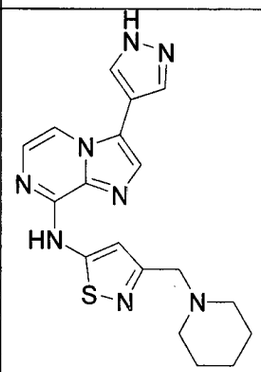
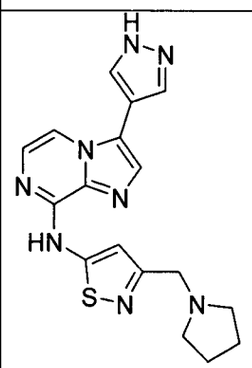
15 16

Siguiendo básicamente el mismo procedimiento indicado en el Ejemplo 11, se prepararon los compuestos ilustrados en la columna 2 de la Tabla 2 (ilustrados inmediatamente a continuación) reemplazando el compuesto 10 con el compuesto 15, y reemplazando pirrolidina con otras aminas alifáticas respectivas en el paso A.

TABLA 2

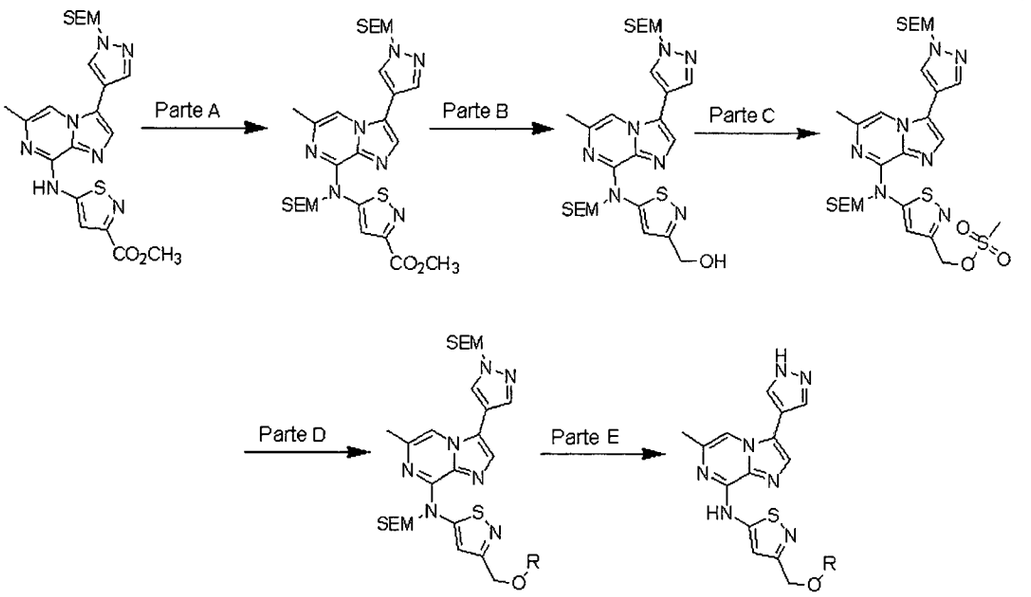
Ejemplo	Columna 2	PM	LCMS MH^+ m/z	HPLC MS t_R
16–1		394,5	395,2	2,02

16–2		394,5	395,2	2,13
16–3		434,6	435,2	2,50
16–4		428,5	429,2	2,22
16–5		408,5	409,2	2,18

16–6		408,5	409,2	2,21
16–7		381,2	382,2	2,55
16–8		366,14	367,14	2,43

1) Walsh R.J.A.; Wooldridge, K. R. H. *J. Chem. Soc. Perkin Trans.* 1972, 1247.

EJEMPLO 17



Parte A: Una solución de éster (2,38 g, 4,91 mmol, 1 equivalente) en DMF (40 mL) se trató con NaH (60% dispersión en aceite, 1,5 equivalentes) durante 20 min a temperatura ambiente, en cuyo tiempo, la mezcla de reacción se enfrió hasta –10C y se agregó cloruro de 2–(trimetilsilil)etoximetilo (0,87 mL, 1 equivalente) a la mezcla de reacción. La solución resultante se dejó calentar lentamente a ta (temperatura ambiente) y continuó agitándose a temperatura ambiente durante 1 h adicional. El análisis por LC–MS indicó que la reacción se había completado. La reacción se templó con metanol (15 mL), se diluyó con acetato de etilo (300 mL) y se lavó con bicarbonato de sodio saturado, agua, salmuera, se secó (sulfato de sodio) y se concentró. La purificación por cromatografía en columna (SiO_2 40% acetato de etilo / hexanos) proporcionó el producto deseado en forma de un sólido de color amarillo 1,2 g (40%). HPLC–MS t_R = 2,79 Min (UV $_{254nm}$). La masa se calculó para la fórmula $C_{27}H_{41}N_7O_4SSi_2$ 615,25; se observó LC/MS m/z 616,2 (M+H).

Parte B: A una solución del compuesto de la Parte A (1,2 g, 1,90 mmol, 1 equivalente) en THF (100 mL) se agregó solución superhidruro (4 equivalentes) a

temperatura ambiente. La solución resultante se agitó a temperatura ambiente durante 30 minutos en cuyo tiempo el análisis por LC–MS indicó que la reacción se había completado. La reacción se templó con cloruro de amonio ac. sat. y luego se extrajo con diclorometano (x2). Las capas orgánicas combinadas se secaron (sulfato de sodio) y concentraron. La purificación por cromatografía en columna (SiO_2 60 % acetato de etilo / hexanos) proporcionó alcohol en forma de un aceite límpido (47%). HPLC–MS t_R = 2,49 Min (UV $_{254nm}$). La masa se calculó para la fórmula $C_{26}H_{41}N_7O_3SSi_2$ 587,25; se observó LC/MS m/z 588,3 (M+H).

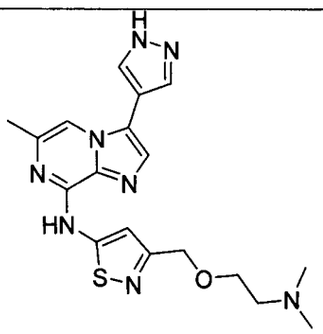
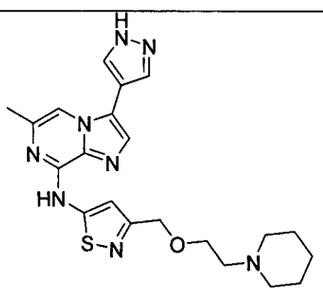
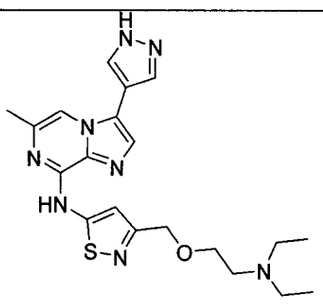
Parte C: Una solución de alcohol de la Parte B (0,52 g, 0,88 mmol, 1 equivalente) en DCM (15 mL) se trató con trietilamina (1,5 equivalentes) durante 15 min a 0C (baño de hielo), en cuyo tiempo, se agregó a la reacción cloruro de metansulfonilo (1,2 equivalentes) a 0C. La solución resultante se dejó calentar lentamente a ta (temperatura ambiente) y continuó agitándose a temperatura ambiente durante 3 h adicionales. El análisis por LC–MS indicó que la reacción se había completado. La mezcla de reacción se diluyó con acetato de etilo (100mL) y se lavó con agua, salmuera, se secó (sulfato de sodio anh.) y se concentró para proporcionar mesilato en forma de un aceite de color rojo/marrón 0,59 g (100%) que se usó sin purificación posterior. HPLC–MS t_R = 2,66 Min (UV $_{254nm}$). La masa se calculó para la fórmula C27H43N7O5S2Si2 665,23; se observó LC/MS m/z 666,1 (M+H).

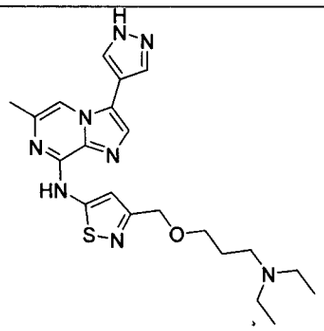
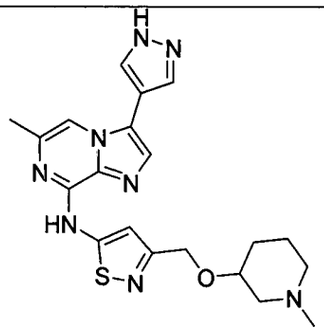
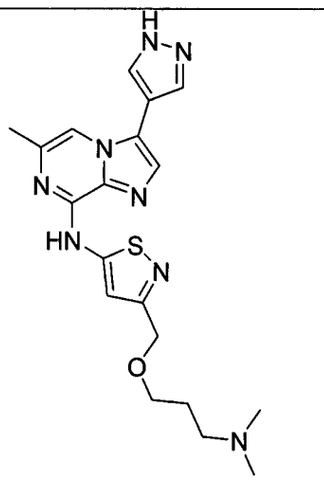
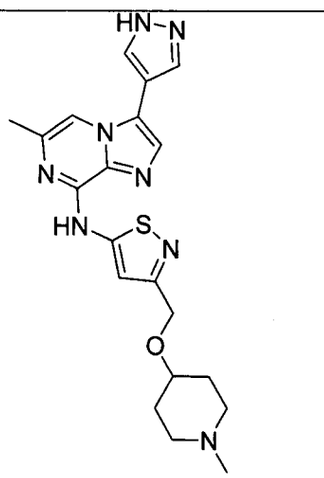
Parte D: Una solución del alcohol respectivo (3 equivalentes) en THF (1,5 mL) se trató con NaH (60% dispersión en aceite, 2 equivalentes) durante 15 min a temperatura ambiente, en cuyo tiempo, se agregó mesilato de la Parte C (40 mg, 0,06 mmol, 1 equivalente) a la mezcla de reacción. Luego de agitar a temperatura ambiente durante 1 h, el análisis por LC–MS indicó que la reacción se había completado. La reacción se templó con cloruro de amonio ac. sat. y luego se extrajo con acetato de etilo (dos veces). La capa orgánica combinada se secó

(sulfato de sodio) y se concentró para proporcionar éter en bruto, que se usó sin purificación posterior.

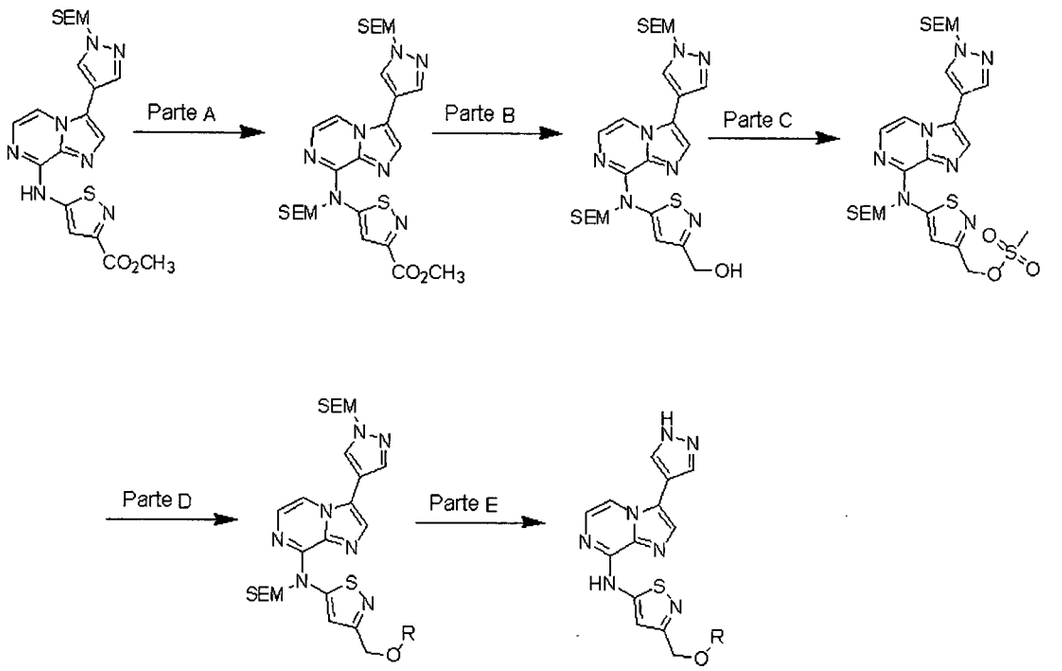
Parte E: Una solución del compuesto de la Parte D en 1,4–dioxano (1 mL) se trató con HCL 4N en solución de 1,4–dioxano (1 mL) a 60C durante 10 min en cuyo tiempo HPLC–MS indicó que la reacción se había completado. El disolvente se removió y el residuo se purificó mediante CL–Prep. La conversión en una sal clorhídrica proporcionó los compuestos indicados en la Tabla 3 (ilustrados inmediatamente a continuación):

TABLA 3

Ejemplo	Columna 2	PM	LCMS MH^+ m/z	HPLC MS t_R
17–1		398,16	399,2	2,55
17–2		438,2	439,3	2,79
17–3		426,2	427,3	2,68

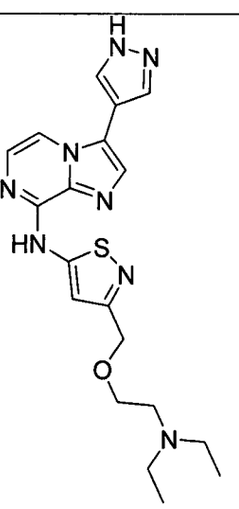
17–4		440,21	441,2	2,75
17–5		424,18	425,2	2,59
17–6		412,18	413,2	2,54
17–7		424,18	425,2	2,61

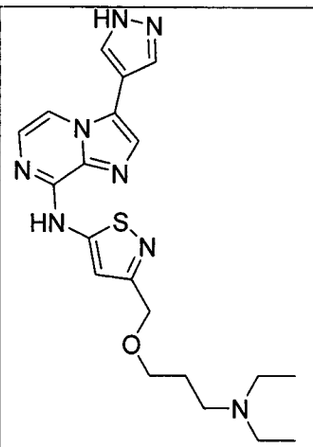
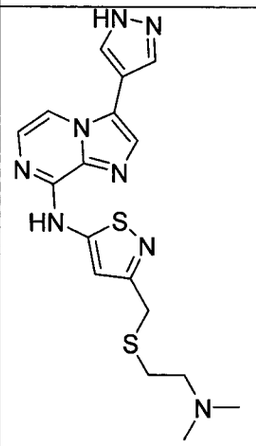
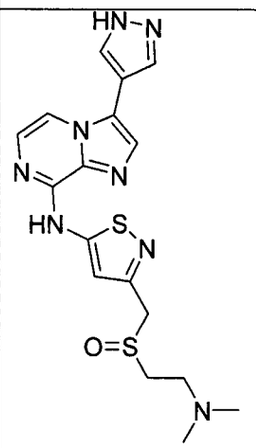
EJEMPLO 18



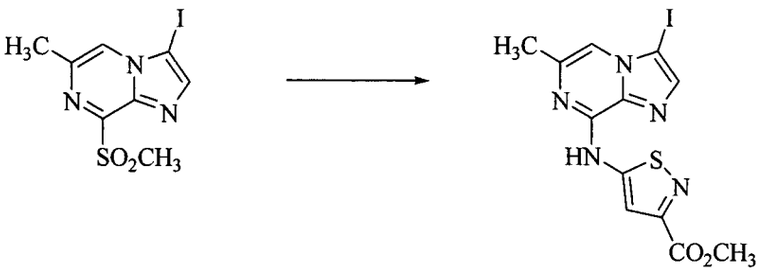
Siguiendo básicamente los mismos procedimientos proporcionados en el Ejemplo de preparación 17 pueden prepararse los compuestos indicados en la Tabla 4 (que se ilustran inmediatamente a continuación).

TABLAE 4

Ejemplo	Columna 2	Masa exacta	MS m/z (M+H)	HPLC MS t_R
18–1		412,18	413,2	2,36

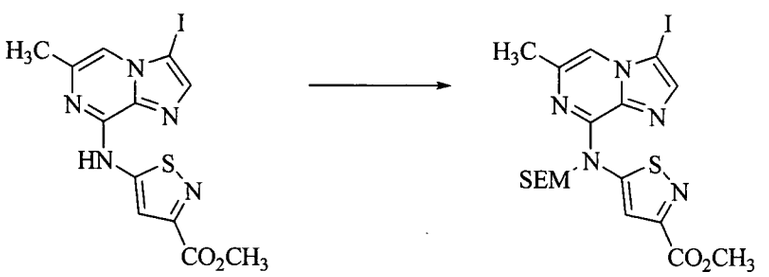
18–2		426,2	427,1	2,71
18–3		400,13	401,1	2,47
18–4		416,12	417,1	2,23

EJEMPLO 19



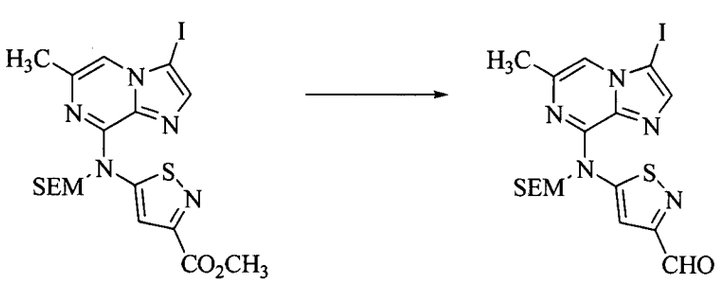
El Ejemplo 19 se preparó de manera similar al Ejemplo 4. ^{1}H RMN (300 MHz, DMSO–d_6) δ 12,4 (bs, 1H), 7,81 (s, 1H), 7,75 (s, 1H), 7,59 (s, 1H), 3,85 (s, 3H), 2,49 (s, 3H).

EJEMPLO 20



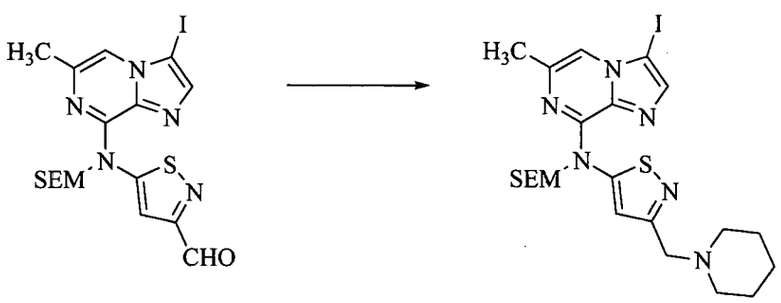
El Ejemplo 20 se preparó de manera similar al Ejemplo 17, Parte A. ^{1}H RMN (300 MHz, $CDCl_3$) δ 7,81 (s, 1H), 7,73 (s, 1H), 7,63 (s, 1H), 6,61 (s, 2H), 3,98 (s, 3H), 3,74 (t, J = 8 Hz, 2H), 2,62 (s, 3H), 0,94 (t, J = 8 Hz, 2H), –0,83 (s, 9H).

EJEMPLO 21



A una solución agitada de éster (2,40 g, 4,40 mmol) en tetrahidrofurano (96 mL) a –78 °C se agregó DIBAL–H (1M en diclorometano, 11,0 mL, 11,0 mmol) por goteo. La mezcla se agitó a –78 °C durante 3 horas en cuyo tiempo la cromatografía de capa fina (30% acetato de etilo/hexanos) indicó que la reacción se había completado. La mezcla se vertió rápidamente en tartrato de potasio y sodio acuoso saturado con agitación y se agitó a temperatura ambiente durante 14 horas. La mezcla se extrajo con acetato de etilo (2×250 mL), las capas orgánicas se combinaron, se lavaron con salmuera (100 mL), se secaron sobre sulfato de magnesio, se filtraron, y concentraron bajo presión reducida proporcionando el compuesto 21 en forma de un sólido de color amarillo 2,20 g (97%). ^{1}H RMN (300 MHz, $CDCl_3$) δ 9,99 (s, 1H), 7,74 (s, 1H), 7,73 (s, 1H), 7,65 (s, 1H), 6,60 (s, 2H), 3,74 (t, *J* = 8 Hz, 2H), 2,64 (s, 3H), 0,94 (t, *J* = 8 Hz, 2H), –0,07 (s, 9H).

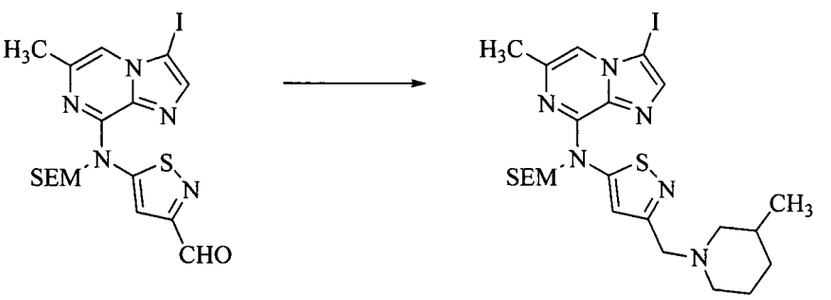
EJEMPLO 22



A una solución agitada de aldehído (1,30 g, 2,52 mmol), piperidina (257 mg, 3,02 mmol), y ácido acético (150 µL, 2,52 mmol) en 1,2–dicloroetano (17 mL) a temperatura ambiente se agregó triacetoxiborohidruro de sodio (801 mg, 3,78 mmol) en una porción. La mezcla se agitó a temperatura ambiente durante 2 horas en cuyo tiempo la cromatografía de capa fina (40% acetato de etilo/hexanos) indicó que la reacción se había completado. La reacción se templó con hidróxido de sodio 1 N (25 mL) y se agitó durante 20 minutos. La mezcla se

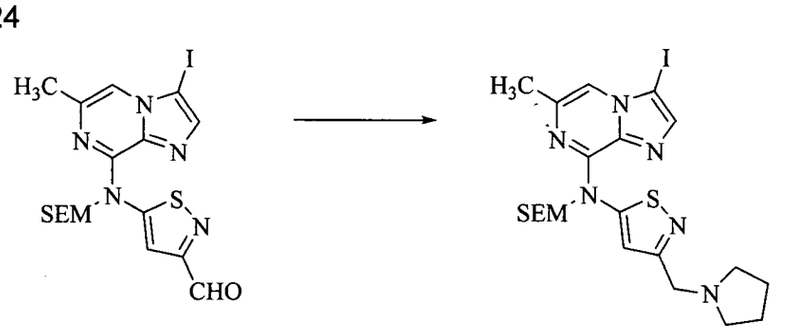
extrajo con cloroformo (3×20 mL), las capas orgánicas se combinaron, se secaron sobre sulfato de sodio, se filtraron y concentraron bajo presión reducida. Proporcionó el compuesto 22 en forma de un sólido de color amarillo 1,35 g (92%). ^{1}H RMN (300 MHz, $CDCl_3$) δ 7,70 (s, 1H), 7,59 (s, 1H), 7,23 (s, 1H), 6,58 (s, 2 H), 3,72 (t, *J* = 8 Hz, 2H), 3,62 (s, 2H), 2,58 (s, 3H), 2,47 (m, 4H), 1,58 (m, 6H), 0,93 (t, *J* = 8 Hz, 2H), –0,086 (s, 9H).

EJEMPLO 23



El Ejemplo 23 se preparó de manera similar al Ejemplo 22 utilizando 3–metilpiperidina en lugar de piperidina. ^{1}H RMN (300 MHz, $CDCl_3$) δ 7,70 (s, 1H), 7,59 (s, 1H), 7,23 (s, 1H), 6,58 (s, 2H), 3,72 (t, *J* = 8 Hz, 2H), 3,62 (s, 2H), 2,85 (m, 2H), 2,59 (s, 3H), 1,98 (m, 1H), 1,65 (m, 6H), 0,93 (t, *J* = 8 Hz, 2H), 0,84 (d, *J* = 6 Hz, 3H), –0,076 (s, 9H).

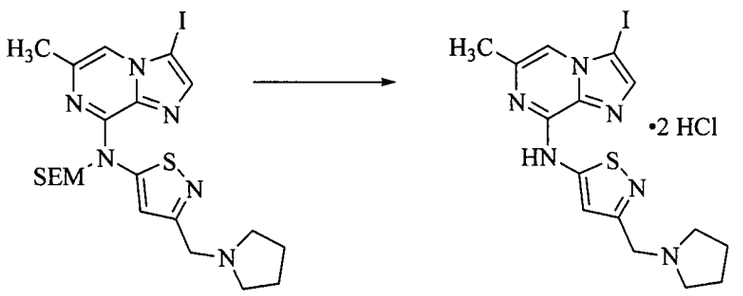
EJEMPLO 24



El Ejemplo 24 se preparó de manera similar al Ejemplo 23 utilizando pirrolidina en lugar de piperidina. ^{1}H RMN (300 MHz, $CDCl_3$) δ 7,70 (s, 1H), 7,59

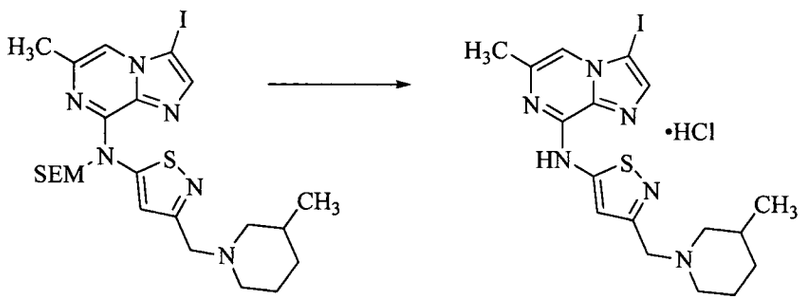
(s, 1H), 7,23 (s, 1H), 6,58 (s, 2H), 3,77 (s, 2H), 3,72 (t, *J* = 8 Hz, 2H), 2,61 (m, 4H), 2,59 (s, 3H), 1,81 (m, 4H), 0,92 (t, *J* = 8 Hz, 2H), –0,90 (s, 9H).

EJEMPLO 25



Una solución de yoduro del Ejemplo 24 (20 mg, 0,035 mmol) en 1,4–dioxano (1 mL) se trató con HCL 4N en 1,4–dioxano (1 mL). La mezcla se sometió a tratamiento de ultrasonido a temperatura ambiente durante 2,5 horas, en cuyo tiempo HPLC determinó que la reacción se había completado. La mezcla se concentró bajo presión reducida y el residuo resultante se purificó mediante HPLC preparativa y la conversión en la sal de clorhidrato proporcionó el compuesto 25 en forma de un sólido de color blanco 15 mg (83%). ^{1}H RMN (300 MHz, CD_3OD) δ 7,88 (s, 1H), 7,79 (s, 1H), 7,17 (s, 1H), 4,51 (s, 2H), 3,71 (m, 2H), 3,22 (m, 2H), 2,57 (s, 3H), 2,07 (m, 4H). HPLC t_R = 4,83 min (UV $_{254\ nm}$). La masa se calculó para la fórmula $C_{15}H_{17}IN_6S$ 440,03; se observó MH^+ (MS) 441,5 (m/z).

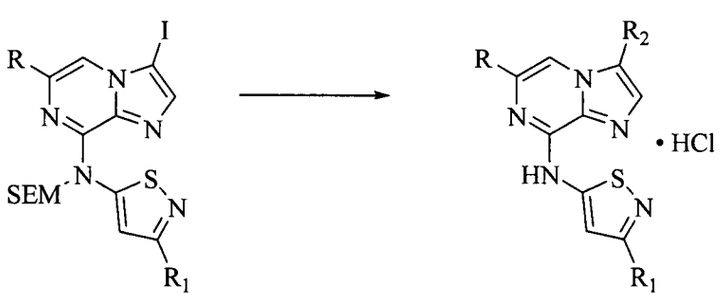
EJEMPLO 26



El Ejemplo 26 se preparó de manera similar al Ejemplo 25. ^{1}H RMN (300 MHz, CD_3OD) δ 7,87 (s, 1H), 7,79 (s, 1H), 7,22 (s, 1H), 4,39 (s, 2H), 3,52 (m, 2H), 2,96 (m, 1H), 2,70 (m, 1H), 2,57 (s, 3H), 1,90 (m, 4H), 1,21 (m, 1H), 0,99 (d, J = 6 Hz, 3H). HPLC t_R = 5,06 min (UV $_{254nm}$). La masa se calculó para $C_{17}H_{21}IN_6S$ 468,3; observed MH^+ (MS) 469,7 (m/z).

EJEMPLO 27

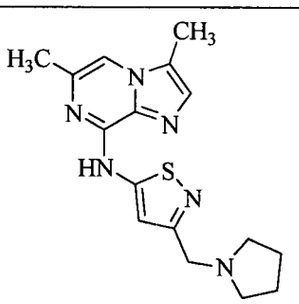
Los compuestos ilustrados en la columna 2 de la Tabla 5 (ilustrados inmediatamente a continuación) se prepararon del siguiente modo:



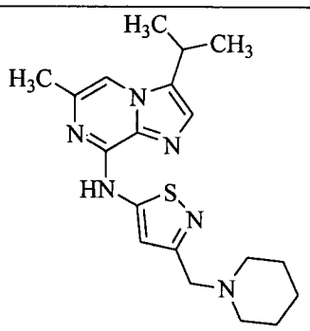
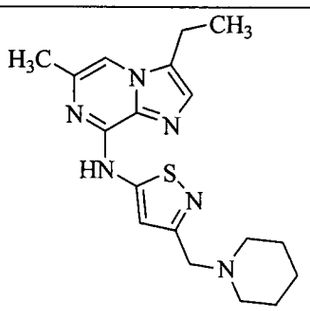
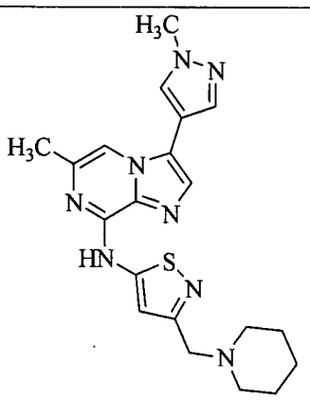
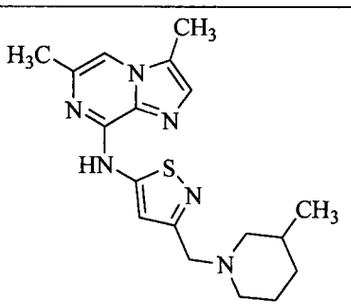
Un frasco que contenía matrices biodegradables preparadas de yoduro de arilo (compuesto del Ejemplo 22, 23, o 24, 1 equivalente), disponibles en el comercio o de fácil preparación en 1 a 3 pasos aril/heteroaril/alquil ácido borónico/éster/boroxina o aril/heteroaril/alquil bromuro de magnesio o aril/heteroaril/alquil cloruro de zinc (1,5 – 3 equivalentes), fosfato de potasio o

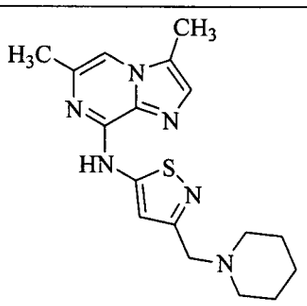
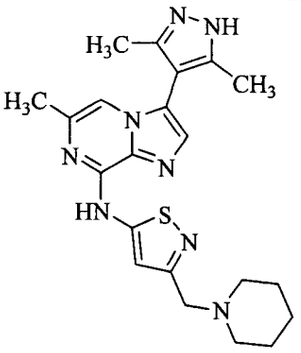
carbonato de potasio (2– 3 equivalentes) y $Pd(PPh_3)_4$ o $PdCl_2dppf$ (0,05 – 0,10 equivalentes) se evacuó, rellenó con nitrógeno y repitió. Se agregó 1,4–dioxano o N,N–dimetilformamida o 1,2–dimetoxietano (1 – 3 mL) y la mezcla se agitó a 50 – 130 °C hasta que la reacción se completó según se determinó mediante cromatografía de capa fina (acetato de etilo/hexanos) o HPLC. La mezcla se diluyó con agua (3 – 10 mL) y se extrajo con acetato de etilo (2–3 × 10–30 mL). Las capas orgánicas se combinaron, se lavaron con salmuera (15 – 30 mL), se secaron sobre sulfato de magnesio, se filtraron, concentraron, y purificaron mediante cromatografía en columna (SiO_2, acetato de etilo/hexanos). El producto obtenido se disolvió en 1,4–dioxano (1 mL) y se trató con HCl 4 N en 1,4–dioxano (1 mL) y se sometió a tratamiento de ultrasonido a temperatura ambiente durante 1–5 horas, en cuyo tiempo HPLC determinó que la reacción se había completado. La mezcla se concentró bajo presión reducida y el residuo resultante se purificó mediante HPLC preparativa y la conversión en la sal de clorhidrato proporcionó los compuestos 27–1 a 27–7.

TABLA 5

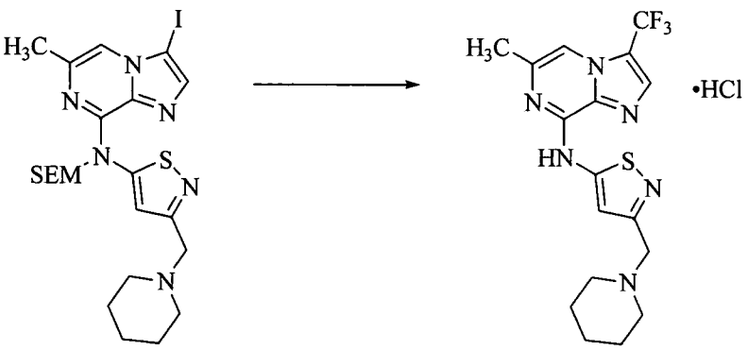
Ejemplo	Columna 2	PM	MS MH^+ m/z	HPLC t_R
27–1		328,4	329,1	3,52

296

27–2		370,5	371,1	4,34
27–3		356,4	357,4	3,98
27–4		408,5	409,6	4,21
27–5		356,4	357,4	3,91

27–6		342,4	343,2	3,71
27–7		422,5	423,2	3,87

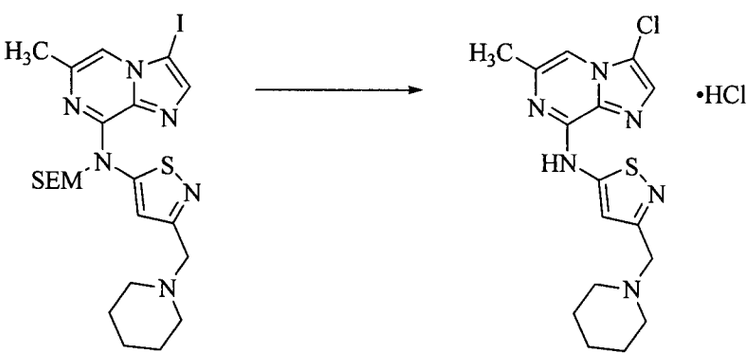
EJEMPLO 28



Una mezcla de yoduro (60 mg, 0,103 mmol), trimetil(trifluorometil)silano (44 mg, 0,308 mmol), yoduro de cobre (73 mg, 0,385 mmol), fluoruro de potasio (15 mg, 0,257 mmol), y DMF anhidro (1,0 mL) se desgasificó con nitrógeno, luego se calentó a 80 °C en un tubo sellado hasta la mañana siguiente. La mezcla se enfrió hasta temperatura ambiente, se diluyó con agua (30 mL), y se extrajo con acetato de etilo (100 mL). La capa orgánica se secó sobre sulfato de sodio, se filtró, concentró bajo presión reducida, y purificó mediante cromatografía en columna (SiO_2, 90:10:0.25 cloruro de metileno/metanol/hidróxido de amonio concentrado). El residuo resultante se disolvió en 1,4–dioxano anhidro (1mL) y se

agregó HCl 4 M en dioxano (1 mL). La solución resultante se sometió a tratamiento de ultrasonido a temperatura ambiente durante 2 horas y se concentró bajo presión reducida hasta sequedad. La purificación mediante HPLC preparativa y la conversión en la sal de clorhidrato proporcionó el compuesto del título en forma de un sólido de color blancuzco 3,1 mg (6%). ^{1}H RMN (300 MHz, CD_3OD) δ 8,07 (s, 1H), 7,85 (s, 1H), 7,24 (s, 1H), 4,40 (s, 2H), 3,61 (d, *J* = 12,3 Hz, 2H), 3,07 (t, *J*= 12,3 Hz, 2H), 2,55 (s, 3H), 1,75–2,03 (m, 5H), 1,56 (m, 1H). HPLC t_R = 7,19 min. La masa se calculó para la fórmula $C_{17}H_{19}F_3N_6S$ 396,13; se observó MH^+ 397,2 (m/z).

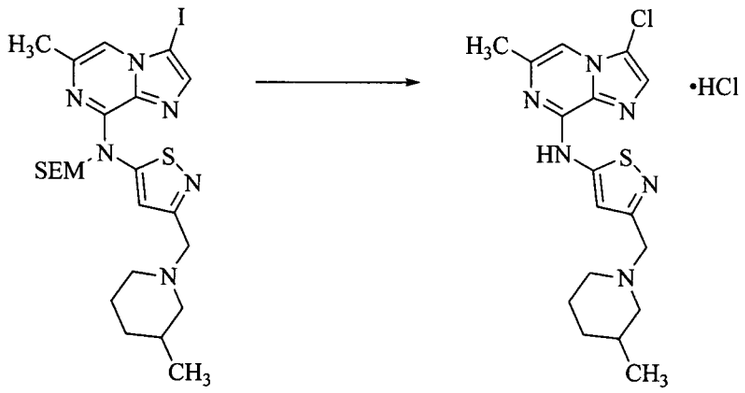
EJEMPLO 29



Una mezcla de yoduro (100 mg, 0,171 mmol) en THF anhidro (2,0 mL) se enfrió hasta –78 °C y se agregó por goteo *n–butil* litio (solución 2,5 M en hexanos, 89 µL, 0,222 mmol). Luego de agitar durante 15 minutos se agregó por goteo una solución de hexacloroetano (45 mg, 0,188 mmol) en THF (1,0 mL). Luego de agitar la reacción a –78 °C durante 30 minutos, la solución se templó con una solución acuosa saturada de cloruro de amonio (3,0 mL) y se calentó hasta temperatura ambiente. La reacción se concentró bajo presión reducida, se extrajo con acetato de etilo (50 mL) y la capa orgánica se secó sobre sulfato de sodio, se filtró, concentró bajo presión reducida, y purificó mediante cromatografía en columna (SiO_2, 90:10:0.25 cloruro de metileno/metanol/hidróxido de amonio concentrado). El residuo resultante se disolvió en 1,4–dioxano anhidro (1mL) y se

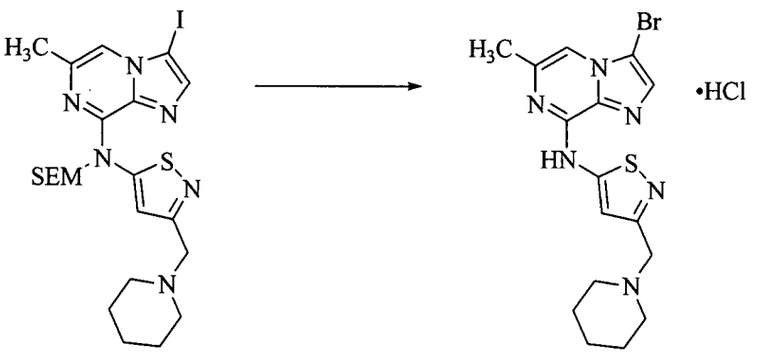
agregó HCl 4 M en dioxano (1 mL). La solución resultante se sometió a tratamiento de ultrasonido a temperatura ambiente durante 2 horas y se concentró bajo presión reducida hasta sequedad. La purificación mediante HPLC preparativa y la conversión en la sal de clorhidrato proporcionó el compuesto del título en forma de un sólido de color blancuzco 30 mg (40%). ^{1}H RMN (300 MHz, CD_3OD) δ 7,80 (s, 1H), 7,73 (s, 1H), 7,22 (s, 1H), 4,39 (s, 2H), 3,59 (d, *J* = 12,3 Hz, 2H), 3,08 (t, *J*= 12,3 Hz, 2H), 2,55 (s, 3H), 1,75–2,03 (m, 5H), 1,56 (m, 1H). HPLC t_R = 4,79 min. La masa se calculó para la fórmula $C_{16}H_{19}ClN_6S$ 362,11; se observó MH^+ 363,7 (m/z).

EJEMPLO 30



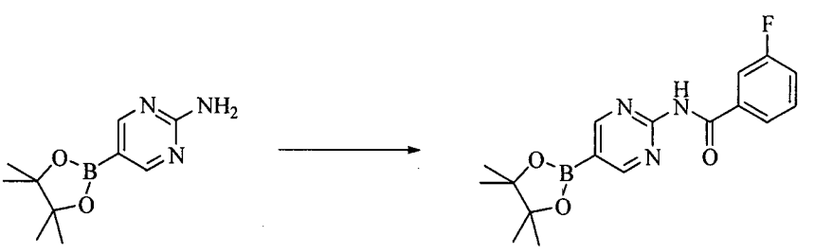
El Ejemplo 30 se preparó de manera similar que el Ejemplo 29. ^{1}H RMN (300 MHz, CD_3OD) δ 7,77 (s, 1H), 7,68 (s, 1H), 7,20 (s, 1H), 4,39 (s, 2H), 3,47–3,67 (m, 2H), 2,97 (m, 1H), 2,71 (m, 1H), 2,55 (s, 3H), 1,77–2,01 (m, 4H), 1,20 (m, 1H), 1,00 (d, *J* = 6,4 Hz, 3H). HPLC t_R = 4,98 min. La masa se calculó para la fórmula $C_{17}H_{21}ClN_6S$ 376,12; se observó MH^+ 377,6 (m/z).

EJEMPLO 31



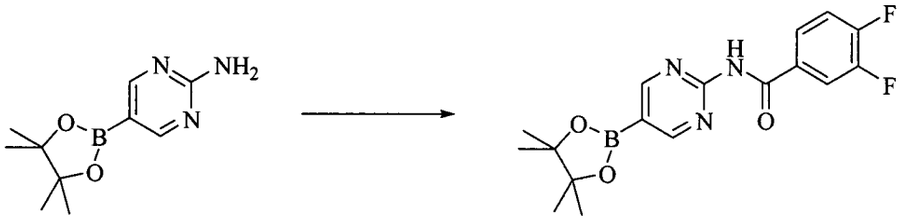
El Ejemplo 31 se preparó de manera similar al compuesto 29 utilizando tetraclorodibromoetano en lugar de hexacloroetano. ^{1}H RMN (300 MHz, CD_3OD) δ 7,84 (s, 1H), 7,83 (s, 1H), 7,25 (s, 1H), 4,41 (s, 2H), 3,61 (d, *J* = 12,3 Hz, 2H), 3,08 (t, *J*= 12,3 Hz, 2H), 2,57 (s 3H), 1,77–2,03 (m, 5H), 1,55 (m, 1H). HPLC t_R = 5,19 min. La masa se calculó para la fórmula $C_{16}H_{19}BrN_6S$ 406,06; se observó MH^+ 407,4 (m/z).

EJEMPLO 32



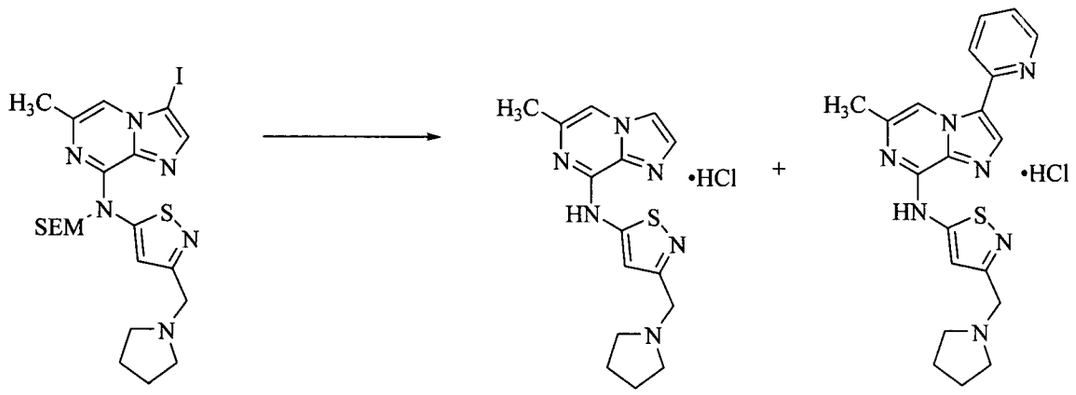
A una solución de aminopirimidina (100 mg, 0,452 mmol) en piridina anhidro (2,0 mL) se agregó cloruro de 3–fluorobenzoílo (72 mg, 0,452 mmol). Luego de agitar a temperatura ambiente hasta la mañana siguiente, la reacción se concentró bajo presión reducida, se diluyó con agua (30 mL), y se extrajo con cloruro de metileno (100 mL). La capa orgánica se secó sobre sulfato de sodio, se filtró y se concentró para proporcionar el compuesto del título en forma de un sólido de color blancuzco 124 mg (80%). ^{1}H RMN (300 MHz, $CDCl_3$) δ 8,95 (s, 2H), 8,72 (s, 1H), 7,66–7,72 (m, 2H), 7,49 (m, 2H), 1,36 (s, 12H).

EJEMPLO 33



Se preparó de manera similar al compuesto 31 proporcionando el compuesto del título en forma de un sólido de color blancuzco 131 mg (80%). ^{1}H RMN (300 MHz, $CDCl_3$) δ 8,93 (s, 2H), 8,65 (s, 1H), 7,83 (m, 1H), 7,69 (m, 1H), 7,30 (m, 1H), 1,34 (s, 12H).

EJEMPLO 34

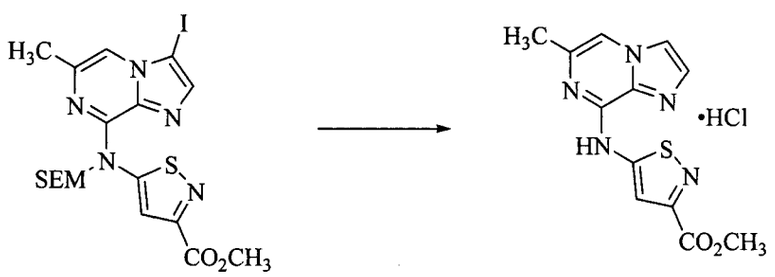


Una mezcla de yoduro (60 mg, 0,103 mmol), tri–*n*–butil(piridil)estaño (57 mg, 0,154 mmol), aducto de dicloro[1,1'–bis(difenilfosfino)ferroceno]paladio(II) diclorometano (8 mg, 0,0103 mmol), y fluoruro de potasio (18 mg, 0,309 mmol) en 1,4–dioxano anhidro (1.0 mL) se desgasificó con nitrógeno, luego se calentó a 85 °C en un tubo sellado hasta la mañana siguiente. La mezcla se enfrió hasta temperatura ambiente, se diluyó con agua (30 mL), y se extrajo con acetato de etilo (2 × 100 mL). La capa orgánica luego se separó, se secó sobre sulfato de sodio, se filtró, concentró bajo presión reducida hasta obtener un residuo, y se purificó mediante cromatografía en columna (SiO_2, 90:10:0,25 cloruro de metileno/metanol/ hidróxido de amonio concentrado). El residuo resultante luego

se disolvió en 1,4–dioxano anhidro (1mL) y se agregó HCl 4 M en dioxano (1 mL). La solución resultante se sometió a tratamiento de ultrasonido a temperatura ambiente durante 2 horas y luego se concentró bajo presión reducida hasta sequedad. La purificación mediante HPLC preparativa y la conversión en la sal de clorhidrato proporcionó el producto deshalogenado 3,2 mg (10%) en forma de un sólido de color blancuzco: ^{1}H RMN (300 MHz, CD_3OD) δ 8,23 (s, 1H), 8,13 (s, 2H), 7,29 (s, 1H), 4,55 (s, 2H), 3,72 (s ancho, 2H), 3,29 (m, 2H), 2,61 (s, 3H), 2,05–2,18 (m, 4H). HPLC t_R =3,49 min. La masa se calculó para la fórmula $C_{15}H_{16}N_6S$ 314,13; se observó MH^+ 315,2 (m/z).

También proporcionó un producto de acoplamiento 5,0 mg (10%) en forma de un sólido de color blancuzco: ^{1}H RMN (300 MHz, CD_3OD) δ 8,95 (s, 1H), 8,86 (d, *J* = 5,1 Hz, 1H), 8,50 (s, 1H), 8,28 (t, *J* = 7,5 Hz, 1H), 8,18 (d, *J* = 7,8 Hz, 1H), 7,70 (t, *J* = 6,3 Hz, 1H), 7,26 (s, 1H), 4,54 (s, 2H), 3,74 (m, 2H), 3,29 (m, 2H), 1,99–2,30 (m, 4H). HPLC t_R =4,80 min. La masa se calculó para la fórmula $C_{20}H_{21}N_7S$ 391,16; se observó MH^+ 392,5 (m/z).

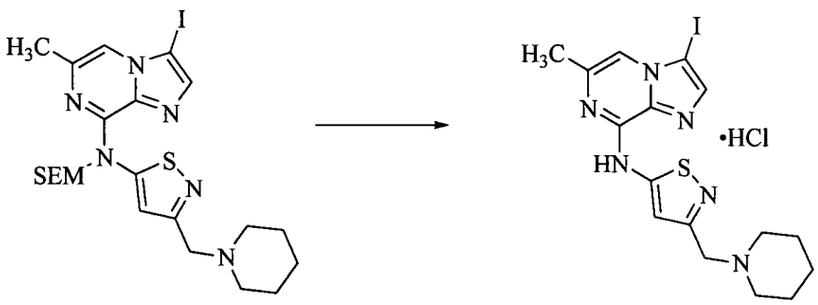
EJEMPLO 35



Se agregó borohidruro de sodio (3 mg, 0,073 mmol) a una suspensión de yoduro a temperatura ambiente (15 mg, 0,037) en metanol (1 mL). La reacción se dejó agitar durante 30 minutos, luego se templó con agua (20 mL). La mezcla se diluyó con éter dietílico (20 mL) y se permitió que las fases se separaran. La capa orgánica se secó (sulfato de sodio), se filtró y se concentró para proporcionar un intermediario deshalogenado protegido. El producto reducido (7 mg, 0,017 mmol)

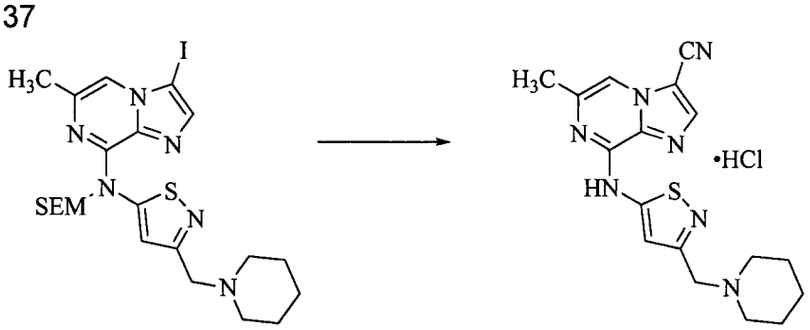
se sometió a las condiciones ácidas indicadas previamente para proporcionar el compuesto del título en forma de un sólido de color amarillo 2 mg (17%). ^{1}H RMN (300 MHz, CD_3OD) δ 7,94 (s, 1H), 7,90 (s, 1H), 7,74 (s, 1H), 7,55 (s, 1H), 3,94 (s, 3H), 2,50 (s, 3H). HPLC t_R = 4,67 min (UV $_{254nm}$). La masa se calculó para la fórmula $C_{12}H_{11}N_5O_2S$ 289,06; se observó MH^- (ESI MS) 288,0 (m/z).

EJEMPLO 36



El Ejemplo 36 se preparó de manera similar al Ejemplo 31. ^{1}H RMN (300 MHz, CD_3OD) δ 7,72 (s, 1H), 7,69 (s, 1H), 7,15 (s, 1H), 4,38 (s, 2H), 3,69–3,52 (m, 2H), 3,17–2,96 (m, 2H), 2,54 (s, 3H), 2,06–1,70 (m, 5H), 1,65–1,44 (m, 1H). HPLC t_R = 5,00 min (UV $_{254nm}$). La masa se calculó para la fórmula $C_{16}H_{19}IN_6S$ 454,04; se observó MH^+ (ESI MS) 455,0 (m/z).

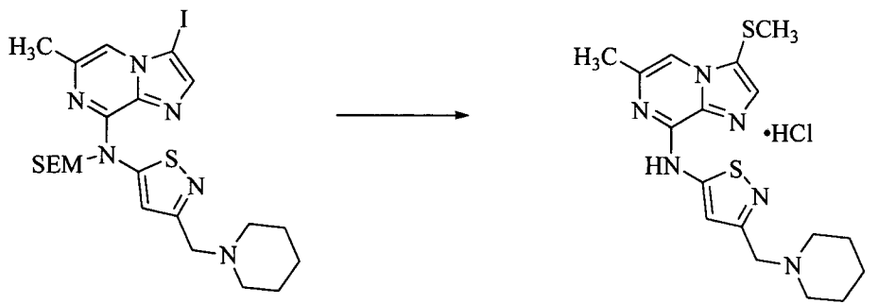
EJEMPLO 37



Se agregó $Pd_2(dba)_3$ (5 mg, 0,005 mmol) a una solución de DPPF a temperatura ambiente (6 mg, 0,103 mmol) en *N,N'*–dimetilformamida (1 mL) y se agitó durante 10 minutos. La mezcla luego se agregó a una solución de yoduro (60 mg, 0,103 mmol), $Zn(CN)_2$ (12 mg, 0,103 mmol) en *N,N'*dimetilformamida (4

mL). La reacción se calentó hasta 150 °C en microondas durante 30 minutos, se enfrió hasta temperatura ambiente, luego se concentró hasta sequedad. La purificación del residuo resultante mediante cromatografía instantánea (SiO_2; 12 g; 10% metanol en cloruro de metileno) proporcionó nitrilo impuro en forma de un sólido de color amarillo. El nitrilo impuro (22 mg, 0,045 mmol) se disolvió en HCl 2 N (4 mL) sin purificación posterior. La solución resultante se sometió a tratamiento de ultrasonido a 45 °C durante 2 horas. Luego de completarse, la reacción se concentró hasta sequedad. La purificación del residuo resultante mediante HPLC preparativa proporcionó el compuesto del título en forma de un sólido de color blanco 8 mg (18%). ^{1}H RMN (300 MHz, CD_3OD) δ 8,22 (s, 1H), 7,93 (s, 1H), 7,22 (s, 1H), 4,40 (s, 2H), 3,73–3,52 (m, 2H), 3,20–2,97 (m, 2H), 2,55 (s, 3H), 2,06–1,71 (m, 5H), 1,66–1,42 (m, 1H). HPLC t_R = 4,50 min (UV $_{254nm}$). La masa se calculó para la fórmula $C_{17}H_{19}N_7S$ 353,14; se observó MH^+ (ESI MS) 354,3 (m/z).

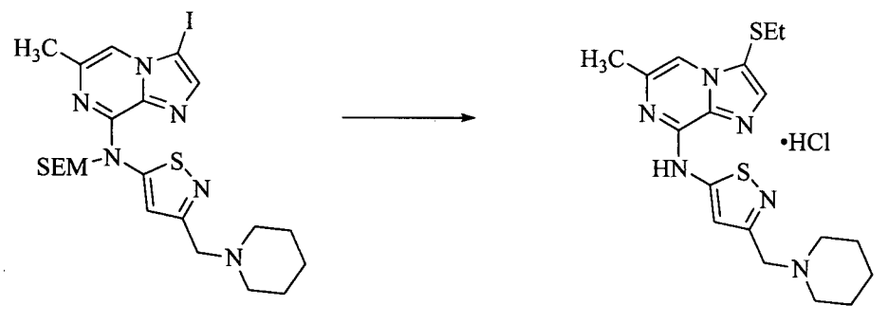
EJEMPLO 38



Una mezcla de yoduro (70 mg, 0,12 mmol), $Pd(dppf)Cl_2$ (9 mg, 0,012 mmol), terc–butóxido de sodio (35 mg, 0,36 mmol) y tiometóxido de sodio (17 mg, 0,24 mmol) se purgó con nitrógeno, luego se disolvió en 1,4–dioxano (5 mL). La solución se calentó hasta 95 °C en microondas durante 90 minutos. La reacción se enfrió hasta temperatura ambiente, se diluyó con acetato de etilo (100 mL), y se filtró a través de Celite. La capa orgánica se lavó con agua (50 mL) y salmuera

(50 mL), luego se secó (sulfato de sodio), se filtró y concentró hasta sequedad. La purificación del residuo resultante mediante HPLC preparativa proporcionó el tiometiléter protegido. El tiometiléter (35 mg, 0,07 mmol) se sometió a las condiciones de reacción indicadas en el ejemplo 110 para proporcionar el compuesto del título en forma de un sólido de color blanco 6 mg (11%). ^{1}H RMN (300 MHz, CD_3OD) δ 8,28 (s, 1H), 8,25 (s, 1H), 7,34 (s, 1H), 4,43 (s, 2H), 3,68–3,52 (m, 2H), 3,18–2,98 (m, 2H), 2,67 (s, 3H), 2,49 (s, 3H), 2,05–1,71 (m, 5H), 1,65–1,44 (m, 1H). HPLC t_R = 4,74 min (UV $_{254nm}$). La masa se calculó para la fórmula $C_{17}H_{22}N_6S_2$ 374,13; se observó MH^+ (ESI MS) 375,3 (m/z).

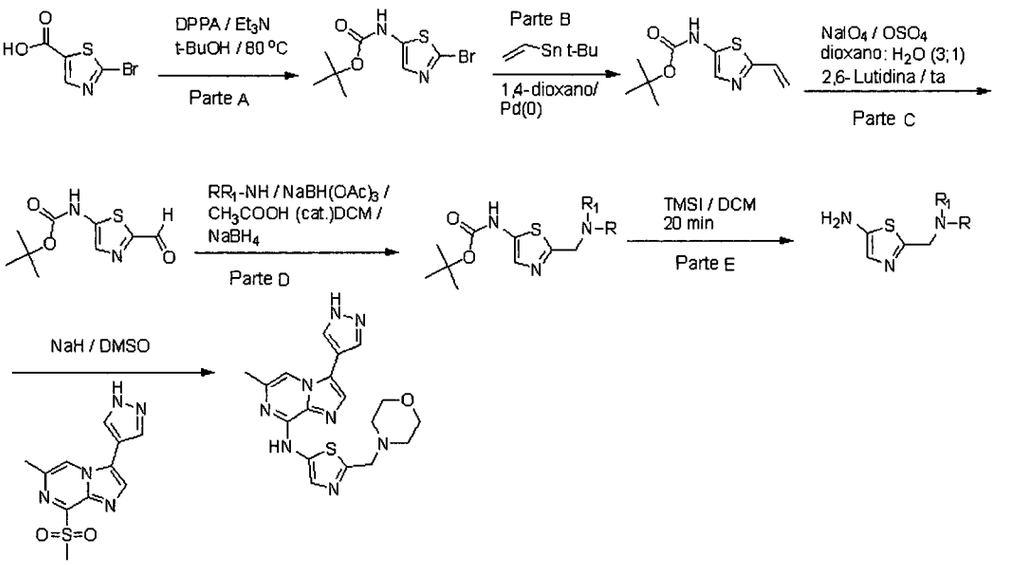
EJEMPLO 39



Una mezcla combinada de yoduro (70 mg, 0,12 mmol), tioetóxido de sodio (20 mg, 0,24 mmol), $Pd(dppf)Cl_2$ (9 mg, 0,012 mmol) y terc–butóxido de sodio (35 mg, 0,36 mmol) se purgó con gas nitrógeno, luego se disolvió en 1,4–dioxano (5 mL). La reacción se calentó hasta 95 °C y se agitó durante 72 horas. La reacción luego se enfrió hasta temperatura ambiente, se diluyó con acetato de etilo (100 ml), y se filtró a través de Celite. El filtrado se lavó con agua (50 mL) y salmuera (50 mL), luego se secó (sulfato de sodio), se filtró y concentró hasta sequedad. La purificación del residuo resultante mediante cromatografía instantánea (SiO_2; 12 g; 0% a 10% metanol en cloruro de metileno) proporcionó un intermediario tioetiléter en forma de un sólido de color amarillo. El tioetiléter (10 mg, 0,019 mmol) se sometió a las condiciones de reacción indicadas en el ejemplo 110 para

proporcionar el compuesto del título en forma de un sólido de color blanco 2 mg (4%). ^{1}H RMN (300 MHz, CD_3OD) δ 8,32 (s, 1H), 8,28 (s, 1H), 7,35 (s, 1H), 4,43 (s, 2H), 3,68–3,55 (m, 2H), 3,17–3,01 (m, 2H), 2,90 (q, *J* = 7,3 Hz, 2H), 2,67 (s, 3H), 2,07–1,71 (m, 5H), 1,65–1,42 (m, 1H), 1,28 (t, *J* = 7,3 Hz, 3H). HPLC t_R = 5,27 min (UV $_{254nm}$). La masa se calculó para la fórmula $C_{18}H_{24}N_6S_2$ 388,15; se observó MH^+ (ESI MS) 389,7 (m/z).

EJEMPLO 40



Parte A: A una solución agitada de ácido 2–bromo–tiazol–5–carboxílico (2,0 g, 9,615 mmol) en *t*–Butanol (30 mL) y trietilamina (1,5 mL, 10,57 mmol) se agregó azida de difenilfosforilo (2,9 g, 10,57 mmol) y la mezcla de reacción se calentó hasta 80 °C y se agitó durante 12 horas. LCMS mostró la desaparición completa del material de partida. La mezcla de reacción se enfrió hasta temperatura ambiente, el disolvente se removió al vacío, se agregó agua (100 mL) y se extrajo con acetato de etilo (3 x 100 mL). La capa orgánica se lavó con agua, salmuera, se secó sobre sulfato de sodio y concentró. El material en bruto se pasó a través de una pequeña almohadilla de gel de sílice y el terc–butil éster del ácido (2–Bromo–tiazol–5–il)–carbámico (sólido) resultante se usó como tal en el paso siguiente, rendimiento 2,5 g (90%). ^{1}H RMN (400 MHz, DMSO–d_6 δ 7,10 (s, 1H),

7,05 (s, 1H), 1,51 (s, 9H). La masa se calculó para la fórmula $C_8H_{11}BrN_2O_2S$ 277,97; se observó MH^+ (LCMS) 279,0 (m/z).

Parte B: A una solución agitada de terc–butil éster del ácido (2–Bromo–tiazol–5–il)–carbámico (2,5 g, 8,9928 mmol) en 1,4–dioxano (20,0 mL) se agregaron tributil(vinil)estaño (2,9 mL, 9,892 mmol), 2,6–di–terc–butil–4–metilphenol (cat. amt) y tetrakis(trifenil fosfina) paladio(0) (506,0 mg, 0,4496 mmol). La mezcla de reacción se calentó hasta 100 °C y se agitó durante 12 horas. LCMS mostró la desaparición completa del material de partida. La mezcla de reacción se enfrió hasta temperatura ambiente, se filtró y el sólido se lavó con acetato de etilo, el filtrado combinado (disolvente orgánico) se removió al vacío, el material en bruto se purificó usando HPLC Biotage usando gradiente de hexano / acetato de etilo 0,0 a 100 % para proporcionar terc–butil éster del ácido (2–Vinil–tiazol–5–il)–carbámico (sólido) 1,1 g (54%). ^1H RMN (400 MHz, $CDCl_3$ δ 7,27 (d, J = 12,7 Hz,2H), 7,19 (s ancho, 1H), 6,84–6,77 (m, 1H), 6,87 (d, J = 17,0 Hz, 1H), 5,43 (d, J = 10,5 Hz,1H), 1,52 (s, 9H). La masa se calculó para la fórmula $C_{10}H_{14}N_2O_2S$ 226,08; se observó MH^+ (LCMS) 227,1 (m/z).

Parte C: A una solución agitada de terc–butil éster del ácido (2–Vinil–tiazol–5–il)–carbámico (0,76 g, 2,857 mmol) en 1,4–dioxano : agua (30 : 9 mL), se agregaron periodato de sodio (2,5 g, 11,43 mmol), tetróxido de osmio (solución 2,5% en 2–propanol) (0,5 mL) y 2,6–lutidina (0,663 mL, 5,714 mmol) y la mezcla de reacción se agitó durante 4 horas. LCMS indicó una desaparición casi total del material de partida. La mezcla de reacción se diluyó con agua (100 mL) y se extrajo con acetato de etilo, la capa orgánica se lavó con agua, salmuera, se secó sobre sulfato de sodio y concentró bajo alto vacío para proporcionar aldehído 710 mg (92%). El producto en bruto se usó como tal en la reacción siguiente. ^1H RMN (400 MHz, DMSO–d_6 δ 11,45 (s, 1H), 9,76 (s, 1H), 7,58 (s, 1H), 1,40 (s, 9H). La masa se calculó para la fórmula $C_9H_{12}N_2O_3S$ 228,06; se observó MH^+ (LCMS) 229,1 (m/z).

Parte D: A una solución agitada de terc–butil éster del ácido (2–Formil–tiazol–5–il)–carbámico (0,76 g, 2,857 mmol) en 1,2–dicloroetano (10 mL) se agregaron morfolina (250 mg, 1,1135 mmol), triacetoxiborohidruro de sodio (472 mg, 2,227 mmol) y una cantidad de ácido acético (tres gotas) y se agitó durante dos horas a temperatura ambiente. A la mezcla de reacción se agregó borohidruro de sodio (126 mg, 3.3405 mmol) y se agitó durante una hora. LCMS mostró la desaparición del material de partida. La mezcla de reacción se diluyó con agua (100 mL) y se extrajo con diclorometano, la capa orgánica se lavó con agua, salmuera, se secó sobre sulfato de sodio y concentró bajo alto vacío para proporcionar terc–butil éster del ácido (2–Morfolin–4–ilmetil–tiazol–5–il)–carbámico 298 mg (91%). El producto en bruto se usó como tal en la reacción siguiente. La masa se calculó para la fórmula C14H25N3O3S 315.43; se observó MH^+ (LCMS) 300,3 (m/z).

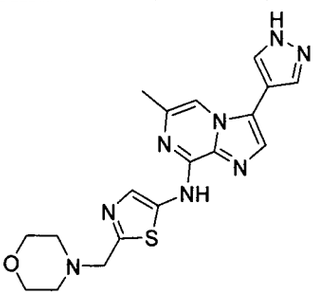
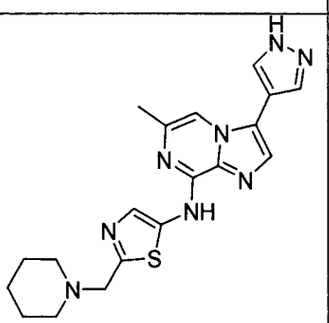
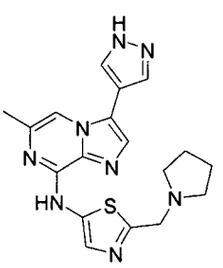
Parte E: A una solución agitada de terc–butil éster del ácido (2–Morfolin–4–ilmetil–tiazol–5–il)–carbámico (80,0 mg, 0,268 mmol) en diclorometano (5 mL) se agregó yodometilsilano (44 µL, 0,321 mmol) y se agitó durante 10 min. LCMS mostró la desaparición del material de partida. La mezcla de reacción se diluyó con agua (10 mL), solución acuosa de NaOH 1N (5 mL) y se extrajo con 10% 2–propanol en DCM (3 x 25 mL) y la capa orgánica se secó sobre sulfato de sodio y concentró bajo alto vacío para proporcionar 2–Morfolin–4–ilmetil–tiazol–5–ilamina 30,0 mg (56%). El producto en bruto se usó como tal en la reacción siguiente. La masa se calculó para la fórmula C8H13N3OS 199,27; se observó MH^+ (LCMS) 200,1 (m/z).

Parte F: A una solución agitada de 2–Morfolin–4–ilmetil–tiazol–5–ilamina (30,0 mg, 0,151 mmol) en DMSO (2.5 mL) se agregó 8–Metansulfonil–6–metil–3–(1H–pirazol–4–il)–imidazo[1,2–a]pirazina (25,0 mg, 0,09045 mmol) seguido por NaH 60% en aceite mineral (48 mg, 1,206 mmol) y se agitó durante 30 min. LCMS mostró la desaparición del material de partida. La mezcla de reacción se templó 1:1 mezcla de acetonitrilo y cloruro de amonio saturado (10 mL), y se extrajo con 10% 2–propanol en DCM (3 x 25 mL) y la capa orgánica se concentró bajo alto

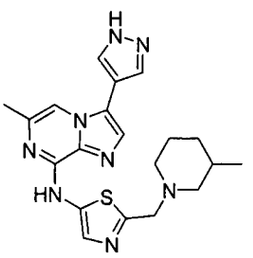
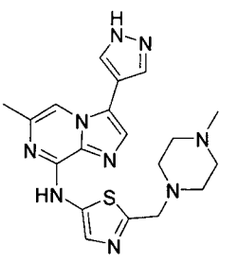
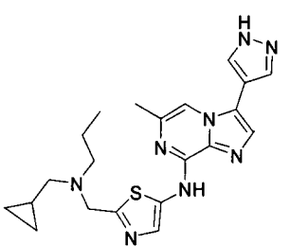
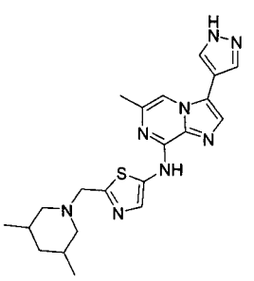
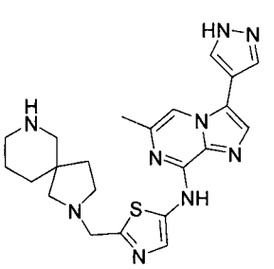
vacío para proporcionar [6–Metil–3–(1H–pirazol–4–il)–imidazo[1,2–a]pirazin–8–il]–(2–morfolin–4–ilmetil–tiazol–5–il)–amina en bruto que se purificó posteriormente por HPLC Agilent de fase reversa usando el método de ácido fórmico para proporcionar 10 mg (28%). HPLC–MS (método 10 min) t_R = 2,06 min (UV $_{254nm}$). La masa se calculó para la fórmula $C_{18}H_{20}N_8OS$ 396,47; se observó MH^+ (LCMS) 397,5 (m/z).

Los compuestos indicados en la Tabla 6 (ilustrados inmediatamente a continuación) se prepararon usando los procedimientos descriptos en el Ejemplo 40.

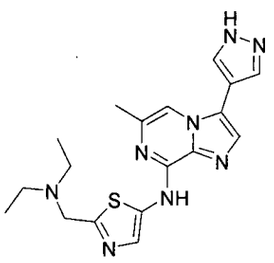
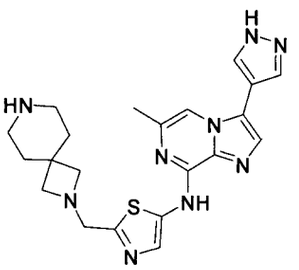
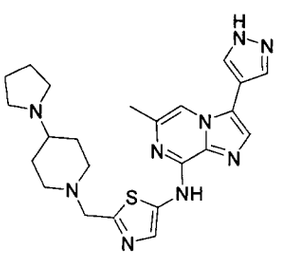
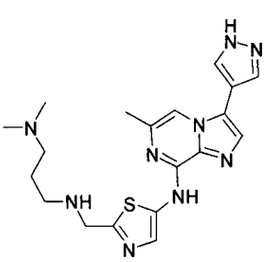
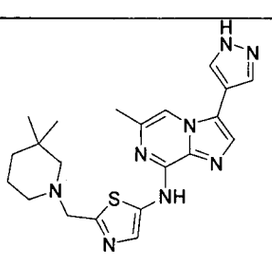
TABLA 6

Ejemplo	Columna 2	PM	LCMS MH^+ m/z	HPLC MS t_R
40–1		396,47	397,5	2,06
40–2		394,50	395,5	2,38
40–3		380,47	381,5	2,25

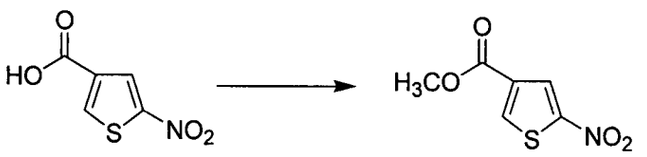
410

40–4		408,52	409,2	2,56
40–5		409,51	410,3	2,14
40–6		422,55	423,5	2,74
40–7		422,55	423,3	2,75
40–8		449,58	450,3	1,85

411

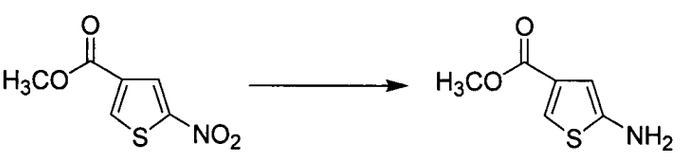
40–9		382,49	383,2	2,28
40–10		435,55	436,44	1,78
40–11		463,60	464,27	1,90
40–12		411,53	412,25	1,76
40–13		422,55	423,28	2,74

EJEMPLO 41



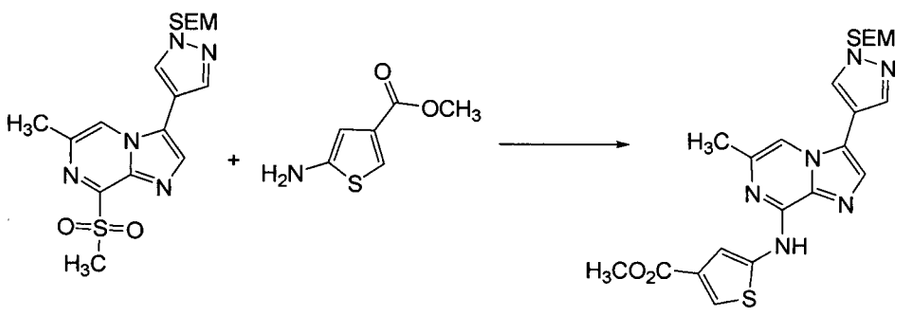
A una solución de ácido 5–nitrotiofeno–3–carboxílico (5,00 g, 28,88 mmol) en dimetilformamida (40 mL) se agregó carbonato de potasio (11,98 g, 86,71 mmol) y yodometano (2,70 mL, 43,37 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 16 horas. Luego de haberse consumido el material, la reacción se diluyó con 50% acetato de etilo/hexanos (350 mL) y se extrajo con H_2O (350 mL). La capa orgánica se lavó con salmuera (150 mL) y concentró. Se agregó hexanos (50 mL) al sólido y se concentró nuevamente para proporcionar 5,456 g (99%) de producto. ^1H RMN (400 MHz) $CDCl_3$ δ 8,30 (s, 1H), 8,25 (s, 1H), 3,93 (s, 3H). La masa se calculó para la fórmula $C_6H_5NO_4S$ 187,17; se observó $M4H^+$ (MS) 191,15 (m/z).

EJEMPLO 42



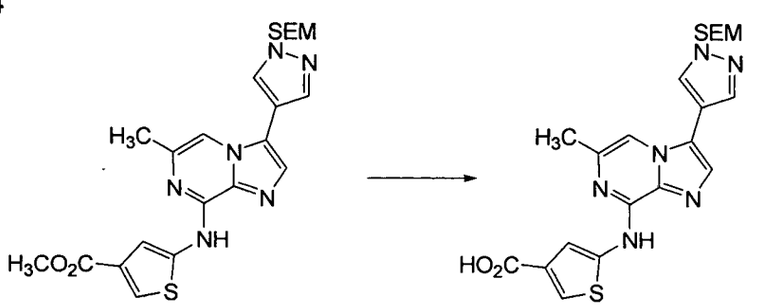
A una solución de nitro–éster (1,006 g, 5,375 mmol) en TFA (15 mL), se agregó lentamente polvo de Fe (1,5135 g, 27,10 mmol) al balón. La reacción se calentó hasta 60°C durante 45 min en cuyo tiempo TLC (1:1, acetato de etilo en hexanos) demostró el consumo del material de partida. La reacción se diluyó con acetato de etilo y el Fe se separó por filtración. El filtrado se neutralizó con Na_2CO_3 acuoso y se dejó agitar durante 1 h. La capa acuosa se extrajo con EtOAc. La capa orgánica se lavó con salmuera, se secó sobre Na_2SO_4, y concentró para proporcionar 0,701 g (83%) de un sólido de color amarillo. ^1H RMN (400 MHz) CD_3OD δ 7,29 (s, 1H), 6,44 (s, 1H), 3,79 (s, 3H). La masa se calculó para la fórmula $C_6H_7NO_2S$ 157,19; se observó MH^+ (LCMS) 158,1 (m/z).

EJEMPLO 43



Una solución de la sulfona (1,27 g, 3,11 mmol) y metil éster 2–aminotiofeno–4–carboxilato (0,701 g, 4,46 mmol) en DMF (35 mL) se trataron con NaH (60% dispersión en aceite, 0,402 g, 10,05 mmol) a temperatura ambiente hasta que la espectrometría de masa y la cromatografía de capa fina (50% acetato de etilo/hexanos) indicaron que la reacción se había completado. Se agregaron cloruro de amonio saturado (15 mL) y agua (50 mL) a la reacción. La reacción se agitó durante 10 minutos. El sólido precipitado se recolectó mediante filtración para proporcionar el producto deseado. ^{1}H RMN (400 MHz) $CDCl_3$ δ 8,78 (s, 1H), 7,88 (s, 1H), 7,82 (s, 3H), 7,68 (s, 1H), 7,58 (s, 1H), 7,44 (s, 1H), 7,16 (s, 3H), 5,54 (s, 2H), 3,87 (s, 3H), 3,67 (t, 2H), 2,46 (s, 3H), 0,97 (t, 2H), 0,01 (s, 9H). La masa se calculó para la fórmula $C_{22}H_{28}N_6O_3SSi$ 484,65; se observó MH^+ (MS) 485,1 (m/z).

EJEMPLO 44

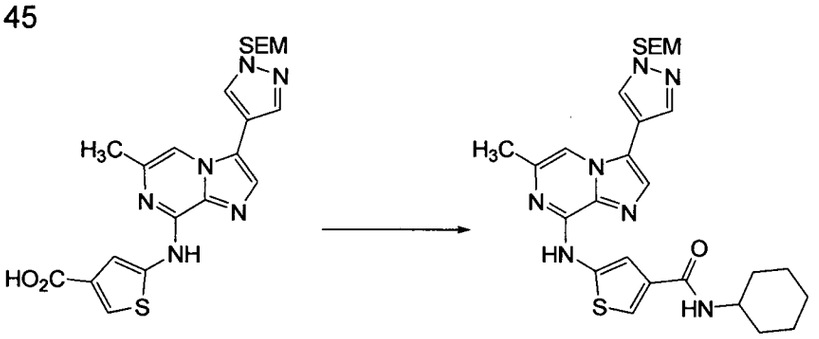


Una solución del éster preparado en el Ejemplo 43 (0,565 g, 1,17 mmol) en THF (10 mL) y MeOH (3 mL) se trató con NaOH sólido (9 microgránulos) seguido por H_2O (5 mL). La reacción se agitó enérgicamente a temperatura ambiente durante 16 horas. El THF y MeOH se removieron al vacío y el residuo se extrajo

814

con EtOAc (3 x 20 mL). La fase acuosa se ajustó hasta un pH de 3–4 con HCl acuoso. La fase acuosa acidificada se extrajo con EtOAc (5 x 20 mL) y concentró al vacío para proporcionar 0,393 g (71%) del ácido carboxílico deseado.

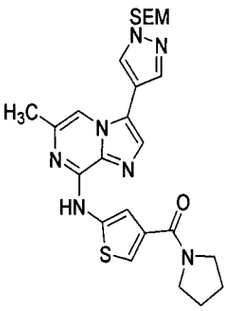
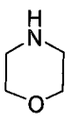
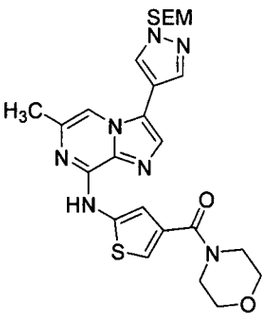
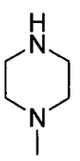
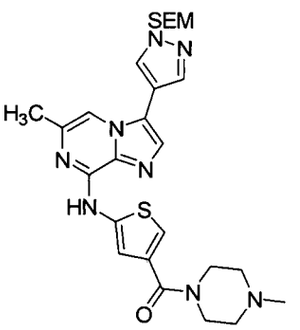
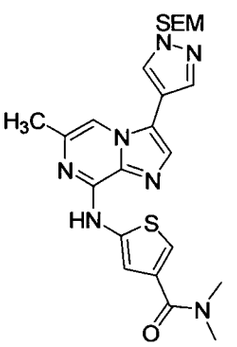
EJEMPLO 45

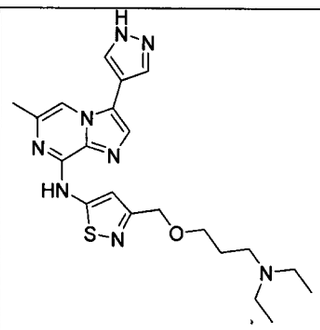
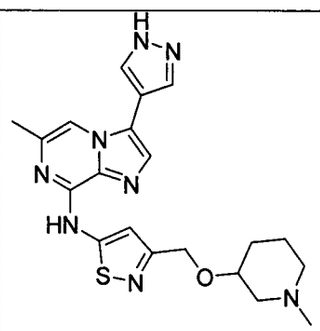
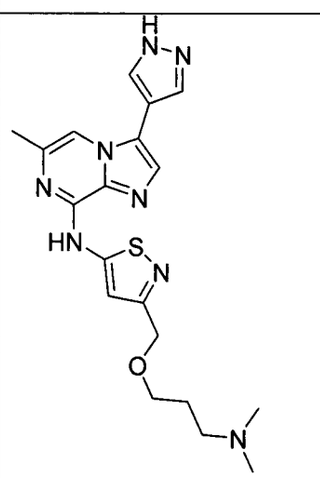
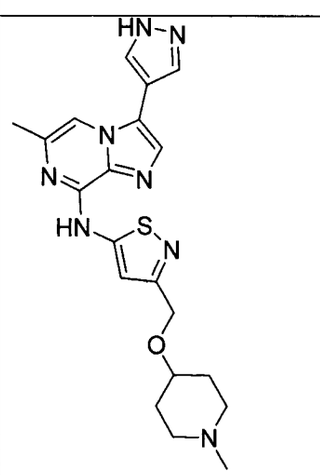


Una solución del ácido carboxílico (preparado en el Ejemplo 4) (0,054 g, 0,115 mmol) en DMF (3 mL) se trató con amina (0,03 mL, 0,262 mmol), NMM (0,07 mL, 0,637 mmol) y luego HATU (0,141 g, 0.372 mmol). La reacción se agitó a temperatura ambiente durante 16 horas. Se agregó agua (15 mL) y la reacción se agitó durante 10 minutos. El sólido precipitado se recolectó mediante filtración para proporcionar 0,038 g (60%) de la amida deseada. ^{1}H RMN (400 MHz) $CDCl_3$ δ 9,13 (s, 1H), 7,86 (s, 1H), 7,80 (s, 3H), 7,54 (s, 1H), 7,41 (s, 1H), 7,31 (s, 1H), 7,08 (s, 3H), 5,83 (d, 1H), 5,53 (s, 2H), 3,93 (m, 1H), 3,67 (t, 2H), 2,44 (s, 3H), 1,70 (m, 10H), 0,96 (t, 2H), 0,00 (s, 9H). La masa se calculó para la fórmula $C_{27}H_{37}N_7O_2SSi$ 551,78; se observó MH^+ (MS) 552,1 (m/z).

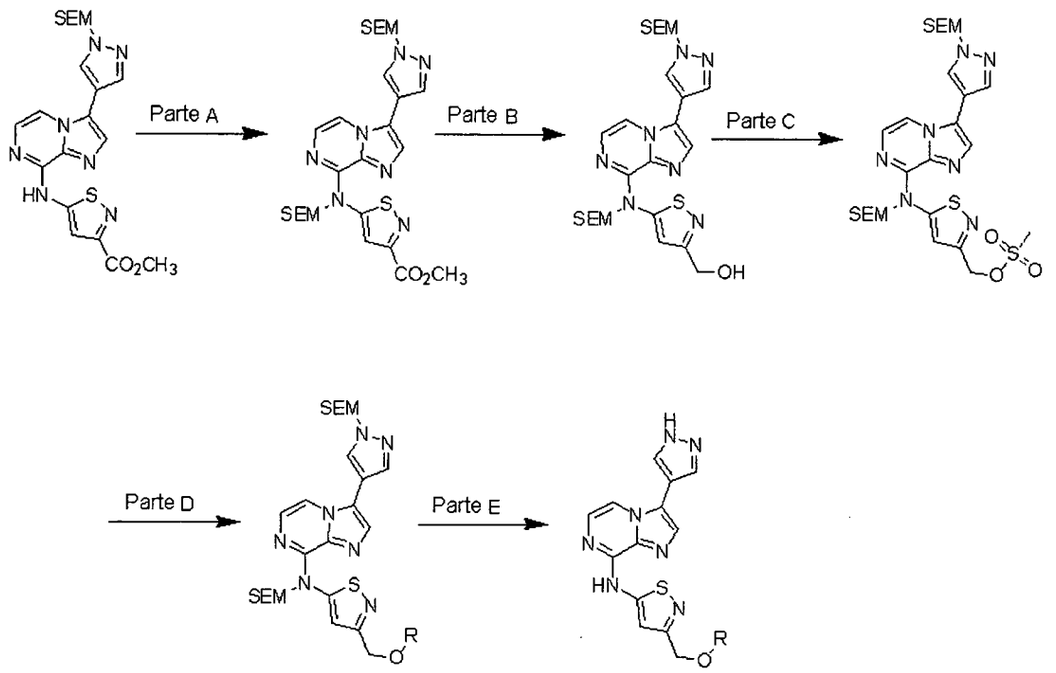
Se prepararon los compuestos en la Columna 3 siguiendo básicamente el mismo procedimiento indicado en el Ejemplo 45 y sólo sustituyendo las aminas ilustradas en la columna 2 de la Tabla 7a (ilustradas inmediatamente a continuación):

TABLA 7a

Ejemplo	Columna 2	Columna 3	PM	MH^+ m/z	LCMS MS t_R
45–1			523,7	524,1	
45–2			539,7	540,2	
45–3			552,8	553,3	
45–4			497,7	498,3	4,16

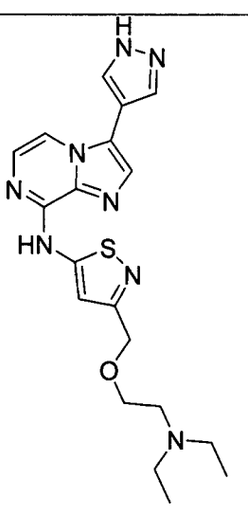
17–4		440,21	441,2	2,75
17–5		424,18	425,2	2,59
17–6		412,18	413,2	2,54
17–7		424,18	425,2	2,61

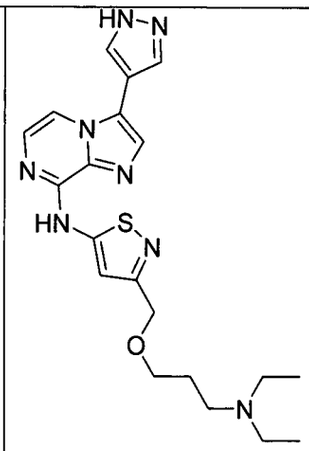
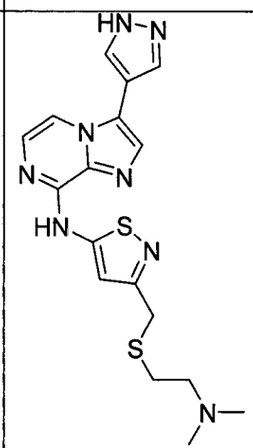
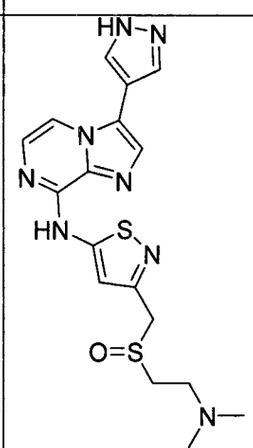
EJEMPLO 18



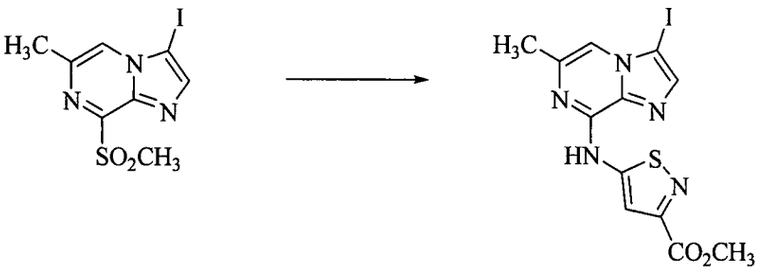
Siguiendo básicamente los mismos procedimientos proporcionados en el Ejemplo de preparación 17 pueden prepararse los compuestos indicados en la Tabla 4 (que se ilustran inmediatamente a continuación).

TABLAE 4

Ejemplo	Columna 2	Masa exacta	MS m/z (M+H)	HPLC MS t_R
18–1		412,18	413,2	2,36

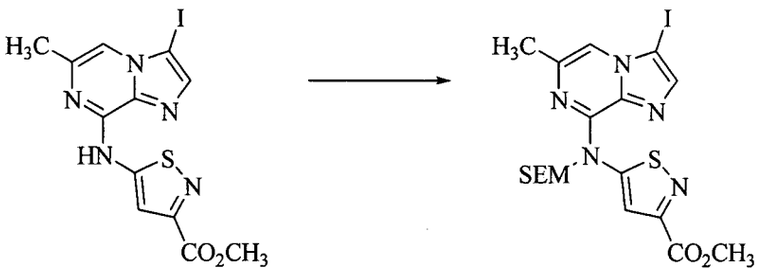
18–2		426,2	427,1	2,71
18–3		400,13	401,1	2,47
18–4		416,12	417,1	2,23

EJEMPLO 19



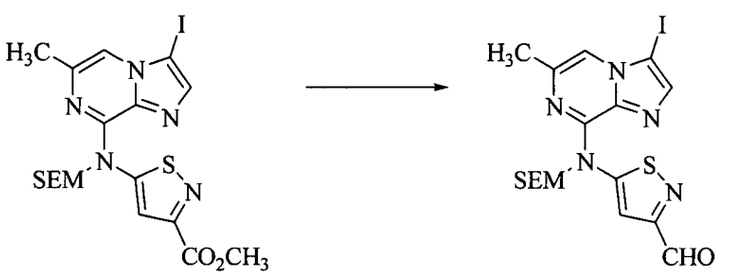
El Ejemplo 19 se preparó de manera similar al Ejemplo 4. ^{1}H RMN (300 MHz, DMSO–d_6) δ 12,4 (bs, 1H), 7,81 (s, 1H), 7,75 (s, 1H), 7,59 (s, 1H), 3,85 (s, 3H), 2,49 (s, 3H).

EJEMPLO 20



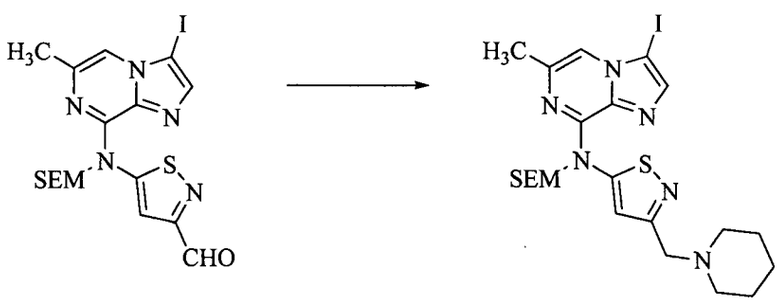
El Ejemplo 20 se preparó de manera similar al Ejemplo 17, Parte A. ^{1}H RMN (300 MHz, $CDCl_3$) δ 7,81 (s, 1H), 7,73 (s, 1H), 7,63 (s, 1H), 6,61 (s, 2H), 3,98 (s, 3H), 3,74 (t, *J* = 8 Hz, 2H), 2,62 (s, 3H), 0,94 (t, *J* = 8 Hz, 2H), –0,83 (s, 9H).

EJEMPLO 21



A una solución agitada de éster (2,40 g, 4,40 mmol) en tetrahidrofurano (96 mL) a –78 °C se agregó DIBAL–H (1M en diclorometano, 11,0 mL, 11,0 mmol) por goteo. La mezcla se agitó a –78 °C durante 3 horas en cuyo tiempo la cromatografía de capa fina (30% acetato de etilo/hexanos) indicó que la reacción se había completado. La mezcla se vertió rápidamente en tartrato de potasio y sodio acuoso saturado con agitación y se agitó a temperatura ambiente durante 14 horas. La mezcla se extrajo con acetato de etilo (2×250 mL), las capas orgánicas se combinaron, se lavaron con salmuera (100 mL), se secaron sobre sulfato de magnesio, se filtraron, y concentraron bajo presión reducida proporcionando el compuesto 21 en forma de un sólido de color amarillo 2,20 g (97%). ^{1}H RMN (300 MHz, $CDCl_3$) δ 9,99 (s, 1H), 7,74 (s, 1H), 7,73 (s, 1H), 7,65 (s, 1H), 6,60 (s, 2H), 3,74 (t, *J* = 8 Hz, 2H), 2,64 (s, 3H), 0,94 (t, *J* = 8 Hz, 2H), –0,07 (s, 9H).

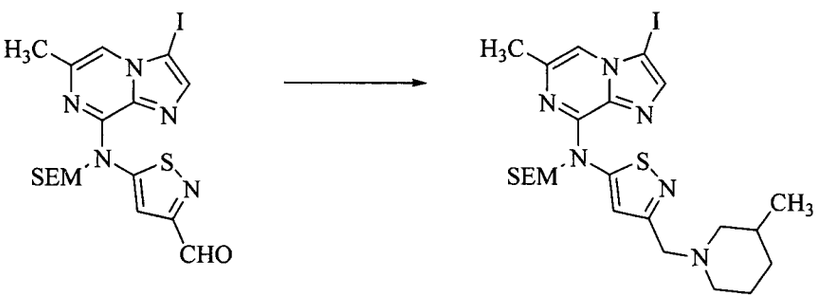
EJEMPLO 22



A una solución agitada de aldehído (1,30 g, 2,52 mmol), piperidina (257 mg, 3,02 mmol), y ácido acético (150 μL, 2,52 mmol) en 1,2–dicloroetano (17 mL) a temperatura ambiente se agregó triacetoxiborohidruro de sodio (801 mg, 3,78 mmol) en una porción. La mezcla se agitó a temperatura ambiente durante 2 horas en cuyo tiempo la cromatografía de capa fina (40% acetato de etilo/hexanos) indicó que la reacción se había completado. La reacción se templó con hidróxido de sodio 1 N (25 mL) y se agitó durante 20 minutos. La mezcla se

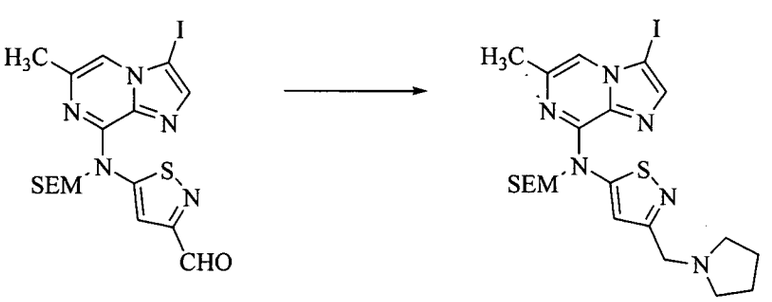
extrajo con cloroformo (3×20 mL), las capas orgánicas se combinaron, se secaron sobre sulfato de sodio, se filtraron y concentraron bajo presión reducida. Proporcionó el compuesto 22 en forma de un sólido de color amarillo 1,35 g (92%). ^{1}H RMN (300 MHz, $CDCl_3$) δ 7,70 (s, 1H), 7,59 (s, 1H), 7,23 (s, 1H), 6,58 (s, 2 H), 3,72 (t, *J* = 8 Hz, 2H), 3,62 (s, 2H), 2,58 (s, 3H), 2,47 (m, 4H), 1,58 (m, 6H), 0,93 (t, *J* = 8 Hz, 2H), –0,086 (s, 9H).

EJEMPLO 23



El Ejemplo 23 se preparó de manera similar al Ejemplo 22 utilizando 3–metilpiperidina en lugar de piperidina. ^{1}H RMN (300 MHz, $CDCl_3$) δ 7,70 (s, 1H), 7,59 (s, 1H), 7,23 (s, 1H), 6,58 (s, 2H), 3,72 (t, *J* = 8 Hz, 2H), 3,62 (s, 2H), 2,85 (m, 2H), 2,59 (s, 3H), 1,98 (m, 1H), 1,65 (m, 6H), 0,93 (t, *J* = 8 Hz, 2H), 0,84 (d, *J* = 6 Hz, 3H), –0,076 (s, 9H).

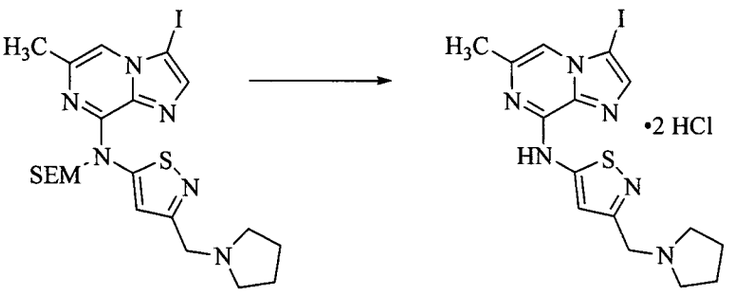
EJEMPLO 24



El Ejemplo 24 se preparó de manera similar al Ejemplo 23 utilizando pirrolidina en lugar de piperidina. ^{1}H RMN (300 MHz, $CDCl_3$) δ 7,70 (s, 1H), 7,59

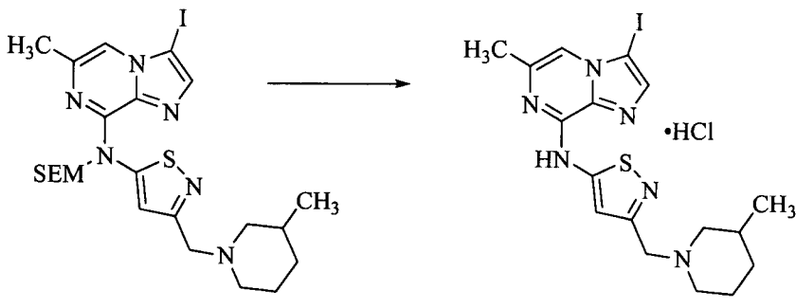
(s, 1H), 7,23 (s, 1H), 6,58 (s, 2H), 3,77 (s, 2H), 3,72 (t, *J* = 8 Hz, 2H), 2,61 (m, 4H), 2,59 (s, 3H), 1,81 (m, 4H), 0,92 (t, *J* = 8 Hz, 2H), –0,90 (s, 9H).

EJEMPLO 25



Una solución de yoduro del Ejemplo 24 (20 mg, 0,035 mmol) en 1,4–dioxano (1 mL) se trató con HCL 4N en 1,4–dioxano (1 mL). La mezcla se sometió a tratamiento de ultrasonido a temperatura ambiente durante 2,5 horas, en cuyo tiempo HPLC determinó que la reacción se había completado. La mezcla se concentró bajo presión reducida y el residuo resultante se purificó mediante HPLC preparativa y la conversión en la sal de clorhidrato proporcionó el compuesto 25 en forma de un sólido de color blanco 15 mg (83%). ^{1}H RMN (300 MHz, CD_3OD) δ 7,88 (s, 1H), 7,79 (s, 1H), 7,17 (s, 1H), 4,51 (s, 2H), 3,71 (m, 2H), 3,22 (m, 2H), 2,57 (s, 3H), 2,07 (m, 4H). HPLC t_R = 4,83 min (UV $_{254\ nm}$). La masa se calculó para la fórmula $C_{15}H_{17}IN_6S$ 440,03; se observó MH^+ (MS) 441,5 (m/z).

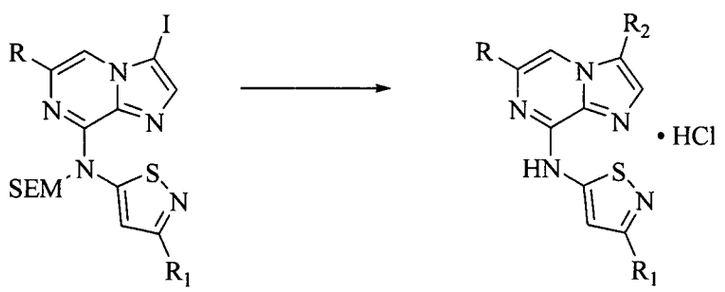
EJEMPLO 26



El Ejemplo 26 se preparó de manera similar al Ejemplo 25. ^{1}H RMN (300 MHz, CD_3OD) δ 7,87 (s, 1H), 7,79 (s, 1H), 7,22 (s, 1H), 4,39 (s, 2H), 3,52 (m, 2H), 2,96 (m, 1H), 2,70 (m, 1H), 2,57 (s, 3H), 1,90 (m, 4H), 1,21 (m, 1H), 0,99 (d, J = 6 Hz, 3H). HPLC t_R = 5,06 min (UV $_{254nm}$). La masa se calculó para $C_{17}H_{21}IN_6S$ 468,3; observed MH^+ (MS) 469,7 (m/z).

EJEMPLO 27

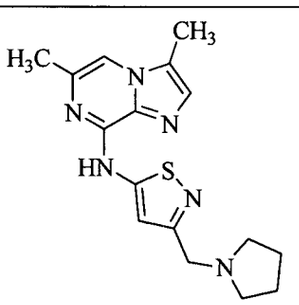
Los compuestos ilustrados en la columna 2 de la Tabla 5 (ilustrados inmediatamente a continuación) se prepararon del siguiente modo:



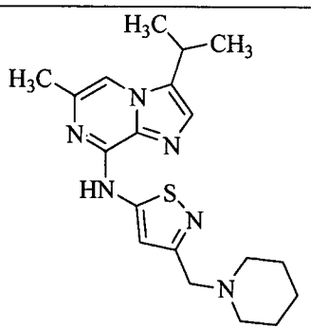
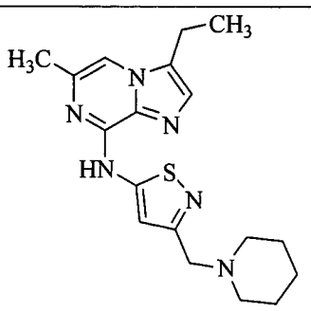
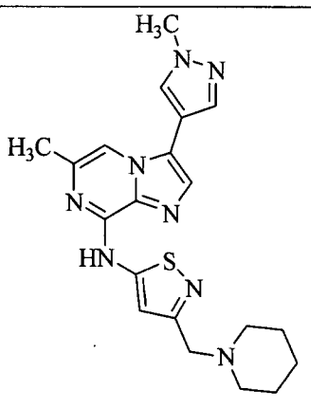
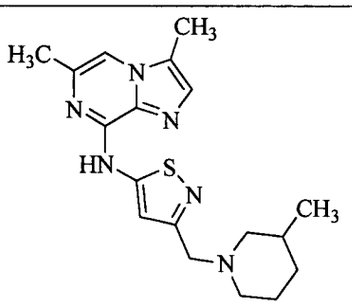
Un frasco que contenía matrices biodegradables preparadas de yoduro de arilo (compuesto del Ejemplo 22, 23, o 24, 1 equivalente), disponibles en el comercio o de fácil preparación en 1 a 3 pasos aril/heteroaril/alquil ácido borónico/éster/boroxina o aril/heteroaril/alquil bromuro de magnesio o aril/heteroaril/alquil cloruro de zinc (1,5 – 3 equivalentes), fosfato de potasio o

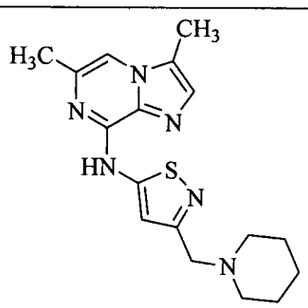
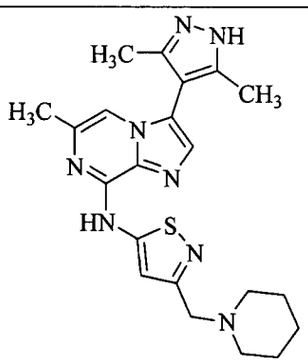
carbonato de potasio (2– 3 equivalentes) y $Pd(PPh_3)_4$ o $PdCl_2$dppf (0,05 – 0,10 equivalentes) se evacuó, rellenó con nitrógeno y repitió. Se agregó 1,4–dioxano o N,N–dimetilformamida o 1,2–dimetoxietano (1 – 3 mL) y la mezcla se agitó a 50 – 130 °C hasta que la reacción se completó según se determinó mediante cromatografía de capa fina (acetato de etilo/hexanos) o HPLC. La mezcla se diluyó con agua (3 – 10 mL) y se extrajo con acetato de etilo (2–3 × 10–30 mL). Las capas orgánicas se combinaron, se lavaron con salmuera (15 – 30 mL), se secaron sobre sulfato de magnesio, se filtraron, concentraron, y purificaron mediante cromatografía en columna (SiO_2, acetato de etilo/hexanos). El producto obtenido se disolvió en 1,4–dioxano (1 mL) y se trató con HCl 4 N en 1,4–dioxano (1 mL) y se sometió a tratamiento de ultrasonido a temperatura ambiente durante 1–5 horas, en cuyo tiempo HPLC determinó que la reacción se había completado. La mezcla se concentró bajo presión reducida y el residuo resultante se purificó mediante HPLC preparativa y la conversión en la sal de clorhidrato proporcionó los compuestos 27–1 a 27–7.

TABLA 5

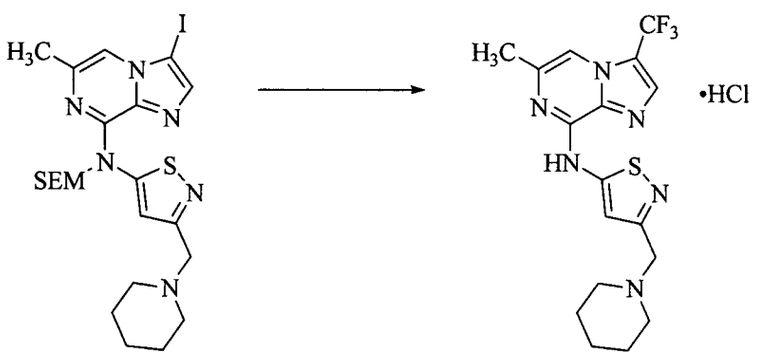
Ejemplo	Columna 2	PM	MS MH^+ m/z	HPLC t_R
27–1		328,4	329,1	3,52

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27–2		370,5	371,1	4,34
27–3		356,4	357,4	3,98
27–4		408,5	409,6	4,21
27–5		356,4	357,4	3,91

27–6		342,4	343,2	3,71
27–7		422,5	423,2	3,87

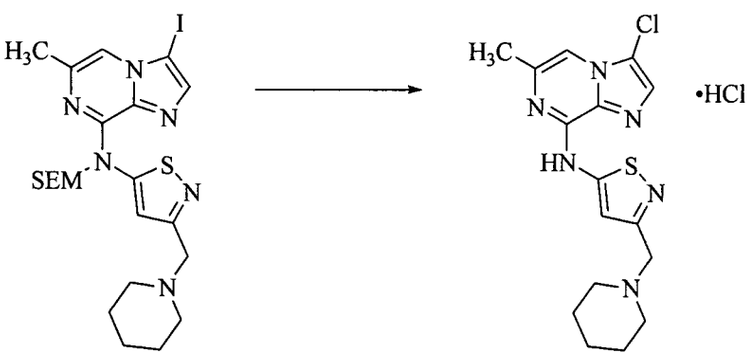
EJEMPLO 28



Una mezcla de yoduro (60 mg, 0,103 mmol), trimetil(trifluorometil)silano (44 mg, 0,308 mmol), yoduro de cobre (73 mg, 0,385 mmol), fluoruro de potasio (15 mg, 0,257 mmol), y DMF anhidro (1,0 mL) se desgasificó con nitrógeno, luego se calentó a 80 °C en un tubo sellado hasta la mañana siguiente. La mezcla se enfrió hasta temperatura ambiente, se diluyó con agua (30 mL), y se extrajo con acetato de etilo (100 mL). La capa orgánica se secó sobre sulfato de sodio, se filtró, concentró bajo presión reducida, y purificó mediante cromatografía en columna (SiO_2, 90:10:0.25 cloruro de metileno/metanol/hidróxido de amonio concentrado). El residuo resultante se disolvió en 1,4–dioxano anhidro (1mL) y se

agregó HCl 4 M en dioxano (1 mL). La solución resultante se sometió a tratamiento de ultrasonido a temperatura ambiente durante 2 horas y se concentró bajo presión reducida hasta sequedad. La purificación mediante HPLC preparativa y la conversión en la sal de clorhidrato proporcionó el compuesto del título en forma de un sólido de color blancuzco 3,1 mg (6%). ^{1}H RMN (300 MHz, CD_3OD) δ 8,07 (s, 1H), 7,85 (s, 1H), 7,24 (s, 1H), 4,40 (s, 2H), 3,61 (d, *J* = 12,3 Hz, 2H), 3,07 (t, *J*= 12,3 Hz, 2H), 2,55 (s, 3H), 1,75–2,03 (m, 5H), 1,56 (m, 1H). HPLC t_R = 7,19 min. La masa se calculó para la fórmula $C_{17}H_{19}F_3N_6S$ 396,13; se observó MH^+ 397,2 (m/z).

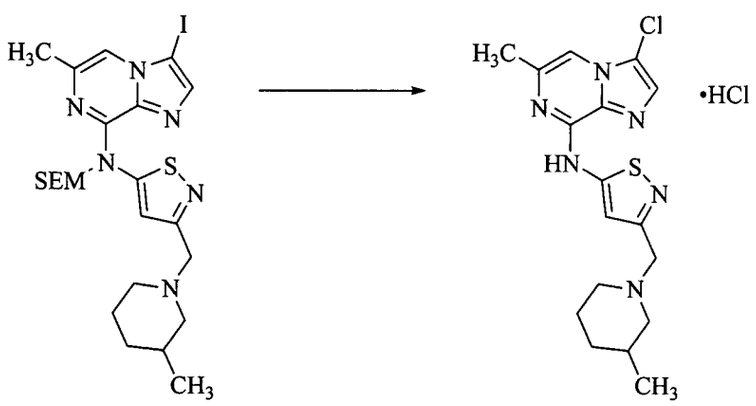
EJEMPLO 29



Una mezcla de yoduro (100 mg, 0,171 mmol) en THF anhidro (2,0 mL) se enfrió hasta –78 °C y se agregó por goteo *n–butil* litio (solución 2,5 M en hexanos, 89 µL, 0,222 mmol). Luego de agitar durante 15 minutos se agregó por goteo una solución de hexacloroetano (45 mg, 0,188 mmol) en THF (1,0 mL). Luego de agitar la reacción a –78 °C durante 30 minutos, la solución se templó con una solución acuosa saturada de cloruro de amonio (3,0 mL) y se calentó hasta temperatura ambiente. La reacción se concentró bajo presión reducida, se extrajo con acetato de etilo (50 mL) y la capa orgánica se secó sobre sulfato de sodio, se filtró, concentró bajo presión reducida, y purificó mediante cromatografía en columna (SiO_2, 90:10:0.25 cloruro de metileno/metanol/hidróxido de amonio concentrado). El residuo resultante se disolvió en 1,4–dioxano anhidro (1mL) y se

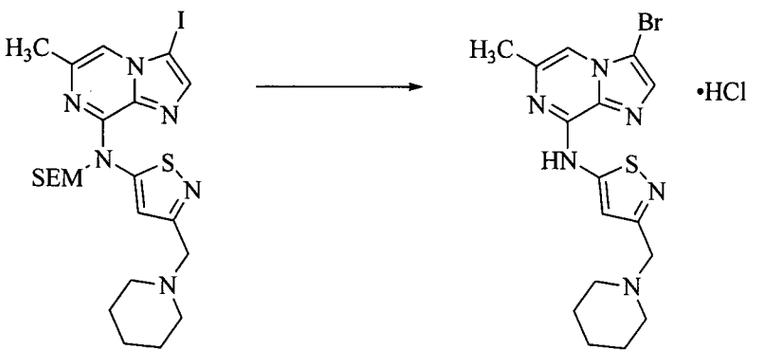
agregó HCl 4 M en dioxano (1 mL). La solución resultante se sometió a tratamiento de ultrasonido a temperatura ambiente durante 2 horas y se concentró bajo presión reducida hasta sequedad. La purificación mediante HPLC preparativa y la conversión en la sal de clorhidrato proporcionó el compuesto del título en forma de un sólido de color blancuzco 30 mg (40%). ^{1}H RMN (300 MHz, CD_3OD) δ 7,80 (s, 1H), 7,73 (s, 1H), 7,22 (s, 1H), 4,39 (s, 2H), 3,59 (d, *J* = 12,3 Hz, 2H), 3,08 (t, *J*= 12,3 Hz, 2H), 2,55 (s, 3H), 1,75–2,03 (m, 5H), 1,56 (m, 1H). HPLC t_R = 4,79 min. La masa se calculó para la fórmula $C_{16}H_{19}ClN_6S$ 362,11; se observó MH^+ 363,7 (m/z).

EJEMPLO 30



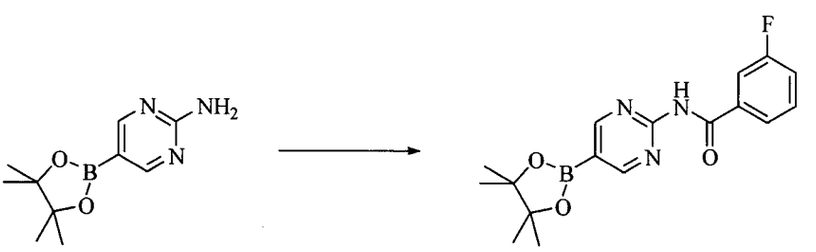
El Ejemplo 30 se preparó de manera similar que el Ejemplo 29. ^{1}H RMN (300 MHz, CD_3OD) δ 7,77 (s, 1H), 7,68 (s, 1H), 7,20 (s, 1H), 4,39 (s, 2H), 3,47–3,67 (m, 2H), 2,97 (m, 1H), 2,71 (m, 1H), 2,55 (s, 3H), 1,77–2,01 (m, 4H), 1,20 (m, 1H), 1,00 (d, *J* = 6,4 Hz, 3H). HPLC t_R = 4,98 min. La masa se calculó para la fórmula $C_{17}H_{21}ClN_6S$ 376,12; se observó MH^+ 377,6 (m/z).

EJEMPLO 31



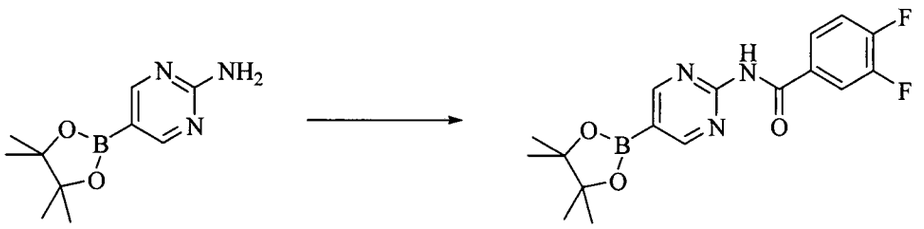
El Ejemplo 31 se preparó de manera similar al compuesto 29 utilizando tetraclorodibromoetano en lugar de hexacloroetano. ^{1}H RMN (300 MHz, CD_3OD) δ 7,84 (s, 1H), 7,83 (s, 1H), 7,25 (s, 1H), 4,41 (s, 2H), 3,61 (d, *J* = 12,3 Hz, 2H), 3,08 (t, *J*= 12,3 Hz, 2H), 2,57 (s 3H), 1,77–2,03 (m, 5H), 1,55 (m, 1H). HPLC t_R = 5,19 min. La masa se calculó para la fórmula $C_{16}H_{19}BrN_6S$ 406,06; se observó MH^+ 407,4 (m/z).

EJEMPLO 32



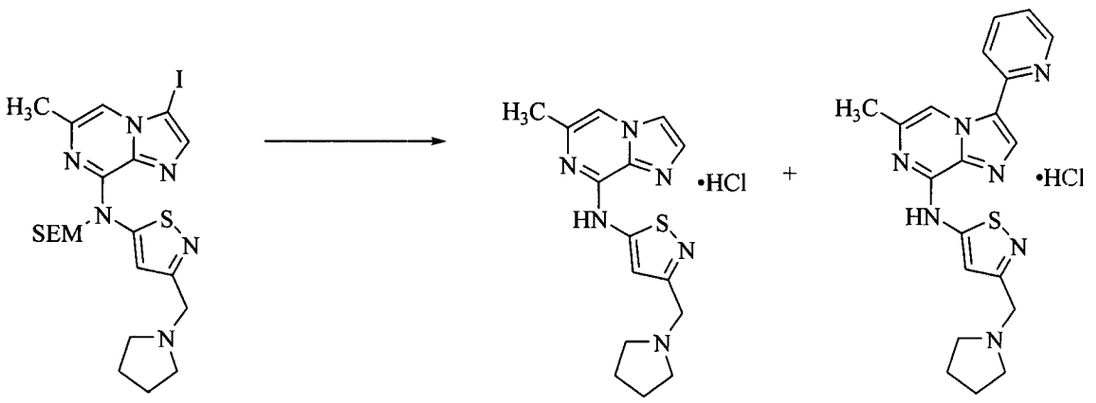
A una solución de aminopirimidina (100 mg, 0,452 mmol) en piridina anhidro (2,0 mL) se agregó cloruro de 3–fluorobenzoílo (72 mg, 0,452 mmol). Luego de agitar a temperatura ambiente hasta la mañana siguiente, la reacción se concentró bajo presión reducida, se diluyó con agua (30 mL), y se extrajo con cloruro de metileno (100 mL). La capa orgánica se secó sobre sulfato de sodio, se filtró y se concentró para proporcionar el compuesto del título en forma de un sólido de color blancuzco 124 mg (80%). ^{1}H RMN (300 MHz, $CDCl_3$) δ 8,95 (s, 2H), 8,72 (s, 1H), 7,66–7,72 (m, 2H), 7,49 (m, 2H), 1,36 (s, 12H).

EJEMPLO 33



Se preparó de manera similar al compuesto 31 proporcionando el compuesto del título en forma de un sólido de color blancuzco 131 mg (80%). ^{1}H RMN (300 MHz, $CDCl_3$) δ 8,93 (s, 2H), 8,65 (s, 1H), 7,83 (m, 1H), 7,69 (m, 1H), 7,30 (m, 1H), 1,34 (s, 12H).

EJEMPLO 34

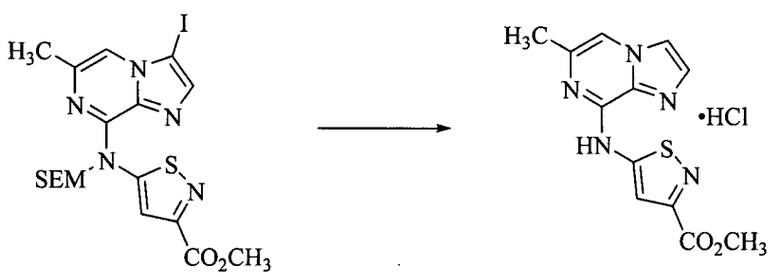


Una mezcla de yoduro (60 mg, 0,103 mmol), tri–*n*–butil(piridil)estaño (57 mg, 0,154 mmol), aducto de dicloro[1,1'–bis(difenilfosfino)ferroceno]paladio(II) diclorometano (8 mg, 0,0103 mmol), y fluoruro de potasio (18 mg, 0,309 mmol) en 1,4–dioxano anhidro (1.0 mL) se desgasificó con nitrógeno, luego se calentó a 85 °C en un tubo sellado hasta la mañana siguiente. La mezcla se enfrió hasta temperatura ambiente, se diluyó con agua (30 mL), y se extrajo con acetato de etilo (2 × 100 mL). La capa orgánica luego se separó, se secó sobre sulfato de sodio, se filtró, concentró bajo presión reducida hasta obtener un residuo, y se purificó mediante cromatografía en columna (SiO_2, 90:10:0,25 cloruro de metileno/metanol/ hidróxido de amonio concentrado). El residuo resultante luego

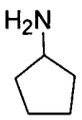
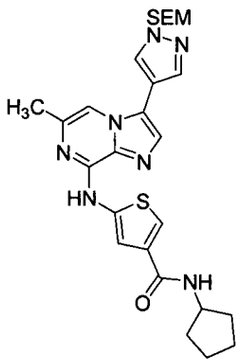
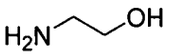
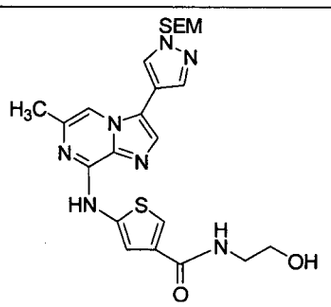
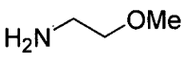
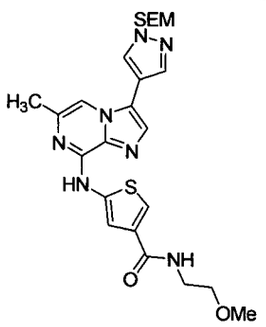
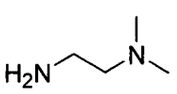
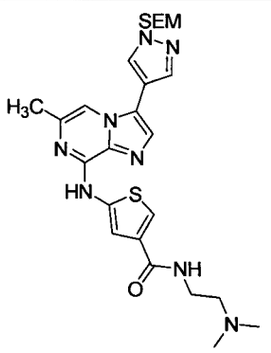
se disolvió en 1,4–dioxano anhidro (1mL) y se agregó HCl 4 M en dioxano (1 mL). La solución resultante se sometió a tratamiento de ultrasonido a temperatura ambiente durante 2 horas y luego se concentró bajo presión reducida hasta sequedad. La purificación mediante HPLC preparativa y la conversión en la sal de clorhidrato proporcionó el producto deshalogenado 3,2 mg (10%) en forma de un sólido de color blancuzco: ^{1}H RMN (300 MHz, CD_3OD) δ 8,23 (s, 1H), 8,13 (s, 2H), 7,29 (s, 1H), 4,55 (s, 2H), 3,72 (s ancho, 2H), 3,29 (m, 2H), 2,61 (s, 3H), 2,05–2,18 (m, 4H). HPLC t_R =3,49 min. La masa se calculó para la fórmula $C_{15}H_{16}N_6S$ 314,13; se observó MH^+ 315,2 (m/z).

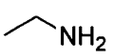
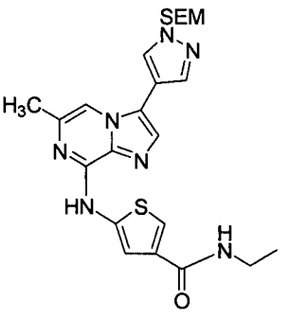
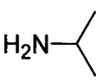
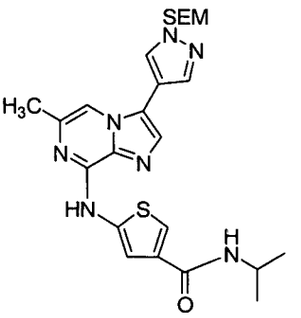
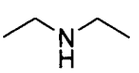
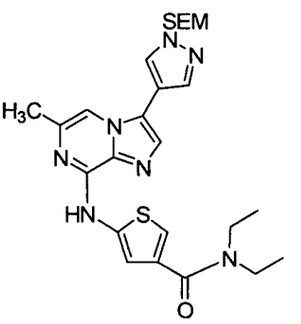
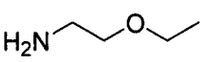
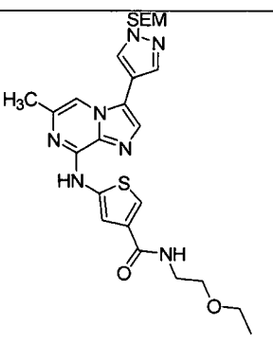
También proporcionó un producto de acoplamiento 5,0 mg (10%) en forma de un sólido de color blancuzco: ^{1}H RMN (300 MHz, CD_3OD) δ 8,95 (s, 1H), 8,86 (d, *J* = 5,1 Hz, 1H), 8,50 (s, 1H), 8,28 (t, *J* = 7,5 Hz, 1H), 8,18 (d, *J* = 7,8 Hz, 1H), 7,70 (t, *J* = 6,3 Hz, 1H), 7,26 (s, 1H), 4,54 (s, 2H), 3,74 (m, 2H), 3,29 (m, 2H), 1,99–2,30 (m, 4H). HPLC t_R =4,80 min. La masa se calculó para la fórmula $C_{20}H_{21}N_7S$ 391,16; se observó MH^+ 392,5 (m/z).

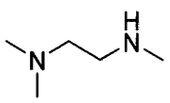
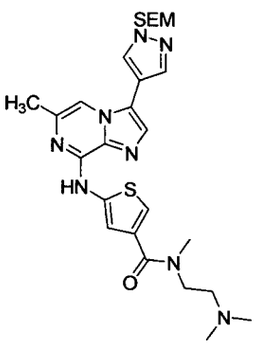
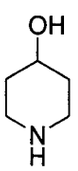
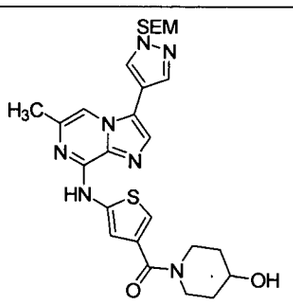
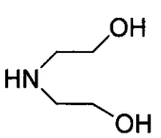
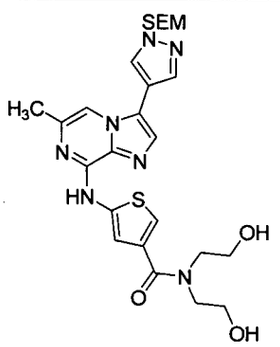
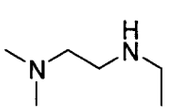
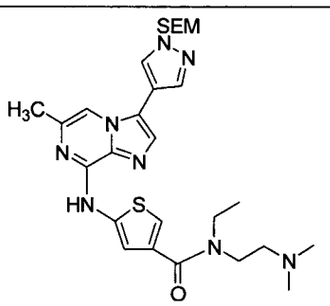
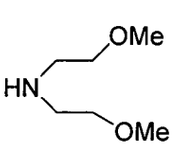
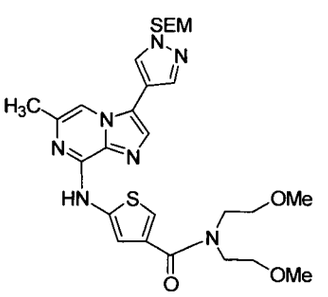
EJEMPLO 35

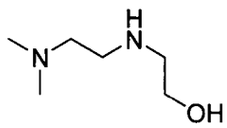
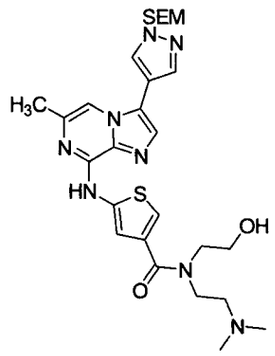
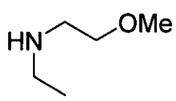
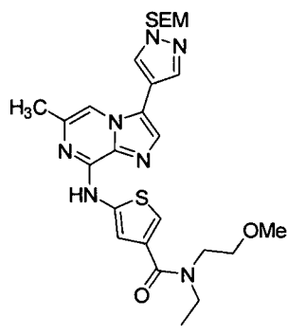


Se agregó borohidruro de sodio (3 mg, 0,073 mmol) a una suspensión de yoduro a temperatura ambiente (15 mg, 0,037) en metanol (1 mL). La reacción se dejó agitar durante 30 minutos, luego se templó con agua (20 mL). La mezcla se diluyó con éter dietílico (20 mL) y se permitió que las fases se separaran. La capa orgánica se secó (sulfato de sodio), se filtró y se concentró para proporcionar un intermediario deshalogenado protegido. El producto reducido (7 mg, 0,017 mmol)

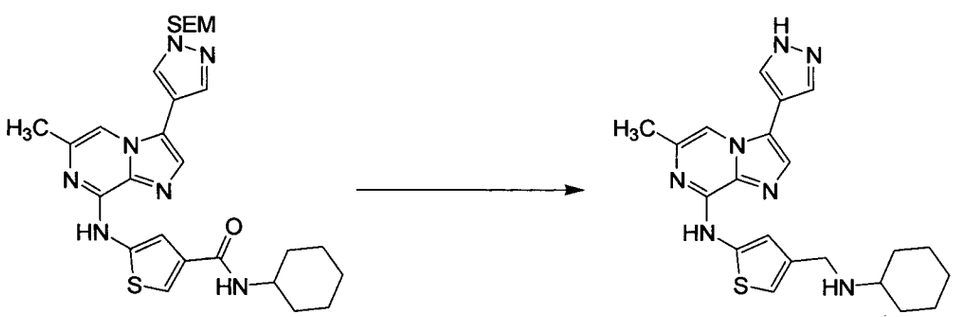
45–5			537,8	538,1	
45–6			513,7	514,3	
45–7			527,7	528,2	
45–8			540,8	541,2	

45–9			497,7	498,1	
45–10			511,7	512,1	
45–11			525,7	526,1	
45–12			541,7	542,2	

45–13			554,8	555,3	
45–14			553,8	554,2	
45–15			557,7	558,2	
45–16			568,8	569,2	
45–17			585,8	586,2	

45–18			584,8	585,2	
45–19			555,8	556,3	4,37

EJEMPLO 46

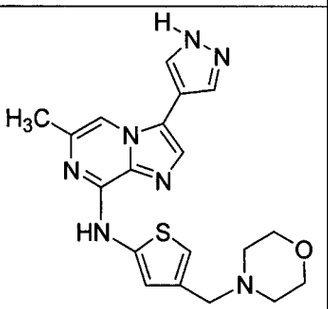
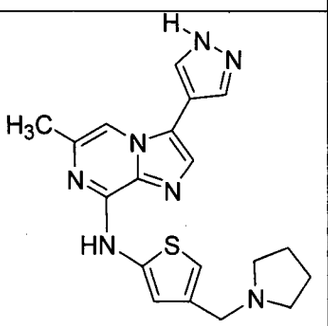
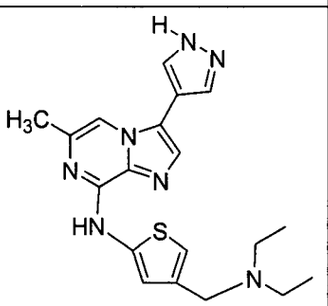


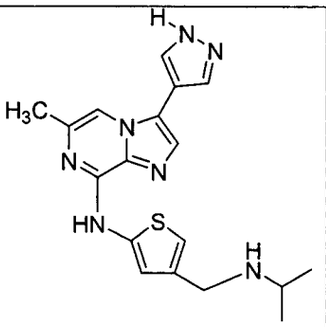
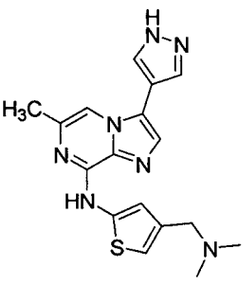
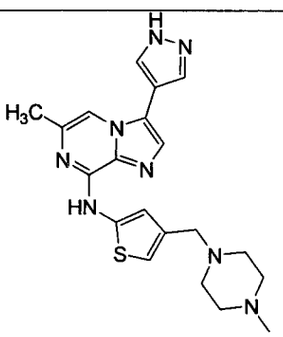
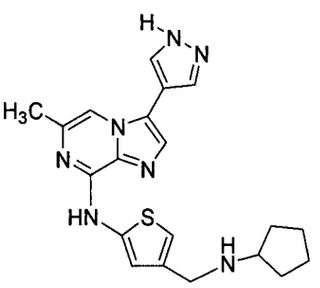
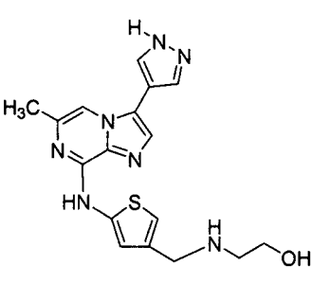
A una solución de la amida (0,038 g, 0,069 mmol) en diclorometano (4 mL) se agregó hidruro de litio y aluminio (0,029 g, 0,775 mmol) y éter de etilo (0,8 mL). La mezcla de reacción se agitó a temperatura ambiente durante 10 min, luego se sometió a reflujo a 40° C durante 5 horas. La reacción se monitoreó mediante espectrometría de masa. Luego de consumirse la amida de partida, la reacción se enfrió hasta TA (temperatura ambiente) y se templó con H_2O (2 mL). La reacción se diluyó con DCM y se filtró. El filtrado se lavó con H_2O (≤ 8 mL). La capa orgánica se concentró para proporcionar 0,019 g (52 %) de la amina. La amina anterior en THF se trató posteriormente con HCl 4 N/dioxano a 60 °C durante 1 h.

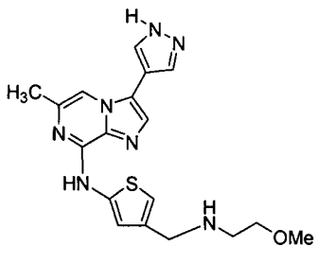
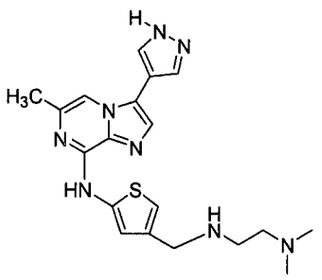
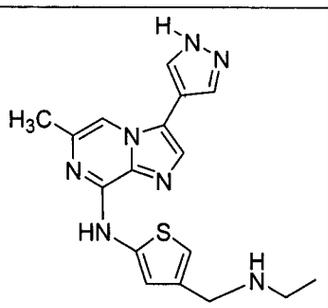
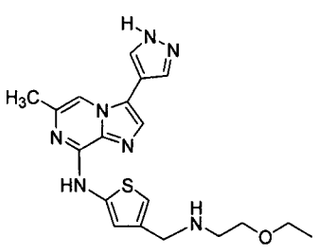
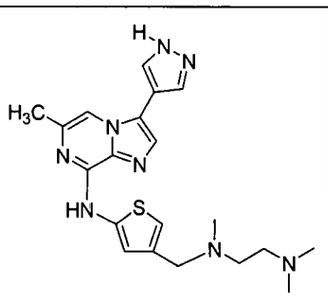
Luego de enfriarse a TA, se agregó Et_2O y la mezcla se agitó durante 10 min. El sólido precipitado se recolectó proporcionando 13,9 mg (96 % de rendimiento) de la amina deseada.

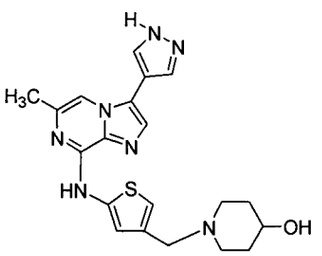
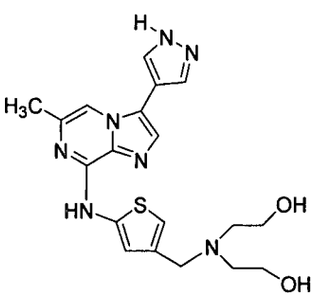
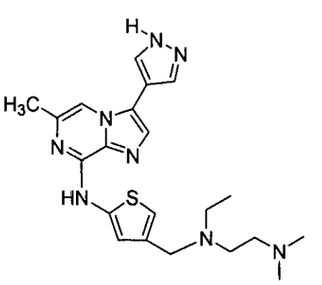
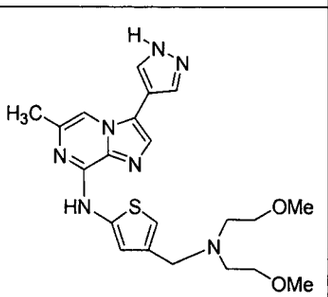
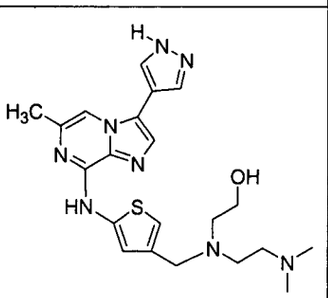
Siguiendo básicamente el mismo procedimiento indicado en el Ejemplo 46, se prepararon los siguientes compuestos ilustrados en la columna 2 de la Tabla 7 (que aparecen inmediatamente a continuación):

TABLA 7

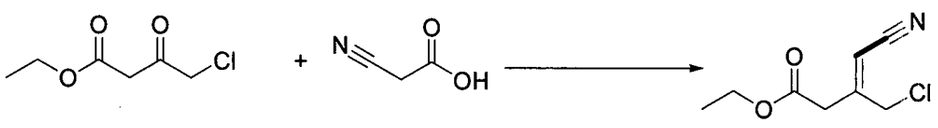
Ejemplo	Columna 2	PM	LCMS MH^+ m/z	LCMS MS t_R
46–1		395,5	396,2	2,06
46–2		379,5	381,2	2,12
46–3		381,5	382,2	2,03

46–4		367,5	368,2	1,95
46–5		353,4	354,2	1,97
46–6		408,5	409,2	1,77
46–7		393,5	394,2	2,06
46–8		369,4	370,2	1,76

46–9		383,5	384,2	1,78
46–10		396,5	397,2	1,52
46–11		353,4	354,2	1,79
46–12		397,5	398,2	1,93
46–13		410,5	411,2	1,76

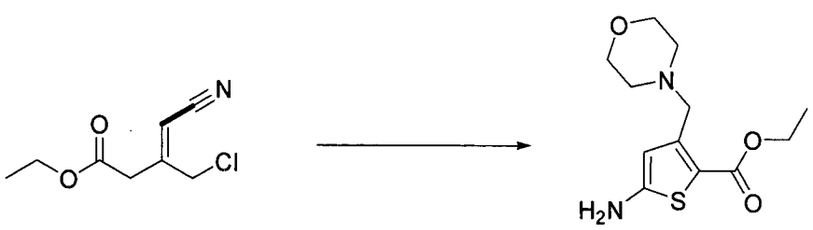
46–14		409,5	410,2	1,94
46–15		413,5	414,2	1,87
46–16		424,6	425,2	1,80
46–17		441,6	442,2	2,23
46–18		440,6	441,2	1,78

EJEMPLO 47



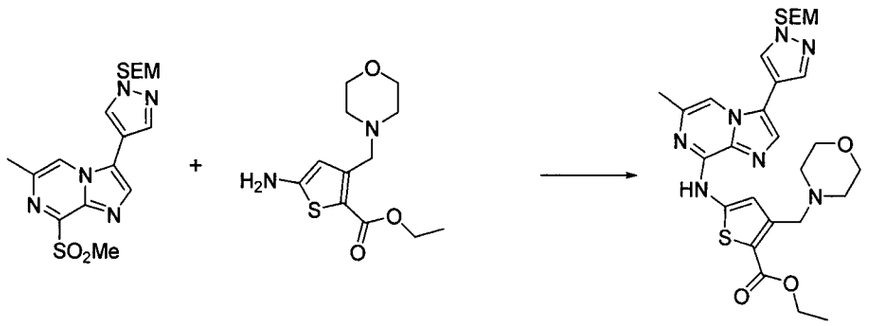
4–Cloro–3–oxobutanoato de etilo (14,15 g, 86 mmol), ácido cianoacético (8,00 g, 86 mmol), NH_4OAc (1,32 g, 17,2 mmol), AcOH (2,46 mL, 43 mmol), y benceno (40 mL) se agitaron hasta la mañana siguiente a reflujo con una trampa Dean–Stark. La mezcla se enfrió hasta temperatura ambiente, se diluyó con EtOAc, se lavó con $NaHCO_3$ sat., salmuera, se secó con Na_2SO_4, y se concentró para proporcionar el producto en bruto 1 (9,29g, 58%). HPLC–MS t_R =1,67 Min (UV $_{254nm}$). La masa se calculó para M+ 187,0; se observó LC/MS m/z 188,1(M+H).

EJEMPLO 48



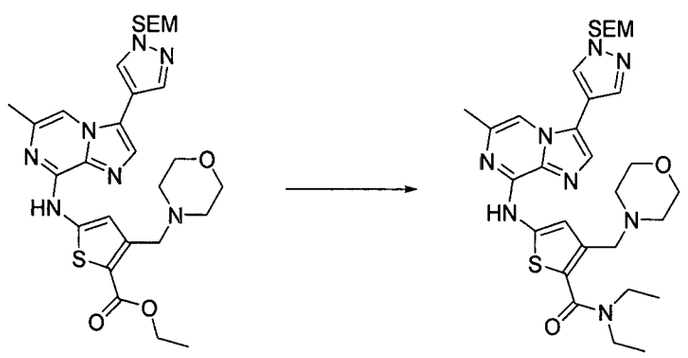
Se agregó morfolina (580 µL, 6,65 mmol) por goteo a una mezcla de 3–(clorometil)–4–cianobut–3–enoato de etilo (622 mg, 3,33 mmol) y copos de S–(116 mg, 3,63 mmol) en EtOH (5 mL). La reacción se agitó a temperatura ambiente hasta la mañana siguiente. La mezcla se concentró. La mezcla se diluyó con EtOAc, se lavó con salmuera, se secó con Na_2SO_4, y se concentró para proporcionar el producto en bruto. La purificación mediante LC preparativa proporcionó el compuesto del título (182 mg, 20%). HPLC–MS t_R = 0,80 Min (UV $_{254nm}$). La masa se calculó para M+ 270,1; se observó LC/MS m/z 271,1(M+H).

EJEMPLO 49



Una solución de 5–amino–3–(morfolinometil)tiofeno–2–carboxilato de etilo (61,0 mg, 0,225 mmol) y sulfona (71,0 mg, 0,173 mmol) en DMF (2 mL) se trató con NaH (60% dispersión en aceite, 20,9 mg, 0,521 mmol) a temperatura ambiente. La mezcla se agitó a temperatura ambiente hasta que LCMS indicó que la reacción se había completado. La mezcla de reacción se diluyó con EtOAc, se lavó con NH_4Cl sat., se secó con Na_2SO_4, y se concentró para proporcionar el compuesto del título. HPLC–MS t_R = 1,79 Min (UV $_{254nm}$). La masa se calculó para M+ 597,2; se observó LC/MS m/z 598,3(M+H).

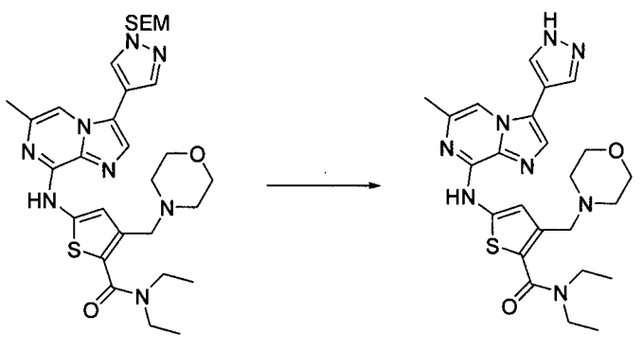
EJEMPLO 50



Una solución de *i*–PrMgCl en THF (0,78 µL, 1,56 mmol) se agregó por goteo a una solución del compuesto en bruto del Ejemplo 49 (104,2 mg, 0,173 mmol) y dietilamina (91 µL, 0,782 mmol) en THF (3 mL) a –20°C. La mezcla se calentó lentamente hasta temperatura ambiente y se agitó a dicha temperatura hasta que LCMS indicó que la reacción se había completado. La mezcla de

reacción se enfrió hasta 0°C y se templó con NH_4Cl saturado. La mezcla de reacción se extrajo con EtOAc y la capa orgánica se secó con Na_2SO_4 y se concentró para proporcionar el producto en bruto 4. HPLC–MS t_R = 1,81 Min (UV $_{254nm}$). La masa se calculó para M+ 624,3; se observó LC/MS m/z 625,3(M+H).

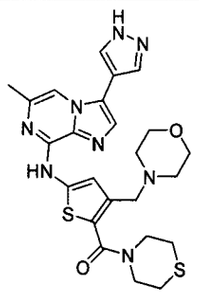
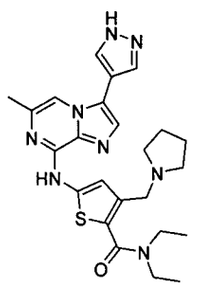
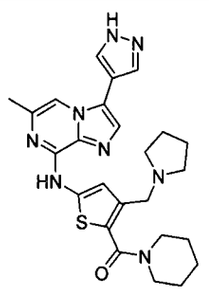
EJEMPLO 51



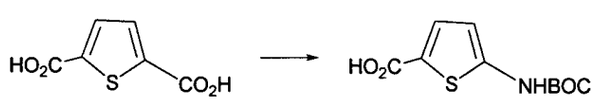
Se agregó HCL 4N en dioxano (1mL) al compuesto en bruto 4 (17mg, 0,027 mmol) a 0°C. La mezcla se calentó hasta temperatura ambiente y se agitó a dicha temperatura hasta que LCMS indicó que la reacción se había completado. La concentración y purificación mediante LC preparativa y la conversión a una sal clorhidrica proporcionaron el compuesto del título. HPLC–MS t_R = 1,14 Min (UV $_{254nm}$). La masa se calculó para M+ 494,2; se observó LC/MS m/z 495,2(M+H).

Siguiendo básicamente el mismo procedimiento, pueden prepararse los compuestos proporcionados en la Columna 2 de la Tabla 8 (ilustrados inmediatamente a continuación).

Tabla 8

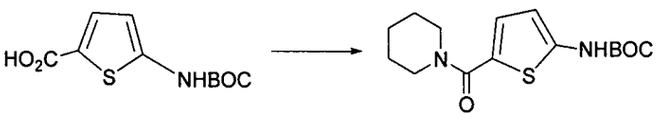
Ejemplo	Columna 2	PM	LCMS MH^+ m/z	LCMS MS t_R
51–1		524,2	525,2	1,328
51–2		478,2	479,2	1,355
51–3		490,2	491,2	1,099

EJEMPLO 52



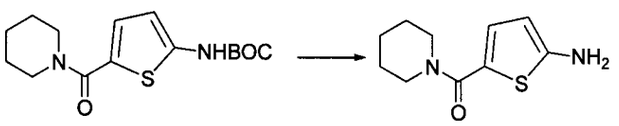
Una solución del ácido tiofeno–2,5–dicarboxílico (2,73 g, 15,84 mmol), azida de difenilfosforilo (3,41 mL g, 15,84 mmol) y trietilamina (4,4 mL, 31,68 mmol) en terc–butanol (80 mL) se calentó a reflujo durante 5 h. La mezcla de reacción se enfrió hasta temperatura ambiente y luego se concentró para proporcionar el compuesto en bruto del título. HPLC–MS t_R =1,52 Min (UV $_{254nm}$). La masa se calculó para M+ 243,0; se observó LC/MS m/z 244,1(M+H).

EJEMPLO 53



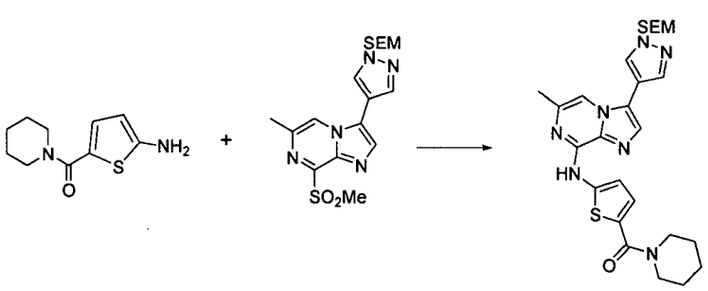
Se agregó Et_3N (1261,6 µL, 9.05 mmol) a 0°C a una mezcla del ácido 5–terc–butoxicarbonilamino–tiofeno–2–carboxílico (550 mg, 2,26mmol), EDCI (1086 mg, 5,65 mmol), y piperidina (447 µL, 4,52 mmol) en DMF (6 ml). La mezcla de reacción se calentó hasta temperatura ambiente y se agitó a dicha temperatura hasta la mañana siguiente. La mezcla se diluyó con EtOAc, se lavó con salmuera (2X), se secó sobre Na_2SO_4 y se concentró para proporcionar el residuo en bruto. La purificación mediante Biotage proporcionó el compuesto 2 (368 mg, 53%). HPLC–MS t_R =1,89 Min (UV $_{254nm}$). La masa se calculó para M+ 310,1; se observó LC/MS m/z 311,2 (M+H). HPLC–MS t_R =2,4 Min (UV $_{254nm}$).

EJEMPLO 54



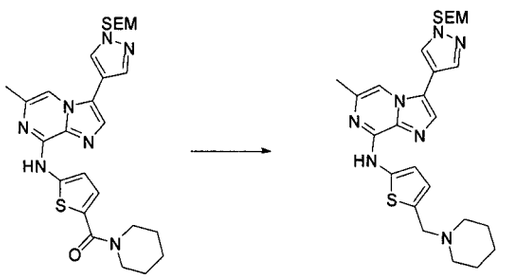
El Compuesto del Ejemplo 53 (90 mg, 0,29 mmol) se agitó en solución 20% de TFA / CH_2Cl_2 (5 mL) a temperatura ambiente durante 1,5 horas. La mezcla de reacción se concentró para proporcionar el compuesto 3. El producto en bruto se usó sin purificación posterior. HPLC–MS t_R =1,16 Min (UV $_{254nm}$). La masa se calculó para M+210,0; se observó LC/MS m/z 211,1 (M+H).

EJEMPLO 55



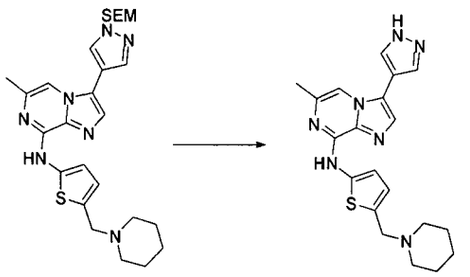
Una solución de material en bruto del Ejemplo 54 y sulfona (98,0 mg, 0,241 mmol) en DMF (2 mL) se trató con NaH (60% dispersión en aceite, 29,0 mg, 0,725 mmol) a temperatura ambiente. La mezcla se agitó hasta que LCMS indicó que la reacción se había completado. La mezcla de reacción se diluyó con EtOAc, se lavó con NH_4Cl sat., se secó con Na_2SO_4, y se concentró para proporcionar el producto en bruto 4. La purificación mediante Biotage proporcionó el compuesto del título (82 mg, 63%). HPLC–MS t_R = 2,30 Min (UV $_{254nm}$). La masa se calculó para M+ 537,2; se observó LC/MS m/z 538,2(M+H).

EJEMPLO 56



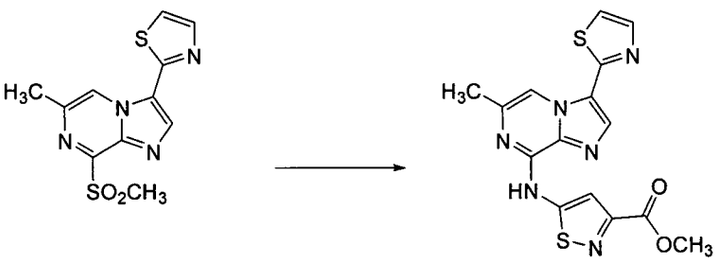
A una solución de la amida (47,6 mg, 0,089 mmol) en diclorometano (5 mL) se agregó hidruro de litio y aluminio (39,9 mg, 1,0 mmol) y éter de etilo (1 mL). La mezcla de reacción se agitó a temperatura ambiente durante 10 min, luego se sometió a reflujo a 40° C hasta que LCMS indicó que la reacción se había completado. La reacción se enfrió hasta temperatura ambiente y se templó con H_2O (0.5 mL). La reacción se diluyó con diclorometano, se secó sobre Na_2SO_4 y se concentró para proporcionar el compuesto en bruto del título. HPLC–MS t_R = 1,52 Min (UV $_{254nm}$). La masa se calculó para M+ 523,2; se observó LC/MS m/z 524,2 (M+H).

EJEMPLO 57



Se agregó HCL 4N en dioxano (2mL) al compuesto en bruto del Ejemplo 56 a 0°C. La mezcla se calentó hasta temperatura ambiente y se agitó a dicha temperatura hasta que LCMS indicó que la reacción se había completado. La concentración proporcionó el compuesto en bruto del título. La purificación mediante LC preparativa y la conversión a una sal clorhidrica proporcionaron el compuesto del título. HPLC–MS t_R = 0,91 Min (UV $_{254nm}$). La masa se calculó para M+ 393,1; se observó LC/MS m/z 394,1 (M+H).

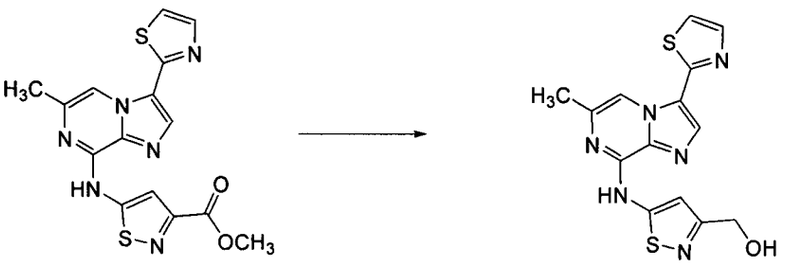
EJEMPLO 58



A una solución de 8–metansulfonil–6–metil–3–tiazol–2–il–imidazo [1, 2–a] pirazina (0,070 g; 0,24 mmol) y 5–amino–3–carbometoxi–isotiazol (0,039 g; 0,25 mmol) en dimetilformamida (DMF; 0.8 mL) se agregó hidruro de sodio (NaH; 60% en aceite; 0,024 g). La mezcla de reacción se agitó a temperatura ambiente durante 0,5 h y luego se templó con solución acuosa saturada de cloruro de amonio (NH_4Cl). Se diluyó con una cantidad adicional de agua y se filtró. La torta de filtración se lavó con agua y hexanos. La torta de filtración se secó al vacío para obtener el compuesto del título en forma de un sólido de color amarillo (0,078 g; 87%). ^{1}H RMN (400 MHz, DMSO–d_6): 8,85 (s, 1H), 8,42 (s, 1H), 8,1 (s, 1H), 7,9

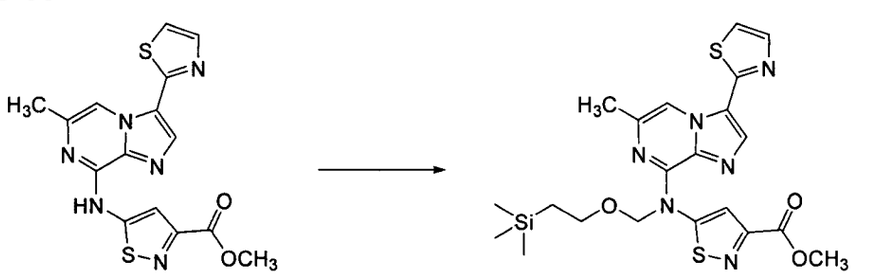
(s, 1H), 7,65 (s, 1H), 3,85 (s, 3H) 2,5 (s, 3H). HPLC–MS t_R = 4,35 (UV_{254nm}). Masa calculada para $C_{15}H_{12}N_6O_2S_2$ 372,04; se observó MH^+ (LCMS) 373,2 (m/z).

EJEMPLO 59



Una solución de trietilborohidruro de litio (Super Hidruro; 1M en THF; 0,32 mL) se agregó por goteo a una solución de metil éster (0,03 g; 0,08 mmol) en THF seco (0.8 mL). Luego de agitar a temperatura ambiente durante 1,5 horas, la mezcla de reacción se templó con solución acuosa saturada de NH_4Cl (8 mL) y se diluyó con agua. Una pequeña cantidad del sólido precipitado de color amarillo se filtró y se lavó con agua y éter. El sólido se secó al vacío para obtener ~10 mg (36%) del alcohol. ^1H RMN (400 MHz, DMSO–d_6): 8,8 (s, 1H), 8,4 (s, 1H), 8,1 (s, 1H), 7,9 (s, 1H), 7,2 (s, 1H), 5,4 (t, 1H), 4,5 (d, 2H), 2,5 (s, 3H). HPLC–MS t_R = 2,98 (UV_{254nm}). Masa calculada para $C_{14}H_{12}N_6OS_2$ 344,05; se observó MH^+ (LCMS) 345,2 (m/z).

EJEMPLO 60

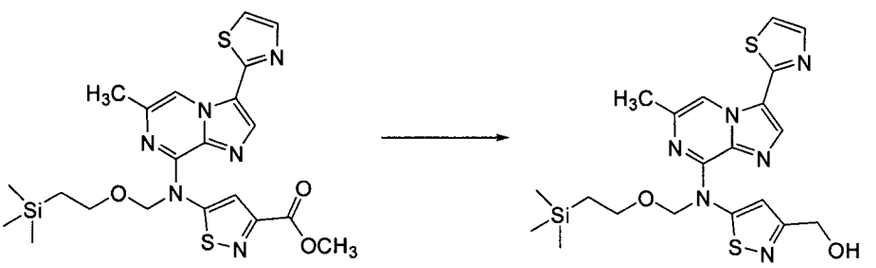


Una solución de éster (0,113 g; 0,3 mmol) en DMF (1.5 mL) se trató con NaH (60% en aceite; 0,03 g; 0,76 mmol) seguido por cloruro de 2–(trimetilsilil) etoximetilo (SEM–Cl; 0,1 mL; 0,61 mmol). La mezcla de reacción se agitó a

temperatura ambiente durante 3 horas y se templó con solución saturada de NH_4Cl y agua. El sólido precipitado de color amarillo se recolectó mediante filtración, se lavó con agua y se secó. El compuesto del título se obtuvo en forma de un sólido de color amarillo (0,142 g; 92%). ^1H RMN (400 MHz, CDCl3): 9,1 (s, 1H), 8,1 (s, 1H), 7,98 (s, 1H), 7,8 (s, 1H), 7,4 (s, 1H), 6,65 (s, 2H), 4,0 (s, 3H), 3,78 (t, 2H), 2,65 (s, 3H), 1,0 (t, 2H), 0,0 (s, 9H).

HPLC–MS t_R = 5,98 (UV_{254nm}). Masa calculada para $C_{21}H_{26}N_6O_3S_2Si$ 502,13; se observó MH^+ (LCMS) 503,3 (m/z).

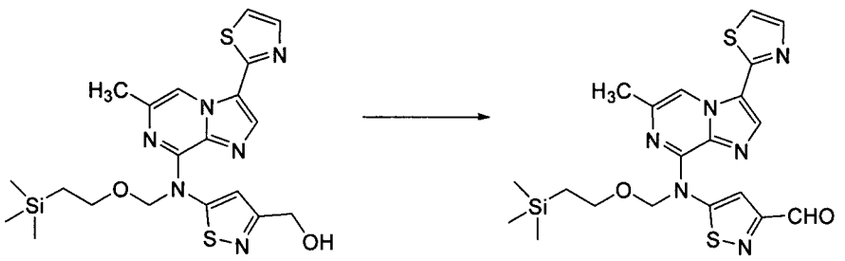
EJEMPLO 61



Una solución de trietilborohidruro de litio (Super Hidruro; 1M en THF; 1 mL) se agregó por goteo a una solución del metil éster 2 en THF seco. Luego de agitar a temperatura ambiente durante 1 h, la mezcla de reacción se templó con solución acuosa saturada de NH_4Cl (8 mL) y solución acuosa saturada de sal de Rochelle. El producto orgánico se extrajo con diclorometano (CH_2Cl_2), se lavó con agua y salmuera. La concentración al vacío proporcionó ~120 mg (100%) del alcohol.

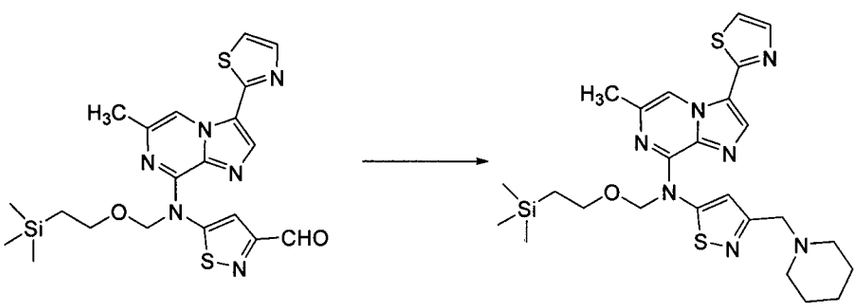
HPLC–MS t_R = 4,22 (UV_{254nm}). Masa calculada para $C_{20}H_{26}N_6O_2S_2Si$ 474,13; se observó MH^+ (LCMS) 475,3 (m/z).

EJEMPLO 62



Se agregó periodinano Dess–Martin (0,147 g; 0,35 mmol) a una solución de alcohol (0,11 g; 0,23 mmol) en THF seco y se agitó a temperatura ambiente durante 40 minutos. La mezcla de reacción se diluyó con 30 mL de CH_2Cl_2, se lavó con solución de bicarbonato de sodio saturado ($NaHCO_3$), agua y se secó. La concentración proporcionó un sólido de color amarillo que se disolvió nuevamente en CH_2Cl_2 y se filtró. El filtrado se concentró para obtener 120 mg de compuesto en bruto del título en forma de un sólido de color amarillo que se usó tal cual estaba en el paso siguiente. ^{1}H RMN (400 MHz, CDCl3): 10 (s, 1H), 9,1 (s, 1H), 8,1 (s, 1H), 7,98 (s, 1H), 7,78 (s, 1H), 7,4 (s, 1H), 6,6 (s, 2H), 3,78 (t, 2H), 2,65 (s, 3H), 1,0 (t, 2H), 0,0 (s, 9H). HPLC–MS t_R = 6,14 (UV_{254nm}). Masa calculada para $C_{20}H_{24}N_6O_2S_2Si$ 472,12; se observó MH^+ (LCMS) 473,3 (m/z).

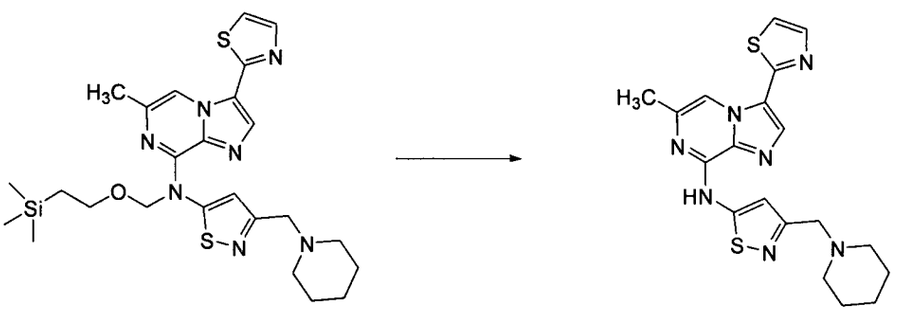
EJEMPLO 63



Una solución de aldehído (0,05 g; 0,1 mmol) y piperidina (0,05 mL; 0,5 mmol) en CH_2Cl_2 (1 mL) se trató con ácido acético glacial (AcOH; 1 gota) y se agitó a temperatura ambiente (RT) durante 3 horas. Se agregó borohidruro de sodio sólido ($NaBH_4$; 0,016 g; 0,42 mmol) y la mezcla de reacción se enfrió en un

baño de hielo/salmuera (–5°C) y se agregó metanol (0,2 mL) por goteo. Luego de agitar a baja temperatura durante 30 minutos, la reacción se templó con NH_4Cl saturada y se extrajo en CH_2Cl_2. El extracto orgánico se lavó con NH_4Cl saturada, agua y salmuera. La remoción del disolvente proporcionó el producto en bruto que se purificó mediante cromatografía de capa fina preparativa (TLC Prep) usando CH_2Cl_2 con 4% CH_3OH y 1% hidróxido de amonio. El compuesto del título se aisló en forma de una película de color amarillo (25 mg; 45%). ^1H RMN (400 MHz, CDCl3): 9,1 (s, 1H), 8,1 (s, 1H), 7,98 (s, 1H), 7,4 (s, 1H),7,3 (s, 1H), 6,6 (s, 2H), 3,8 (t, 2H), 3,6 (s, 2H), 2,65 (s, 3H), 2,5 (s ancho, 4H),1,7 (s ancho, 4H), 1,45 (s ancho, 2H), 0,98 (t, 2H), 0,0 (s, 9H). HPLC–MS t_R = 3,82 (UV_{254nm}). Masa calculada para $C_{25}H_{35}N_7OS_2Si$ 541,21; se observó MH^+ (LCMS) 542,3 (m/z).

EJEMPLO 64

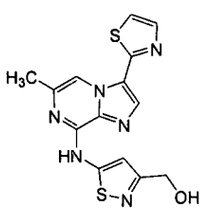
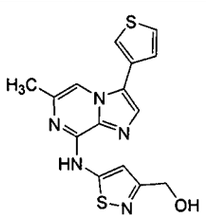
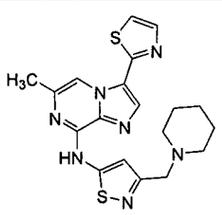
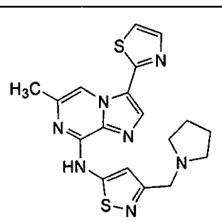


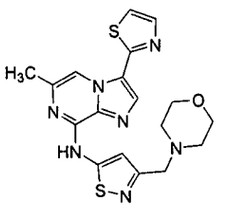
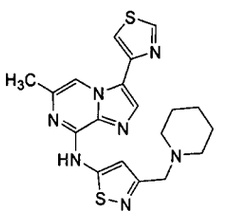
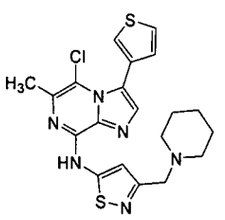
Una solución del compuesto del Ejemplo 63 (0,013 g; 0,02 mmol) en 0,5 mL de THF se trató con HCl en dioxano (4M; 0,5 mL) y se colocó en un baño de aceite a 70°C. Luego de calentar durante 30 min, se formó un precipitado que se disolvió luego de agregar 0,5 mL de metanol. La mezcla de reacción se calentó a una temperatura del baño de 70°C durante 1 h adicional. Los contenidos de la reacción se enfriaron hasta TA y se removieron todos los volátiles en un evaporador rotativo. El residuo se suspendió en THF y se trituró con éter. El precipitado se recolectó mediante filtración, se lavó con ~ 10 mL de éter y se secó en aire (0,5 h) y al vacío (16 horas) para proporcionar 10 mg (93%) del compuesto

del título en forma de un sólido de color amarillo. ^{1}H RMN (400 MHz, CD_3OD): 9,0 (s, 1H), 8,3 (s, 1H), 8,05 (s, 1H), 7,7 (s, 1H), 7,25 (s, 1H), 4,4 (s, 2H), 3,6 (d, 2H), 3,1 (t, 2H), 2,6 (s, 3H), 2,0 (d, 2H), 1,85 (t, 4H), 1,6 (t, 1H). HPLC–MS t_R = 2,96 (UV_{254nm}). Masa calculada para $C_{19}H_{21}N_7S_2$ 411,13; se observó MH^+ (LCMS) 412,2 (m/z).

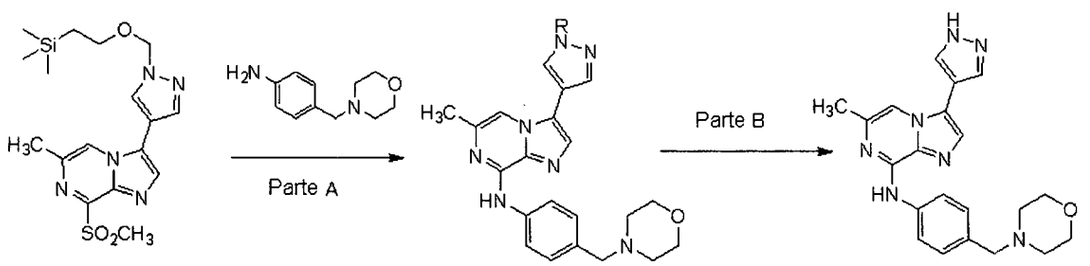
Los compuestos en la Tabla 9 (ilustrados inmediatamente a continuación) se prepararon de acuerdo con los ejemplos descriptos anteriormente:

Tabla 9

Ejemplo	Estructura	PM	LCMS MH^+ (m/z)	HPLC MS t_R
59–1		344,05	345,2	2,98
59–2		343,06	344,2	2,78
64–1		411,13	412,2	2,96
64–2		397,11	398,2	3,11

64–3		413,11	414,2	2,86
64–4		411,13	412,2	2,99
64–5		444,09	445,2	3,29

EJEMPLO 65

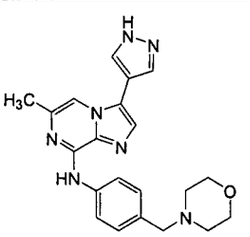
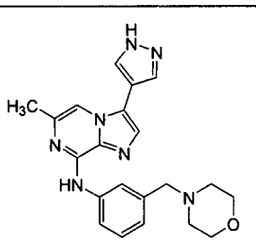


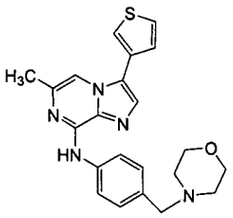
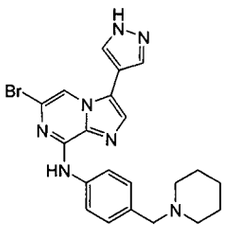
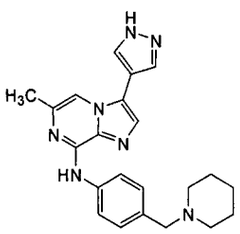
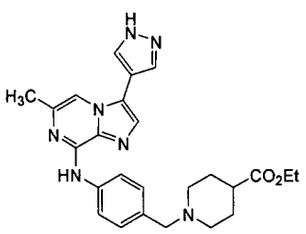
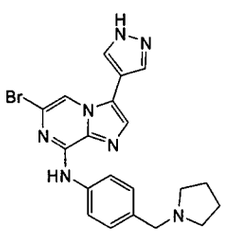
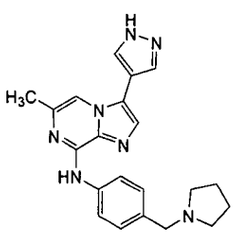
Parte A: se agregó hexametildisilazida de litio (1M en THF; 0,18 mL) a una solución de color ámbar de 4–morfolin–4–ilmetil fenilamina (0,013g; 0,068 mmol) y 8–metansulfonil–6–metil–3–[1–(2–trimetilsilanil–etoximetil)–1*H*–pirazol–4–il]–imidazo[1, 2–*a*]pirazina (0,025g; 0,061 mmol) en 2 mL de THF a temperatura ambiente dando como resultado una solución de color bordó. Luego de agitar a temperatura ambiente durante 20 minutos, la mezcla de reacción se templó con solución acuosa saturada de NH_4Cl. Los contenidos se diluyeron con acetato de etilo y se lavaron con agua y salmuera. El material en bruto del extracto orgánico se purificó mediante TLC preparativa (5% metanol–CH_2Cl_2) para obtener el compuesto del título en forma de un aceite de color amarillo pálido (0,025 g; 80%).

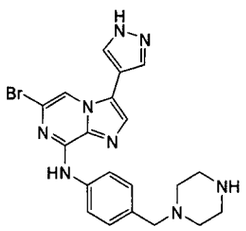
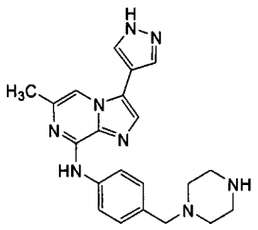
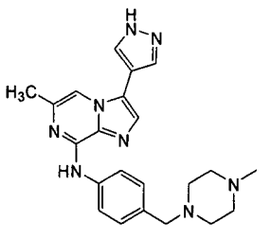
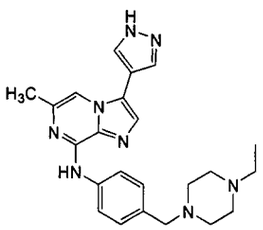
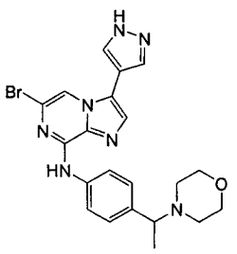
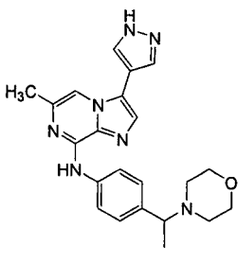
^{1}H RMN (400 MHz, CDCl3): 8 (s, 1H), 7,9 (d, 2H), 7,85 (s, 1H), 7,8 (s, 1H), 7,5 (s, 1H), 7,4 (s, 1H), 7,35 (d, 2H), 5,55 (s, 2H), 3,75 (s ancho, 4H), 3,7 (t, 2H), 3,5 (s ancho, 2H), 2,5 (s ancho, 2H), 2,4 (s, 3H), 1,6 (s ancho, 2H), 0,95 (t, 2H), 0,0 (s, 9H). HPLC–MS t_R = 3,05 (UV_{254nm}). Masa calculada para $C_{27}H_{37}N_7O_2Si$ 519,27; se observó MH^+ (LCMS) 520,3 (m/z).

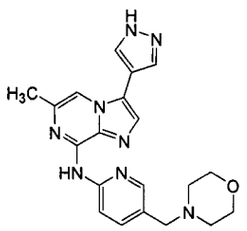
Parte B: El compuesto de la Parte A (0,025g; 0,048 mmol) se suspendió en THF seco y se trató con HCl en dioxano (4M; 1 mL) y se calentó en un baño de aceite fijado a 70°C durante 15 minutos en cuyo tiempo se formó un precipitado de color blanco. Se agregó metanol para disolver una parte del sólido y la mezcla de reacción se continuó calentando durante otros 45 minutos. Luego de enfriarse hasta TA, los volátiles se removieron en un evaporador rotativo. El residuo se suspendió en THF y el sólido precipitado se recolectó mediante filtración, se lavó con éter y se secó al vacío hasta la mañana siguiente. El compuesto del título se aisló en forma de un sólido de color beige (14 mg; 78%). Todos los análogos de la Tabla 10 se prepararon de manera similar.

Tabla 10

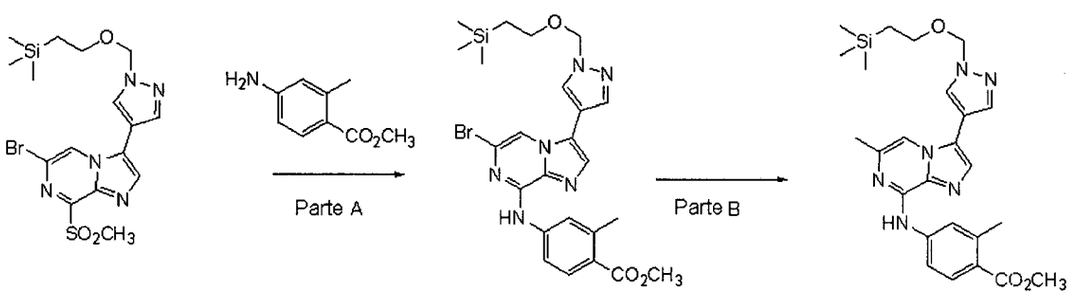
Ejemplo	Estructura	PM	LCMS MH^+ (m/z)	HPLC MS t_R
65–1		389,19	390,2	1,7
65–2		389,19	390,2	1,76

65–3		405,16	406,2	2,38
65–4		451,11	452,2	2,51
65–5		387,22	388,2	1,85
65–6		459,24	460,3	2,03
65–7		437,1	438,2	2,38
65–8		373,2	374,2	1,65

65–11		452,11	453,3	1,93
65–12		388,21	389,2	1,59
65–13		402,23	403,2	1,51
65–14		416,24	417,2	1,54
65–15		467,1	468,3	2,27
65–16		403,21	404,2	1,9

65–17		390,19	391,2	1,36

EJEMPLO 66



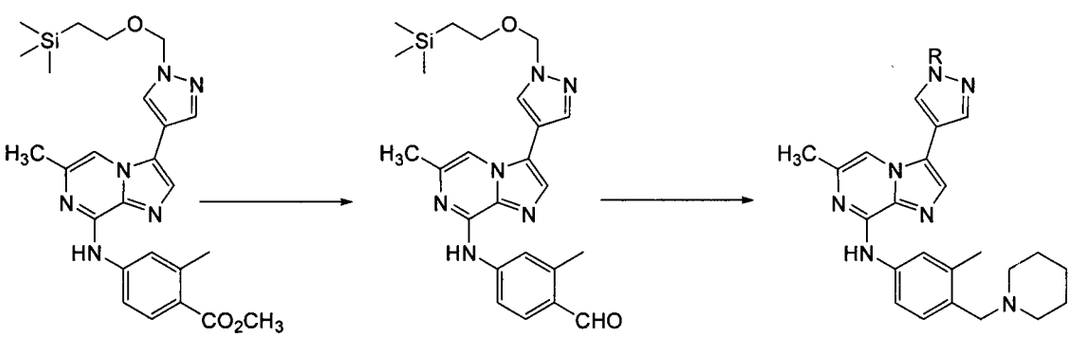
Parte A: Una solución de metil éster del ácido 4–Amino–2–metil–benzoico (0,33 g; 2 mmol; preparada a partir del ácido 4–nitro–2–metil–benzoico disponible en el comercio) y 8–metansulfonil–6–bromo–3–[1–(2–trimetilsilanil–etoximetil)–1*H*–pirazol–4–il]–imidazo[1, 2–*a*]pirazina (0,472 g; 1,0 mmol) se trató con LiHMDS (1M en THF; 2 mL) a temperatura ambiente La solución de color bordó se agitó a temperatura ambiente durante 20 minutos y luego se templó con solución acuosa saturada de NH_4Cl. La preparación estándar tal como se describió para el Ejemplo 65 y la cromatografía instantánea en gel de sílice (25% EtOAc en CH_2Cl_2) proporcionaron el compuesto del título en forma de una espuma de color amarillo pálido (0,48 g; 86%).

RMN (400 MHz, CDCl3): 8,18 (s, 1H), 8 (d, 1H), 7,9 (s, 1H), 7,85 (d, 1H), 7,78 (s, 1H), 7,7 (s, 1H), 7,62 (s, 1H), 7,58 (s, 1H), 5,5 (s, 2H), 3,9 (s, 3H), 3,65 (t, 2H), 2,6 (s, 3H), 0,98 (t, 2H), 0,0 (s, 9H). Masa calculada para $C_{24}H_{29}BrN_6O_3Si$ 556,13; se observó MH^+ (CI–MS) 557 / 559 (m/z).

Parte B: Una solución del compuesto de la Parte A (0,48 g; 0,86 mmol) en 2 mL de THF seco se trató con una solución de dimetil zinc (2M; 4 mL) por goteo.

Luego de cesar la efervescencia, se agregó $Pd(PPh_3)_4$ sólido y la reacción se purgó con nitrógeno, se equipó con un condensador de reflujo y se calentó en un baño de aceite a 65–70°C. Al cabo de 0,5 h, la mezcla de reacción se transformó desde anaranjado amarillo a rojo profundo y luego de otras 4 horas, se tornó de color negro opaco. TLC (25% EtOAc– CH_2Cl_2) indicó la formación de una mancha más ligeramente polar. La reacción se enfrió hasta TA, se templó con solución acuosa saturada de NH_4Cl y se extrajo con EtOAc. La cromatografía instantánea en gel de sílice del material en bruto proporcionó el compuesto del título 6–metilo en forma de un sólido de color amarillo (0,38 g; 90%). RMN (400 MHz, CDCl3): 8,1 (s, 1H), 8 (d, 1H), 7,9 (d, 1H), 7,85 (s, 1H), 7,8 (s, 1H), 7,7 (s, 1H), 7,58 (s, 1H), 7,4 (s, 1H), 5,5 (s, 2H), 3,9 (s, 3H), 3,65 (t, 2H), 2,65 (s, 3H), 2,4 (s, 3H), 0,98 (t, 2H), 0,0 (s, 9H). Masa calculada para $C_{25}H_{32}N_6O_3Si$ 492,23; se observó MH^+ (CI–MS) 493,11 (m/z).

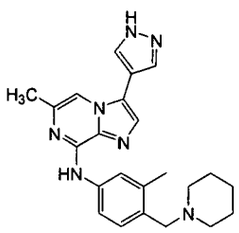
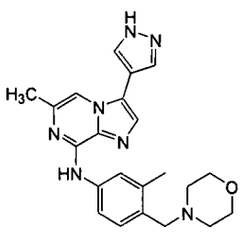
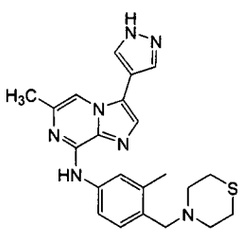
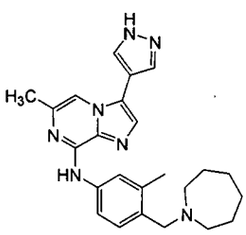
EJEMPLO 67



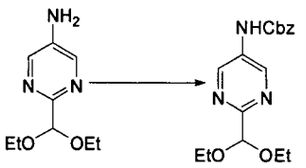
Parte A: Primero, se redujo el éster al alcohol usando $LiBEt_3H$ en THF a temperatura ambiente y luego se oxidó usando periodinano Dess–Marin hasta el aldehído tal como se describió anteriormente. La aminación reductiva de aldehído con varias aminas secundarias proporcionó el compuesto del título SEM–protegido. La remoción del grupo de protección SEM se llevó a cabo en las condiciones descriptas anteriormente.

De manera similar, también se prepararon otras aminas terciarias indicadas en la Tabla 11 (ilustrados inmediatamente a continuación) mediante un esquema de reacción similar con las aminas secundarias correspondientes seguido por la remoción del grupo de protección SEM.

TABLA 11

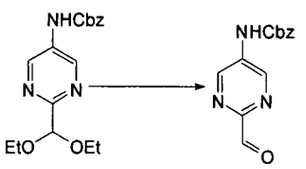
Ejemplo	Estructura	PM	LCMS MH^+ (m/z)	HPLC MS t_R
67–1		401,23	402,2	1,87
67–2		403,21	404,2	1,71
67–3		419,19	420,2	1,95
67–4		415,25	416,2	2,0

EJEMPLO 68



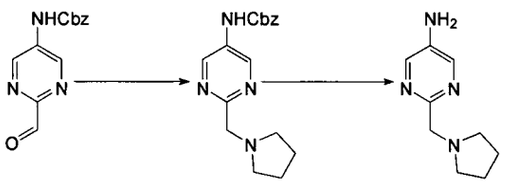
El sustrato (1 g, 5,07 mmol) se disolvió en THF:H_2O (12 mL, 1:1, v/v) y se trató con K_2CO_3 (1,4 g, 10,15 mmol) a temperatura ambiente. Luego se agregó lentamente cloroformato de bencilo (0,79 ml, 5,58 mmol) en THF (2 mL). La mezcla se agitó durante 16 horas. Se diluyó con acetato de etilo (25 mL). Las dos capas se separaron, y la capa acuosa se extrajo con acetato de etilo (2 × 25 mL). La capa orgánica combinada se lavó con salmuera (1 × 30 mL), se secó (Na_2SO_4), se filtró y evaporó bajo presión reducida para proporcionar el producto en bruto que se purificó mediante cromatografía en columna (SiO_2) eluyendo con acetato de etilo–hexano.

EJEMPLO 69



El sustrato acetal (1,2 g, 3,64 g) se disolvió en acetona (20 mL), y se trató con HCl 1 N acuosa (2 mL) a temperatura ambiente, y la mezcla se agitó durante 7 horas. Luego la acetona se separó por evaporación, y el residuo se diluyó con $NaHCO_3$ acuosa saturada (30 mL). La capa acuosa se extrajo con acetato de etilo (2 × 30 mL). La capa orgánica combinada se lavó con salmuera (1 × 30 mL), se secó (Na_2SO_4), se filtró y evaporó bajo presión reducida para proporcionar el producto en bruto en forma de sólido que se usó en el paso siguiente sin purificación posterior.

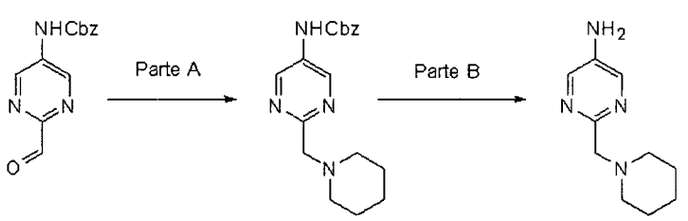
EJEMPLO 70



El sustrato (1 eq.), la amina (4 eq.), AcOH catalítico, $NaB(OAc)_3H$ (2 eq.) en 1,2–dicloroetano se agitaron a temperatura ambiente durante 2 h. Luego se agregó borohidruro de sodio (3 eq.) y la mezcla se agitó durante 30 min en cuyo tiempo el análisis por LC–MS indicó el consumo total del material de partida a producto. Luego, la reacción se templó con NaOH 2N acuosa, y la mezcla se agitó enérgicamente hasta que se separaron dos capas límpidas. La capa orgánica se lavó con agua, salmuera, se secó (Na_2SO_4), se filtró y concentró bajo presión reducida para proporcionar el producto.

El producto en bruto se hidrogenó en acetato de etilo usando 10% Pd/C a una presión de hidrógeno de 1 atmósfera. El catalizador se separó por filtración, y el disolvente se evaporó bajo presión reducida para proporcionar el producto en bruto.

EJEMPLO 71

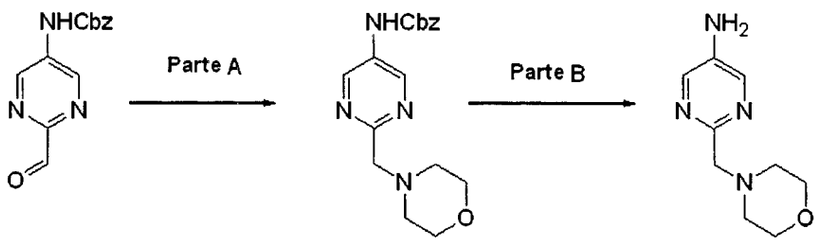


Parte A: El sustrato (1 eq.), la amina (4 eq.), AcOH catalítico, $NaB(OAc)_3H$ en 1,2–dicloroetano se agitaron a temperatura ambiente durante 2 h. Luego se agregó borohidruro de sodio (3 eq.) y la mezcla se agitó durante 30 min en cuyo tiempo el análisis por LC–MS indicó el consumo total del material de partida a producto. Luego la reacción se templó con NaOH 2N acuosa, y la mezcla se agitó

enérgicamente hasta que se separaron dos capas límpidas. La capa orgánica se lavó con agua, salmuera, se secó (Na_2SO_4), se filtró y concentró bajo presión reducida para proporcionar el producto.

Parte B: El producto en bruto se hidrogenó en acetato de etilo usando 10% Pd/C a una presión de hidrógeno de 1 atmósfera. El catalizador se separó por filtración, y el disolvente se evaporó bajo presión reducida para proporcionar el producto en bruto.

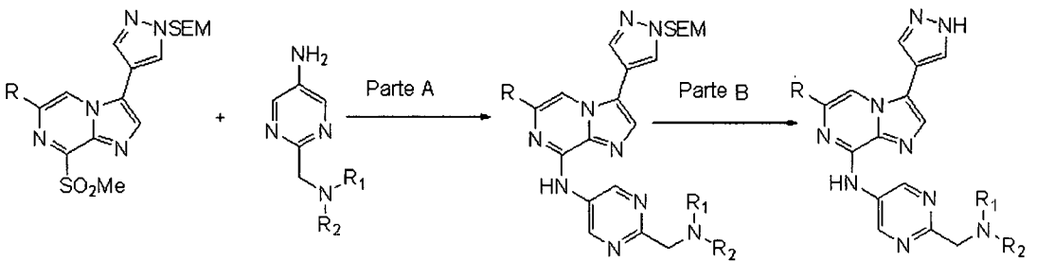
EJEMPLO 72



Parte A: El sustrato (1 eq.), la amina (4 eq.), AcOH catalítico, $NaB(OAc)_3H$ en 1,2–dicloroetano se agitaron a temperatura ambiente durante 2 horas. Luego se agregó borohidruro de sodio (3 eq.) y la mezcla se agitó durante 30 min en cuyo tiempo el análisis por LC–MS indicó el consumo total del material de partida a producto. Luego la reacción se templó con NaOH 2N acuosa, y la mezcla se agitó enérgicamente hasta que se separaron dos capas límpidas. La capa orgánica se lavó con agua, salmuera, se secó (Na_2SO_4), se filtró y concentró bajo presión reducida para proporcionar el producto.

Parte B: El producto en bruto se hidrogenó en acetato de etilo usando 10% Pd/C a una presión de hidrógeno de 1 atmósfera. El catalizador se separó por filtración, y el disolvente se evaporó bajo presión reducida para proporcionar el producto en bruto.

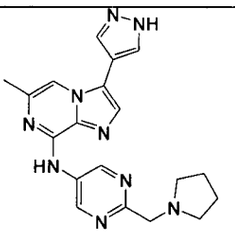
EJEMPLO 73

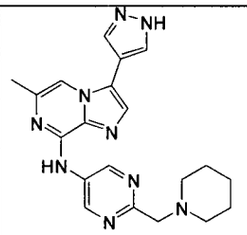
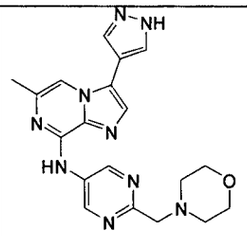
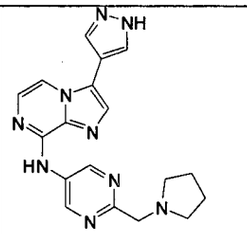
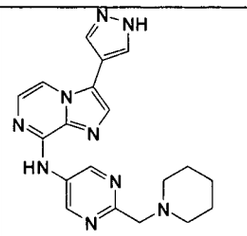
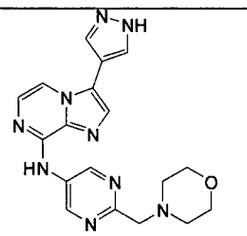


Parte A: El sustrato (1 eq.) y la amina (1,5–2 eq.) se disolvió en DMSO bajo argón, y se trató con NaH (5 eq., 60% dispersión en aceite). Al cabo de 30 min, el análisis por LC–MS indicó el consumo total del material de partida. La reacción se templó agregando NH_4Cl acuosa saturada–acetonitrilo (1:1, v/v). Las dos capas se separaron, y la capa acuosa se extrajo con acetato de etilo. La capa orgánica combinada se lavó con salmuera, se secó (Na_2SO_4), se filtró y concentró bajo presión reducida para proporcionar el producto en bruto.

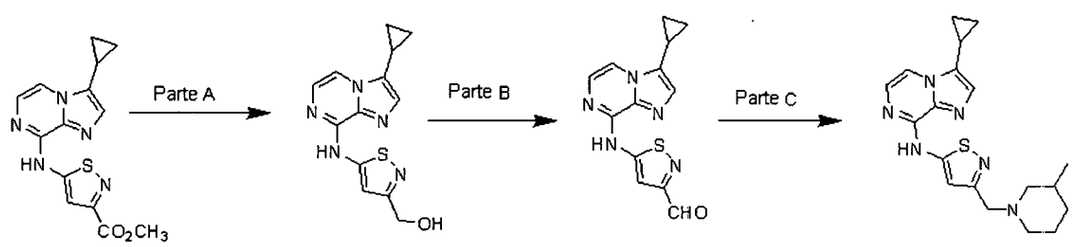
Parte B: El sustrato se disolvió en HCL 4N en dioxano, y se agitó a temperatura ambiente durante 30 min. El disolvente luego se evaporó, y el residuo se purificó mediante CL–Prep. La conversión en la sal clorhídrica proporcionó el producto en forma de un sólido. Por consiguiente, se prepararon los compuestos en la Tabla 12 (ilustrados inmediatamente a continuación):

TABLA 12

Ejemplo	Columna	PM	LCMS MH^+ m/z	HPLC MS t_R
73–1		375,4	376,1	0,83

73–2		389,4	390,2	1,05
73–3		391,4	392,1	0,78
73–4		361,4	362,2	0,74
73–5		375,4	376,2	0,85
73–6		377,4	378,3	0,87

EJEMPLO 74

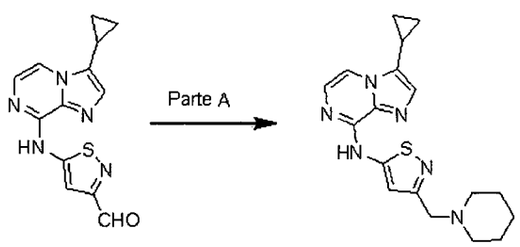


Parte A: Siguiendo básicamente el mismo procedimiento tal como se describió para el Ejemplo 1 y 13.

Parte B: A una solución del compuesto del Ejemplo 74, Parte A (0,16 g, 0,57 mmol) en THF (20 mL) y agua (0,025 mL) se agregó periodinano Dess–Martin (3 equivalentes). La solución resultante se agitó a temperatura ambiente durante 1,5 h en cuyo tiempo el análisis por LC–MS indicó que la reacción se había completado. La mezcla de reacción se diluyó con diclorometano (75 mL), se lavó con agua, se secó (sulfato de sodio) y concentró. La purificación por cromatografía en columna (SiO_2 10% metanol / DCM) proporcionó el compuesto del título en forma de un sólido de color amarillo 0,08 g (49%). HPLC–MS t_R = 1,59 Min (UV $_{254nm}$). La masa se calculó para la fórmula C13H11N5OS 285,07; se observó LC/MS m/z 286,1 (M+H).

Parte C: A una solución del compuesto de la Parte B (30 mg, 0,105 mmol, 1 equivalente), 3–metilpiperidina (10 equivalentes) en diclorometano:metanol (5:1) (3 ml) se agregó ácido acético (1 gota). La solución resultante se agitó a temperatura ambiente durante 30 minutos, y luego se agregó borohidruro de sodio (8 equivalentes) a la reacción. La mezcla de reacción se agitó a temperatura ambiente durante 1 hora en cuyo tiempo el análisis por LC–MS indicó que la reacción se había completado. La reacción se templó con bicarbonato de sodio ac. sat., y luego se extrajo con diclorometano (x2). La capa orgánica combinada se secó (sulfato de sodio) y concentró. La purificación mediante LC preparativa y la conversión a una sal clorhidrica proporcionó el compuesto del título. HPLC–MS t_R = 3,73 Min (UV $_{254nm}$). La masa se calculó para la fórmula $C_{19}H_{24}N_6S$ 368,18; se observó LC/MS m/z 369,2 (M+H).

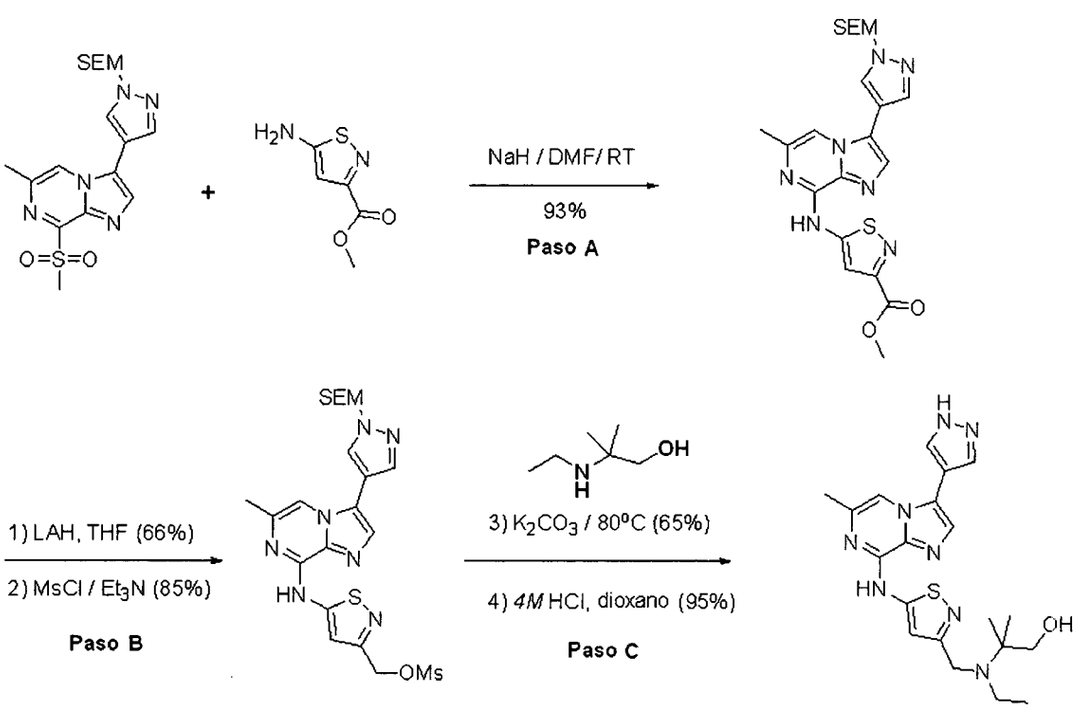
EJEMPLO 75



849

Parte A: A una solución del compuesto 1 (30 mg, 0,105 mmol, 1 equivalente), piperidina (10 equivalentes) en diclorometano:metanol (5:1) (3 ml) se agregó ácido acético (1 gota). La solución resultante se agitó a temperatura ambiente durante 30 minutos, y luego se agregó borohidruro de sodio (8 equivalentes) a la reacción. La mezcla de reacción se agitó a temperatura ambiente durante 1 h en cuyo tiempo el análisis por LC–MS indicó que la reacción se había completado. La reacción se templó con bicarbonato de sodio ac. sat., y luego se extrajo con diclorometano (x2). La capa orgánica combinada se secó (sulfato de sodio) y concentró. La purificación mediante LC preparativa y la conversión en una sal clorhídrica proporcionó el compuesto 2. HPLC–MS t_R = 3,47 Min (UV $_{254nm}$). La masa se calculó para la fórmula $C_{18}H_{22}N_6S$ 354.16; se observó LC/MS m/z 355,1 (M+H).

EJEMPLO 76:



Paso A: Se agregó lentamente hidruro de sodio (60% dispersión en aceite mineral, 6,68 g, 3,40 equiv.) en una porción a una mezcla agitada del compuesto sulfona (20,0 g, 1,00 equiv.) y aminoisotiazol (11,5 g, 1,20 equiv, como sal HCl) en DMF (490 mL) a temperatura ambiente (con ayuda de un baño de agua a temperatura ambiente). La reacción se dejó agitar durante 1 hora en cuyo tiempo el análisis mediante HPLC indicó que la reacción se había completado. La reacción se templó cuidadosamente con bicarbonato de sodio acuoso saturado (200 mL) y luego se diluyó con agua (1L). Dicha mezcla se agitó durante 20 minutos a temperatura ambiente, y luego el precipitado resultante se recolectó mediante filtración, se lavó con agua (200 mL), y se secó bajo alto vacío durante 16 horas. El sólido ceroso resultante se disolvió en 1,8 L de 1:1 cloroformo : metanol, se secó sobre sulfato de sodio, se filtró, y concentró bajo presión reducida para proporcionar el compuesto del título (22,3 g, 93%) en forma de un sólido de color amarillo oscuro. ^{1}H RMN (300 MHz, DMSO–d_6) δ 12,3 (s ancho, 1H), 8,60 (s, 1H), 8,10 (s, 1H), 7,88 (s, 2H), 7,59 (s, 1H), 5,51 (s, 2H), 3,85 (s, 3H), 3,63 (d, J = 8 Hz, 2H), 2,48 (s, 3H), 0,88 (d, J = 8 Hz, 2H), –0,026 (s, 9H). La masa se calculó para la fórmula $C_{21}H_{27}N_7O_3SSi$ 485,63; se observó MH^+ (MS) 486,6 (m/z).

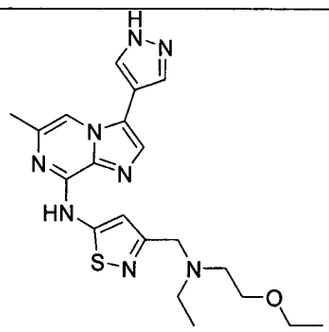
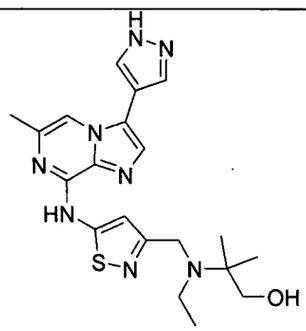
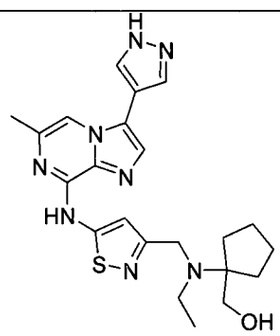
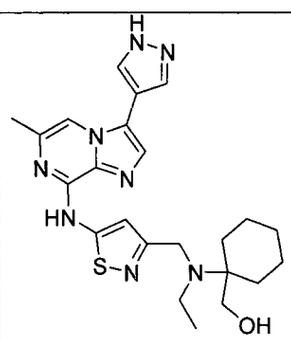
Paso B: Una mezcla del compuesto del Paso A (4,27g, 3,73 mmol) se disolvió en 180 mL de THF. La solución resultante se enfrió hasta 0 °C y se agregó cuidadosamente polvo de $LiAlH_4$ (2,6 g, 68,5 mmol). El baño de enfriamiento se removió y la reacción se agitó a temperatura ambiente bajo una atmósfera N_2 durante 1,5 horas. La reacción se enfrió hasta 0 °C y se templó cuidadosamente mediante el agregado consecutivo de 2,6 mL de H_2O; 2,6 mL de 15 % NaOH (ac.); 7,8 mL H_2O. Luego de agitar durante 10 min, la reacción se filtró a través de una almohadilla muy delgada de Celite (enjuagando con THF, EtOAc y DCM). La

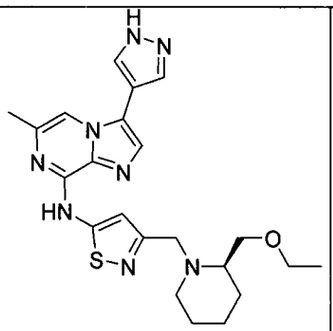
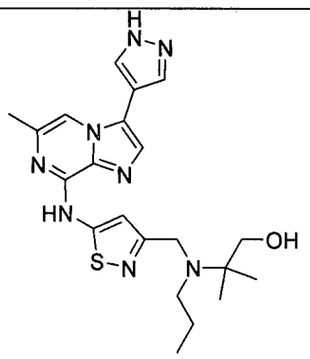
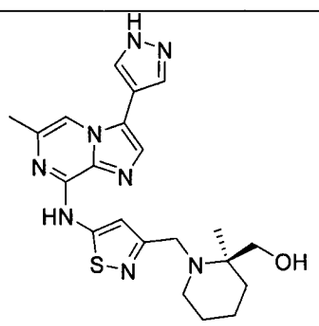
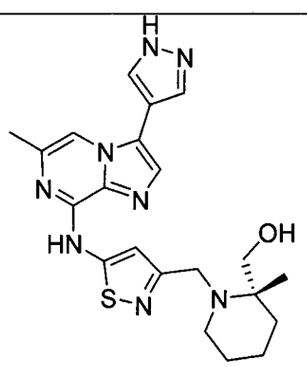
concentración del filtrado proporcionó un sólido de color amarillo claro. Se obtuvo alcohol puro (2,66 g, 66 % de rendimiento) mediante trituración con MeOH y se usó directamente en el paso siguiente.

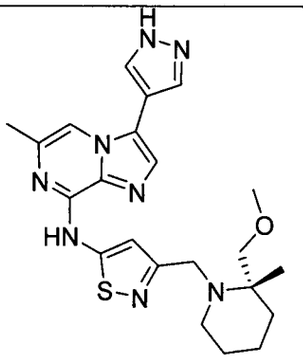
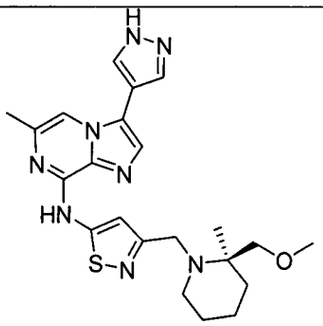
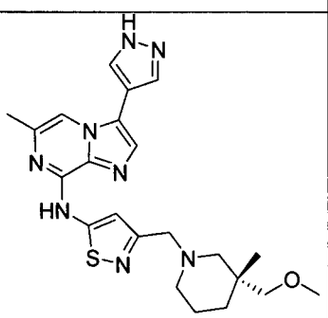
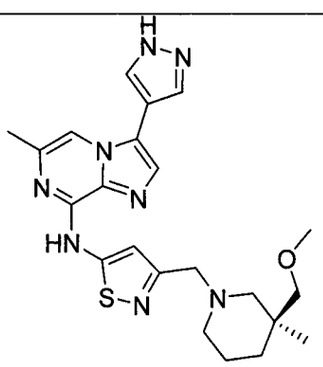
Paso C: Una mezcla del compuesto del Paso B (2,40 g, 4,49 mmol), amina (1,57 g, 13,46 mmol), y NaI (63,0 mg, 0,449 mmol) en 45 mL de THF se calentó a 80 °C durante 12 horas. Se diluyó con 200 mL de CH_2Cl_2, y se lavó con 100 mL de solución acuosa saturada de $NaHCO_3$, luego con salmuera (100 mL). El disolvente se removió al vacío. El residuo se purificó mediante cromatografía instantánea eluyendo con 5% a 10% $MeOH/CH_2Cl_2$ para proporcionar 1,68 g del compuesto del título. ^1H RMN (400 MHz, $CDCl_3$) δ 9,49 (s ancho, 1H), 7,89 (s, 1H), 7,82 (s, 1H), 7,60 (s, 1H), 7,49 (s, 1H), 6,86 (s, 1H), 5,54 (s, 2H), 3,79 (s ancho, 3H), 3,67 (t, *J* = 8,3 Hz, 2H), 3,36 (s, 2H), 2,65–2,80 (m, 2H), 2,50 (s, 3H), 1,11 (s, 6H), 1,02(t, *J* = 7,1 Hz, 2H), 0,96 (t, *J* = 8,2 Hz, 2H), 0,01 (s, 9H). A una solución del compuesto SEM–protegido (2,0 g, 3,6 mmol) en 36 mL de $MeOH/CH_2Cl_2$ (1:1) agitado a 80 °C, se agregó 36 mL de HCl 4 N en dioxano. La reacción se agitó a 80 °C durante 30 min. Luego se enfrió hasta temperatura ambiente y se agregó 120 mL de éter. El sólido se recolectó mediante filtración, se lavó con éter y se secó al vacío para proporcionar 2,0 g del compuesto del título como su sal HCl. La masa se calculó para la fórmula $C_{20}H_{26}N_8OS$ 426,2; se observó MH^+ (LCMS) 427,2 (m/z).

Usando básicamente los mismos procedimientos descriptos para el Ejemplo 76, se prepararon los siguientes compuestos en la Tabla 13 (ilustrados inmediatamente a continuación).

TABLA 13

Ejemplo	Columna 2	EM	LCMS MH^+ m/z	HPLC MS t_R
76–1		426,2	427,2	2,28
76–2		426,2	427,2	2,21
76–3		452,2	453,2	2,26
76–4		466,3	467,3	2,48

76–5		452,2	453,2	2,35
76–6		440,2	441,2	2,39
76–7		438,1	439,1	1,81
76–8		438,1	439,1	1,03

76–9		452,2	453,3	1,48
76–10		452,2	453,1	1,48
76–11		452,2	453,3	1,35
76–12		452,2	453,2	1,36

Ejemplo 76–1: ^{1}H RMN (400 MHz, CD_3OD) δ 8,24 (s, 1H), 8,23 (s, 2H), 8,07 (s, 1H), 7,35 (s, 1H), 4,57 (d, *J* = 12,8 Hz, 2H), 3,81 (t, *J* = 4,8, 2H), 3,57 (q, *J* = 14,0, 6,8 Hz, 2H), 3,52 (m, 2H), 3,41 (m, 2H), 2,60 (s, 3H), 1,38 (t, *J* = 7,2 Hz, 3H), 1,21

(t, J = 6,8 Hz, 3H). HPLC–MS t_R = 2,28 min (UV $_{254nm}$). La masa se calculó para la fórmula $C_{20}H_{26}N_8OS$ 426,2; se observó MH^+ (LCMS) 427,2 (m/z).

Ejemplo 76–2: ^{1}H RMN (400 MHz, CD_3OD) δ 8,31 (s, 1H), 8,29 (s, 2H), 7,32 (s, 1H), 4,88 (d, 1H), 4,46 (d, J = 16,1 Hz, 1H), 3,82 (d, J = 12,3 Hz, 1H), 3,71 (d, J = 12,3 Hz, 1H), 3,64 (m, 1H), 2,65 (s, 3H), 1,42 (s, 3H), 1,40 (s, 3H), 1,31 (t, J = 7,1 Hz, 3H). HPLC–MS t_R = 2,26 min (UV $_{254nm}$).

Ejemplo 76–3: ^{1}H RMN (400 MHz, CD_3OD) δ 8,16 (s, 2H), 8,13 (s, 1H), 7,99 (s, 1H), 7,25 (s, 1H), 4,72 (d, J = 15,6 Hz, 1H), 4,53 (t, J = 15,6, 1H), 3,66 (s, 2H), 3,61 (m, 1H), 3,40 (m, 1H), 2,57 (s, 3H), 1,33–0,95 (8H), 1,17 (t, J = 6,8 Hz, 3H). HPLC–MS t_R = 2,26 min (UV $_{254nm}$). La masa se calculó para la fórmula $C_{20}H_{26}N_8OS$ 452,2; se observó MH^+ (LCMS) 453,2 (m/z).

Ejemplo 76–4: ^{1}H RMN (400 MHz, CD_3OD) δ 8,16 (s, 2H), 8,15 (s, 1H), 8,00 (s, 1H), 7,21 (s, 1H), 4,95 (d, J = 16,0 Hz, 1H), 4,35 (d, J = 16,8 Hz, 1H), 4,07 (d, J = 12,4 Hz 1H), 3,82 (d, J = 12,8 Hz 1H), 3,52 (m, 2H), 2,57 (s, 3H), 1,96–1,58 (10H), 1,26 (t, J = 6,8 Hz, 3H). HPLC–MS t_R = 2,48 min (UV $_{254nm}$). La masa se calculó para la fórmula $C_{20}H_{26}N_8OS$ 466,3; se observó MH^+ (LCMS) 467,3 (m/z).

Ejemplo 76–5: ^{1}H RMN (400 MHz, CD_3OD) δ 8,28 (s, 1H), 8,25 (s, 2H), 8,10 (s, 1H), 7,39 (s, 1H), 4,65 (d, J = 14,0 Hz, 1H), 4,52 (d, J = 10,8 Hz, 1H), 4,24 (d, J = 14,0 Hz 1H), 3,85 (d, J = 18,0 Hz 1H), 3,65–3,44 (4H), 2,65 (s, 3H), 1,97–1,58 (6H), 1,29 (t, J = 7,2 Hz, 3H). HPLC–MS t_R = 2,35 min (UV $_{254nm}$). La masa se calculó para la fórmula $C_{20}H_{26}N_8OS$ 452,2; se observó MH^+ (LCMS) 453,2 (m/z).

Ejemplo 76–6 ^{1}H RMN (400 MHz, CD_3OD) δ 8,21 (s, 3H), 8,03 (s, 1H), 7,23 (s, 1H), 4,38 (d, J = 5,6 Hz, 1H), 3,79 (d, J = 5,4 Hz, 1H), 3,63 (d, J = 12,4 Hz 1H), 3,53 (m, 1H), 3,10 (m, 1H), 2,58 (s, 3H), 1,34 (s, 6H), 0,87 (t, J = 6,2 Hz, 3H). HPLC–MS t_R = 2,39 min (UV $_{254nm}$). La masa se calculó para la fórmula $C_{20}H_{26}N_8OS$ 440,2; se observó MH^+ (LCMS) 441,2 (m/z).

Ejemplo 76–7: ^{1}H–RMN(400 MHz, CD_3OD) δ 8,33 m (3H), 8,15 s (1H), 7,41 s (1H), 4,80 (d, 2H), 4,15 (d, 2H), 4,06 (d, 2H), 3,62 (d, 2H), 3,58 (m, 1H), 2,68 (d, 3H), 2,21 (m, 1H), 1,81 (m , 6H) y 1,45 (s, 3H). HPLC–MS t_R =1,80Min (UV $_{254nm}$). La masa se calculó para la fórmula C21H26N8OS 438,55; se observó LC/MS m/z 439,1 (M+H).

Ejemplo 76–8: ^{1}H–RMN(400 MHz, DMSO–d_6) δ 12,73 s ancho (1H), 9,2 s ancho (1H), 8,28 s (2H), 8,09 s (1H), 8,08 s (1H), 7,36 s (1H), 4,71 m (1H), 4,05 m (1H), 3,82 m (1H), 3,63 m (1H), 3,25 m (2H), 1,97 m (1H), 1,65 m (6H) y 1,30 s (3H).

Ejemplo 76–9: ^{1}H–RMN(400 MHz, DMSO–d_6) δ 8,28 (1H), 8,25 (2H), 8,08 (1 H), 7,32 (1 H), 4,71 (1 H), 4,08 (1 H), 3,84 (1 H), 3,52 (3 H), 3,46 (1 H), 2,63 (3 H), 2,17 (2 H), 1,87–1,73 (6 H), 1,45 (3 H).

Ejemplo 76–10: ^{1}H–RMN(400 MHz, DMSO–d_6) δ 8,28 (1H), 8,25 (2H), 8,08 (1 H), 7,32 (1 H), 4,71 (1 H), 4,08 (1 H), 3,84 (1 H), 3,52 (3 H), 3,46 (1 H), 2,63 (3 H), 2,17 (2 H), 1,87–1,73 (6 H), 1,45 (3 H).

Ejemplo 76–11: ^{1}HRMN (400 MHz, CD_3OD) δ 8,20 (s, 2H), 8,14 (s, 1H), 8,03 (s, 1H), 7,25 (s, 1H), 4,48 (d, 1H), 4,37 (d, 1H), 3,46 (s, 3H), 2,91–3,60 (m, 6H), 2,62 (s, 3H), 1,40 – 1,89 (m, 4H), 0,92 (s, 3H).

Ejemplo 76–12: ^{1}HRMN (400 MHz, CD_3OD) δ 8,20 (s, 2H), 8,14 (s, 1H), 8,03 (s, 1H), 7,25 (s, 1H), 4,48 (d, 1H), 4,37 (d, 1H), 3,46 (s, 3H), 2,91–3,60 (m, 6H), 2,62 (s, 3H), 1,40 – 1,89 (m, 4H), 0,92 (s, 3H).

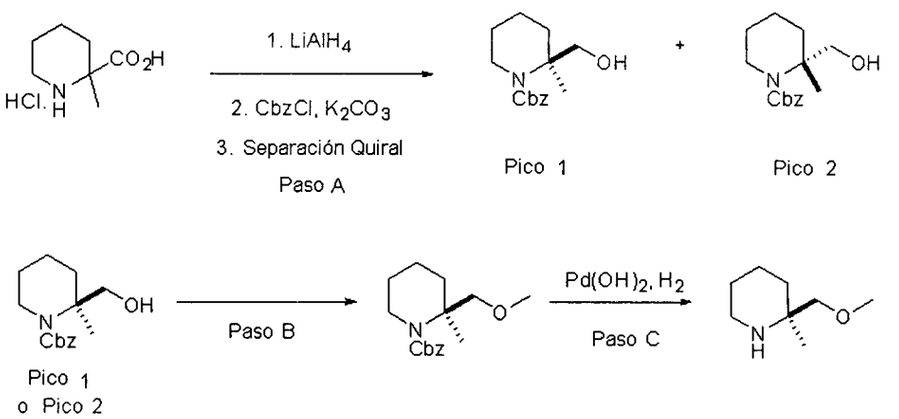
EJEMPLO 77



Una mezcla de yodoetano (52,5 g, 336,5 mmol) y 2–amino–2–metil–1–propanol (30,0 g, 336,5 mmol) se agitó a 60 °C durante 15 min. Se diluyó con 500 mL de éter, y se alcalinizó agregando NaOH 5 N acuosa hasta que alcanzó un pH =10. La capa orgánica se separó. La capa acuosa se extrajo con éter (500 mL X

3). La capa orgánica combinada se lavó consecutivamente con 100 mL de agua, y 100 mL de salmuera, luego se secó sobre Na_2SO_4 anhidro. El disolvente se removió para proporcionar 20 g del producto en bruto, el cual se purificó mediante recristalización en 150 mL de hexanos para proporcionar 13 g de un sólido de color blanco. El sólido luego se purificó mediante sublimación bajo presión reducida para proporcionar 12 g del compuesto del título. ^{1}H RMN (400 MHz, $CDCl_3$) δ 3,28 (s, 2H), 2,54 (ct, *J* = 7,1 Hz, 2H), 1,09 (t, *J* = 7,0 Hz, 3H), 1,07 (s, 6H).

EJEMPLO 78



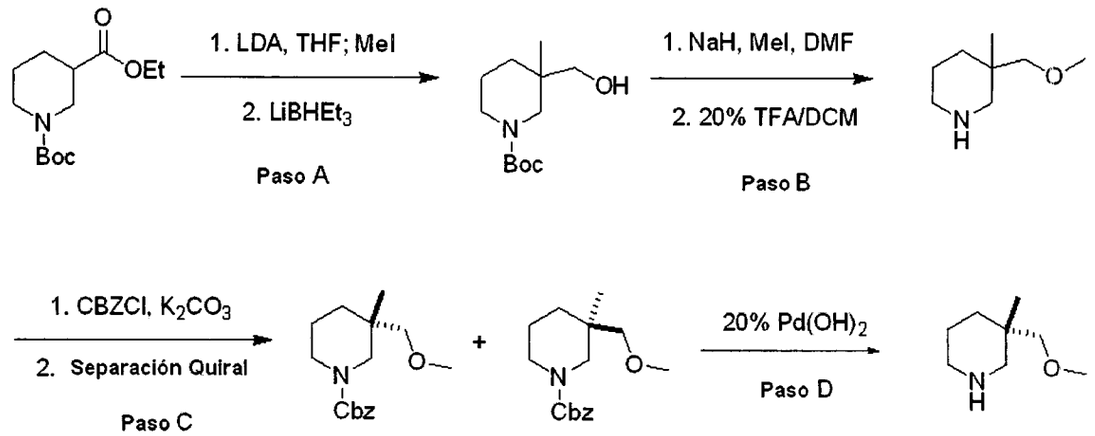
Paso A: El sustrato (10 g) se suspendió en THF (200 mL). Luego se agregó lentamente solución de hidruro de litio y aluminio (110 mL, 2M en THF). La mezcla se agitó a temperatura ambiente durante 12 horas. La solución se enfrió hasta 0 °C, y se agregó lentamente Na_2SO_4 acuosa saturada (200 mL). La mezcla se filtró a través de Celite, y torta de filtración se lavó con acetato de etilo (400 mL). La capa orgánica se lavó con agua (200 mL) y salmuera (200 mL). La capa orgánica se secó (Na_2SO_4 anhidro), se filtró y evaporó para proporcionar el aminoalcohol (6,9 g). El aminoalcohol (6,9 g) se disolvió en THF (80 mL) y agua (80 mL) a temperatura ambiente. Se agregó carbonato de potasio (14,76 g). Luego se agregó por goteo cloroformato de bencilo (8,28 mL) en THF (40 mL). La mezcla se agitó a temperatura ambiente durante 30 min. El disolvente se separó por

evaporación bajo presión reducida, y se agregó acetato de etilo (100 mL). Se separaron dos capas, y la capa acuosa se extrajo con acetato de etilo (2 × 100 mL). La capa orgánica combinada se lavó con salmuera (200 mL), se secó (Na_2SO_4), se filtró y evaporó bajo presión reducida para proporcionar el producto en bruto que se purificó mediante cromatografía en columna. El aminoalcohol racémico se separó quiralmente mediante el método HPCL SFC. Los enantiómeros correspondientes al pico 1 y al pico 2 se tomaron por separado para preparar los componentes básicos correspondientes.

Paso B: El alcohol del Paso A (1,936 g) se disolvió en diclorometano (80 mL), y se trató con esponja de protones (8,32 g) a temperatura ambiente. Luego se agregó tetrafluoroborato de trimetiloxonio (5,69 g). La mezcla se agitó durante 1 h. La reacción se templó con solución acuosa saturada de cloruro de amonio (100 mL). Las dos capas se separaron, y la capa acuosa se extrajo con diclorometano (2 × 100 mL). La capa orgánica combinada se lavó consecutivamente con ácido clorhídrico (200 mL, 1 N), solución de bicarbonato de sodio saturado (200 mL), salmuera (200 mL), se secó (Na_2SO_4), se filtró y evaporó bajo presión reducida para proporcionar el producto en bruto que se purificó mediante cromatografía en columna.

Paso C: El éter de metilo enantiómericamente puro del Paso B en EtOH se trató con $Pd(OH)_2$ sobre carbono (20% en peso) y se agitó en atmósfera de hidrógeno a presión atmosférica, a temperatura ambiente durante 2 h. La mezcla se separó por filtración, y el filtrado se evaporó bajo presión reducida para proporcionar la amina.

EJEMPLO 79



Paso A: A –78°C se agregó por goteo éster (6359 mg, 24,7 mmol) en THF (50ml) a LDA (1,8 M en THF, 27,5 ml, 49,4 mmol) en THF (200ml). La mezcla de reacción se calentó lentamente hasta temperatura ambiente y se agitó a dicha temperatura hasta la mañana siguiente. La reacción se enfrió hasta 0°C y se templó con solución saturada de NH_4Cl. La mezcla se diluyó con H_2O y se extrajo con EtOAc (x2). La capa orgánica combinada se secó sobre Na_2SO_4 anhidro y concentró. La purificación por cromatografía en columna proporcionó el compuesto del título (6221 mg, 93%). LCMS t_R =2,27 Min. La masa se calculó para, M+ 271,1; se observó LC/MS m/z 216,1 (M+H–C_4H_8). A una solución de éster (4659 mg, 17,2 mmol) en THF (300 ml) se agregó $LiBHEt_3$ (69 ml, 1M en THF). La reacción se agitó a temperatura ambiente durante 30 min. Se templó agregando NH_4Cl saturado. La mezcla se extrajo con CH_2Cl_2. La capa orgánica combinada se secó sobre Na_2SO_4 anhidro y concentró. La purificación por cromatografía en columna proporcionó el compuesto del título (3032mg, 77%). LCMS t_R =1,82 Min. La masa se calculó para M+ 229,1; se observó LC/MS m/z 174,1 (M+H–C_4H_8).

Paso B: NaH (1324 mg, 60% dispersión en aceite mineral, 33,1 mmol) se agregó en porciones a una mezcla del compuesto del Paso A y MeI (3,3 ml, 52,9 mmol) en DMF (66 mL) a 0°C. La mezcla de reacción se calentó lentamente hasta

temperatura ambiente y se agitó a dicha temperatura hasta la mañana siguiente. La reacción se enfrió hasta 0°C y se templó con solución saturada de NH_4Cl. La mezcla se diluyó con H_2O y se extrajo con EtOAc (x2). La capa orgánica combinada se secó sobre Na_2SO_4 anhidro y concentró. La purificación por cromatografía en columna proporcionó el compuesto del título (2633 mg, 82%). LCMS t_R =2,32 Min. La masa se calculó para M+ 243,1; se observó LC/MS m/z 188,1 (M+H–C_4H_8). Una solución del compuesto 4 (901 mg, 3,71 mmol) se agitó en 20 % TFA en CH_2Cl_2 (20 mL) a 0°C durante 30 min y luego a temperatura ambiente durante 15 min. La mezcla de reacción se concentró. El residuo en bruto se usó, por ejemplo, sin purificación posterior. LCMS t_R =0,26 Min. La masa se calculó para M+ 143,1; se observó LC/MS m/z 144,1 (M+H).

Paso C: CbzCl (604 µl, 4,08 mmol) en THF (1 ml) se agregó a una mezcla del compuesto del Paso B y K_2CO3 (1125 mg, 8,15 mmol) en THF (20 ml) y H_2O (20 ml) a 0°C. Luego de agitar a temperatura ambiente durante 30 min, la mezcla de reacción se extrajo con EtOAc (x2). La capa orgánica combinada se secó sobre Na_2SO_4 anhidro y concentró. La purificación por cromatografía en columna proporcionó el compuesto del título (965mg, 94%). LCMS t_R =2,28 Min (UV $_{254nm}$). La masa se calculó para M+ 277,1; se observó LC/MS m/z 278,1 (M+H). Las aminas del título se separaron quiralmente usando un sistema manipulador de líquidos Gilson GX–281 con capacidad para HPLC. La separación se llevó a cabo en las siguientes condiciones: columna Chiral PAK AD (5 x 50 cm; 20 µ) de Chiral Technologies; flujo = 50 mL/min; 7,5% isopropanol en hexanos (isocrático); se observó a 210 nm.

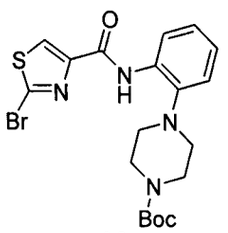
Paso D: Los isómeros enantioméricamente puros del Paso C se disolvieron en (1mmol, 277 mg) en EtOH (6 ml), se mezcló (sic) con 20% $Pd(OH)_2$ (51mg) y se agitó bajo balón de H_2 a temperatura ambiente durante 2 horas. La filtración a través de Celite y la concentración proporcionó el compuesto del título, el cual se usó para el paso siguiente sin purificación posterior. LCMS t_R =0,26 Min. La masa

461

se calculó para M+ 143,1; se observó LC/MS m/z 144,1 (M+H).

La síntesis de los compuestos del párrafo (j), tal como se divulgó en la Solicitud de Patente Provisional de EEUU, Serie Nº 60/855421, se describe a continuación:

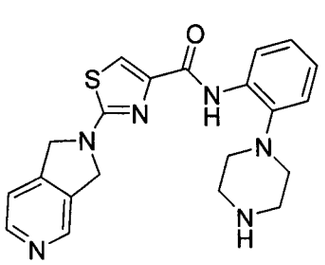
Ejemplo 1
Preparación del Compuesto Intermediario JA



JA

A una solución del ácido 2–bromo–tiazol–4–carboxílico (2,0 mmol, 0,42 g), *N,N*–diisopropiletilamina (3,0 mmol, 0,52 mL) y HATU (2,0 mmol, 0,76 g) en DMF (10 mL) se agregó terc–butil éster del ácido 4–(2–aminofenil)–piperazina–1–carboxílico (2,0 mmol, 0,56 g). La mezcla de reacción se agitó a 80 °C durante 3 horas, y luego se concentró al vacío. El residuo resultante se purificó usando cromatografía instantánea en columna sobre gel de sílice (eluyente: Hexano:EtOAc (4.5:1)) para proporcionar el Compuesto JA en forma de un sólido de color amarillo (0,67 g , 72%). ^{1}H RMN (400 MHz, $CDCl_3$) □ 10,38 (s, 1H), 8,49 (dd, *J* = 8,0, 1,2 Hz, 1H), 8,14 (s, 1H), 7,23–7,10 (m, 3 H), 3,72 (s ancho, 4H), 2,89–2,87 (m, 4H), 1,50 (s, 9H). HPLC–MS TA= 2,39 min, la masa se calculó para la fórmula $C_{19}H_{23}BrN_4O_3S$ 466,07; se observó LCMS m/z 467,05 (M+H).

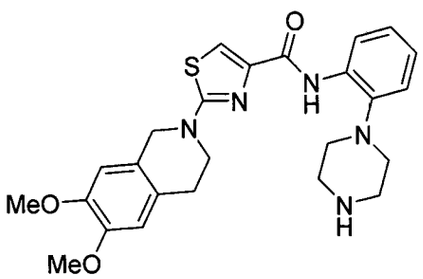
Ejemplo 2
Preparación del compuesto 1



1

Una solución del compuesto **JA** (0,050 mmol, 23 mg), *N,N*–diisopropiletilamina (0,20 mmol, 35 µL) y 2,3–dihidro–1*H*–pirrolo[3,4–c]piridina (0,1 mmol) en DMF (1 mL) se irradió usando microondas durante 15 minutos a una temperatura de 180 °C. La mezcla de reacción luego se concentró al vacío, y al residuo resultante se agregó TFA (0,5 mL). La solución resultante se dejó agitar a temperatura ambiente durante 10 minutos y luego se concentró al vacío. El residuo resultante se purificó usando HPLC en fase reversa para proporcionar el Compuesto **1**.

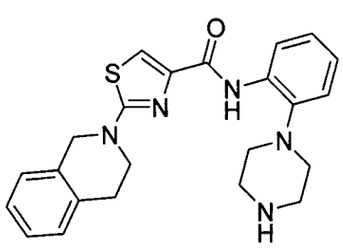
Ejemplo 3
Preparación del compuesto 2



2

Se preparó el Compuesto **2** usando el método descripto en el Ejemplo 2 y utilizando 6,7–dimetoxi–1,2,3,4–tetrahidro–isoquinolina en lugar de 2,3–dihidro–1*H*–pirrolo[3,4–c]piridina.

Ejemplo 4
Preparación del compuesto 3

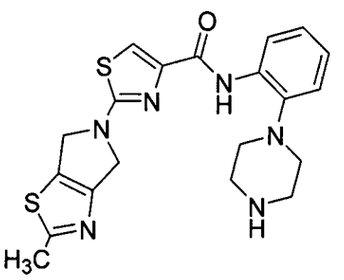


3

Se preparó el Compuesto **3** usando el método descripto en el Ejemplo 2 y utilizando 1,2,3,4–tetrahidro–isoquinolina en lugar de 2,3–dihidro–1*H*–pirrolo[3,4–c]piridina.

Ejemplo 5

Preparación del compuesto 4

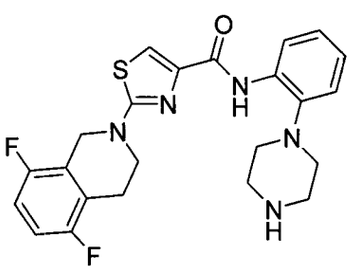


4

Se preparó el Compuesto **4** usando el método descripto en el Ejemplo 2 y utilizando 2–metil–5,6–dihidro–4*H*–pirrolo[3,4–d]tiazol en lugar de 2,3–dihidro–1*H*–pirrolo[3,4–c]piridina.

Ejemplo 6

Preparación del compuesto 5



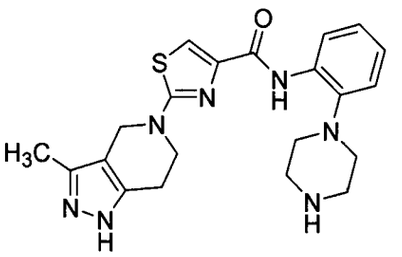
5

Se preparó el Compuesto **5** usando el método descripto en el Ejemplo 2 y utilizando 5,8–difluoro–1,2,3,4–tetrahidro–isoquinolina en lugar de 2,3–dihidro–1*H*–pirrolo[3,4–c]piridina.

464

Ejemplo 7

Preparación del compuesto 6

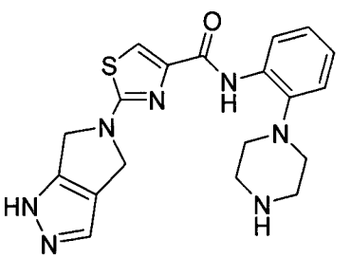


6

Se preparó el Compuesto **6** usando el método descripto en el Ejemplo 2 y utilizando 3–metil–4,5,6,7–tetrahidro–1*H*–pirazolo[4,3–c]piridina en lugar de 2,3–dihidro–1*H*–pirrolo[3,4–c]piridina.

Ejemplo 8

Preparación del compuesto 7

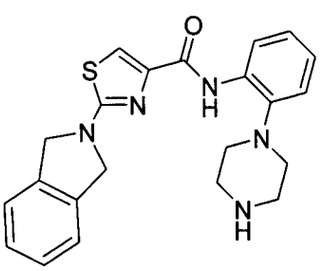


7

Se preparó el Compuesto **7** usando el método descripto en el Ejemplo 2 y utilizando 1,4,5,6–tetrahidro–pirrolo[3,4–c]pirazol en lugar de 2,3–dihidro–1*H*–pirrolo[3,4–c]piridina.

Ejemplo 9

Preparación del compuesto 8

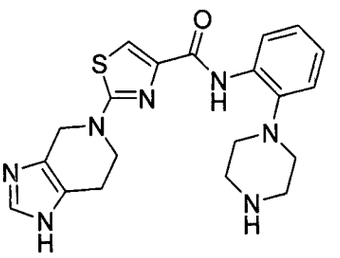


8

Se preparó el Compuesto **8** usando el método descripto en el Ejemplo 2 y utilizando 2,3–dihidro–1*H*–isoindol en lugar de 2,3–dihidro–1*H*–pirrolo[3,4–c]piridina.

Ejemplo 10

Preparación del compuesto 9

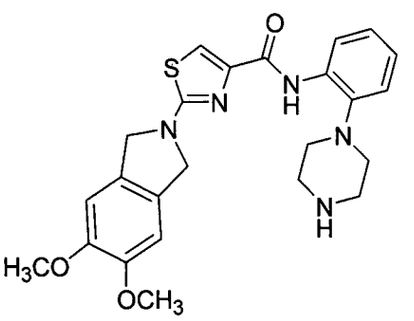


9

Se preparó el Compuesto **9** usando el método descripto en el Ejemplo 2 y utilizando 4,5,6,7–tetrahidro–1*H*–imidazo[4,5–c]piridina en lugar de 2,3–dihidro–1*H*–pirrolo[3,4–c]piridina.

Ejemplo 11

Preparación del compuesto 10

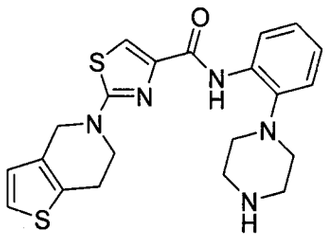


10

Se preparó el Compuesto **10** usando el método descripto en el Ejemplo 2 y utilizando 5,6–dimetoxi–2,3–dihidro–1*H*–isoindol en lugar de 2,3–dihidro–1*H*–pirrolo[3,4–c]piridina.

Ejemplo 12

Preparación del compuesto 11

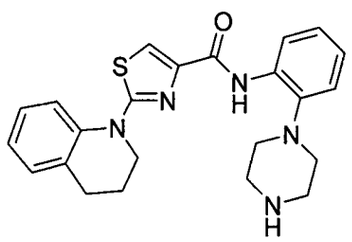


11

Se preparó el Compuesto **11** usando el método descripto en el Ejemplo 2 y utilizando 4,5,6,7–tetrahidro–1*H*–tieno[3,2–c]piridina en lugar de 2,3–dihidro–1*H*–pirrolo[3,4–c]piridina.

Ejemplo 13

Preparación del compuesto 12

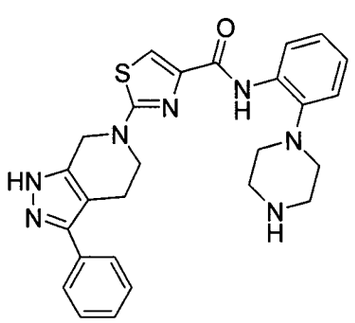


12

Se preparó el Compuesto **12** usando el método descripto en el Ejemplo 2 y utilizando 1,2,3,4–tetrahidroquinoline en lugar de 2,3–dihidro–1*H*–pirrolo[3,4–c]piridina.

Ejemplo 14

Preparación del compuesto 13

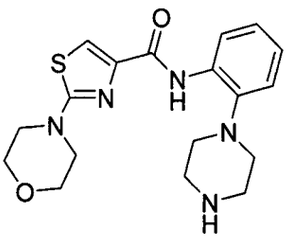


13

Se preparó el Compuesto **13** usando el método descripto en el Ejemplo 2 y utilizando 3–fenil–4,5,6,7–tetrahidro–1*H*–pirazolo[3,4–c]piridina en lugar de 2,3–dihidro–1*H*–pirrolo[3,4–c]piridina.

Ejemplo 15

Preparación del compuesto 14

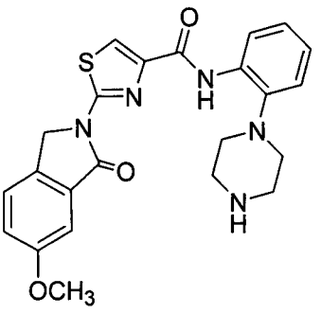


14

Un tubo que contenía una barra de agitación se cargó con una solución del compuesto **JA** (0,050 mmol, 23 mg), $Pd_2(DBA)_3$ (5.0 □mol, 4,6 mg), y X--Phos (0,010 mmol, 4,8 mg) en dioxano (1 mL). Se agregó K_3PO_4 (0,10 mmol, 21 mg) a la solución y la reacción resultante se colocó bajo una atmósfera de nitrógeno. Se agregó morfolina (8,7 mg, 0,10 mmol) a la mezcla de reacción mediante una jeringa bajo una atmósfera de N_2. El tubo se colocó en un baño de aceite a 100 °C y la reacción se dejó agitar a dicha temperatura durante alrededor de 15 horas, luego se enfrió hasta temperatura ambiente. La mezcla de reacción luego se diluyó con acetonitrilo (5 mL), la solución resultante se centrifugó durante alrededor de 2 horas a una velocidad de alrededor de 1000 rpm, y el sobrenadante se recolectó y concentró al vacío. Al residuo resultante se agregó TFA (0,5 mL) y la solución resultante se dejó reposar durante 10 minutos, luego se concentró al vacío. El residuo resultante se purificó usando HPLC en fase reversa para proporcionar el Compuesto **14**.

Ejemplo 16

Preparación del compuesto 15

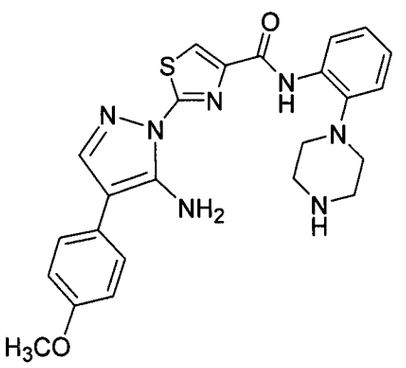


15

Se preparó el Compuesto **15** usando el método descripto en el Ejemplo 15 y utilizando 6–metoxi–2,3–dihidro–isoindol–1–ona en lugar de morfolina.

Ejemplo 17

Preparación del compuesto 16



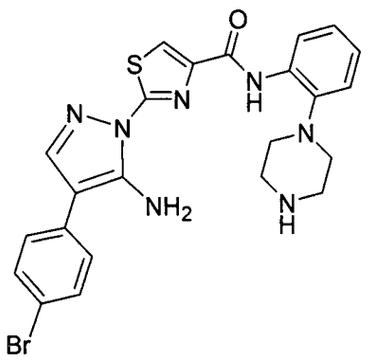
16

Un tubo que contenía una barra de agitación se cargó con una solución de 4–(4–metoxi–fenil)–2*H*–pirazol–3–ilamina (0,10 mmol), $Pd_2(DBA)_3$ (5,0 □mol, 4,6 mg), Xantphos (0,010 mmol, 5,8 mg) y el Compuesto **JA** (0,050 mmol, 23 mg) en dioxano (1 mL). A la solución luego se agregó K_3PO_4 (0,10 mmol, 21 mg) y el tubo de reacción se purgó con N_2, luego se cerró herméticamente. La reacción resultante se calentó hasta 100 °C y se dejó agitar a dicha temperatura durante alrededor de 15 horas, luego se enfrió hasta temperatura ambiente. La mezcla de reacción luego se diluyó con acetonitrilo (5 mL), la solución resultante se centrifugó durante alrededor de 2 horas a una velocidad de alrededor de 1000

rpm, y el sobrenadante se recolectó y concentró al vacío. Al residuo resultante se agregó TFA (0,5 mL) y la solución resultante se dejó reposar durante 10 minutos, luego se concentró *al vacío*. El residuo resultante se purificó usando HPLC en fase reversa para proporcionar el Compuesto **16**.

Ejemplo 18

Preparación del compuesto 17

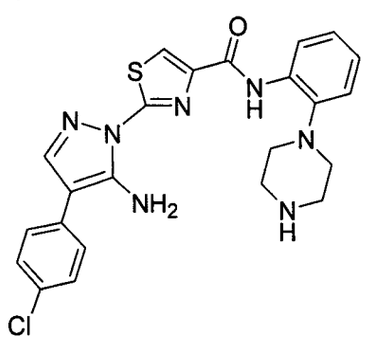


17

Se preparó el Compuesto **17** usando el método descripto en el Ejemplo 17 y utilizando 4–(4–bromo–fenil)–2*H*–pirazol–3–ilamina en lugar de 4–(4–metoxi–fenil)–2*H*–pirazol–3–ilamina.

Ejemplo 19

Preparación del compuesto 18

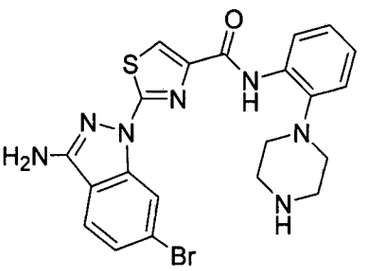


18

Se preparó el Compuesto **18** usando el método descripto en el Ejemplo 17 y utilizando 4–(4–cloro–fenil)–2*H*–pirazol–3–ilamina en lugar de 4–(4–metoxi–fenil)–2*H*–pirazol–3–ilamina.

Ejemplo 20

Preparación del compuesto 19

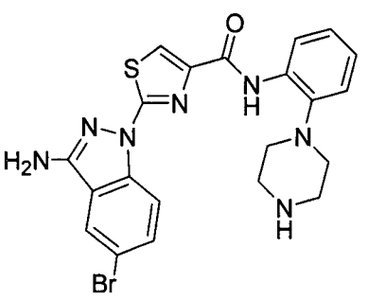


19

Se preparó el Compuesto **19** usando el método descripto en el Ejemplo 17 y utilizando 6–bromo–1*H*–indazol–3–ilamina en lugar de 4–(4–metoxi–fenil)–2*H*–pirazol–3–ilamina.

Ejemplo 21

Preparación del compuesto 20

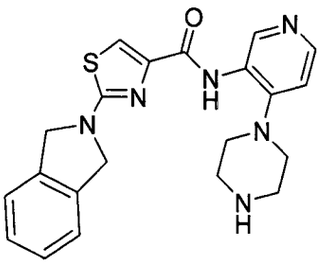


20

Se preparó el Compuesto **20** usando el método descripto en el Ejemplo 17 y utilizando 5–bromo–1*H*–indazol–3–ilamina en lugar de 4–(4–metoxi–fenil)–2*H*–pirazol–3–ilamina.

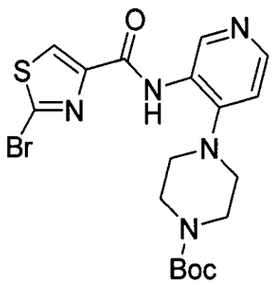
Ejemplo 22

Preparación del compuesto 21



21

*Paso 1 – Síntesis del Compuesto Intermediario **B***



B

Una solución de 4–cloro–3–nitro–piridina (2,0 mmol, 0,32 g), trietilamina (3,0 mmol, 0,42 mL) y terc–butil éster del ácido piperazina–1–carboxílico (2,5 mmol, 0,47 g) en dioxano (2 mL) se irradió usando microondas durante 8 minutos a una temperatura de 150 °C. La solución luego se enfrió hasta temperatura ambiente y concentró al vacío y el residuo resultante se purificó usando cromatografía instantánea en columna sobre gel de sílice (eluyente: acetato de etilo) para proporcionar terc–butil éster del ácido 4–(3–nitro–piridin–4–il)–piperazina–1–carboxílico en forma de un sólido de color amarillo (633 mg, rendimiento cuantitativo). ^{1}H RMN (400 MHz, $CDCl_3$) □ 8,87 (s, 1H), 8,40 (d, *J* = 5,6 Hz, 1H), 6,87 (d, *J* = 6,0 Hz, 1H), 3,68–3,56 (m, 4H), 3,32–3,18 (m, 4H), 1,48 (s, 9H).

El terc–butil éster del ácido 4–(3–nitro–piridin–4–il)–piperazina–1–carboxílico (633 mg) luego se diluyó con MeOH/EtOAc (1:1, 10 mL) y a la solución resultante se agregó Pd sobre carbono (5% Pd). La mezcla de reacción

resultante se agitó bajo una atmósfera de hidrógeno a temperatura ambiente durante alrededor de 15 horas. La mezcla de reacción se filtró a través de una almohadilla de celite y el filtrado se concentró al vacío para proporcionar terc–butil éster del ácido 4–(3–amino–piridin–4–il)–piperazina–1–carboxílico en forma de un sólido. HPLC–MS RT= 1.10 min, la masa se calculó para la fórmula $C_{14}H_{22}N_4O_2$ 278,17; se observó LCMS m/z 279,28 (M+H).

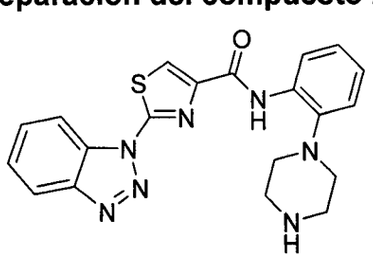
A una solución del ácido 2–bromo–tiazol–4–carboxílico (0,78 mmol, 0,16 g), *N,N*–diisopropiletilamina (1,5 mmol, 0,26 mL) y HATU (0,78 mmol, 0,30 g) en DMF (10 mL) se agregó terc–butil éster del ácido 4–(3–amino–piridin–4–il)–piperazina–1–carboxílico (0,78 mmol, 0,22 g). La mezcla de reacción se calentó hasta 80 °C y se dejó agitar a dicha temperatura durante alrededor de 15 horas, luego de cuyo tiempo la mezcla de reacción se enfrió hasta temperatura ambiente y concentró al vacío. El residuo en bruto resultante se purificó usando cromatografía instantánea en columna sobre gel de sílice (eluyente: acetato de etilo) para proporcionar el Compuesto **B** en forma de un sólido de color amarillo. HPLC–MS TA= 1,40 min, la masa se calculó para la fórmula $C_{18}H_{22}BrN_5O_3S$ 467,06; se observó LCMS m/z 468,05 (M+H).

*Paso 2 – Síntesis del compuesto **21***

Se preparó el Compuesto **21** usando el método descripto en el Ejemplo 2 y utilizando el Compuesto **B** en lugar del Compuesto **A**, y 2,3–dihidro–1*H*–isoindol en lugar de 2,3–dihidro–1*H*–pirrolo[3,4–c]piridina.

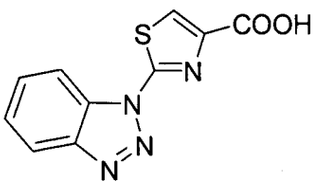
Ejemplo 23

Preparación del compuesto 22



22

Paso 1 – Síntesis del compuesto ***C***



C

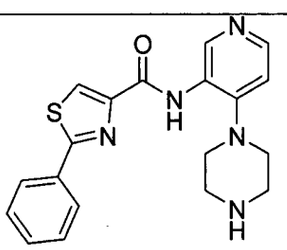
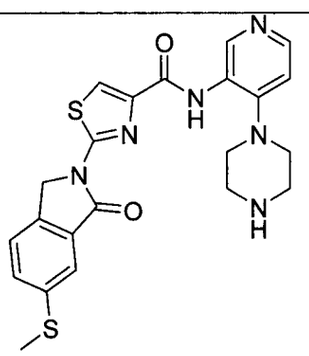
Benzotriazol (1,20 mmol, 143 mg), K_3PO_4 (1,5 mmol, 0,32 g), $Pd_2(DBA)_3$ (40,0 □mol, 36,6 mg), X–Phos (0,12 mmol, 57 mg) y etil éster del ácido 2–bromo–tiazol–5–carboxílico (1,00 mmol, 236 mg) se cargaron en un tubo Schlenk que contenía una barra de agitación. El tubo Schlenk se tapó con un septo de caucho, se evacuó y se colocó bajo una atmósfera de nitrógeno. Se agregó tolueno (2 mL) a través del septo mediante una jeringa, luego el tubo se cerró con una tapa a rosca de Teflón bajo un flujo de nitrógeno, y se colocó en un baño de aceite a 100 °C. La reacción se calentó hasta 100 °C y se dejó agitar a dicha temperatura durante alrededor de 15 horas, luego de cuyo tiempo, la mezcla de reacción se enfrió hasta temperatura ambiente y se filtró a través de una almohadilla de celite. El filtrado se concentró al vacío y el residuo resultante se purificó usando cromatografía instantánea en columna sobre gel de sílice (eluyente: Hexano/EtOAc (6:1)) para proporcionar etil éster del ácido 2–benzotriazol–1–il–tiazol–4–carboxílico en forma de un sólido de color blanco. ^{1}H RMN (400 MHz, $CDCl_3$) □ 8,57 (d, *J* = 8,4 Hz, 1H), 8,14 (d, *J* = 8,0 Hz, 1H), 8,06 (s, 1H), 7,73–7,68 (m, 1H), 7,54–7,49 (m, 1H), 4,46 (q, *J* = 7,2 Hz, 2H), 1,45 (t, *J* = 7,2 Hz, 3H).

Etil éster del ácido 2–benzotriazol–1–il–tiazol–4–carboxílico se diluyó con ácido clorhídrico acuoso concentrado y la solución resultante se calentó hasta reflujo y se dejó agitar a dicha temperatura durante alrededor de 15 horas. La mezcla de reacción luego se enfrió hasta temperatura ambiente y liofilizó para proporcionar el Compuesto **C** en forma de una sal de cloruro de amonio.

Paso 2 – Síntesis del compuesto ***22***

vacío. El residuo en bruto resultante se diluyó con diclorometano (2 mL), se filtró a través de Celite y el filtrado se purificó usando cromatografía instantánea en columna sobre gel de sílice (eluyente: gradiente de 100% hexanos en 30% acetato de etilo en hexanos) proporcionó un producto intermediario sólido de color blanco . ^{1}H RMN (400 MHz, CD_3CN) □10,35–10,25 (s ancho, 1H), 8,49–8,46 (dd, *J* = 8, 1,6 Hz, 1H), 8,39–8,37 (d, *J* = 2,8 Hz, 1H), 8,04 (s, 1H), 7,84–7,83 (d, *J* = 1,6 Hz, 1H), 7,30–7,27 (dd, *J* = 8, 1,6 Hz, 1H), 7,25–7,20 (td, *J* = 8, 1,6 Hz, 1H), 7,18–7,13 (td, *J* = 8, 1,6 Hz, 1H), 3,70–3,63 (t ancho, *J* = 4,8 Hz, 4H), 2,91–2,86 (m, *J* = 4,8 Hz, 4H), 1,48 (s, 9H). El producto intermediario sólido de color blanco se diluyó con una solución 9:1 de TFA:H_2O (2 mL). La solución resultante se agitó durante 2 horas a temperatura ambiente y la mezcla de reacción se concentró al vacío. El residuo resultante se purificó usando HPLC en fase reversa y liofilizó con HCl acuoso (1 M) para proporcionar el Compuesto **23** en forma de sal diclorhidrato (15,43 mg).

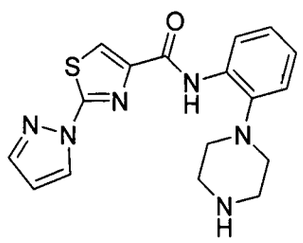
Los siguientes compuestos representativos de la invención se prepararon usando este método con reactivos apropiados:

No.	***Estructura***	***LCMS MH$^+$ m/z***	***HPLC MS t_R***
118		366,21	1,74
204		467,23	2,13

A una solución del ácido 2–benzotriazol–1–il–tiazol–4–carboxílico (0,050 mmol, 14 mg), *N,N*–diisopropiletilamina (0,25 mmol, 44 □L) y HATU (0,050 mmol, 19 mg) en DMF (0,5 mL) se agregó terc–butil éster del ácido 4–(2–aminofenil)–piperazina–1–carboxílico (0,10 mmol, 28 mg). La mezcla de reacción se calentó hasta 80 °C y se dejó agitar a dicha temperatura durante alrededor de 15 horas, luego de cuyo tiempo la mezcla de reacción se enfrió hasta temperatura ambiente y concentró al vacío. Al residuo sólido resultante se agregó TFA (0,5 mL) y la solución resultante se dejó reposar durante 10 minutos, luego se concentró al vacío. El residuo resultante se purificó usando HPLC en fase reversa para proporcionar el Compuesto **22**.

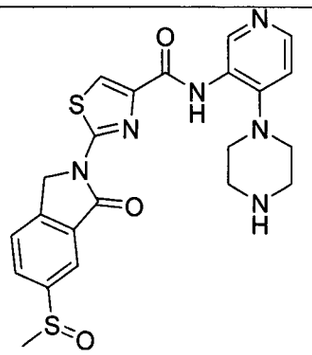
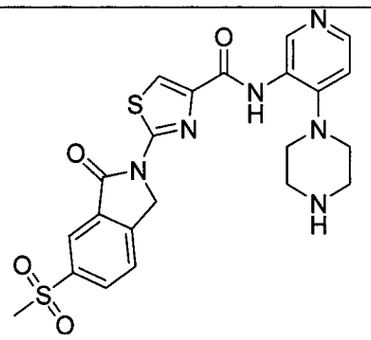
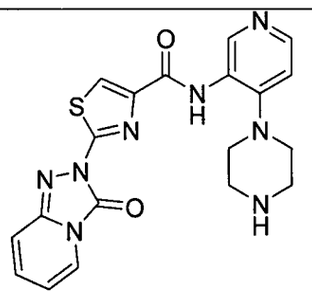
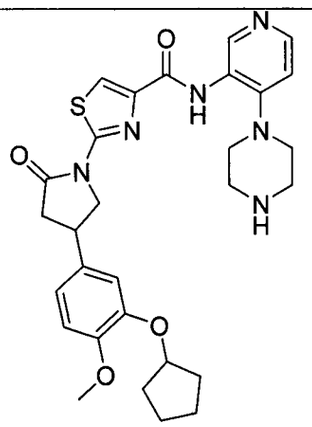
Ejemplo 24

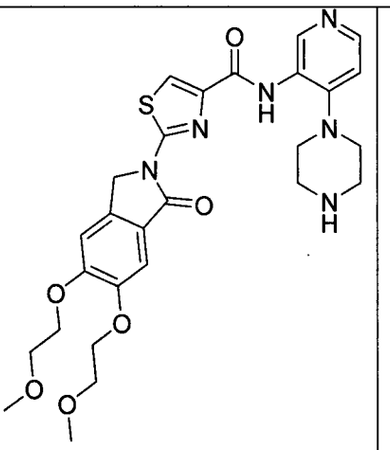
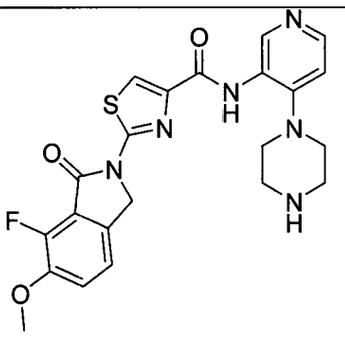
Preparación del compuesto 23



23

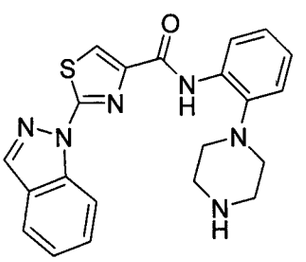
En un vial de 20 mL que contenía una barra de agitación (vial 1) se cargo una solución de terc–butil éster del ácido 4–{2–[(2–bromo–tiazol–4–carbonil)–amino]–fenil}–piperazina–1–carboxílico (107 µmol, 50 mg) y 1,4–dioxano (1 mL). Un segundo vial de 20 mL que contenía una barra de agitación (vial 2) se cargó con una solución de pirazol (4 eq., 428 µmol, 29,1 mg) y 1,–4 dioxano (2 mL). A la solución en el vial 2 se agregó NaH (60% dispersión en aceite mineral, 4 eq., 428 µmol, 17,2 mg). La reacción resultante se dejó agitar durante 15 minutos, luego se agregó a la solución en el vial 1. El vial 1 se cerró y la reacción resultante dentro del vial 1 se calentó hasta 100° C y se dejó agitar a dicha temperatura durante alrededor de 18 horas. El análisis mediante LC/MS confirmó la desaparición del material de partida y la mezcla de reacción se concentró al

242		483,11	1,48
243		499,08	1,26
267		445,69 (M+Na)	0,749
269		563,26	2,71

293		569,37	2,07
333		469,22	1,92

Ejemplo 25

Preparación del compuesto 24

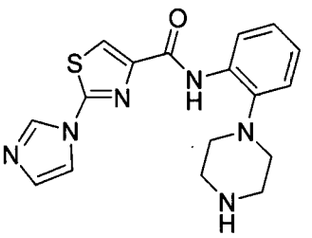


24

Se preparó el Compuesto **24** en forma de sal diclorhidrato usando el método descripto en el Ejemplo 24 y utilizando indazol en lugar de pirazol.

Ejemplo 26

Preparación del compuesto 25

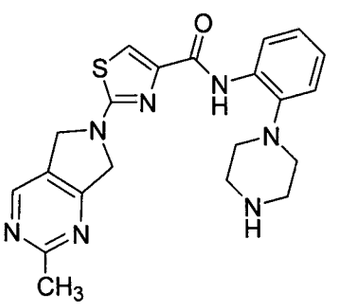


25

Se preparó el Compuesto **25** en forma de sal diclorhidrato usando el método descripto en el Ejemplo 24 y utilizando imidazol en lugar de pirazol.

Ejemplo 27

Preparación del compuesto 26

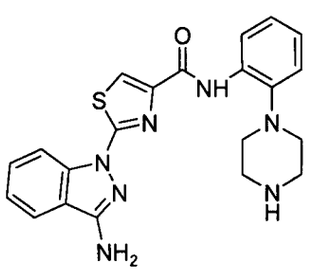


26

Se preparó el Compuesto **26** en forma de sal diclorhidrato usando el método descripto en el Ejemplo 24 y utilizando diclorhidrato de 2–metil–6,7–dihidro–5*H*–pirrolo[3,4–d]pirimidina en lugar de pirazol.

Ejemplo 28

Preparación del compuesto 27

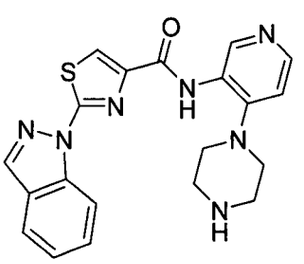


27

Un vial de 20 mL que contenía una barra de agitación se cargó con terc–butil éster del ácido 4–{2–[(2–bromo–tiazol–4–carbonil)–amino]–fenil}–piperazina–1–carboxílico (107 µmol, 50 mg), $Pd_2(DBA)_3$ (0,05 eq., 5,4 µmol, 4,9 mg), Xant–Phos (0,1 eq., 10,7 µmol, 6,2 mg), K_3PO_4 (2 eq., 214 µmol, 45,5 mg), 3–aminoindazol (2 eq., 214 µmol, 28,5 mg) y tolueno (3 mL). El vial se purgó con argón, se tapó y cerró herméticamente y luego se colocó en un baño de aceite a 140 °C. La reacción luego se dejó agitar a dicha temperatura durante alrededor de 18 horas. LC/MS confirmó la presencia de 2 productos. La mezcla de reacción se concentró al vacío y el residuo resultante se diluyó con diclorometano (2 mL) y se filtró a través de Celite. El filtrado luego se purificó usando HPLC en fase reversa y los 2 productos separados se caracterizaron usando LC/MS (el primer producto tuvo un tiempo de retención = 5,76 min, y m+1=520,24; el segundo producto tuvo un tiempo de retención = 5,99 minutos, y m+1=520,35). El segundo producto se diluyó con una mezcla 9:1 de TFA:H_2O (2 mL) y la solución resultante se agitó durante 2 horas a temperatura ambiente. La mezcla de reacción se concentró al vacío y el residuo resultante se purificó usando HPLC en fase reversa y liofilizó con HCl acuoso (1M) para proporcionar el Compuesto **27** en forma de sal diclorhidrato.

Ejemplo 29

Preparación del compuesto 28



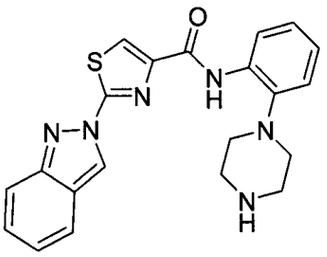
28

Se preparó el Compuesto **28** en forma de sal diclorhidrato usando el método descripto en el Ejemplo 24 y utilizando 4–{3–[(2–Bromo–tiazol–4–

carbonil)–amino]–piridin–4–il}–1–Boc–piperazina en lugar de terc–butil éster del ácido 4–{2–[(2–bromo–tiazol–4–carbonil)–amino]–fenil}–piperazina–1–carboxílico e indazol en lugar de pirazol.

Ejemplo 30

Preparación del compuesto 29

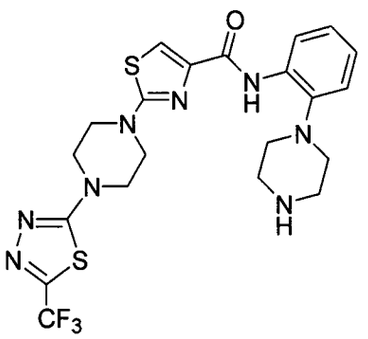


Un vial de 20 mL que contenía una barra de agitación (vial 1) se cargó con una solución de terc–butil éster del ácido 4–{2–[(2–bromo–tiazol–4–carbonil)–amino]–fenil}–piperazina–1–carboxílico (321 µmol, 150 mg). A esto se agregó 2 mL de 1,4–dioxano. Un segundo vial de 20 mL que contenía una barra de agitación (vial 2) se cargó con una solución de indazol (3 eq., 963 µmol, 114 mg) y 4 mL de 1,4–dioxano. A la solución en el vial 2 luego se agregó NaH (60% dispersión en aceite mineral, 3 eq., 963 µmol, 38,5 mg). La reacción resultante se dejó agitar a temperatura ambiente durante alrededor de 15 minutos, luego la mezcla de reacción se agregó a la solución en el vial 1. El vial 1 luego se cerró herméticamente, se colocó en un baño de aceite a 100 °C y la mezcla de reacción se dejó agitar a dicha temperatura durante alrededor de 5 horas. La mezcla de reacción luego se concentró al vacío y el residuo resultante se diluyó con diclorometano (2 mL) y se filtró a través de Celite. El residuo resultante se purificó usando cromatografía instantánea en columna sobre gel de sílice (eluyente: gradiente de 100% hexanos en 70% acetato de etilo en hexanos) proporcionó un producto que se recolectó y se diluyó con una mezcla 9:1 de TFA:H_2O (3 mL) y la solución resultante se dejó agitar durante 2 horas a temperatura ambiente. Se concentró al vacío y el residuo resultante se purificó mediante HPLC en fase

reversa que indicó la presencia de dos productos. El primer producto tenía un tiempo de retención de 3,73 minutos con una masa visible de m+1=405,23. Dicho producto se liofilizó con HCl acuoso para proporcionar el Compuesto **29** en forma de sal diclorhidrato (12,45 mg).

Ejemplo 31

Preparación del compuesto 30



30

Un vial de 2 mL para microondas se cargó con una solución de terc–butil éster del ácido 4–{2–[(2–bromo–tiazol–4–carbonil)–amino]–fenil}–piperazina–1–carboxílico (107 µmol, 50 mg) en acetonitrilo (2 mL). A esta solución se agregó una solución de 1–(5–Trifluorometil–[1,3,4]tiadiazol–2–il)–piperazina (160 µmol, 38 mg) en DIEA (160 µmol, 28 µL) y la reacción resultante se colocó en microondas a 180° C durante alrededor de 15 minutos. La mezcla de reacción luego se concentró al vacío y el residuo resultante se diluyó con una mezcla 9:1 de TFA:H_2O (2 mL) y la solución resultante se agitó durante alrededor de 2 horas a temperatura ambiente. La mezcla de reacción luego se concentró al vacío y el residuo resultante se purificó usando HPLC en fase reversa y liofilizó con HCl acuoso para proporcionar el Compuesto **30** en forma de sal diclorhidrato (53,34 mg).

Los datos de LCMS y los tiempos de retención en HPLC para los Derivados de Anilinopiperazina representativos se proporcionan en la tabla

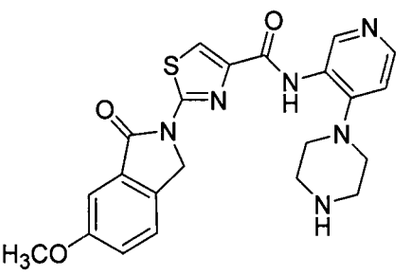
siguiente, en la cual los números de compuesto en la Tabla 1 corresponden a la numeración del compuesto en esta memoria descriptiva.

Compuesto	Se observó LCMS *m/z* (M+H)	HPLC–MS Tiempo de retención (min)
1	407,28	2,56
2	480,33	4,06
3	420,40	4,24
4	427,23	3,72
5	456,29	4,37
6	424,28	2,93
7	396,29	3,27
8	406,26	4,13
9	410,29	2,36
10	466,26	3,91
11	426,26	4,11
12	420,27	4,21
13	486,22	3,82
14	374,25	3,28
15	450,12	3,72
16	476,32	3,75
17	524,26	4,11
18	480,32	4,05
19	498,22	3,84
20	498,25	3,81
21	407,28	2,70
22	406,21	3,48
23	355,33	3,20
24	405,28	3,89
25	355,27	2,31
26	422,27	3,28
27	420,10	3,45
28	406,12	2,31
29	405,23	3,73
30	525,21	3,85
31	487,5	ND

ND = no disponible

Ejemplo 32

Preparación del compuesto 45

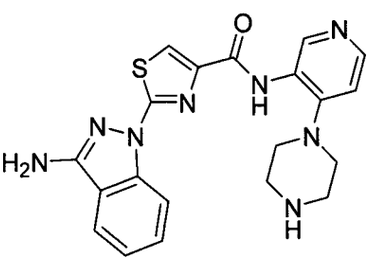


45

Se preparó el Compuesto **45** en forma de sal diclorhidrato usando el método descripto en el Ejemplo 24 y utilizando 4–{3–[(2–Bromo–tiazol–4–carbonil)–amino]–piridin–4–il}–1–Boc–piperazina en lugar de terc–butil éster del ácido 4–{2–[(2–bromo–tiazol–4–carbonil)–amino]–fenil}–piperazina–1–carboxílico (compuesto B) y 6–metoxi–2,3–dihidro–isoindol–1–ona.

Ejemplo 33

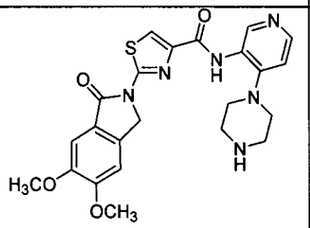
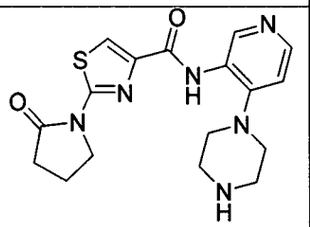
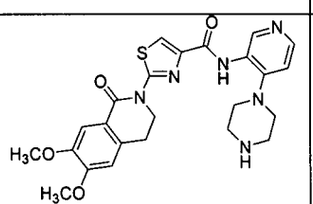
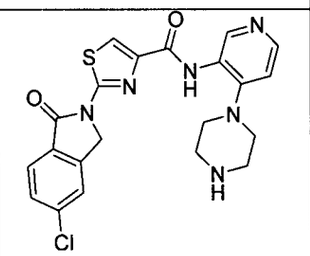
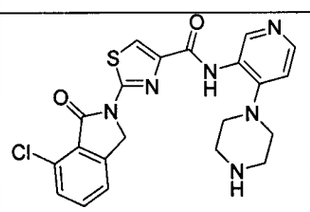
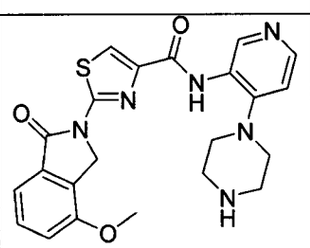
Preparación del compuesto 43

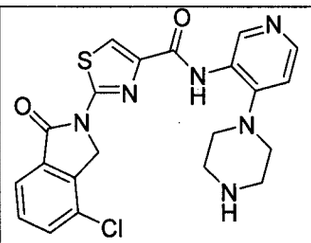
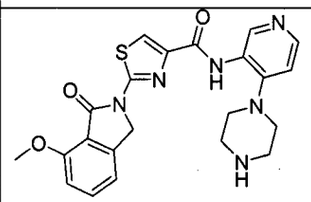
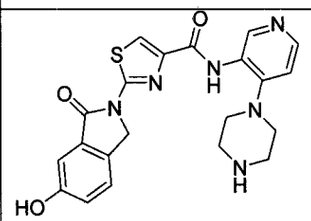
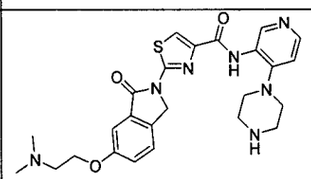
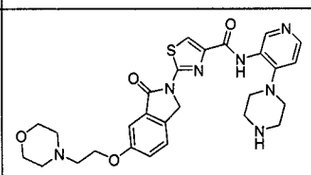
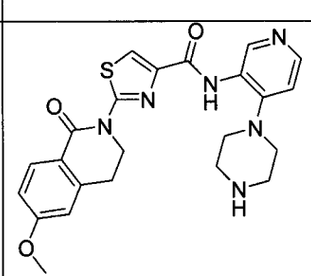
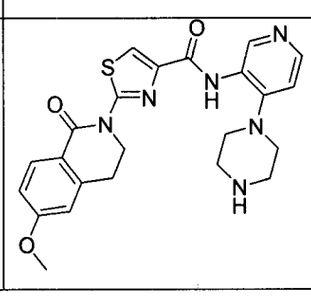


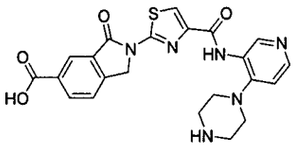
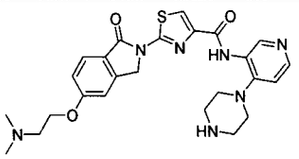
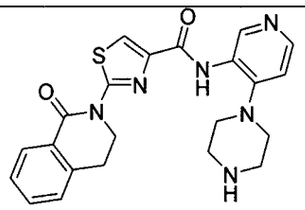
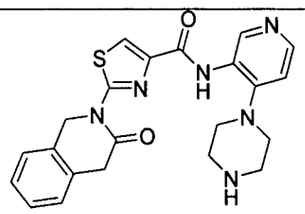
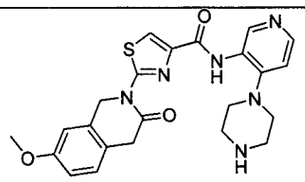
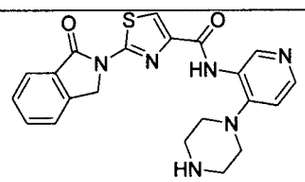
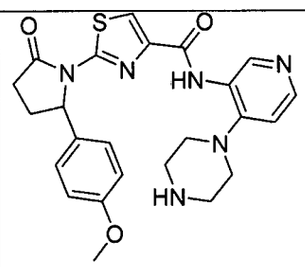
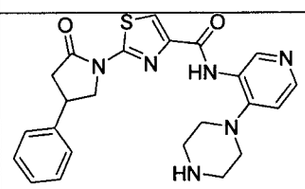
43

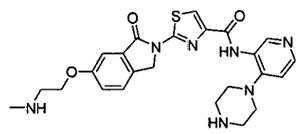
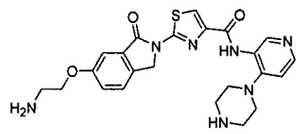
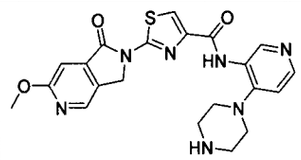
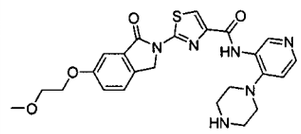
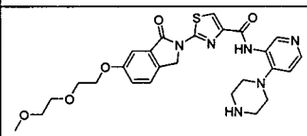
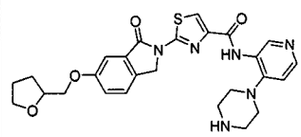
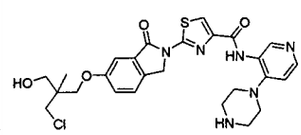
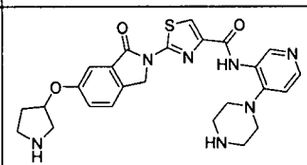
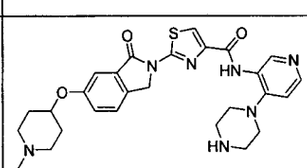
Se preparó el Compuesto **43** en forma de sal triclorhidrato usando el método descripto en el Ejemplo 24 y utilizando 4–{3–[(2–Bromo–tiazol–4–carbonil)–amino]–piridin–4–il}–1–Boc–piperazina en lugar de terc–butil éster del ácido 4–{2–[(2–bromo–tiazol–4–carbonil)–amino]–fenil}–piperazina–1–carboxílico y 3–amino indazol.

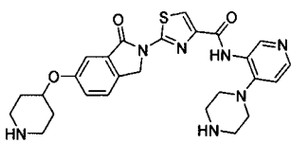
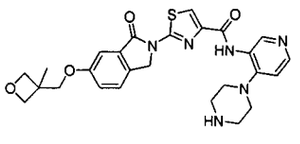
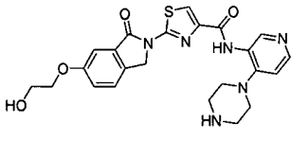
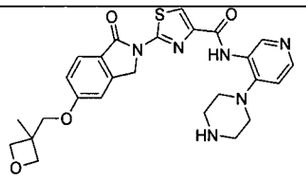
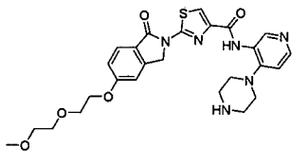
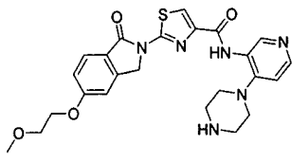
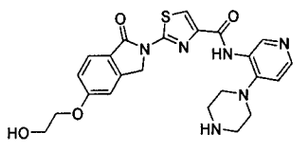
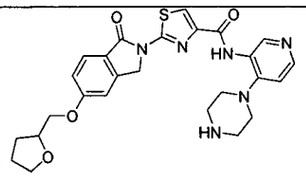
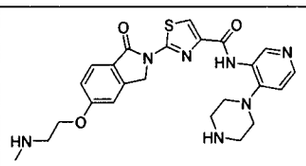
Se prepararon los siguientes compuestos usando el mismo procedimiento y los reactivos apropiados.

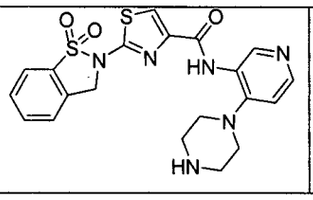
No.	Estructura	MS m/z (M+H)	HPLC MS t_R
84		481,1	1,04
96		373,1	0,60
99		495,1	0,92
100		455,0	0,98
106		455,0	0,97
107		451,1	1,06

108		**455,0**	**0,95**
109		**451,1**	**0,88**
115		**437,1**	**0,74**
116		**508,1**	**0,65**
119		**550,2**	**0,66**
121		**465,1**	**1,00**
86		**465,1**	**1,00**

138		**465,0**	**0,72**
139		**508,1**	**0,69**
147		**435,1**	**0,98**
149		**435,1**	**0,98**
150		**465,1**	**1,00**
164		**421,1**	**0,88**
165		**479,1**	**0,93**
169		**449,2**	**0,97**

186		**494,1**	**0,63**
187		**480,0**	**0,62**
188		**452,1**	**0,88**
190		**495,1**	**0,92**
191		**539,2**	**0,93**
192		**521,2**	**1,00**
196		**557,2**	**0,97**
197		**506,2**	**0,65**
198		**534,2**	**0,86**

199		**520,2**	**0,68**
200		**521,2**	**1,03**
205		**481,1**	**0,93**
234		**521,2**	**1,01**
235		**539,2**	**0,94**
236		**495,1**	**0,92**
237		**481,1**	**0,90**
238		**521,2**	**1,01**
263		**494,1**	**0,64**

287		**457,1**	**0,81**

Ejemplo 34

Preparación del Compuesto Intermediario **34C**



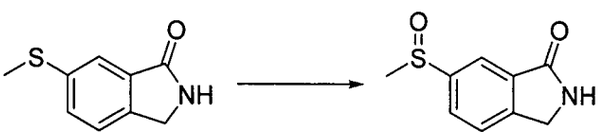
34A **34B** **34C**

En una solución del ácido 2–Metil–5–metilsulfanil–benzoico (250mg, 1,37mmol) en 12mL de mezcla (1:1 benceno/metanol) se agregó 2,74mmol de (Trimetilsilil)diazometano. La reacción se agitó durante 1,5 horas. El disolvente se removió para proporcionar **34A** (metil éster del ácido 2–Metil–5–metilsulfanil–benzoico) en forma de un aceite de color amarillo que se usó tal como estaba en el paso siguiente.

En la solución de **34A** (1,034g, 5,27mmol) en 15 mL de tetracloruro de carbono se agregó *N*–Bromosuccinimida (0,685g, 3,85mmol) y peróxido de benzoílo (46,63mg, 0,19mmol). La mezcla de reacción se sometió a reflujo a 80 °C durante 6 horas. La mezcla se enfrió y el precipitado se removió mediante filtración. La capa orgánica recolectada se concentró al vacío. El compuesto en bruto resultante **34B** se disolvió en NH_3 7N en metanol (20mL) y se calentó hasta 85 °C en un recipiente cerrado herméticamente durante alrededor de 15 horas. El disolvente se removió y el producto en bruto se purificó mediante cromatografía en columna instantánea sobre sílice usando el sistema de disolvente acetato de etilo/hexano para proporcionar 158 mg del compuesto **34A** en forma de un polvo de color blanco. RMN (H^1) □ 2,51(3H), 4,30(2 H), 7,45–7,47(m,3H).

Ejemplo 35

Preparación del Compuesto Intermediario **35A**



34C **35A**

A la solución del compuesto **34C** (40mg, 0,223mmol) en 5 mL de diclorometano se agregó ácido 3–cloroperoxibenzoico (55mg, 0,223mmol) y la reacción se agitó a temperatura ambiente durante 3 horas. La mezcla de reacción luego se enfrió en un baño de hielo y el precipitado formado se removió mediante filtración. El filtrado se lavó con agua, se secó sobre sulfato de sodio anhidro, se filtró y concentró al vacío para proporcionar el compuesto **35A**, que se usó sin purificación posterior. RMN del producto en bruto indicó un desplazamiento del pico S–CH3 desde 2,51 hasta 2,84ppm

Ejemplo 36

Preparación del Compuesto Intermediario **36A**

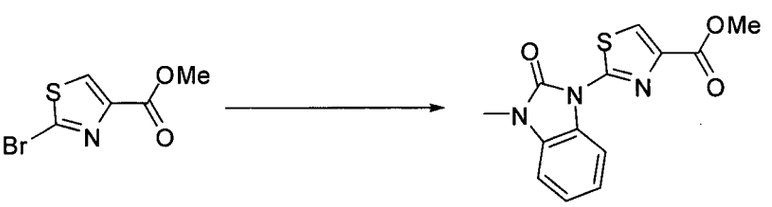


35A **36A**

El compuesto **35A** se convirtió en el compuesto **36A** usando el método descripto en el Ejemplo 35.

Ejemplo 37

Preparación del Compuesto Intermediario **37A**

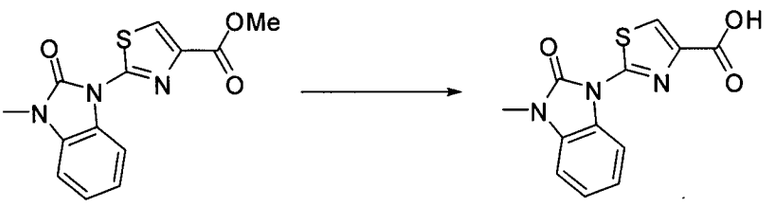


37A

A una solución de 2–bromo–4–carbometoxitiazol (1,5 g, 6,78 mmol) en dioxano (80 mL) a temperatura ambiente se agregó 1–metil–2–benzimidazolona (1,0 g, 6,78 mmol) seguido por CuI (0,13 g, 0,68 mmol), K_2CO_3 (1,0 g, 7,47 mmol), trans–*N*, *N*–dimetilciclohexano (0,21 mL, 1,35 mmol). La mezcla se desgasificó bajo vacío propio del laboratorio y se llenó seis veces con N_2 y se calentó hasta 90 °C. La mezcla se agitó durante 12 horas, se enfrió hasta ta (temperatura ambiente), y se concentró bajo presión reducida. El producto en bruto se purificó usando cromatografía instantánea usando una mezcla 20:1 de CH_2Cl_2/MeOH para proporcionar 1,8 g (92% de rendimiento) del compuesto del título en forma de un sólido de color blancuzco. LC–MS [M+H] = 290,2; 98% de pureza.

Ejemplo 38

Preparación del Compuesto Intermediario **38A**

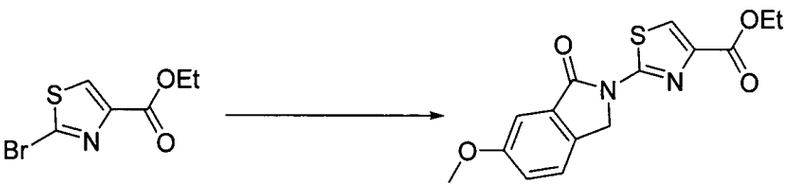


37A **38A**

A una solución del compuesto **37A** (0,18 g, 0,59 mmol) en THF (1,5 mL) a 0 °C se agregó por goteo una solución 1M de LiOH (1,18 mL). La reacción resultante se dejó calentar hasta temperatura ambiente y se dejó agitar durante 12 horas. La mezcla se concentró bajo presión reducida y se absorbió en H_2O (2 mL). La mezcla se trató con HCl concentrado hasta obtener un pH = 4. La mezcla se concentró bajo presión reducida para proporcionar el compuesto **38A** (0,15 g, 92% de rendimiento) en forma de un sólido de color anaranjado que se usó sin purificación posterior. LC–MS [M+H] = 276,2; 96% de pureza.

Ejemplo 39

Preparación del Compuesto Intermediario **39A**

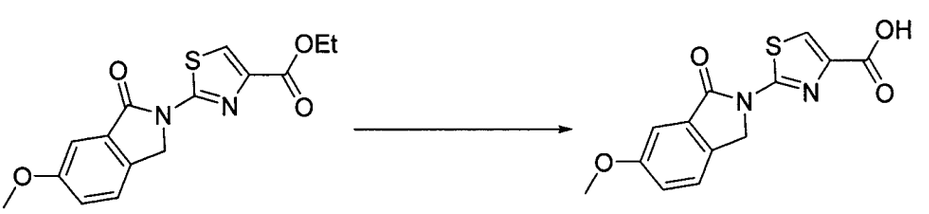


39A

A un tubo de presión cargado con 2–bromo–4–carboetoxitiazol (2,5 g, 10,6 mmol) y una barra de agitación se agregó 6–metoxiisoindolin–1–ona (2,1 g, 12,7 mmol), K_3PO_4 (4,9 g, 23,3 mmol), $Pd_2(dba)_3$ (0,58 g, 0,64 mmol), Xant–Phos (0,62g, 1,1 mmol). Se agregó dioxano (20 mL) y N_2 formó burbujas a través de la solución durante 10 min antes de que el recipiente se tapara. La mezcla se agitó a 105 °C durante 12 horas y se enfrió hasta ta (temperatura ambiente). La mezcla se filtró a través de una almohadilla de Celite y se lavó con CH_2Cl_2/MeOH (20:1; 2 x 10 mL). El filtrado resultante se concentró bajo presión reducida y se colocó bajo alto vacío. El producto en bruto se purificó usando cromatografía instantánea usando un gradiente de CH_2Cl_2 a 97:3 CH_2Cl_2/acetona para proporcionar 3,1 g (91% de rendimiento) del compuesto **39A** en forma de un sólido de color marrón. LC–MS [M+H] = 400,2; 98% de pureza.

Ejemplo 40

Preparación del Compuesto Intermediario **40A**



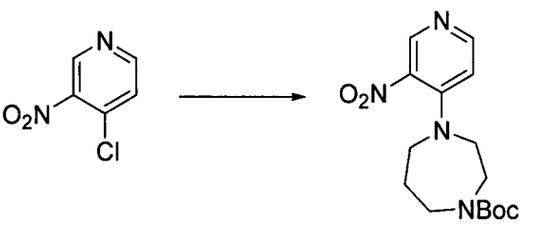
39A **40A**

A una solución del compuesto **39A** (0,67 g, 2,1 mmol) en THF/MeOH/H_2O (2:2:1;12.5 mL total) a temperatura ambiente se agregó $LiOH{\cdot}H_2O$ (97 mg, 2,3

mmol) en una porción. La solución resultante se agitó a 40 °C durante 12, se enfrió hasta ta (temperatura ambiente), y concentró bajo presión reducida. El material en bruto se absorbió en H_2O (20 mL) y se trató con HCl concentrado hasta obtener un pH 3. La mezcla se concentró bajo presión reducida para proporcionar 0,58 g (95 % de rendimiento) del compuesto **40A** en forma de un sólido de color blanco pálido que se usó sin purificación posterior. MS [M+H] = 290,9.

Ejemplo 41

Preparación del Compuesto Intermediario **41A**



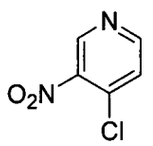
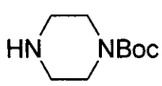
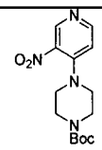
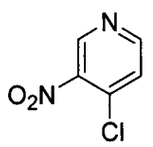
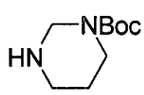
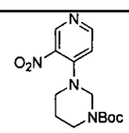
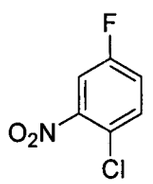
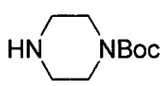
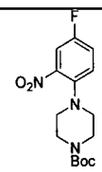
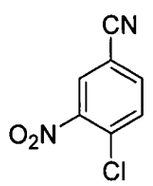
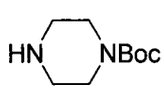
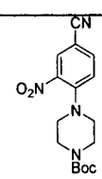
41A

A una solución de 4–cloro–3–nitropiridina (2,0 g, 12,5 mmol) en dioxano (25 mL) se agregó DIPEA (3,2 mL, 18,7 mmol) seguido por Boc–homopiperazina (3,0 g, 15,0 mmol). La mezcla de reacción se agitó a 110°C durante 12 horas, se enfrió hasta ta (temperatura ambiente), y concentró hasta sequedad. La mezcla se dividió entre $NaHCO_3$ ac. sat. (4 mL) y CH_2Cl_2 (15 mL) y las capas se separaron. La capa acuosa se extrajo con CH_2Cl_2 (2 x 15 mL) y las capas orgánicas se combinaron. La capa orgánica se lavó con salmuera (1 x 4 mL), se secó (Na_2SO_4), se filtró, y concentró bajo presión reducida. El producto en bruto se purificó usando cromatografía instantánea usando una mezcla 50:1 de CH_2Cl_2/MeOH como eluyente para proporcionar 3,7g (93% de rendimiento) del compuesto **41A** en forma de un sólido de color amarillo. LC–MS [M+H] = 323,2; 98% de pureza.

Ejemplo 42

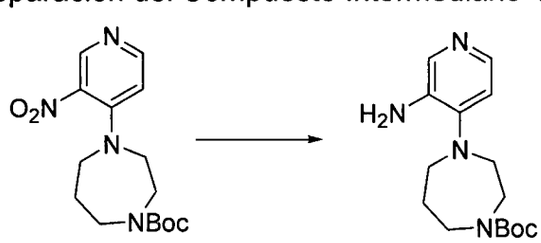
Preparación del Compuesto Intermediarios **42A–42D**

Los compuestos intermediarios 42A–42D, ilustrados en la tabla siguiente, se prepararon haciendo reaccionar los derivados de cloro indicados con las aminas indicadas de acuerdo con el método descripto en el Ejemplo 41.

Derivado de Cloro	***Amina***	***Producto***	***1. Rendimiento (%) 2. LC–MS (M+H)***
		 **42A**	1. 98 2. 309,2
		 **42B**	1. 80 2. 309,2
		 **42C**	1. 94 2. 326,1
		 **42D**	1. 98 2. 333,2

Ejemplo 43

Preparación del Compuesto Intermediario **43A**



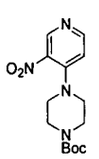
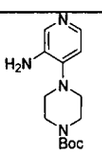
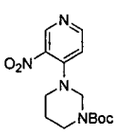
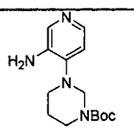
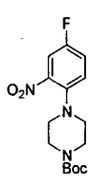
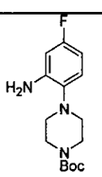
41A **43A**

A una mezcla del compuesto **41A** (3,5 g, 11,1 mmol) en MeOH/EtOAc (1:1; 100 mL) a temperatura ambiente se agregó 5% Pd/C (1,2 g). La mezcla de reacción se desgasificó y llenó con N_2 y finalmente con H_2 (balón). La mezcla se agitó durante 12 horas a temperatura ambiente y se purgó en N_2. La mezcla de reacción se filtró a través de una almohadilla de celite que se lavó con MeOH/EtOAc (1:1; 3 x 25 mL). El filtrado resultante se concentró bajo presión reducida y se colocó bajo alto vacío para proporcionar 3,2 g (99% de rendimiento) del compuesto **43A** en forma de un semisólido de color amarillo. LC–MS [M+H] = 293,2; 87% de pureza. Dicho material se usó sin purificación posterior.

Ejemplo 44

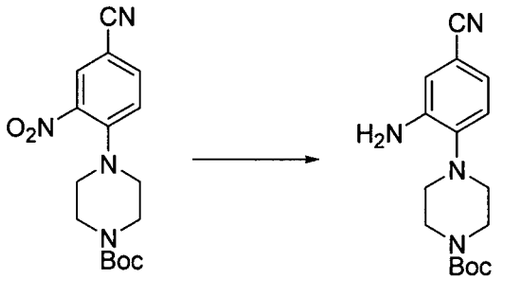
Preparación de los Compuestos Intermediarios **44A–44C**

Siguiendo el método descripto en el Ejemplo 43, los derivados de nitro indicados se convirtieron en los derivados de amino correspondientes 44A–44C.

Derivado de Nitro	**Producto**	**1. Rendimiento (%) 2. LC–MS (M+H)**
	 **44A**	1. 98 2. 309,2
	 **44B**	1. 80 2. 309,2
	 **44C**	1. 94 2. 326,1

Ejemplo 45

Preparación del Compuesto Intermediario **45A**

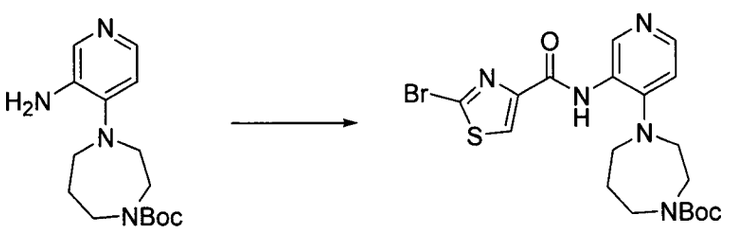


42D **45A**

A una mezcla del compuesto **42D** (0,5 g, 1,5 mmol) en THF (15 mL) a temperatura ambiente se agregó formato de amonio (0,95 g, 15,1 mmol) seguido por 10% Pd/C (50 mg). La mezcla de reacción se calentó hasta 65 °C, se agitó durante 30 min, y se enfrió hasta temperatura ambiente. La mezcla de reacción se filtró a través de una almohadilla de celite que se lavó con EtOH (2 x 5 mL) y CH_2Cl_2 (2 x 5 mL). El filtrado resultante se concentró bajo presión reducida y se colocó bajo alto vacío para proporcionar 0,46 g (99% de rendimiento) del compuesto **45A** en forma de un semisólido de color amarillo. LC–MS [M+H] = 303.2; 99% de pureza. Dicho material se usó sin purificación posterior.

Ejemplo 46

Preparación del Compuesto Intermediario **46A**



43A **46A**

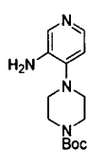
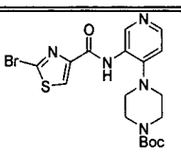
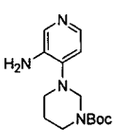
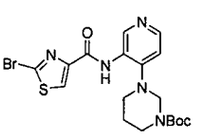
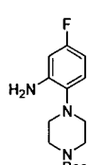
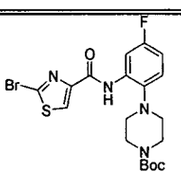
A una solución del compuesto **43A** (1,1 g, 5,2 mmol) en DMF (10 mL) se agregó *N,N*–diisopropiletilamina (2,7 ml, 15,4 mmol) y a HATU (2,2 g, 5,6 mmol) en DMF (10 mL), se agregó anilina (1,5 g, 5,2 mmol) del Ejemplo de preparación 10. La mezcla de reacción se agitó a temperatura ambiente durante 72 horas y

luego se concentró al vacío. El residuo en bruto se absorbió en EtOAc (50 mL) y se agregó $NaHCO_3$ ac. sat. (2 mL). Las capas se separaron y la capa orgánica se lavó con $NaHCO_3$ ac. sat. (1 x 2 mL) y salmuera (1 x 2 mL). La capa orgánica se secó (Na_2SO_4), se filtró, y concentró bajo presión reducida. El producto en bruto se purificó usando cromatografía preparativa en capa delgada usando una mezcla 40:1 de CH_2Cl_2/MeOH como eluyente para proporcionar 1,9 g (75% de rendimiento) del compuesto **46A** en forma de un sólido de color amarillo claro como el compuesto del título. LC–MS [M+H] = 483,2; 89% de pureza.

Ejemplo 47

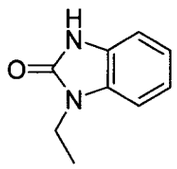
Preparación del Compuesto Intermediarios **47A–47C**

Se prepararon los compuestos intermedios 47A–47C siguiendo el método descripto en el Ejemplo 46, utilizando el ácido 2–bromo–tiazol–4–carboxílico y las aminas indicadas.

Amina	Producto	1. Rendimiento (%) 2. LC–MS (M+H)
	 **47A**	1. 63 2. 470,3
	 **47B**	1. 35 2. 470,3
	 **47C**	1. 67 2. 470,3

Ejemplo 48

Preparación del Compuesto Intermediario **48A**

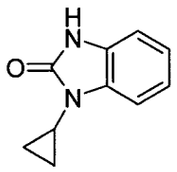


48A

El Compuesto **48A** se preparó usando el método descripto en la Publicación de Patente de EEUU Nº 2007/0072928.

Ejemplo 49

Preparación del Compuesto Intermediario **49A**

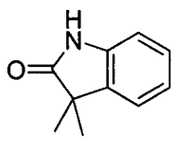


49A

El Compuesto **49A** se preparó usando el método descripto en la Publicación de Patente de EEUU Nº 2007/0072928.

Ejemplo 50

Preparación del Compuesto Intermediario **50A**

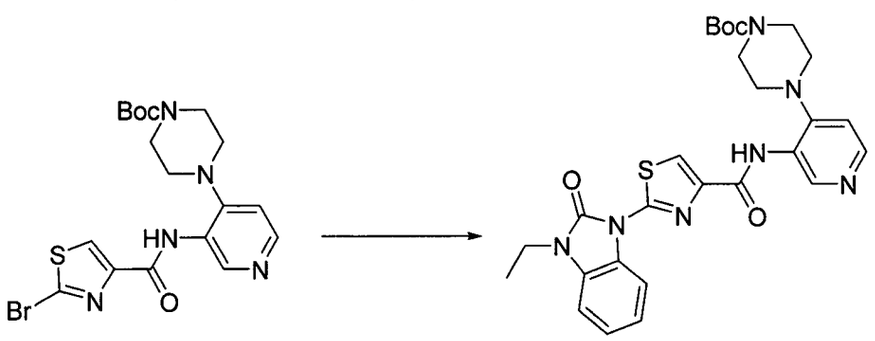


50A

El Compuesto **50A** se preparó usando el método descripto en *J. Med. Chem.* **1986**, *29*, 1832.

Ejemplo 51

Preparación del Compuesto Intermediario **51A**



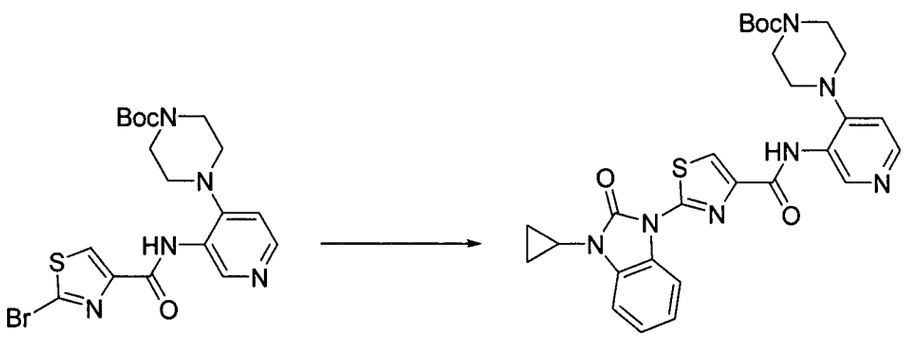
47A **51A**

A una solución del compuesto **47A** (0,35 g, 0,75 mmol) se agregó el compuesto **48A** (0,12 g, 0,75 mmol), CuI (14 mg, 0,075 mmol), K_2CO_3 (114 mg, 0,83 mmol), y trans–N, N–dimetilciclohexano (23 μL, 0,15 mmol). La mezcla se desgasificó bajo vacío propio del laboratorio y se llenó seis veces con N_2 y se calentó hasta 90 °C. La mezcla se agitó durante 12 horas, se enfrió hasta

temperatura ambiente, y se concentró bajo presión reducida. El producto en bruto se absorbió en EtOAc (2 mL) y se filtró. El sólido resultante se lavó con EtOAc (2 x 2 mL) y H_2O (2 x 2 mL), luego se secó bajo alto vacío para proporcionar 0,25 g (61% de rendimiento) del compuesto **51A** en forma de un sólido de color tostado. MS (M+H) = 550,2.

Ejemplo 52

Preparación del Compuesto Intermediario **52A**

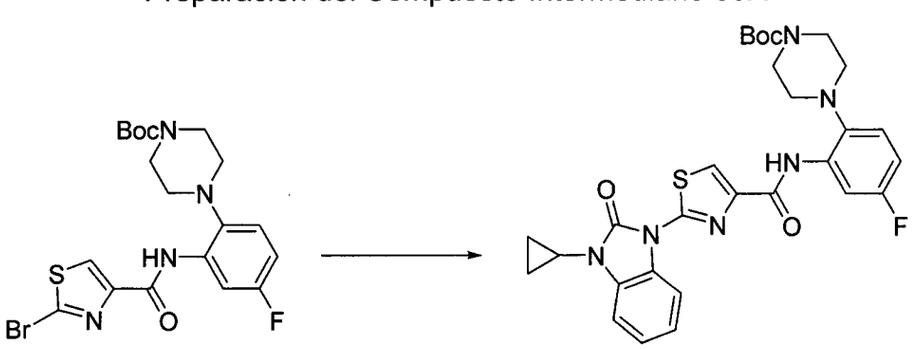


47A **52A**

El Compuesto **47A** (0,35 g, 0,75 mmol) se hizo reaccionar con el compuesto **49A** (0,12 g, 0,75 mmol) de acuerdo con el método descripto en el Ejemplo 51 para proporcionar 0,28 g (66% de rendimiento) del compuesto **52A** en forma de un sólido de color amarillo claro. MS (M+H) = 562,3.

Ejemplo 53

Preparación del Compuesto Intermediario **53A**



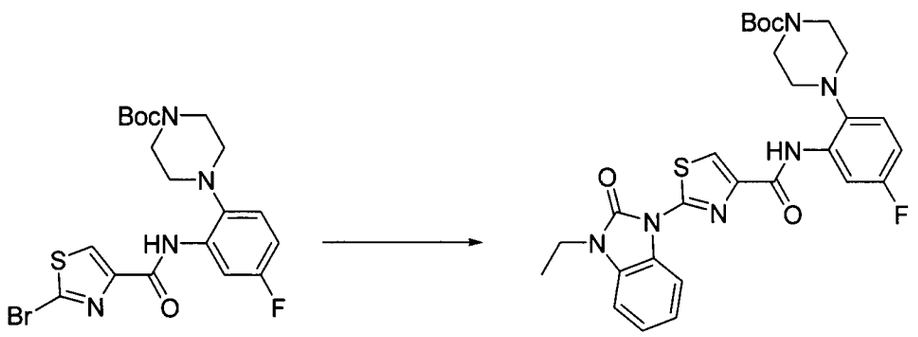
47C **53A**

El Compuesto **47C** (0,35 g, 0,72 mmol) se hizo reaccionar con el compuesto **49A** (0,13 g, 0,72 mmol) de acuerdo con el método descripto en el

Ejemplo 51 para proporcionar 0,28 g (66% de rendimiento) del compuesto **53A** en forma de un sólido de color gris. MS (M+H) = 579,1.

Ejemplo 54

Preparación del Compuesto Intermediario **54A**

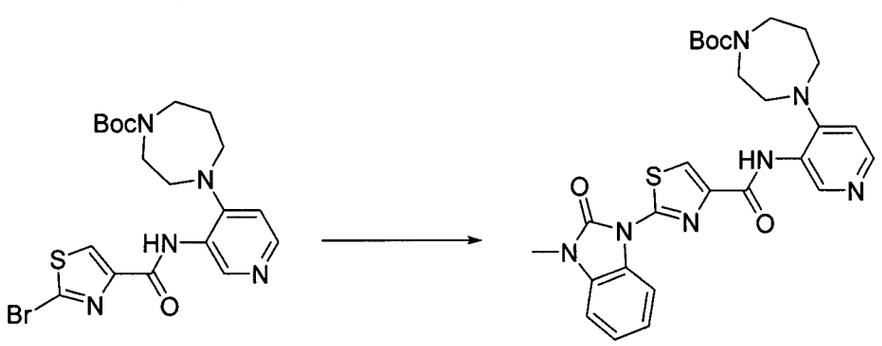


47C **54A**

El Compuesto **47C** (0,35 g, 0,72 mmol) se hizo reaccionar con el compuesto **48A** (0,12 g, 0,72 mmol) de acuerdo con el método descripto en el Ejemplo 51 para proporcionar 0,29 g (71% de rendimiento) del compuesto **54A** en forma de un sólido de color anaranjado. MS (M+H) = 567,1.

Ejemplo 55

Preparación del Compuesto Intermediario **55A**

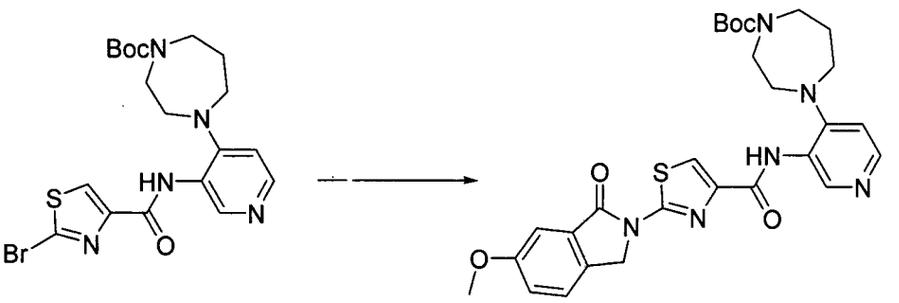


46A **55A**

El Compuesto **46A** (0,10 g, 0,21 mmol) se hizo reaccionar con 1–metil–2–benzimidazolona (31 mg, 0,21 mmol) de acuerdo con el método descripto en el Ejemplo 51 para proporcionar 0,11 g (95% de rendimiento) del compuesto **55A** en forma de un sólido de color anaranjado. LC–MS [M+H] = 550,3; 99% de pureza.

Ejemplo 56

Preparación del Compuesto Intermediario **56A**

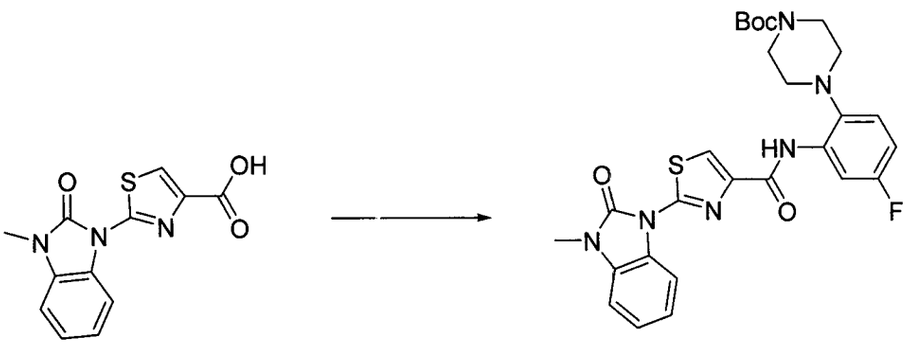


46A **56A**

El Compuesto **46A** (0,25 g, 0,52 mmol) se hizo reaccionar con 6–metoxiisoindolin–1–ona (93 mg, 0,57 mmol) de acuerdo con el método descripto en el Ejemplo 51 para proporcionar 0,28 g (96% de rendimiento) del compuesto **56A** en forma de un sólido de color anaranjado. LC–MS [M+H] = 565,3; 80% de pureza.

Ejemplo 57

Preparación del Compuesto Intermediario **57A**



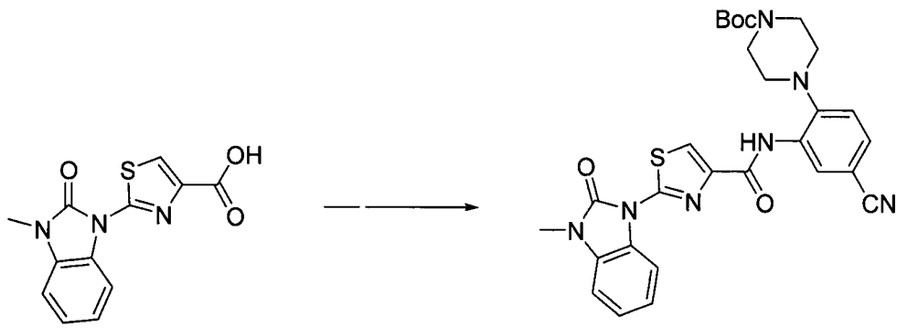
38A **57A**

El Compuesto **38A** (0,15 g, 0,55 mmol) se hizo reaccionar con el compuesto **44C** (0,12 g, 0,72 mmol) de acuerdo con el método descripto en el Ejemplo 58 a continuación para proporcionar 0,29 g (71% de rendimiento) del compuesto **57A** en forma de un sólido de color anaranjado. MS (M+H) = 567,1.

403

Ejemplo 58

Preparación del Compuesto Intermediario **58A**

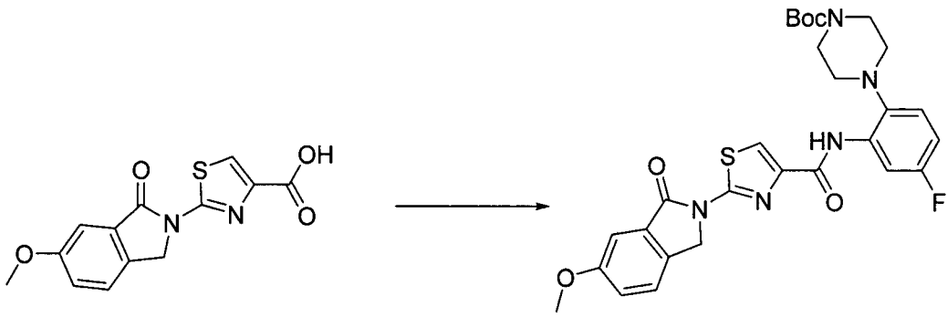


38A **58A**

A una solución del compuesto **38A** (0,10 g, 0,36 mmol) en CH_2Cl_2 (4 mL) a temperatura ambiente se agregó cloruro de oxalilo (61 µL, 0,72 mmol) seguido por DMF (3 gotas). La mezcla se agitó durante 1 h y luego se agregó una cantidad adicional de cloruro de oxalilo (61 µL, 0,72 mmol) y DMF (3 gotas). Al cabo de 1 hora adicional, la mezcla se concentró bajo presión reducida y se disolvió nuevamente en CH_2Cl_2 (3 mL). Se agregó DIPEA (0,19 mL, 1,1 mmol) seguido por el agregado del compuesto **45A** (0,12 g, 0,42 mmol) y la mezcla se agitó durante 12 horas. La mezcla de reacción se concentró hasta sequedad y se dividió entre $NaHCO_3$ ac. sat. (3 mL) y CH_2Cl_2 (10 mL). Las capas se separaron, la capa acuosa se extrajo con CH_2Cl_2 (2 x 10 mL), y las capas orgánicas se combinaron. La capa orgánica se lavó con salmuera (1 x 4 mL), se secó (Na_2SO_4), se filtró, y concentró bajo presión reducida. El producto en bruto se purificó usando cromatografía instantánea usando una mezcla 50:1 de CH_2Cl_2/MeOH como eluyente para proporcionar 0,10 (50% de rendimiento) del compuesto **58A** en forma de un semisólido de color amarillo. MS [M+H] = 560,2.

Ejemplo 59

Preparación del Compuesto Intermediario **59A**

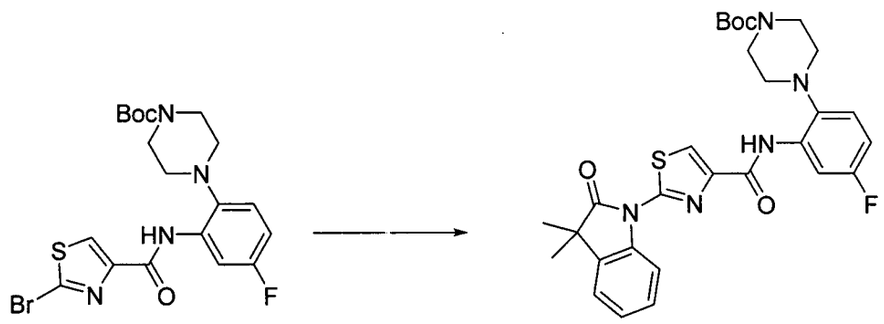


40A **59A**

A una solución del compuesto **40A** (0,15 g, 0,52 mmol) en DMF (2 mL) se agregó el compuesto **44C** (0,17 g, 0,57 mmol), seguido por *N*–metilmorfolina (0,17 mL, 1,56 mmol) y PyBop (0,54 g, 1,1 mmol). La mezcla de reacción se agitó durante 72 horas a temperatura ambiente y se concentró bajo presión reducida. El residuo en bruto se absorbió en EtOAc (8 mL) y se agregó $NaHCO_3$ ac. sat. (3 mL). Las capas se separaron y la capa acuosa se extrajo con EtOAc (2 x 8 mL). Las capas orgánicas se combinaron y se lavaron con salmuera (1 x 5 mL). La capa orgánica se secó (Na_2SO_4), se filtró, y concentró bajo presión reducida. El producto en bruto se purificó usando cromatografía preparativa en capa delgada usando una mezcla 2:1 de hexanos/EtOAc como eluyente para proporcionar 40 mg (14% de rendimiento) del compuesto **59A** en forma de un sólido de color amarillo claro. LC–MS [M+H] = 568,3; 89% de pureza.

Ejemplo 60

Preparación del Compuesto Intermediario **60A**

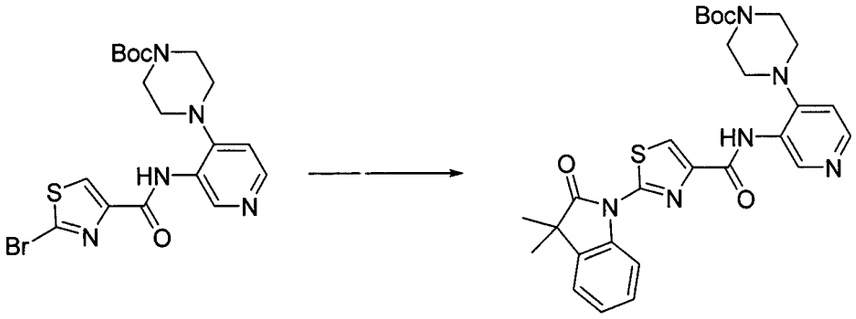


47C **60A**

A una solución del compuesto **47C** (0,30 g, 0,61 mmol) se agregó el compuesto **50A** (98 mg, 0,61 mmol), CuI (58 mg, 0,31 mmol), K_3PO_4 (263 mg, 1,24 mmol), y 1,2–*trans*–diamino ciclohexano (73 □L, 0,61 mmol). La mezcla se diluyó con dioxano (4 mL) y se desgasificó bajo vacío propio del laboratorio y se llenó seis veces con N_2. La mezcla de reacción se calentó hasta 100 °C, se agitó durante 12 horas, se enfrió hasta ta (temperatura ambiente), y concentró bajo presión reducida. El producto en bruto se absorbió en una mezcla 20:1 de CH_2Cl_2/MeOH (5 mL), se filtró y concentró bajo presión reducida. El residuo del filtrado se purificó usando cromatografía preparativa en capa delgada usando una mezcla 3:1 de hexanos/EtOAc como eluyente para proporcionar 125 mg (36% de rendimiento) del compuesto **60A** en forma de un sólido de color blancuzco. LC–MS [M+H] = 566,3; 98% de pureza.

Ejemplo 61

Preparación del Compuesto Intermediario **61A**

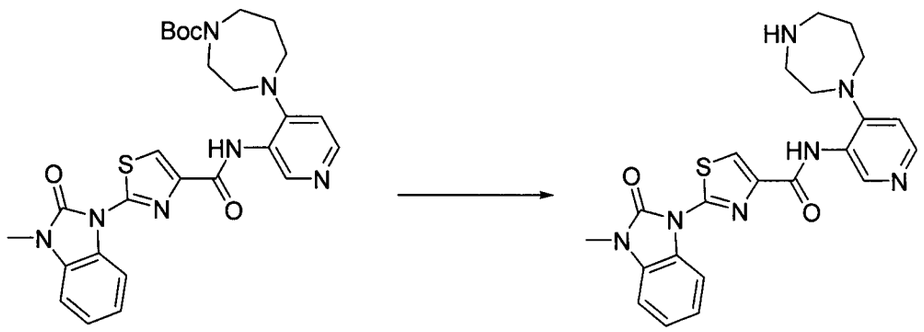


47A **61A**

Usando el método descripto en el Ejemplo 60, el compuesto **47A** (0,35 g, 0,75 mmol) se hizo reaccionar con el compuesto **50A** (0,12 g, 0,75 mmol) para proporcionar 0,15 g (36% de rendimiento) del compuesto **61A** en forma de un sólido de color marrón. LC–MS [M+H] = 549,3; 90% de pureza.

Ejemplo 62

Preparación del compuesto **258**



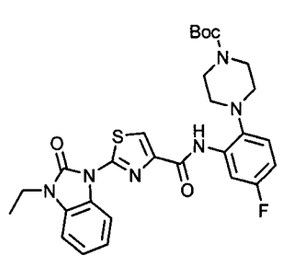
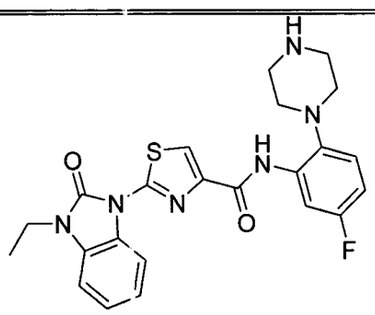
55A **258**

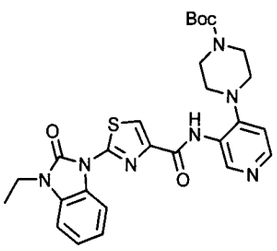
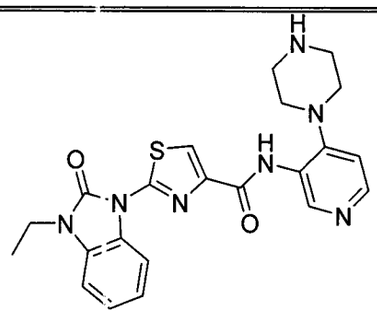
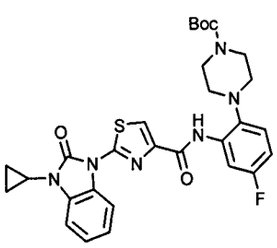
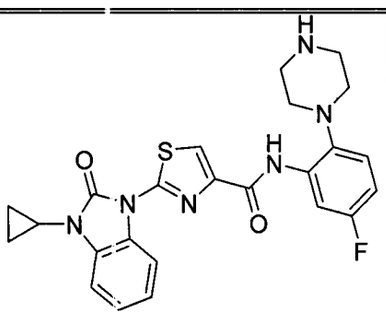
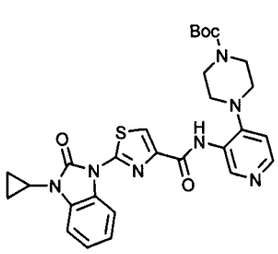
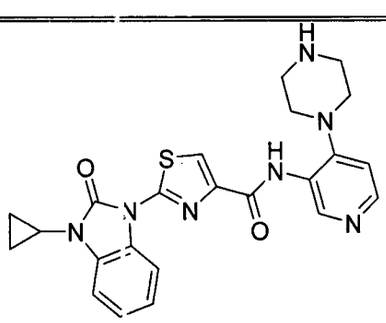
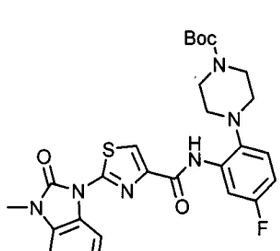
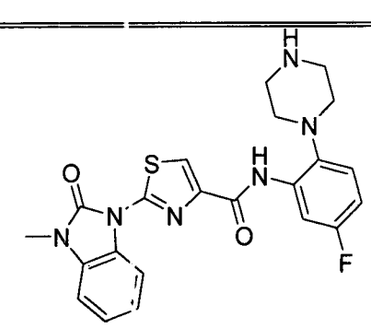
A una solución del compuesto **55A** (42 mg, 0,08 mmol) en CH_2Cl_2 (3 mL) a temperatura ambiente se agregó TFA (1 mL). La mezcla se agitó durante 3 horas a temperatura ambiente y se concentró bajo presión reducida. El producto en bruto se absorbió en NH_3 7M en MeOH (5 mL), se agitó durante 2 horas, y concentró bajo presión reducida. El producto en bruto se purificó usando cromatografía preparativa en capa delgada usando una mezcla 12:1 de CH_2Cl_2/MeOH (7M NH_3) como eluyente para proporcionar 29 mg (85% de rendimiento) del compuesto **258** en forma de un sólido de color amarillo pálido. pf 152–155 °C, LC–MS [M+H] = 450,1; 95% de pureza.

Ejemplo 63

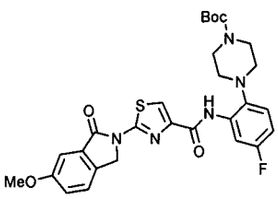
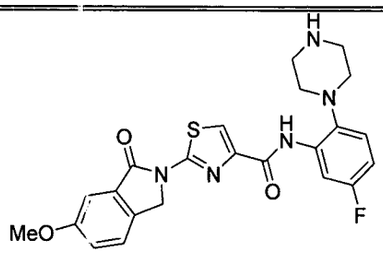
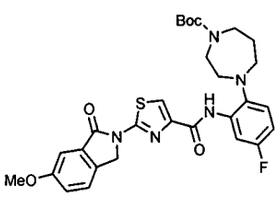
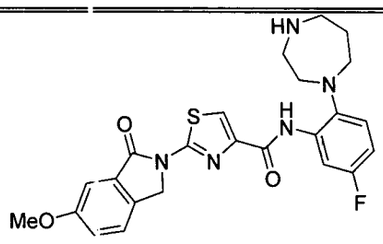
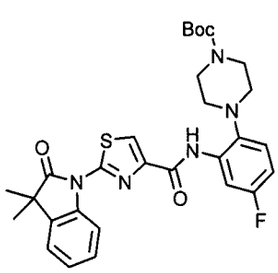
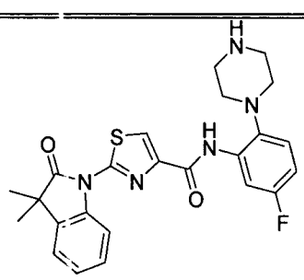
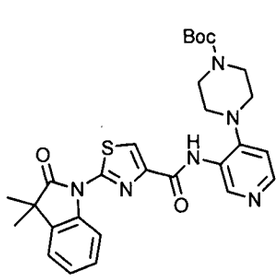
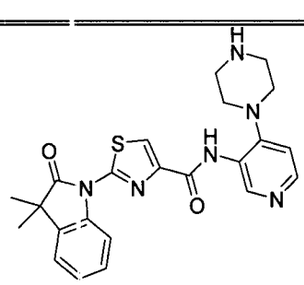
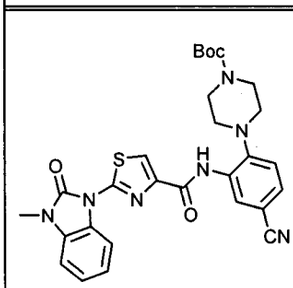
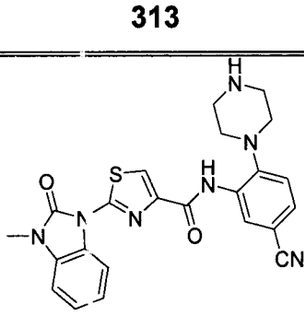
Preparación de los Compuestos **229–232**, **239**, **256**, **288**, **301** y **313**

Los siguientes compuestos representativos de la invención se prepararon usando los métodos descriptos en los Ejemplos 60 y 62, y usando los aductos Boc indicados.

Aducto Boc	**Producto**	1.Rendimiento (%) 2. LC–MS 3. pf (°C)
	 **255**	1. 90 2. 467,3 3. 242–244

	 **239**	1. 73 2. 450,2 3. 172–175
	 **256**	1. 92 2. 479,3 3. 220–223
	 **229**	1. 67 2. 462,3 3. 180–183
	 **232**	1. 62 2. 453,2 3. 140–142

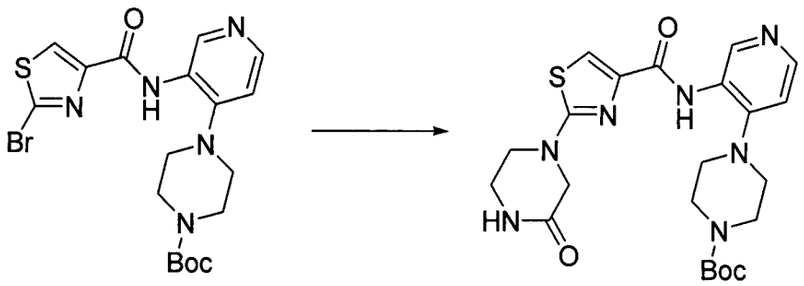
908

	 **230**	1. 86 2. 468,3 3. 168–171
	 **231**	1. 90 2. 465,3 3. 133–135
	 **301**	1. 87 2. 466,3 3. 167–170
	 **313**	1. 92 2. 449,2 3. 200–205
	 **288**	1. 57 2. 460,2 3. 168–171

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Ejemplo 64

Preparación del compuesto **64A**

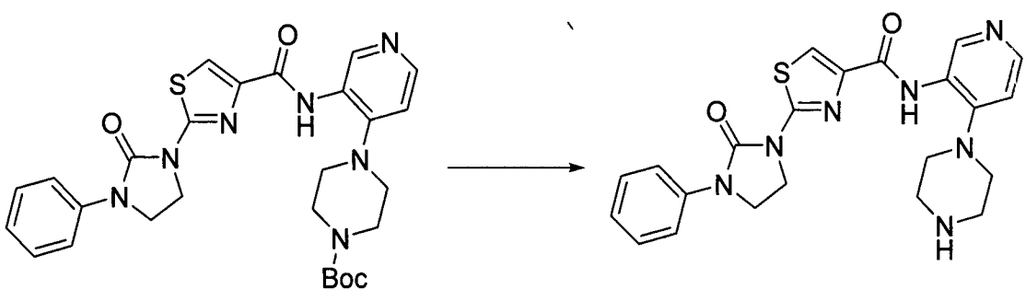


47A **64A**

Usando los métodos descriptos en los Ejemplos 60 y 62, el compuesto **47A** (0,15 g, 0,32 mmol) se hizo reaccionar con piperazin–2–ona (96 mg, 0,96 mmol) en dioxano (2 mL) para proporcionar 84 mg (54% de rendimiento) del compuesto **64A** en forma de un sólido de color amarillo claro. LC–MS [M+H] = 488,3; 98% de pureza.

Ejemplo 65

Preparación del compuesto **112**



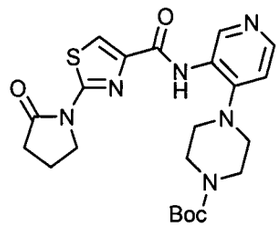
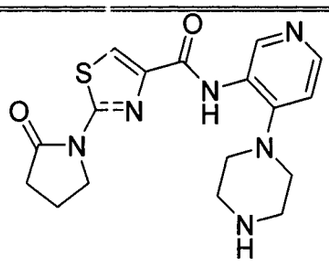
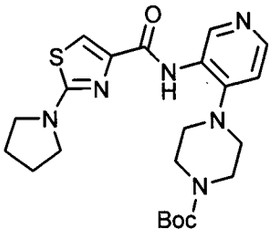
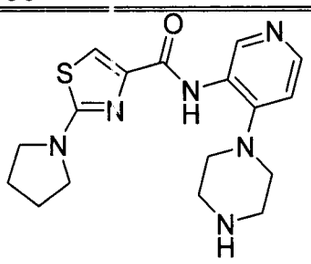
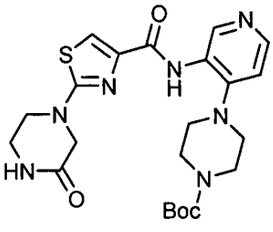
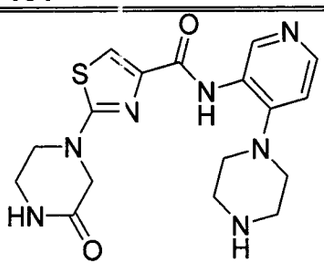
65A **112**

A una solución del compuesto **65A** (0,13 g, 0,22 mmol) en CH_2Cl_2 (3 mL) a temperatura ambiente se agregó TFA (1 mL). La mezcla se agitó durante 2 horas a temperatura ambiente y se concentró bajo presión reducida. El producto en bruto se absorbió en amoníaco 2M en MeOH (3 mL), se agitó durante 2 horas y luego se concentró bajo presión reducida. El producto crudo se purificó con cromatografía preparativa en capa fina usando una mezcla 11:1 de CH_2Cl_2/MeOH (NH_3 7 M) como eluyente para proporcionar 63 mg (64% de rendimiento) de

910

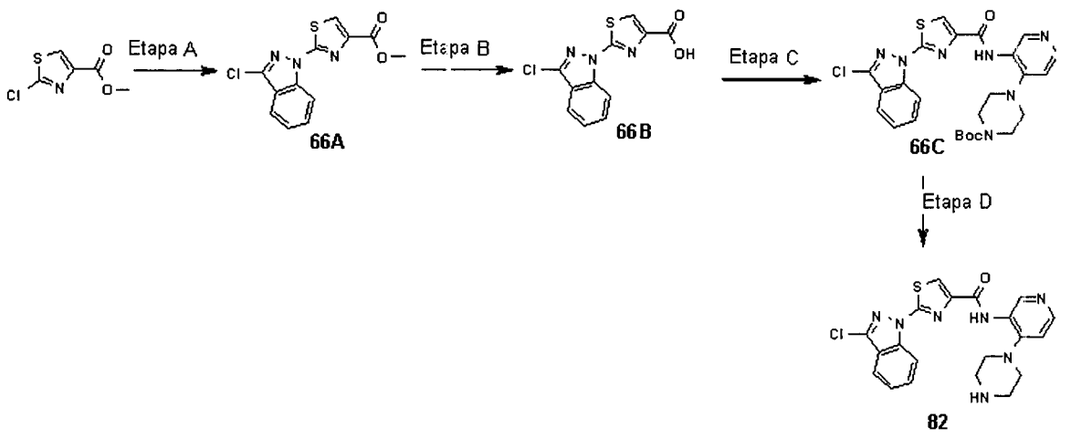
compuesto **112** en forma de un sólido de color amarillo pálido. Punto de fusión 116–118 °C, LC–MS [M+H] = 450,2; 95% de pureza.

Utilizando el método descrito con anterioridad, los aductos de Boc indicados se desprotegieron para proporcionar los compuestos ilustrativos 96, 101 y 111 mostrados en la siguiente tabla.

Aducto de Boc	**Producto>**	1. Rendimiento (%) 2. LC–MS 3. Punto de fusión (°C)
	 **96**	1. 45 2. 373,2 3. 122–124
	 **101**	1. 71 2. 359,2 3. 179–181
	 **111**	1. 77 2. 388,2 3. 215–218

Ejemplo 66

Preparación del compuesto **82**



Etapa A:

Se extrajeron 3–cloroindazol (305 mg, 2,0 mmol) y 2–clorotiazol (355 mg, 2,0 mmol) en DMF (20 mL). Se añadió cuidadosamente NaH (80 mg, 60% en aceite, 2,0 mmol) y la mezcla resultante se calentó hasta 60 °C y se agitó durante 3 horas. Después de enfriar hasta temperatura ambiente, se añadió NH_4Cl (ac.) con cuidado y la solución resultante se extrajo con EtOAc (60 mL x 3). Las sustancias orgánicas se secó sobre Na_2SO_4, se concentró al vacío y se purificó usando cromatografía flash en columna de gel de sílice (EtOAc/hexano = 30:70) para proporcionar el compuesto **66A** (503 mg) en forma de un sólido marrón. HPLC–MS t_R = 2,24 min (UV_{254} nm); masa calculada para la fórmula $C_{12}H_8ClN_3O_2S$ 293,0, LCMS observada m/z 294,0 (M+H).

Etapa B:

El compuesto **66A** (503 mg, 1,7 mmol) se diluyó con THF (10 mL) y a la solución resultante se añadió LiOH (1N, 3,0 mL). La mezcla se agitó a temperatura ambiente durante aproximadamente 15 horas. El solvente se eliminó al vacío y el residuo obtenido se diluyó con H_2O (5 mL). Se añadió HCl 1 N para ajustar el pH en 5 y el sólido formado se recogió por filtración, luego se lavó con

agua y se secó al aire para proporcionar el compuesto **66B**, que se usó en la siguiente etapa sin ulterior purificación. HPLC–MS t_R = 1,71 min (UV_{254} nm); masa calculada para la fórmula $C_{11}H_6ClN_3O_2S$ 279,0, LCMS observada m/z 280,0 (M+H).

Etapa C:

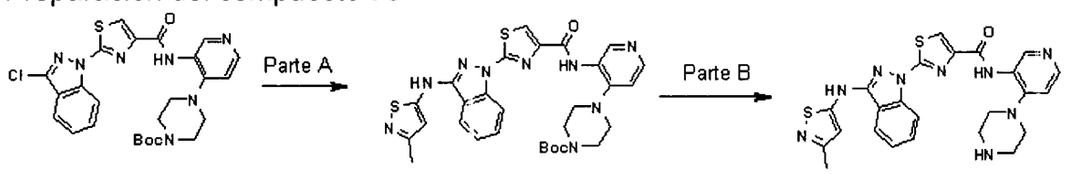
El compuesto **66C** se sintetizó a partir del compuesto **66B** usando el método descrito en el Ejemplo 59. HPLC–MS t_R = 1,75 min (UV_{254} nm); masa calculada para la fórmula $C_{25}H_{26}ClN_7O_3S$ 539,2, LCMS observada m/z 540,1 (M+H).

Etapa D:

El compuesto **82** se preparó a partir del compuesto **66C** usando el método descrito en el Ejemplo 62. HPLC–MS t_R = 1,10 min (UV_{254} nm); masa calculada para la fórmula $C_{20}H_{18}ClN_7OS$ 439,1, LCMS observada m/z 440,0 (M+H).

Ejemplo 67

Preparación del compuesto **78**



66C **67A** **78**

Etapa A:

A un recipiente de base redonda de 25 ml cargado con el compuesto **66C** (270 mg, 0,5 mmol), sal de isotiazol HCl (300 mg, 2,0 mmol), $Pd_2(dba)_3$ (45 mg, 0,05 mmol), 2–di–t–butilfosfino–2',4',6'–tri–i–propil–1,1–bifenilo (42 mg, 0,1 mmol) y K_3PO_4 (616 mg, 3,0 mmol) se añadió tolueno (10 mL). La mezcla se desgasificó cuidadosamente conectando alternativamente el recipiente a vacío y a argón. Esta mezcla resultante luego se calentó hasta 90 °C y se agitó durante aproximadamente 15 horas, luego se diluyó por EtOAc (40 mL) y se lavó con

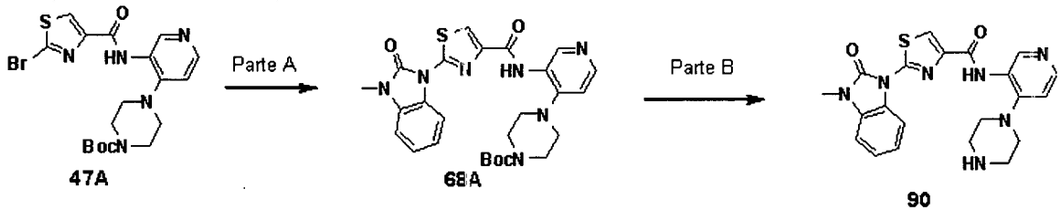
salmuera. Después de concentrar, el residuo obtenido se purificó usando cromatografía líquida preparativa para proporcionar el compuesto **67A**. HPLC–MS t_R = 1,49 min (UV_{254} nm); masa calculada para la fórmula $C_{29}H_{31}N_9O_3S_2$ 617,2, LCMS observada m/z 618,1 (M+H).

Etapa B:

El compuesto **78** se preparó eliminando el grupo protector Boc del compuesto **67A** usando el método descrito en el Ejemplo 62. HPLC–MS t_R = 0,97 min (UV_{254} nm); masa calculada para la fórmula $C_{24}H_{23}N_9OS_2$ 517,1, LCMS observada m/z 518,1 (M+H).

Ejemplo 68

Preparación del compuesto **90**



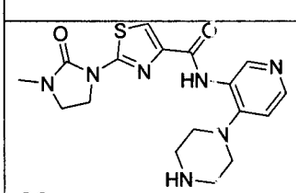
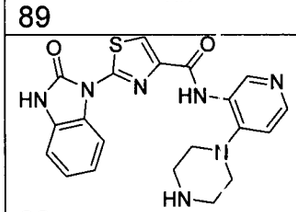
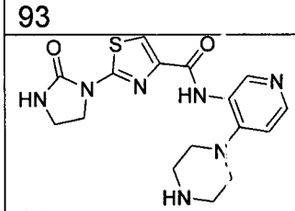
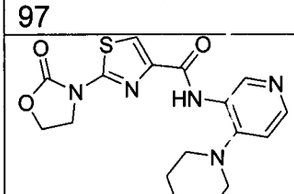
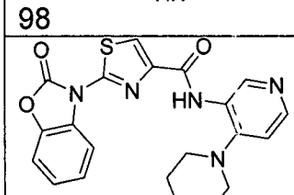
Etapa A:

A un recipiente de base redonda de 25 mL cargado con el compuesto **47A** (100 mg, 0,22 mmol), bencimidazolona (45 mg, 0,3 mmol), CuI (10 mg, 0,05 mmol), trans–1,2–dimetilaminociclohexano (13 mg, 0,1) y K_2CO_3 (51 mg, 0,3 mmol) se añadió dioxano (10 mL). La mezcla se desgasificó cuidadosamente conectando alternativamente el recipiente a vacío y a argón. Esta mezcla resultante luego se calentó a 80 °C durante aproximadamente 15 horas. Después de enfriar hasta temperatura ambiente, el solvente se eliminó al vacío. El residuo obtenido se diluyó con H_2O (5 mL) y el compuesto sólido crudo **68A** se recogió por filtración y se usó directamente en la siguiente etapa sin ulterior purificación. HPLC–MS t_R = 1,42 min (UV_{254} nm); masa calculada para la fórmula $C_{26}H_{29}N_7O_4S$ 535,2, LCMS observada m/z 536,2 (M+H).

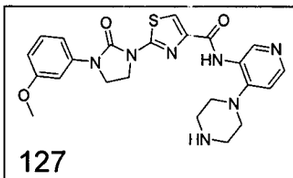
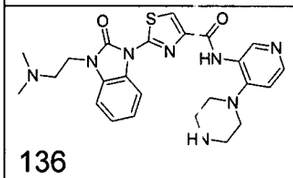
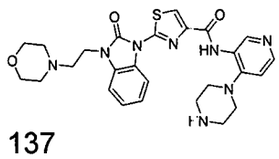
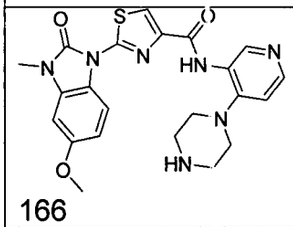
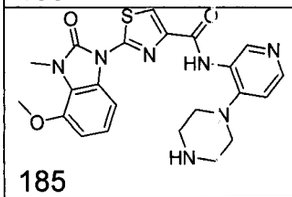
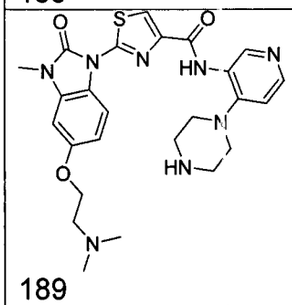
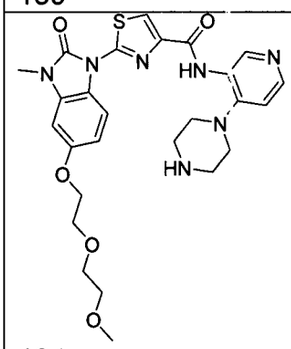
Etapa B:

El compuesto **90** se preparó eliminando el grupo protector Boc del compuesto **68A** usando el método descrito en el Ejemplo 62. HPLC–MS t_R = 0,83 min (UV_{254} nm); masa calculada para la fórmula $C_{21}H_{21}N_7O_2S$ 435,1, LCMS observada m/z 436,1 (M+H).

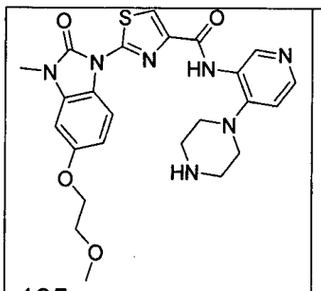
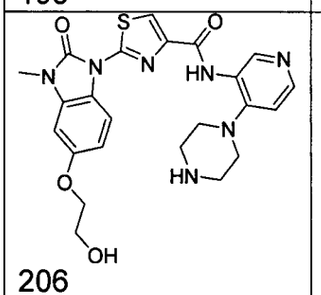
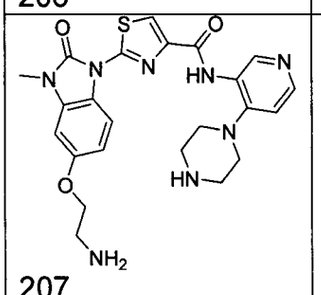
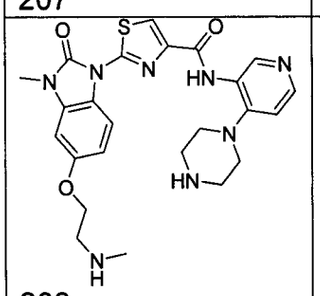
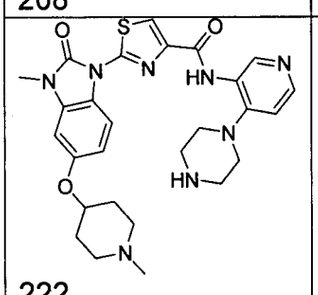
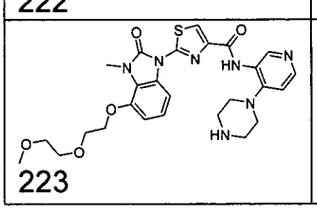
Usando el método descrito en las etapas A y B anteriores y usando las parejas de acoplamiento apropiadas en la Etapa A, se prepararon los siguientes compuestos ilustrativos.

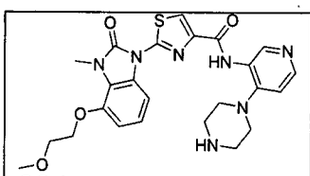
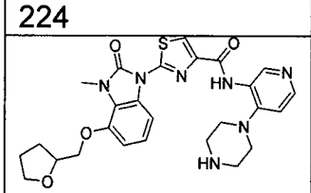
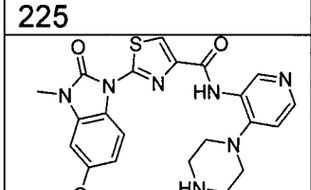
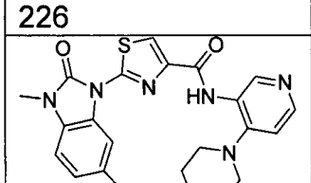
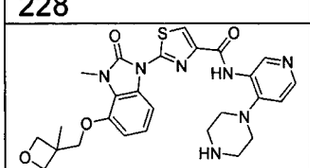
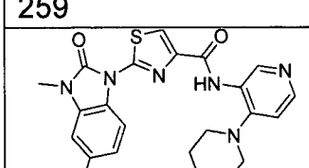
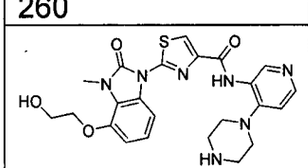
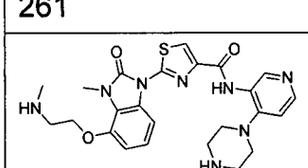
Compuesto	MS m/z (M+H)	HPLC MS tR
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 93	422,1	0,71
 97	374,2	0,47
 98	375,1	0,55
 120	423,1	0,88

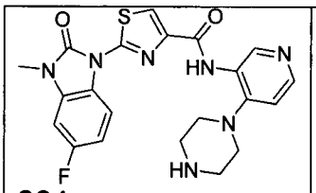
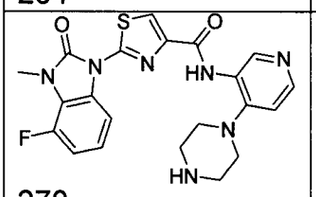
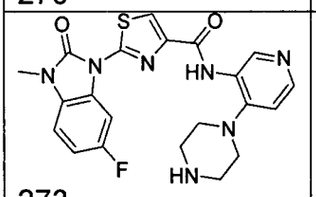
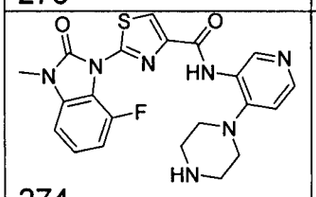
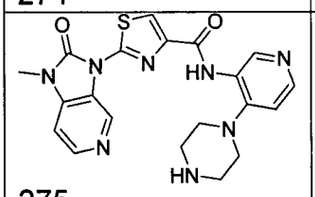
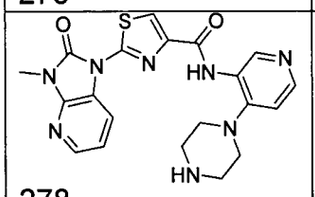
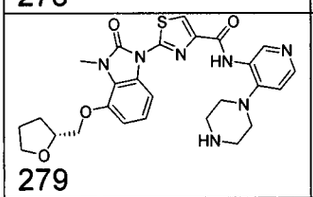
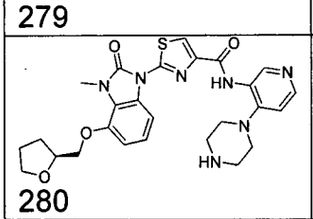
95

 127	480,1	1,00
 136	493,1	0,58
 137	535,1	0,61
 166	466,1	0,86
 185	466,1	0,97
 189	523,1	0,63
 194	554,2	0,93

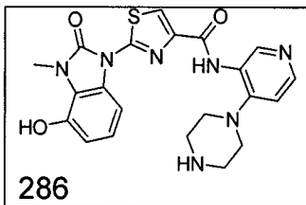
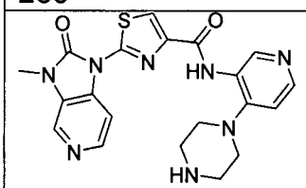
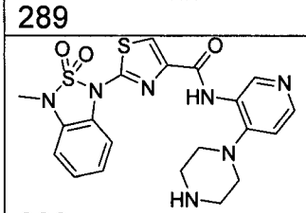
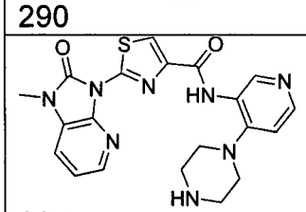
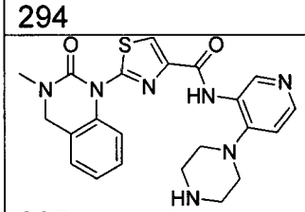
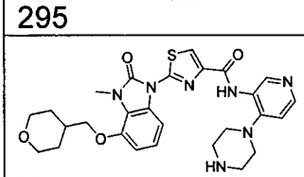
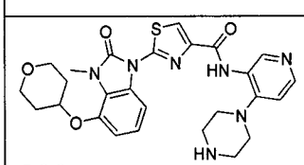
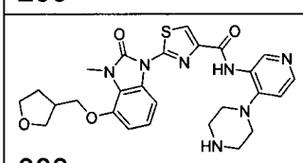
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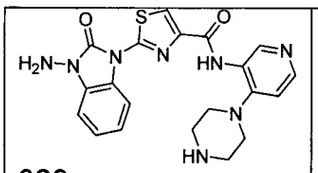
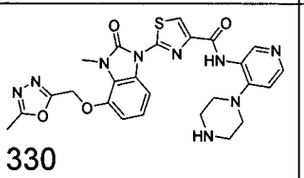
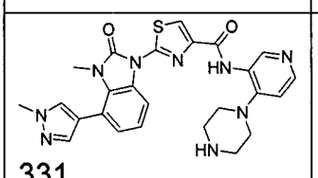
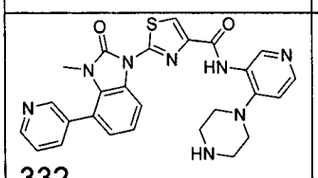
 195	510,1	0,90
 206	496,2	0,97
 207	495,1	0,68
 208	509,2	0,69
 222	549,2	0,75
 223	554,2	1,15

 224	510,2	1,13
 225	536,2	1,21
 226	536,2	1,17
 228	466,1	0,91
 259	536,3	0,98
 260	536,2	1,23
 261	496,1	0,90
 262	509,2	0,67

 264	454,1	1,02
 270	454,1	0,93
 273	454,1	1,02
 274	454,1	1,02
 275	437,2	0,64
 278	437,2	0,93
 279	536,2	1,22
 280	536,2	1,25

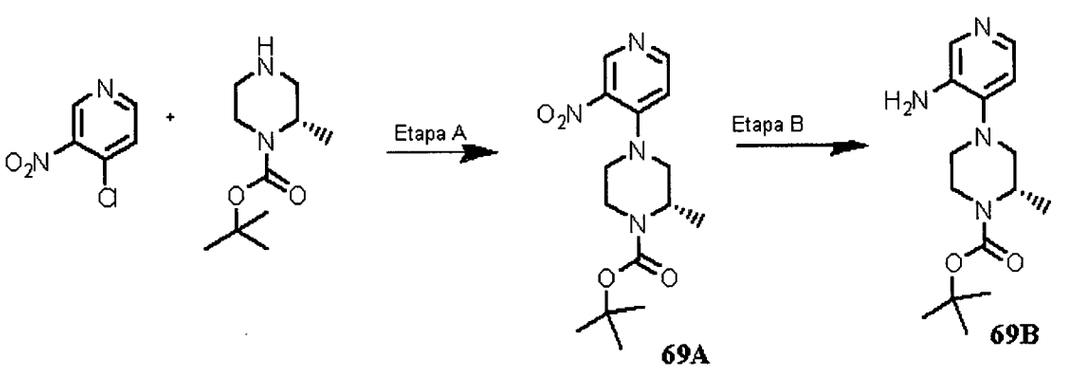
919

 286	452,2	1,12
 289	437,1	0,19
 290	472,1	0,94
 294	437,0	0,92
 295	450,1	1,06
 32	550,2	1,09
 299	536,2	1,06
 300	536,2	1,06

 329	437,1	0,72
 330	548,2	1,11
 331	516,1	0,93
 332	513,1	0,92

Ejemplo 69

Preparación del compuesto **69B**



Etapa A:

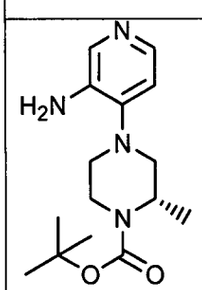
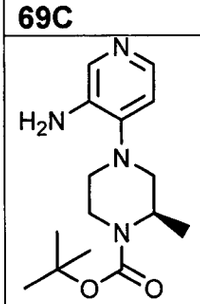
Una solución de 4–cloro–3–nitro–piridina (2,0 mmol, 0,32 g), dietilisopropilamina (3,0 mmol, 0,52 mL) y éster ter–butílico del ácido 2(s)–metil–piperazin–1–carboxílico (2,5 mmol, 0,50 g) en dioxano (2 mL) se irradió usando microondas durante 20 minutos a una temperatura de 120 °C. La mezcla de

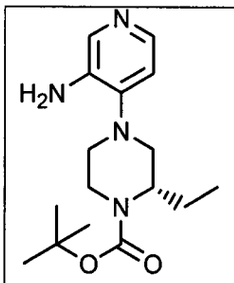
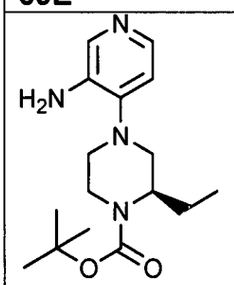
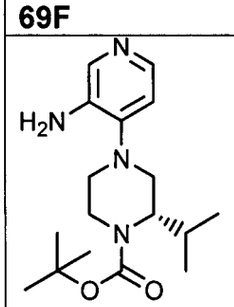
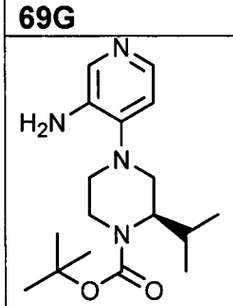
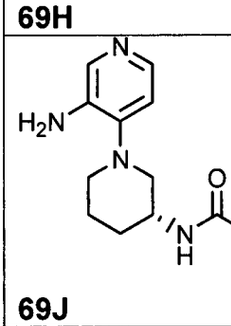
reacción se concentró al vacío y el residuo resultante se purificó usando cromatografía flash en columna de gel de sílice (eluyente: acetato de etilo) para proporcionar el compuesto **69A** en forma de un sólido amarillo con rendimiento cuantitativo. HPLC–MS RT= 1,42 min, masa calculada para la fórmula $C_{15}H_{22}N_4O_4$ 322,16, LCMS observada m/z 323,1 (M+H).

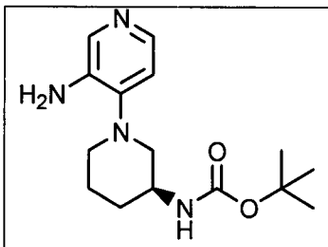
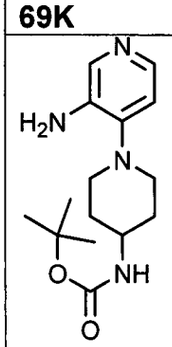
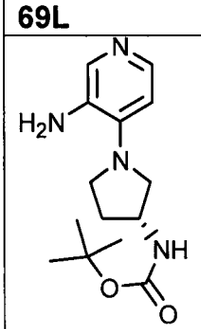
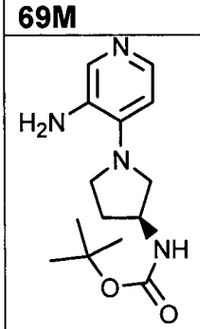
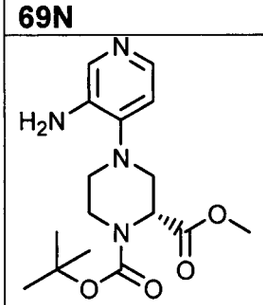
Etapa B:

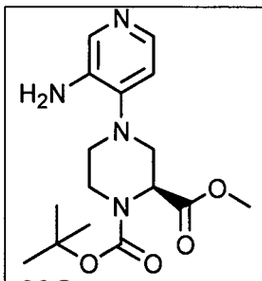
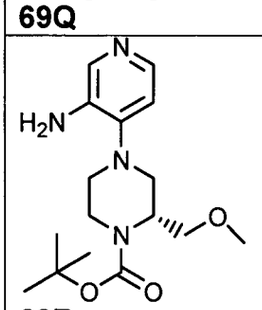
A una solución del compuesto **69A** (600 mg) en etanol/EtOAc (1:1, 10 mL) se añadió Pd sobre carbón (5% de Pd). La mezcla de reacción se agitó bajo una atmósfera de hidrógeno a temperatura ambiente durante aproximadamente 15 horas, luego se filtró a través de un taco de celite. El filtrado se concentró al vacío para proporcionar el compuesto **69B** en forma de un sólido. HPLC–MS RT= 1,10 min, masa calculada para la fórmula $C_{15}H_{24}N_4O_2$ 292,19, LCMS observada m/z 293,20 (M+H).

Usando los métodos descritos en las etapas A y B anteriores y usando los reactivos apropiados, se prepararon los siguientes compuestos intermediarios:

Compuestos	**M+H Observado**	**Tiempo de retención**
 **69C**	293,2	1,10
 **69D**	293,2	1,10

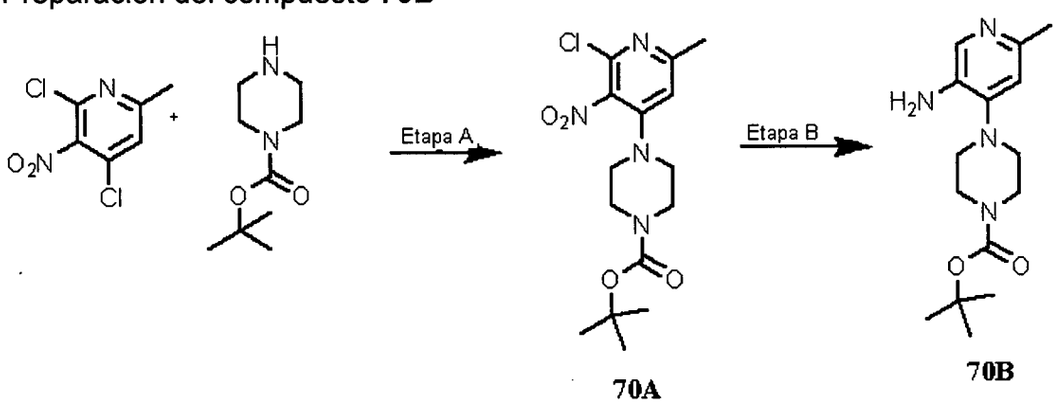
 **69E**	307,3	1,0
 **69F**	307,3	1,0
 **69G**	321,2	1,15
 **69H**	321,2	1,15
 **69J**	293,2	0,09

 **69K**	293,2	0,09
 **69L**	293,3	1,0
 **69M**	279,1	0,85
 **69N**	279,1	0,85
 **69P**	337,12	0,95

 **69Q**	337,12	0,95
 **69R**	323,2	1,05

Ejemplo 70

Preparación del compuesto **70B**



70A **70B**

Etapa A:

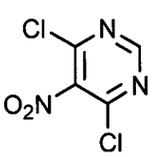
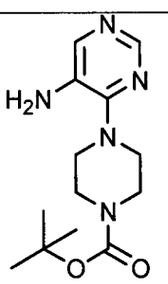
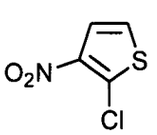
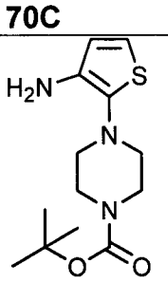
Una solución de 2,4–dicloro–6–metil–3–nitro–piridina (2,0 mmol, 0,42 g), dietilisopropilamina (3,0 mmol, 0,52 mL) y éster ter–butílico del ácido piperazin–1–carboxílico (2 mmol, 0,372 g) en diclorometano (5 mL) se agitó a temperatura ambiente durante 12 horas. La mezcla de reacción se concentró al vacío y el residuo resultante se purificó usando cromatografía flash en columna de gel de sílice (eluyente: hexano y acetato de etilo) para proporcionar el compuesto **70A** en forma de un sólido amarillo con rendimiento cuantitativo. HPLC–MS RT= 2,1 min,

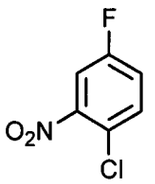
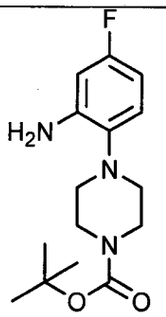
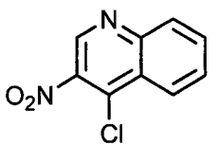
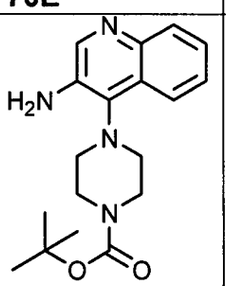
masa calculada para la fórmula $C_{15}H_{21}ClN_4O_4$ 356,13, LCMS observada m/z 357,1 (M+H).

Etapa B:

A una solución del compuesto **70A** (600 mg) en etanol/EtOAc (1:1, 10 mL) se añadió Pd sobre carbón (5% de Pd). La mezcla de reacción se agitó bajo una atmósfera de hidrógeno a 40psi durante aproximadamente 15 horas, luego se filtró a través de un taco de celite. El filtrado se concentró al vacío para proporcionar el compuesto **70B** en forma de un sólido. HPLC–MS RT= 1,10 min, masa calculada para la fórmula $C_{15}H_{24}N_4O_2$ 292,19, LCMS observada m/z 293,20 (M+H).

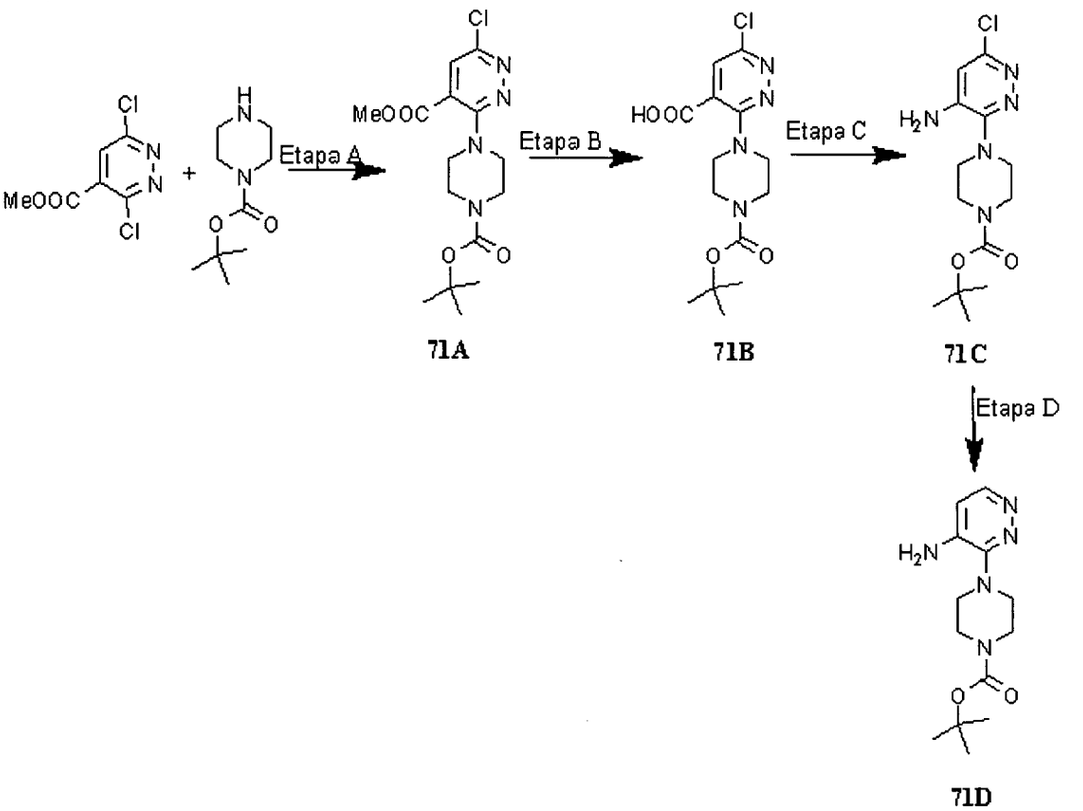
Usando los métodos descritos en las etapas A y B anteriores y usando los reactivos apropiados, se prepararon los siguientes compuestos intermediarios:

Material de partida	**Producto**	**M+H Observado**	**Tiempo de retención**
	 **70C**	**280,3**	**0,9**
	 **70D**	**284,1**	**1,5**

	 **70E**	**296,2**	**2,0**
	 **70F**	**329,2**	**1,2**

Ejemplo 71

Preparación del compuesto **71D**



Etapa A:

Una solución de éster metílico del ácido 3,6–dicloropiridazin–4–carboxílico (2,0 mmol, 0,41 g), dietilisopropilamina (3,0 mmol, 0,52 mL) y éster ter–butílico del ácido piperazin–1–carboxílico (2 mmol, 0,37 g) en dioxano (2 mL) se irradió usando microondas durante 20 minutos a una temperatura de 80 °C. La mezcla de reacción se concentró al vacío y el residuo resultante se purificó usando cromatografía flash en columna de gel de sílice (eluyente: acetato de etilo) para proporcionar el compuesto **71A** en forma de un sólido amarillo con rendimiento

cuantitativo. HPLC–MS RT= 1,9 min, masa calculada para la fórmula $C_{15}H_{21}ClN_4O_4$ 356,13, LCMS observada m/z 357,1 (M+H).

Etapa B:

A una solución del compuesto **71A** (2,0 mmol. ,714 g) en 4 ml de THF se añadió solución 1 N de LiOH en agua 4 mL y se agitó durante aproximadamente 15 horas a temperatura ambiente. Se eliminó el THF y se acidificó en pH 2. Se extrajo la capa acuosa con acetato de etilo, se lavó con salmuera, se secó sobre sulfato de sodio anhidro. Se filtró y se concentró para obtener el compuesto **71B**. HPLC–MS RT= 1,3 min, masa calculada para la fórmula $C_{14}H_{19}ClN_4O_4$ 342,11, LCMS observada m/z 343,1 (M+H).

Etapa C:

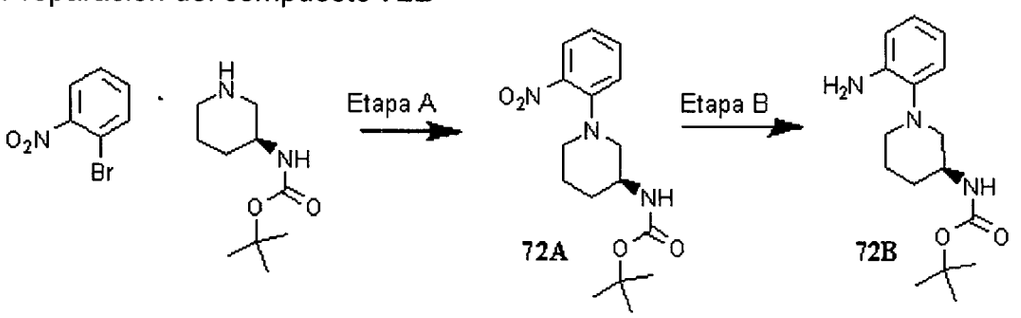
A una solución del compuesto **71B** (1 mmol, 0,34 g.) en DMF (5 mL) se añadió DPPA (1 mmol, 0,275 g.) y trietilamina (1,1 mmol, 0,16 mL) y se agitó bajo Ar durante 4 horas, luego se añadió 1 ml de agua y se calentó hasta 65 °C durante 1 hora. Se enfrió hasta temperatura ambiente y el pH se ajustó en 9 al añadir carbonato de potasio. Se extrajo con acetato de etilo, se lavó con salmuera, se secó sobre sulfato de sodio, se filtró y se concentró para obtener el compuesto **71C**. HPLC–MS RT= 1,35 min, masa calculada para la fórmula $C_{13}H_{20}ClN_5O_2$ 313,13, LCMS observada m/z 314,2 (M+H).

Etapa D:

A una solución del compuesto **71C** (150 mg) en etanol/EtOAc (1:1, 10 mL) se añadió Pd sobre carbón (5% de Pd). La mezcla de reacción se agitó bajo una atmósfera de hidrógeno a 40 psi durante aproximadamente 15 horas, luego se filtró a través de un taco de celite. El filtrado se concentró al vacío para proporcionar el compuesto **71D** en forma de un sólido. HPLC–MS RT= 1,0 min, masa calculada para la fórmula $C_{13}H_{21}N5O_2$ 279,17, LCMS observada m/z 280,30 (M+H).

Ejemplo 72

Preparación del compuesto **72B**



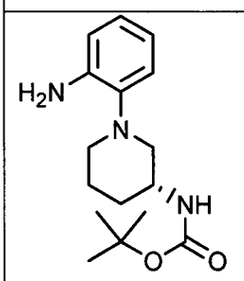
Etapa A:

Una solución de 1–bromo–2–nitro–benceno (2,0 mmol, 0,4 g), dietilisopropilamina (3,0 mmol, 0,52 mL) y el compuesto (2,5 mmol, 0,50 g) en dimetilacetamida (2 mL) se irradió usando microondas durante 30 minutos a una temperatura de 200 °C. La mezcla de reacción se concentró al vacío y el residuo resultante se purificó usando cromatografía flash en columna de gel de sílice (eluyente: acetato de etilo) para proporcionar el compuesto **72A** en forma de un sólido. HPLC–MS RT= 2,15 min, masa calculada para la fórmula $C_{16}H_{23}N_3O_4$ 321,17, LCMS observada m/z 322,2 (M+H).

Etapa B:

A una solución del compuesto **72A** (400 mg) en etanol/EtOAc (1:1, 10 mL) se añadió Pd sobre carbón (5% de Pd). La mezcla de reacción se agitó bajo una atmósfera de hidrógeno a temperatura ambiente durante aproximadamente 15 horas, luego se filtró a través de un taco de celite. El filtrado se concentró al vacío para proporcionar el compuesto **72B** en forma de un sólido. HPLC–MS RT= 1,70 min, masa calculada para la fórmula $C_{16}H_{25}N3O_2$ 291,19, LCMS observada m/z 292,20 (M+H).

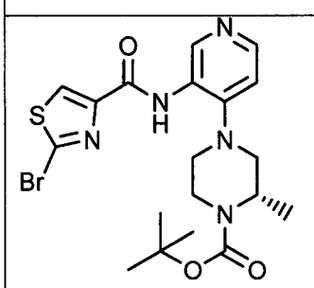
Usando los métodos descritos en las etapas A y B anteriores y utilizando el enantiómero del compuesto **72B**, se preparó el siguiente compuesto intermediario:

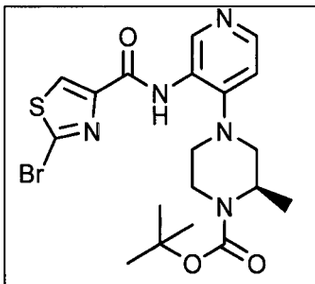
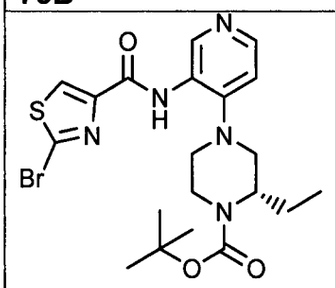
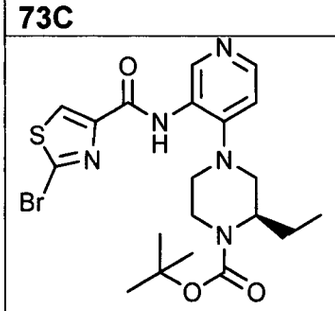
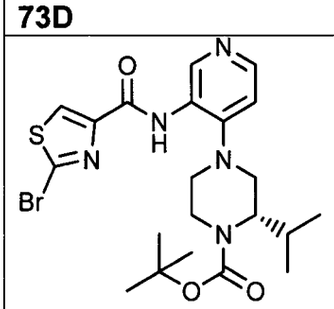
Compuesto	M+H Observado	Tiempo de retención
 **72C**	292,20	1,70

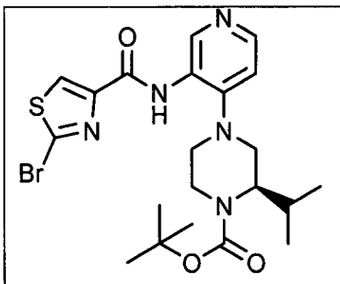
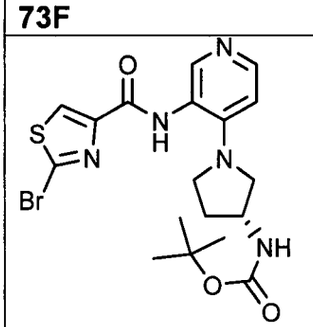
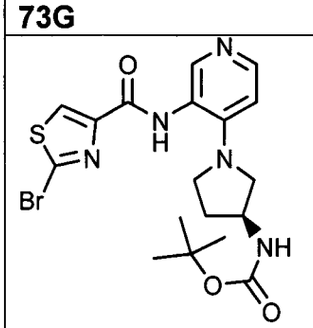
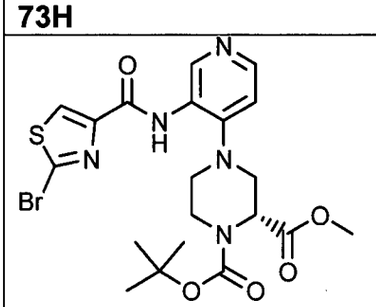
Ejemplo 73

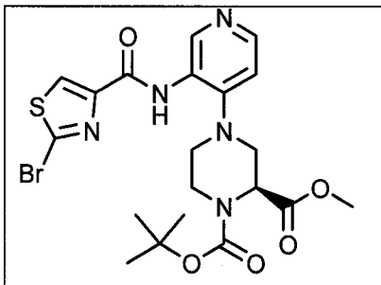
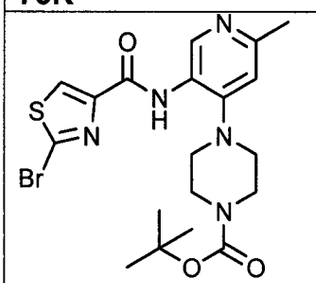
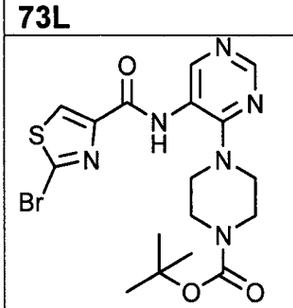
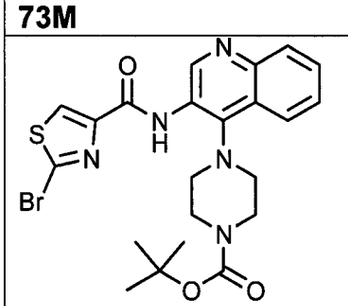
Preparación de los compuestos intermediarios **73A–73Q**

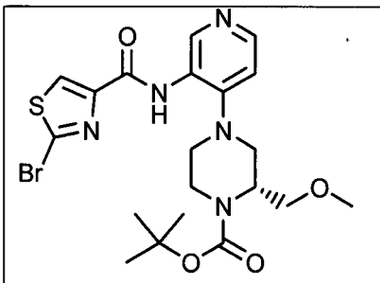
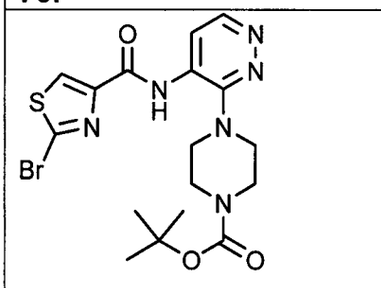
Usando los métodos descritos en el Ejemplo 46 anterior y usando los reactivos apropiados, se prepararon los siguientes compuestos intermediarios:

Compuesto	M+H Observado
 **73A**	482,1

 **73B**	482,1
 **73C**	496,1
 **73D**	496,1
 **73E**	510,1

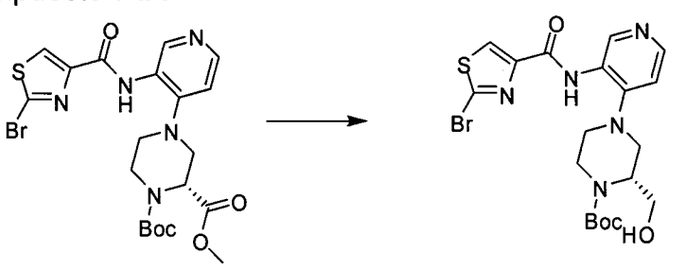
 **73F**	510,1
 **73G**	468,1
 **73H**	468,1
 **73J**	526,1

 **73K**	526,1
 **73L**	**482,1**
 **73M**	**469,1**
 **73N**	518,1

 **73P**	**512,1**
 **73Q**	**469,1**

Ejemplo 74

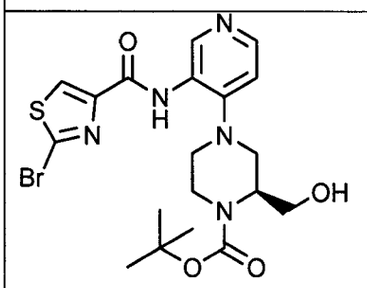
Preparación del compuesto **74A**



73J **74A**

A una solución del compuesto **73J** (0,2 mmol, 0,1 g.) en etanol 2 mL se añadió borhidruro de sodio (0,8 mmol, 0,03 g) y se agitó durante aproximadamente 15 horas. Se añadió agua y se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con agua, salmuera, se secó sobre sulfato de sodio anhidro, se filtró y se concentró al vacío para proporcionar el producto **75A**. HPLC–MS RT= 1,10 min, masa calculada para la fórmula $C_{19}H_{24}BrN_5O_4S$ 497,07, LCMS observada m/z 498,1 (M+H).

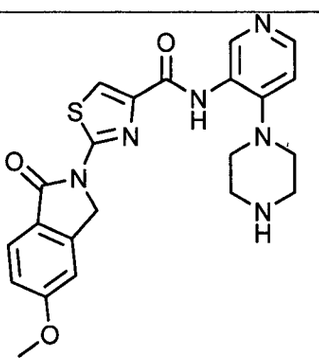
Usando este procedimiento, el compuesto **74B** se sintetizó a partir del compuesto **73K**.

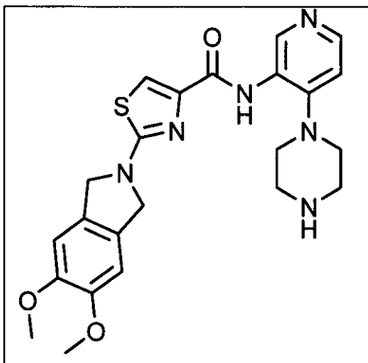
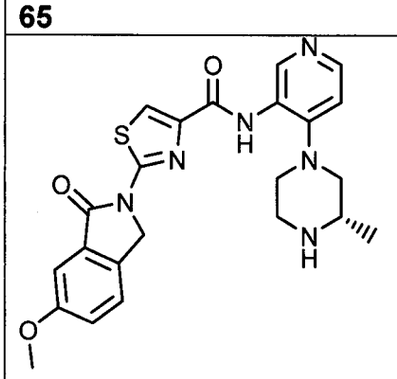
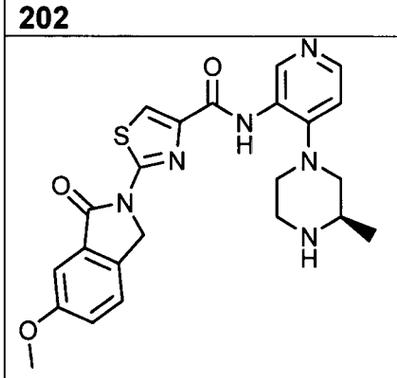
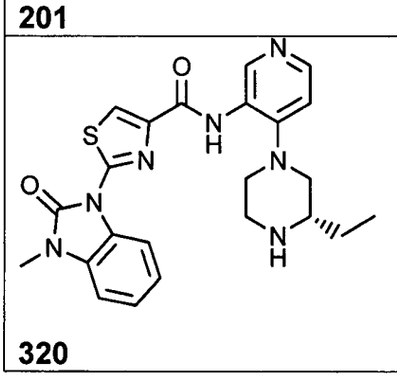
Compuesto	M+H observado
 **74B**	498,31

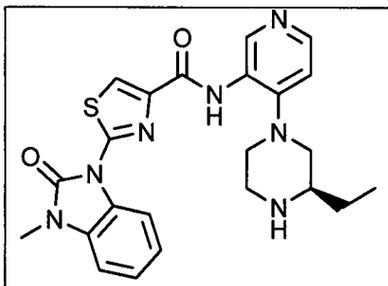
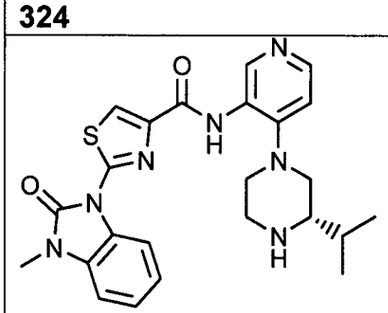
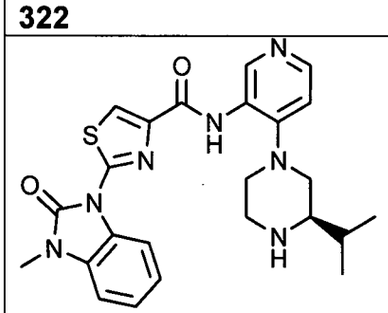
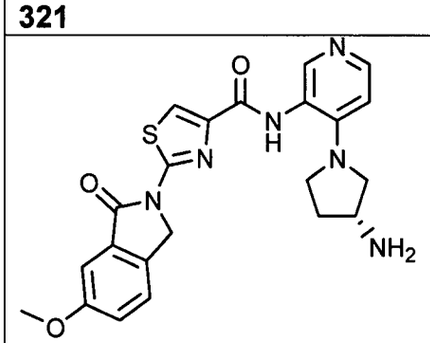
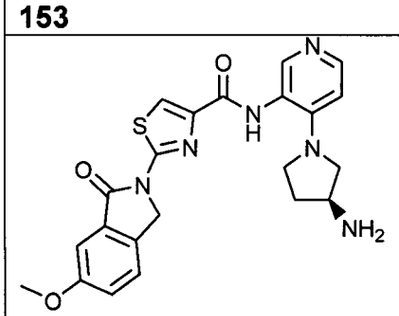
Ejemplo 75

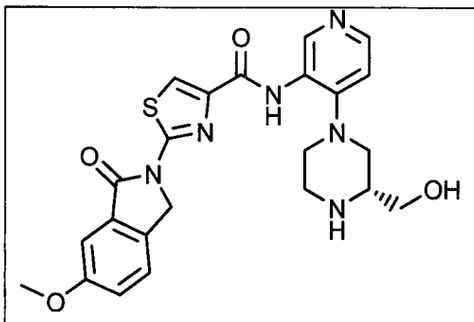
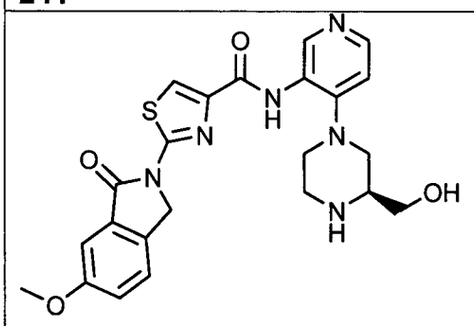
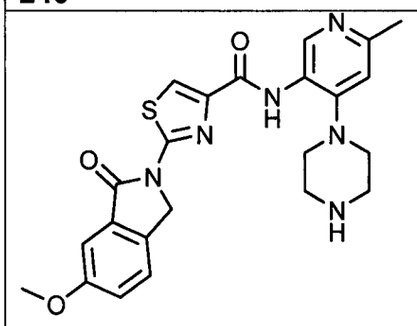
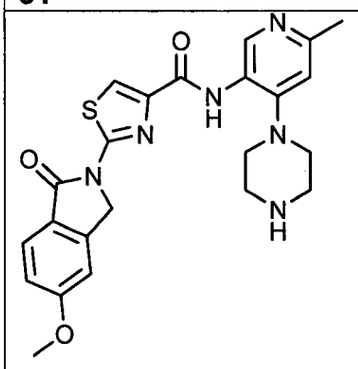
Preparación de los compuestos **65, 71, 75, 81, 83, 86, 87, 151–153, 201, 202, 240, 241, 257, 317, 320–322 y 324**

Los compuestos representados más abajo se prepararon usando el método descrito en el Ejemplo 51 y utilizando los reactivos apropiados.

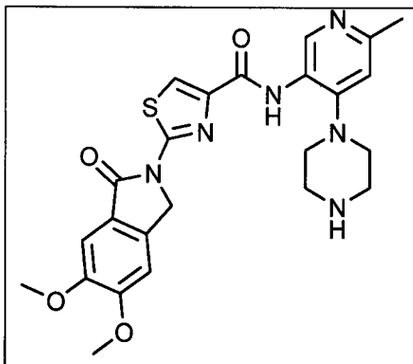
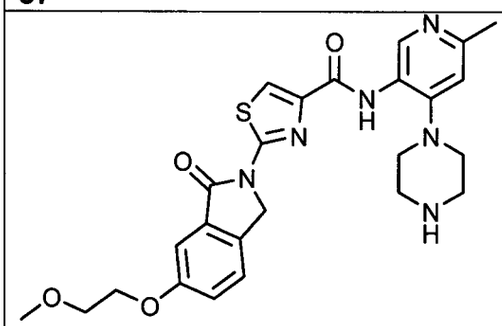
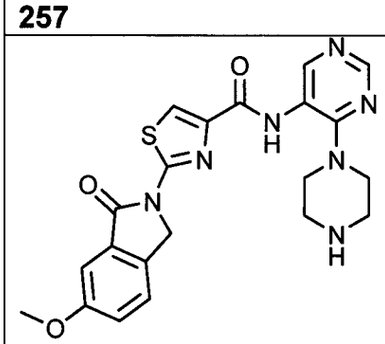
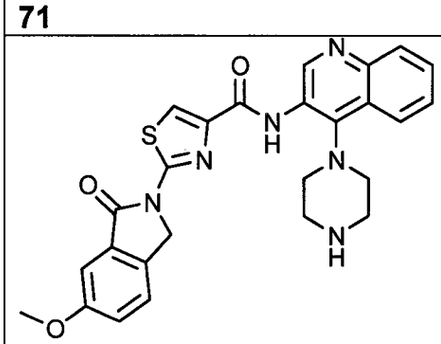
Compuesto	M+H observado	Tiempo de retención
 **83**	451,14	2,07

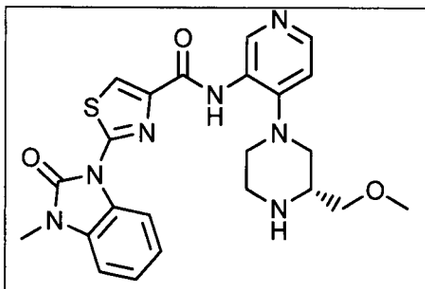
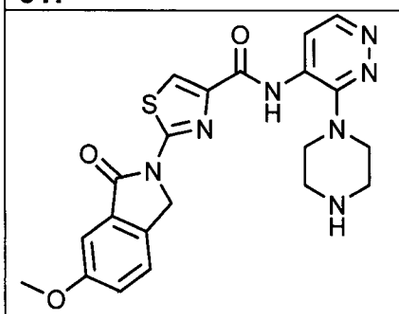
 **65**	467,2	0,5
 **202**	465,1	0,75
 **201**	465,1	0,8
 **320**	464,17	1,81

 **324**	464,17	1,92
 **322**	478,19	1,93
 **321**	478,19	1,86
 **153**	451,1	2,1
 **152**	451,1	2,1

 **241**	481,15	1,71
 **240**	481,15	1,74
 **81**	**465,16**	**2,14**
 **86**	**465,16**	**1,93**

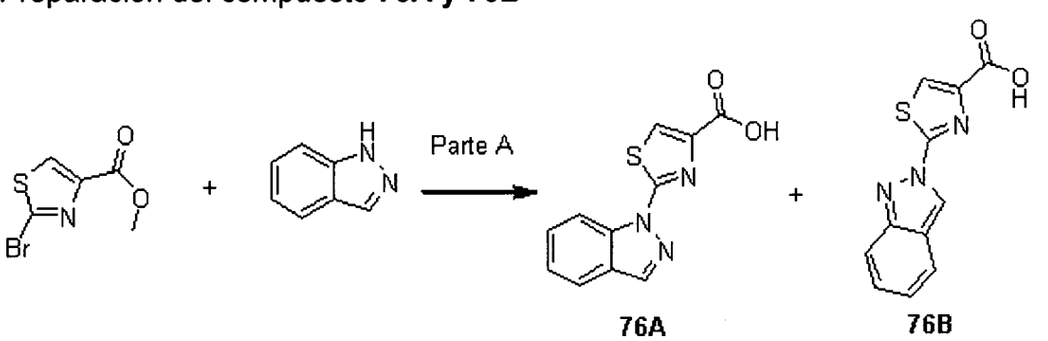
959

 **87**	**495,17**	**1,99**
 **257**	**509,19**	**2,10**
 **71**	**452,1**	**2,45**
 **75**	501,16	2,14

 317	**480,17**	**1,78**
 151	**452,15**	**2,76**

Ejemplo 76

Preparación del compuesto **76A y 76B**



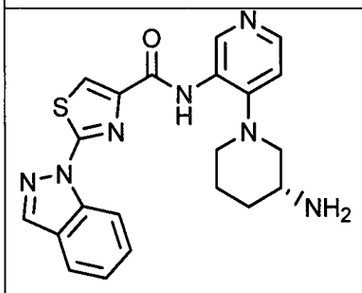
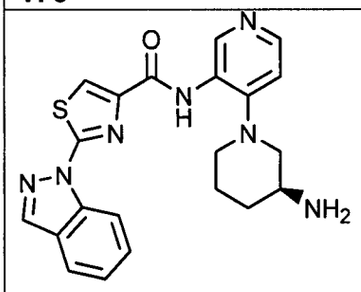
A una suspensión de NaH (60% de dispersión en aceite, 10 mmol, 0,48 g) en dioxano anhidro (5 mL) se añadió una solución de indazol (10 mmol, 1,18 g) en dioxano (5 mL) y la reacción resultante se dejó bajo agitación durante 30 minutos. Una solución de éster metílico del ácido 2–bromo–tiazol–4–carboxílico (10,0 mmol, 2,22 g) en dioxano (5 mL) luego se añadió gota a gota y la mezcla de reacción se calentó hasta 100 °C durante 4 h. La mezcla de reacción se enfrió hasta temperatura ambiente, se neutralizó con agua y la solución se ajustó en pH

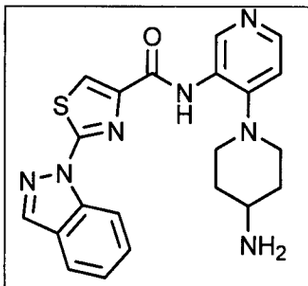
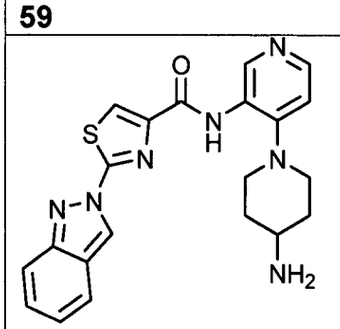
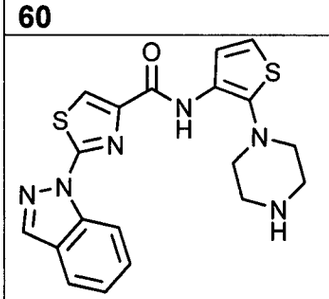
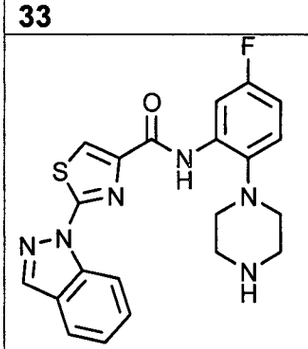
2 usando HCl 1 N. La solución básica resultante se extrajo con acetato de etilo y la fase orgánica se lavó con agua y salmuera, se secó sobre sulfato de sodio anhidro, luego se filtró y se concentró. LCMS del residuo resultante mostró dos picos para el ácido, lo que indicó la formación de dos regioisómeros (compuestos **76A y 76B**). HPLC–MS RT= 1,35 y 1,45 min, masa calculada para la fórmula $C_{11}H_7N_3O_2S$ 245,03, LCMS observada m/z 246,1 (M+H).

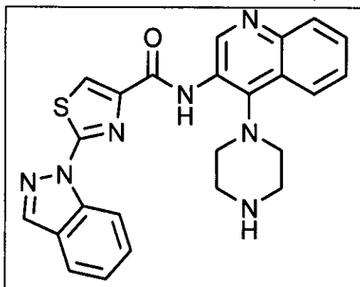
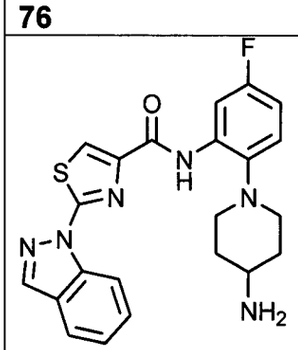
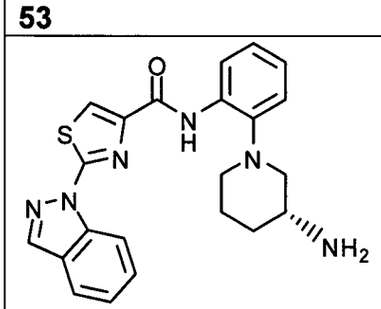
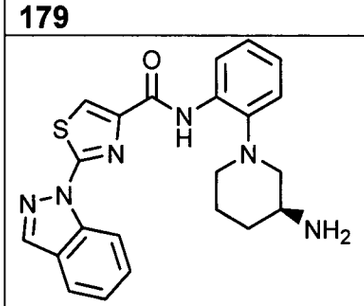
Ejemplo 77

Preparación de los compuestos **33, 40, 53, 59, 60, 76, 173, 176 y 179**

Los compuestos representados más abajo se prepararon haciendo reaccionar el compuesto **76A** o **76B** con la pareja de acoplamiento apropiada usando el método descrito en las etapas C y D de Ejemplo 66.

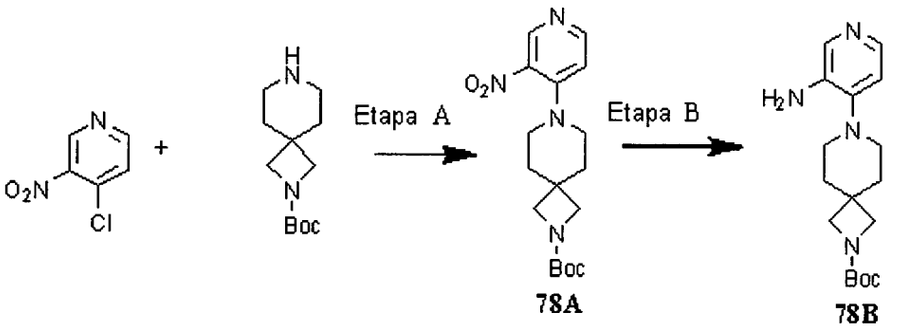
Compuesto	**M+H observado**	**Tiempo de retención**
 **173**	420,1	**2,07**
 **171**	420,1	2,07

 **59**	420,15	2,22
 **60**	420,15	2,16
 **33**	**411,09**	**3,34**
 **40**	**423,1**	**3,75**

 **76**	456,15	2,31
 **53**	**437,2**	**4,0**
 **179**	**419,15**	**3,57**
 **176**	**419,15**	**3,54**

Ejemplo 78

Preparación del compuesto **78B**



78A 78B

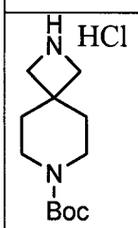
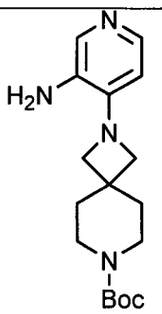
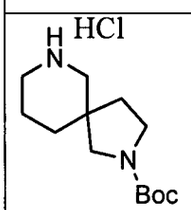
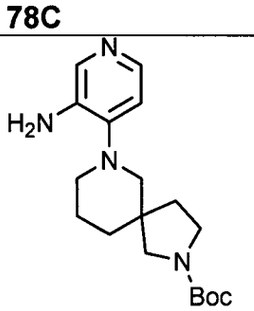
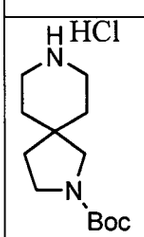
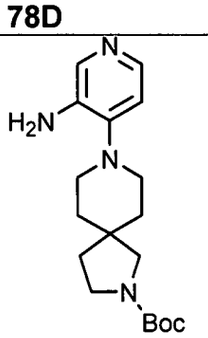
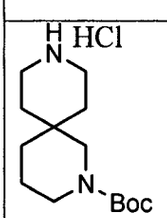
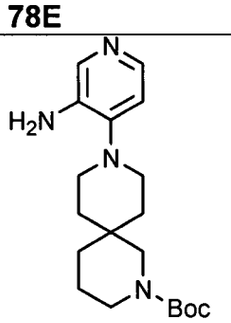
Etapa A:

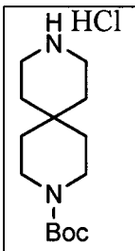
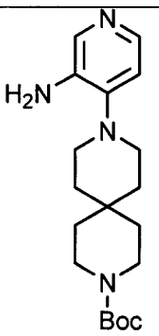
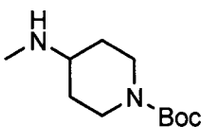
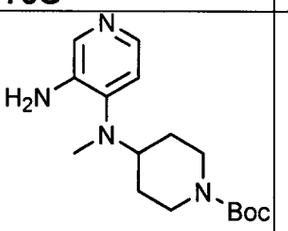
A un recipiente se añadieron 4–cloro–3–nitropiridina (2 mmol) y amina espirocíclica (2 mmol). Los materiales de partida se disolvieron en 4 mL de diclorometano seguido de la adición de DIPEA (6 mmol). La reacción se agitó a 60° durante aproximadamente 15 horas, luego la mezcla de reacción se concentró y se usó cromatografía líquida preparativa (0–5% de metanol en acetato de etilo) para proporcionar el compuesto **78A**. Se recuperaron 1,6 mmol (80%) de 274. Masa calculada para la fórmula $C_{17}H_{24}N_4O_4$ 348,18, LCMS observada m/z 348,20 (M+H).

Etapa B:

A un recipiente de base redonda se añadió una solución del compuesto **78A** en acetato de etilo. A continuación, Pd/C se añadió a la mezcla. El recipiente se selló con un septo y se evacuó. La mezcla se hidrogenó usando un balón durante aproximadamente 15 horas. El producto se confirmó por medio de LCMS. El Pd/C se filtró usando Celite y el filtrado se concentró al vacío para proporcionar el compuesto **78B** con rendimiento cuantitativo. Masa calculada para la fórmula $C_{17}H_{26}N_4O_2$ 318,21, LCMS observada m/z 319,20 (M+H). LCMS calculada para 275: 318,21.

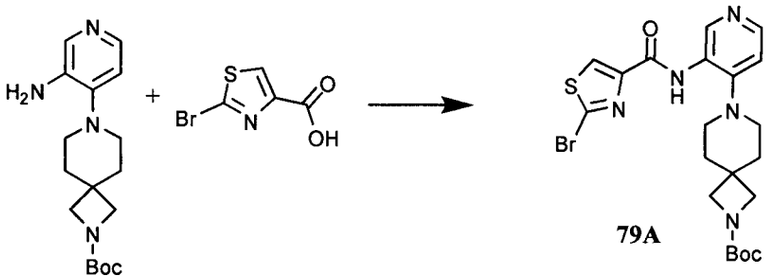
Usando los métodos descritos en las etapas A y B anteriores y usando los reactivos apropiados, se prepararon los siguientes compuestos intermediarios:

Material de partida	Producto	M+1	Tiempo de re–tención (min)
	 **78C**	319,2	0,95
	 **78D**	333,2	1,11
	 **78E**	333,3	1,21
	 **78F**	347,2	1,12

	 **78G**	347,2	1,05
	 **78H**	307,3	0,99

Ejemplo 79

Preparación del compuesto **79A**

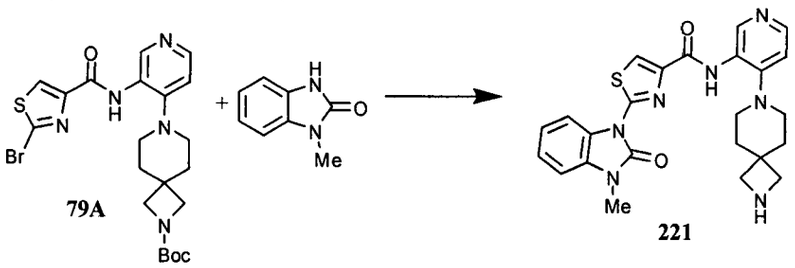


78B **79A**

A una solución de ácido 2–bromotiazol–5 carboxílico (0,57 mmol) y HATU (0,68 mmol) en 1 mL de DMF, se añadió DIPEA (3 equivalentes, 1,6 mmol) y la reacción resultante se agitó durante 10 minutos a temperatura ambiente. A la mezcla de reacción luego se añadió una solución del compuesto **78B** (0,57 mmol) en 0,5 mL de DMF y la reacción resultante se agitó a temperatura ambiente durante 2 horas más. La mezcla de reacción luego se concentró al vacío y el residuo obtenido se purificó usando cromatografía líquida preparativa (5–10% de metanol en diclorometano) para proporcionar 0,54 mmol (95%) del compuesto **79A**.

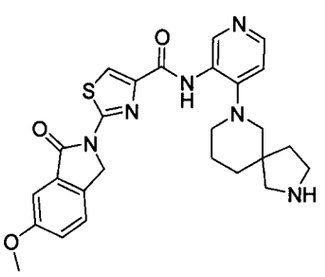
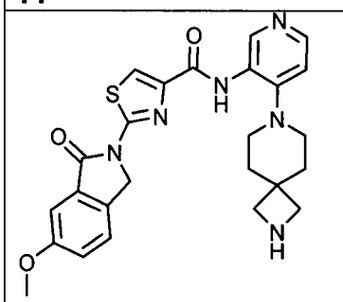
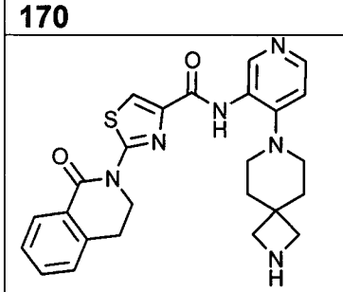
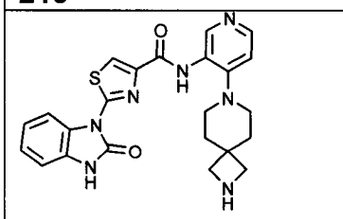
Ejemplo 80

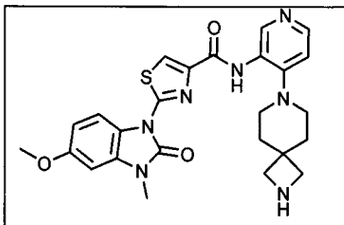
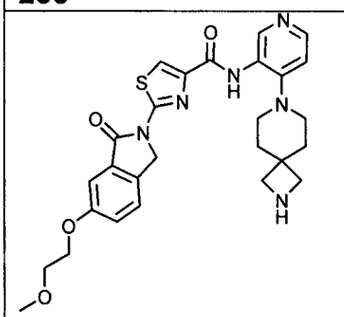
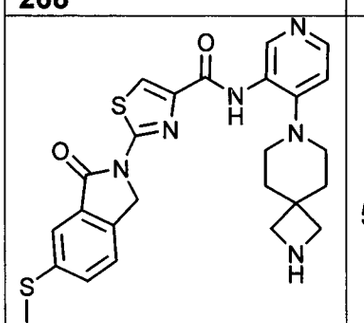
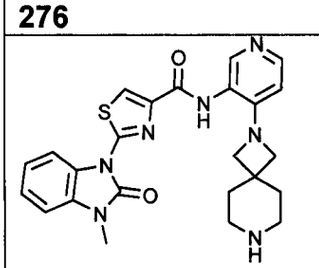
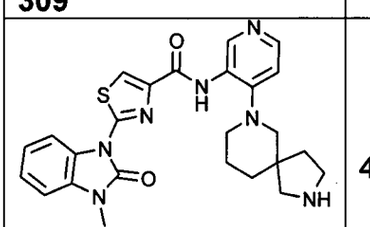
Preparación del compuesto **221**

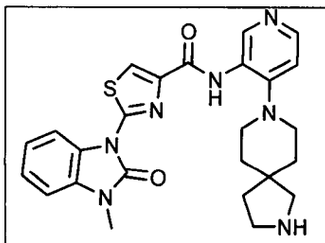
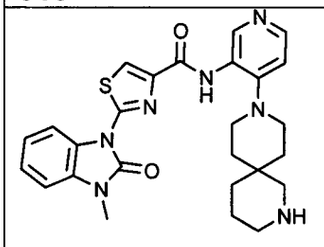
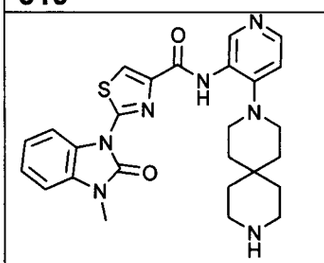


El compuesto **79A** (0,15 mmol), 1–metil–1,3–dihidro–bencimidazol–2–ona (0,1 mmol), Pd_2dba_3 (0,01 mmol), Xantphos (0,02 mmol) y K_3PO_4 (0,3 mmol) se colocaron en un vial y se diluyeron con dioxano (1 mL). La solución resultante se desgasificó y se inundó con argón, luego se tapó y se sonicó. La reacción se calentó hasta 90 °C y se dejó bajo agitación a esta temperatura durante 2 horas, luego la mezcla de reacción se enfrió hasta temperatura ambiente y se diluyó con acetato de etilo. La capa orgánica se lavó secuencialmente con $NaHCO_3$ saturado (ac), salmuera y agua. La capa orgánica luego se secó con sulfato de sodio, se filtró y se concentró al vacío y el residuo crudo obtenido se purificó usando cromatografía líquida preparativa (5–10% de metanol en diclorometano). El producto obtenido luego se liofilizó y el material sólido obtenido se trató con HCl 2 M en exceso en dioxano para proporcionar el compuesto **221**.

Utilizando el método descrito con anterioridad, se prepararon los siguientes compuestos ilustrativos:

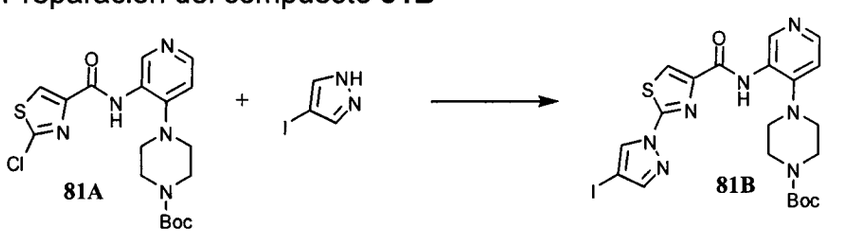
Compuesto	M+ (m/z)	M+H	Tiempo de retención (minutos)
 **77**	504,20	505,20	2,75
 **170**	490,18	491,2	2,60
 **219**	474,18	475,2	2,19
 **220**	461,16	462,1	1,84

 **233**	505,19	506,1	2,26
 **268**	534,21	535,2	2,66
 **276**	506,16	507,1	2,48
 **309**	475,18	476,1	1,75
 **315**	489,19	490,1	2,31

 **316**	489,19	490,1	2,39
 **319**	503,21	504,3	2,18
 **323**	503,21	504,3	2,15

Ejemplo 81

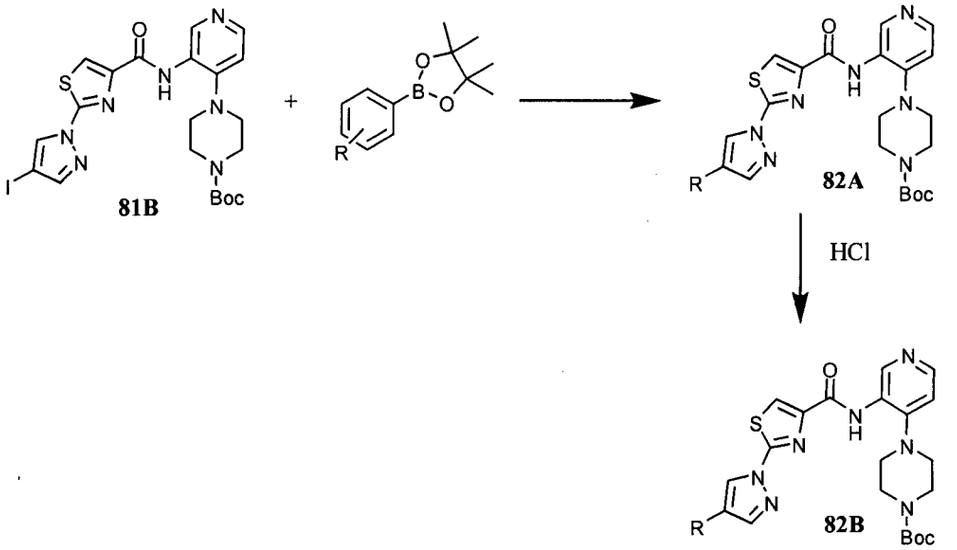
Preparación del compuesto **81B**



Usando el método descrito en el Ejemplo 24, se hizo reaccionar el compuesto **81A** con 4–yodopirazol para preparar el compuesto **81B**. Masa calculada para la fórmula $C_{21}H_{24}N_7O_2SI$ 581,0, LCMS observada m/z 582,20 (M+H).

Ejemplo 82

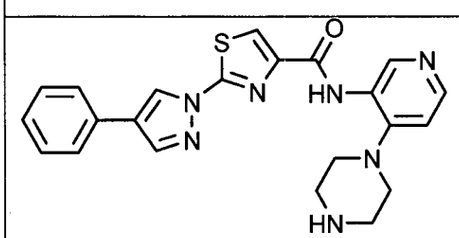
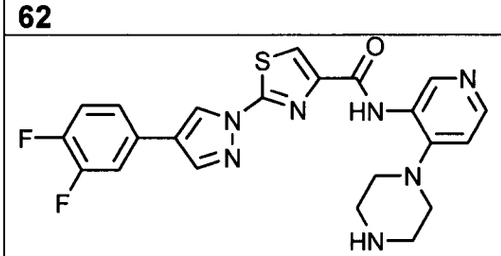
Preparación de los compuestos **62, 63, 66, 70, 272, 277 y 283**

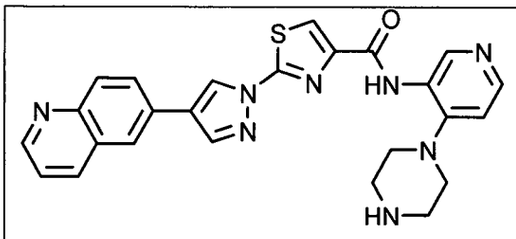
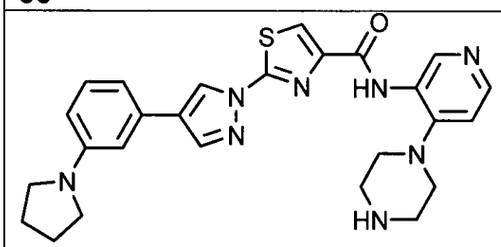
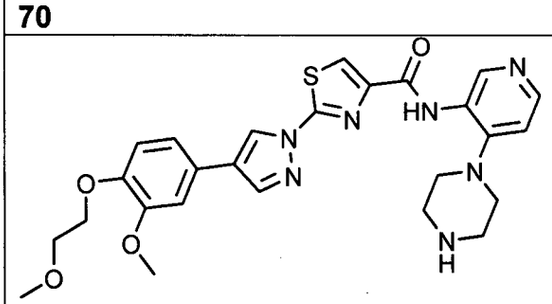
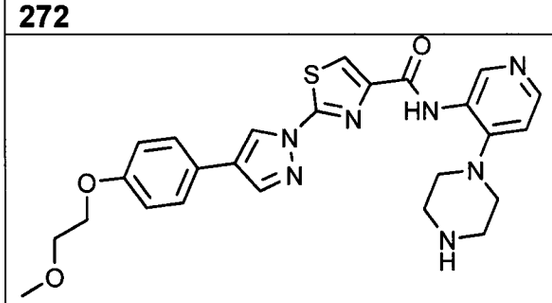
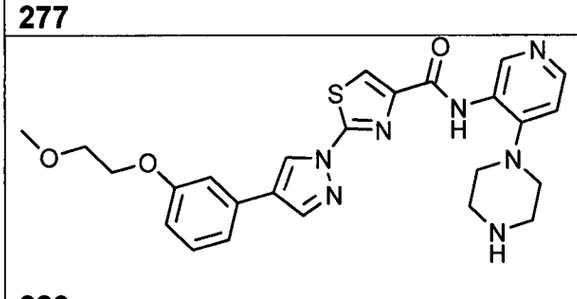


Procedimiento general:

El compuesto **81B** (0,30 mmol), un ácido borónico o éster representativos (0,34 mmol), $Pd(dppf)Cl_2$ (0,034 mmol) y K_3PO_4 (0,9 mmol) se disolvieron en 2 mL de dioxano y 300 µL de agua. La solución resultante se desgasificó y se inundó con argón, luego se calentó hasta 90 °C y se dejó bajo agitación a esta temperatura durante aproximadamente 2 horas. La reacción luego se diluyó con acetato de etilo y la fase orgánica se lavó secuencialmente con $NaHCO_3$ acuoso saturado y agua. La capa orgánica luego se secó sobre Na_2SO_4, se filtró y se concentró al vacío. El residuo obtenido se pudo purificar usando HPLC preparativa para proporcionar el compuesto de la fórmula 82A, que luego se liofiliza y el producto purificado luego se trató con HCl 4 N para eliminar el grupo Boc y se obtuvo el producto deseado **82B**.

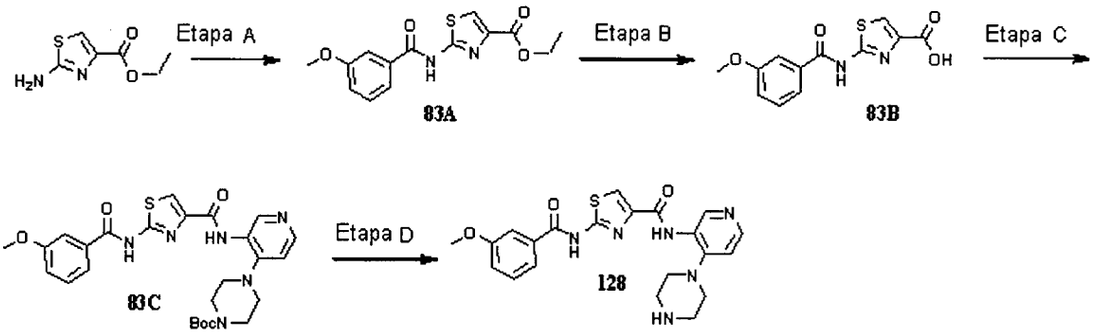
Utilizando este método, se prepararon los siguientes compuestos ilustrativos.

Compuesto	M+H observado	Tiempo de ret (min)
 **62**	432,15	2,60
 **63**	468,1	2,49

 **66**	483,1	1,69
 **70**	501,2	2,63
 **272**	536,2	2,86
 **277**	506,2	2,96
 **283**	506,2	2,95

Ejemplo 83

Preparación del compuesto **128**



Etapa A:

A la mezcla de 2–amino–4–carboxilato de metilo (634 mg, 3,69 mmol), DIEA (0,7 mL, 4,0 mmol) y ácido 3–metoxibenzoico (561 mg, 3,69 mmol) en DMF (10 mL) se añadió HATU (1,52 g, 4,0 mmol). La mezcla resultante se agitó a temperatura ambiente durante aproximadamente 15 horas y se añadió agua (60 mL). El sólido precipitado se recogió por filtración y se lavó con agua, se secó al aire. El producto crudo **83A** se usó en la siguiente etapa directamente sin ninguna purificación ulterior. HPLC–MS t_R = 1,71 min (UV_{254} nm); masa calculada para la fórmula $C_{14}H_{14}N_2O_4S$ 306,1, LCMS observada m/z 307,1 (M+H).

Etapa B:

El compuesto **83B** se preparó hidrolizando el compuesto **83A** usando el método descrito en el Ejemplo 50 anterior. HPLC–MS t_R = 1,45 min (UV_{254} nm); masa calculada para la fórmula $C_{12}H_{10}N_2O_4S$ 278,0, LCMS observada m/z 279,1 (M+H).

Etapa C:

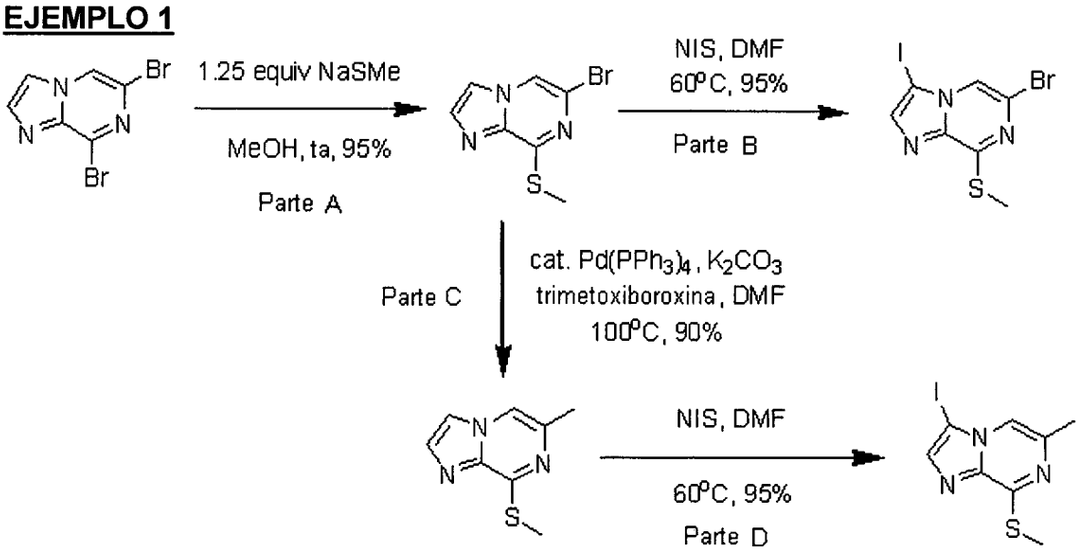
El compuesto **83C** se preparó haciendo reaccionar el compuesto **83B** con la pareja de acoplamiento apropiada de acuerdo con el método descrito en el Ejemplo 58 anterior. HPLC–MS t_R = 1,50 min (UV_{254} nm); masa calculada para la fórmula $C_{26}H_{30}N_6O_5S$ 538,2, LCMS observada m/z 539,2 (M+H).

Etapa D:

El compuesto **128** se preparó desprotegiendo el compuesto **83C** por medio del método descrito en el Ejemplo 62 anterior. HPLC–MS t_R = 0,94 min (UV_{254} nm); masa calculada para la fórmula $C_{21}H_{22}N_6O_3S$ 438,1, LCMS observada m/z 439,1 (M+H).

La síntesis de compuestos (k) de la solicitud de patente provisional U. S., expediente N.º OC06760L01 presentada junto con la presente, se describe más abajo:

EJEMPLO 1



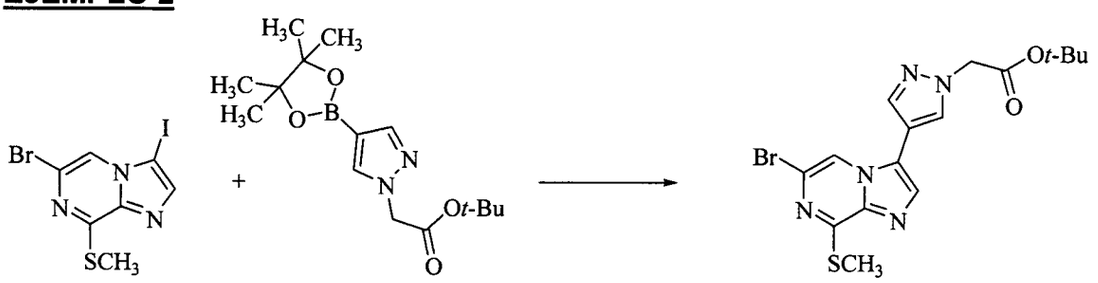
Parte A: El compuesto del título se preparó de acuerdo con US20060106023 (A1).

Parte B: A una solución del compuesto del Ejemplo 1, Parte A (2,00 g, 8,19 mmol) en DMF (50 mL) se añadió N–yodosuccinimida (1,84 g, 8,19 mmol). La mezcla de reacción se agitó a 60 °C durante 16 horas. La mezcla se enfrió hasta 25 °C y se concentró. El residuo se disolvió en DCM con una pequeña cantidad de metanol y luego se cargó en la columna. La purificación por cromatografía en columna (SiO_2, 40% de acetato de etilo/hexanos) dio el compuesto en forma de un sólido blanco 2,30 g (76%). ^{1}H–RMN (400 MHz, DMSO–d_6) δ 8,3 (s, 1H), 7,8 (s, 1H), 2,6 (s, 3H). HPLC–MS t_R = 1,87 Min (UV_{254nm}). Masa calculada para la fórmula $C_7H5BrIN3S$ 370,01, LC/MS observada m/z 370,9 (M+H).

Parte C: Una suspensión de bromuro de la Parte A (45,6 g), $Pd(PPh_3)_4$ (10,8 g), carbonato de potasio (77,4 g), trimetilboroxina (46,9 g) y carbonato de potasio (77,4 g) en DMF (410 mL) se calentó durante la noche bajo nitrógeno a 105 °C. Después de enfriar, la mezcla se diluyó con acetato de etilo (1 L), se lavó con salmuera (2 x 500 mL), se secó (sulfato de magnesio), se filtró, se concentró y se purificó por cromatografía en gel de sílice. El compuesto del título se obtuvo en forma de un sólido de color amarillo pálido (21,4 g, 64%).

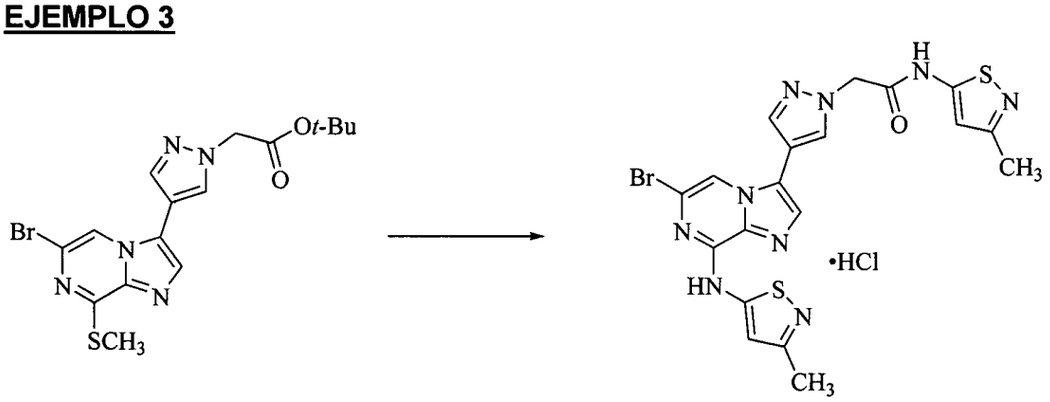
Parte D: A una solución en DMF (400 mL) del compuesto del Ejemplo 1, Parte C (21,8 g) se añadió N–yodosuccinimida (26,9 g) y la mezcla resultante se calentó durante la noche a 60 °C. La mezcla se concentró y se añadió agua (400 mL). Después de agitar durante 1 h a temperatura ambiente, se añadió carbonato de sodio saturado (250 mL) y luego se agitó durante 30 min más a temperatura ambiente. La mezcla se filtró, se lavó con agua, metanol (100 mL) y la torta filtrante se secó durante la noche al vacío. Se obtuvo un sólido marrón (31,4 g, 87%).

EJEMPLO 2



Una solución de 2–(4–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)–1H–pirazol–1–il)acetato de ter–butilo (318 mg, 1,03 mmol) en 1,4–dioxano (3 mL) y se añadió agua (0,30 mL) a una mezcla desgasificada con argón del compuesto del Ejemplo 1, Parte B (292 mg, 0,79 mmol), $Pd(dppf)Cl_2$ (58 mg, 0,079 mmol) y fosfato de potasio (503 mg, 2,37 mmol). La reacción se calentó hasta 40 °C y se dejó bajo agitación durante 12 horas. La reacción se enfrió hasta temperatura ambiente, se filtró a través de Celite eluyendo con acetato de etilo, luego se concentró hasta sequedad. La purificación del residuo crudo por cromatografía flash (SiO_2, 12 g; 5% a 40% de acetato de etilo en hexanos) dio el compuesto del título en forma de un sólido marrón claro 244 mg (73%). ^1H RMN (300 MHz, $CDCl_3$) δ 7,94 (s, 1H), 7,81 (s, 1H), 7,80 (s, 1H), 7,65 (s, 1H), 4,94 (s, 2H), 2,68 (s, 3H), 1,51 (s, 9H).

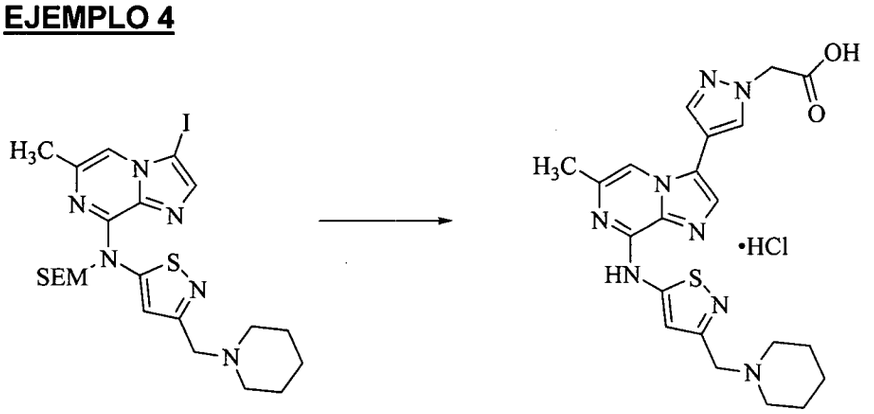
EJEMPLO 3



Se añadió ácido 3–cloroperoxibenzoico (204 mg, 1,18 mmol) a una solución a temperatura ambiente de éster del Ejemplo 2 (244 mg, 0,58 mmol) en

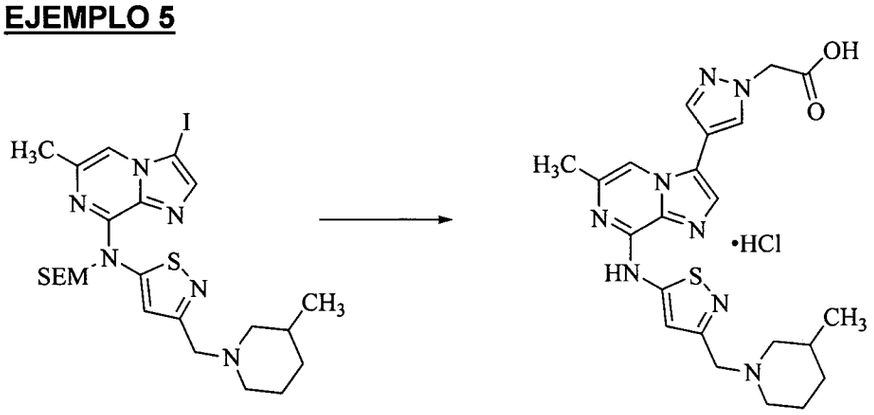
cloruro de metileno (3 mL). La reacción se dejó bajo agitación durante 1 hora. Después de completar, la reacción se concentró hasta sequedad, luego se extrajo en acetato de etilo (50 mL). La solución se lavó con solución acuosa saturada de bicarbonato de sodio (50 mL) y salmuera (2 × 50 mL), luego se secó (sulfato de sodio), se filtró y se concentró hasta sequedad para dar 220 mg de sulfóxido crudo. El sulfóxido crudo (220 mg, 0,48 mmol) en dimetilsulfóxido (2,5 mL) se añadió a una solución premezclada de hidruro de sodio (106 mg, 1,45 mmol) y 2–amino–4–metilisotiazol (78 mg, 0,68 mmol) en dimetilsulfóxido (2,5 mL). La reacción se agitó durante 20 minutos, luego se neutralizó con cloruro de amonio acuoso saturado (50 mL). La capa acuosa se extrajo con éter dietílico (2 × 50 mL) y acetato de etilo (2 × 50 mL). Las capas orgánicas combinadas se lavaron con salmuera (2 × 50 mL), se secaron (sulfato de sodio), se filtraron y se concentraron hasta sequedad. La purificación del residuo resultante por cromatografía flash (SiO_2, 12 g; 5% al 40% de acetato de etilo en cloruro de metileno) y luego en HPLC preparativa dio el compuesto del título en forma de un sólido amarillo 2 mg (0,8%). ^1H RMN (300 MHz, $CDCl_3$) δ 8,35 (s, 1H), 8,32 (s, 1H), 8,02 (s, 1H), 7,93 (s, 1H), 7,17 (s, 1H), 6,90 (s, 1H), 5,37 (s, 2H), 2,63 (s, 3H), 2,46 (s, 3H). HPLC t_R = 4,62 min (UV $_{254nm}$). Masa calculada para la fórmula $C_{19}H_{16}BrN_9OS_2$ 529,01; MH^+ observada (APCI MS) 531,1 (m/z).

EJEMPLO 4



Una solución de 2–(4–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)–1H–pirazol–1–il)acetato de ter–butilo (135 mg, 0,44 mmol) en 1,4–dioxano (3 mL) y agua (0,30 mL) se añadió a una mezcla inundada con nitrógeno de yoduro (200 mg, 0,34 mmol), $Pd(dppf)Cl_2$ (25 mg, 0,034 mmol) y fosfato de potasio (216 mg, 1,02 mmol). La mezcla de reacción se calentó hasta 90 °C y se dejó bajo agitación durante 12 horas. Después de completar, la reacción se dejó enfriar hasta temperatura ambiente y luego se concentró hasta sequedad. La purificación del residuo resultante por cromatografía flash (SiO_2; 12 g; 10% a 80% de acetato de etilo en cloruro de metileno) dio el intermediario acoplado deseado. Se añadió ácido trifluoroacético (1 mL) a una solución a temperatura ambiente del éster acoplado deseado (80 mg, 0,125 mmol) en cloruro de metileno (3 mL). La reacción se agitó durante 12 horas, luego se concentró hasta sequedad. La purificación del residuo resultante por HPLC preparativa dio el compuesto del título en forma de un sólido amarillo 40 mg (45%). ^1H RMN (300 MHz, CD_3OD) δ 8,34 (s, 1H), 8,26 (s, 1H), 8,08 (s, 1H), 8,01 (s, 1H), 7,36 (s, 1H), 5,15 (s, 2H), 4,43 (s, 2H), 3,17–2,99 (m, 2H), 2,71–2,55 (m, 2H), 2,64 (s, 3H), 2,06–1,71 (m, 5H), 1,65–1,46 (m, 1H). HPLC t_R = 3,82 min (UV $_{254nm}$). Masa calculada para la fórmula $C_{21}H_{24}N_8O_2S$ 452,17; MH^+ observada (ESI MS) 453,1 (m/z).

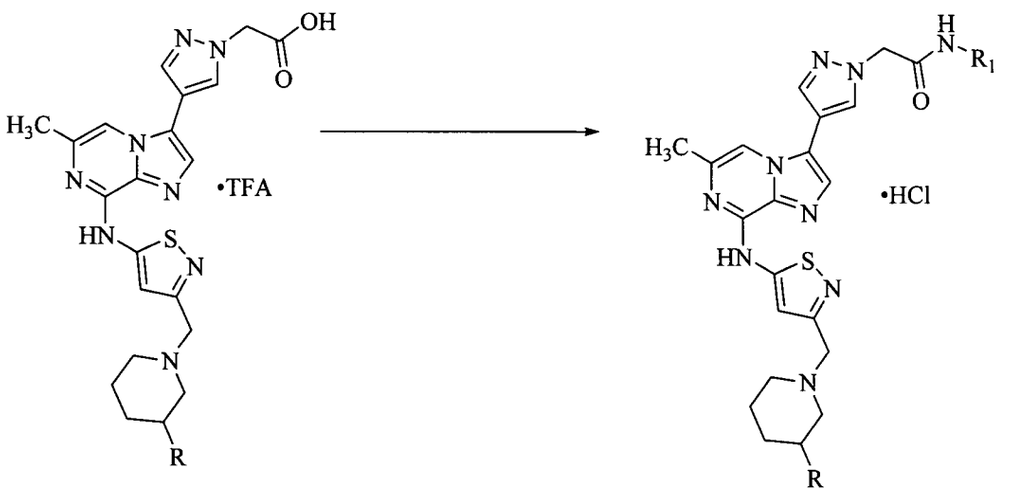
EJEMPLO 5



El Ejemplo 5 se preparó de una manera similar a la del Ejemplo 4. ^{1}H RMN (300 MHz, CD_3OD) δ 8,34 (s, 1H), 8,26 (s, 1H), 8,08 (s, 1H), 8,01 (s, 1H), 7,36 (s, 1H), 5,15 (s, 2H), 4,43 (s, 2H), 3,17–2,99 (m, 2H), 2,71–2,55 (m, 2H), 2,64 (s, 3H), 2,06–1,71 (m, 5H), 1,65–1,46 (m, 1H). HPLC t_R = 3,82 min (UV $_{254nm}$). Masa calculada para la fórmula $C_{21}H_{24}N_8O_2S$ 452,17; MH^+ observada (ESI MS) 453,1 (m/z).

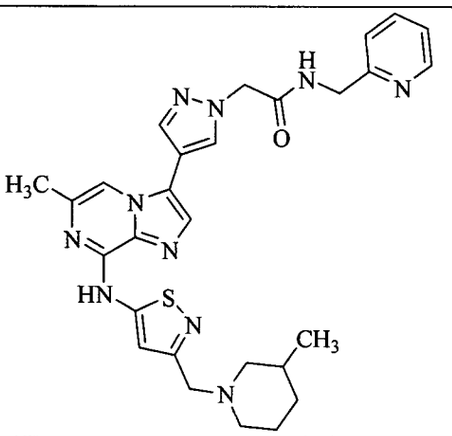
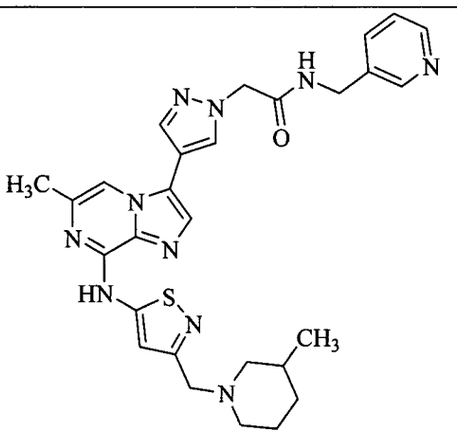
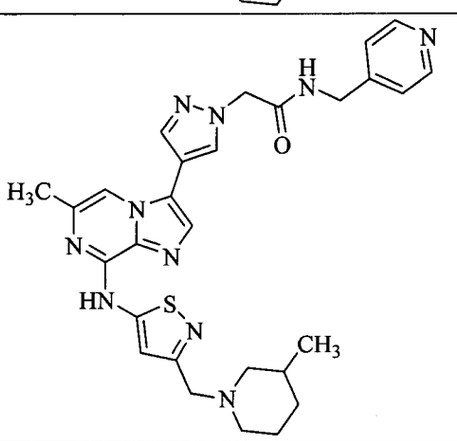
EJEMPLO 6

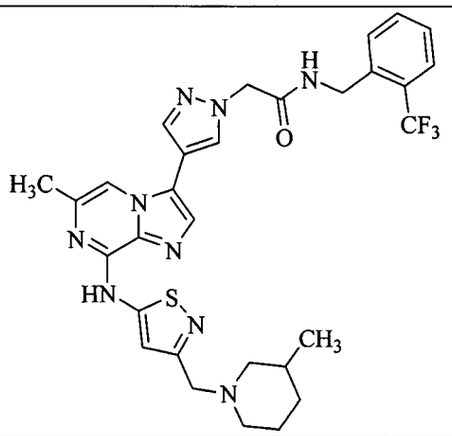
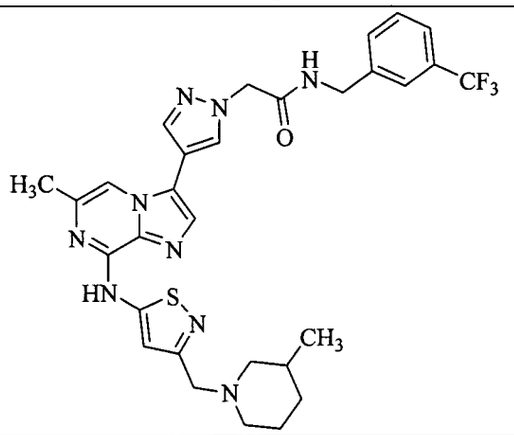
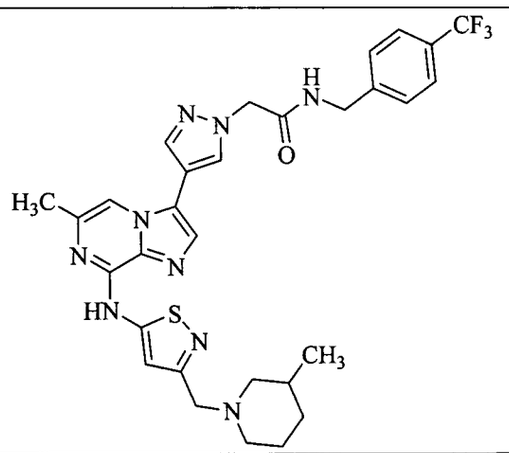
Los compuestos mostrados en la columna 2 de la Tabla 1 (mostrada inmediatamente a continuación) se prepararon de la siguiente manera:

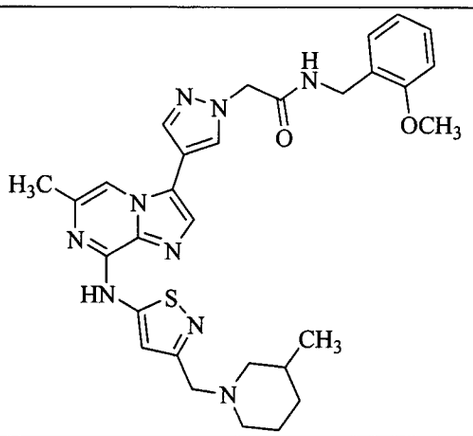
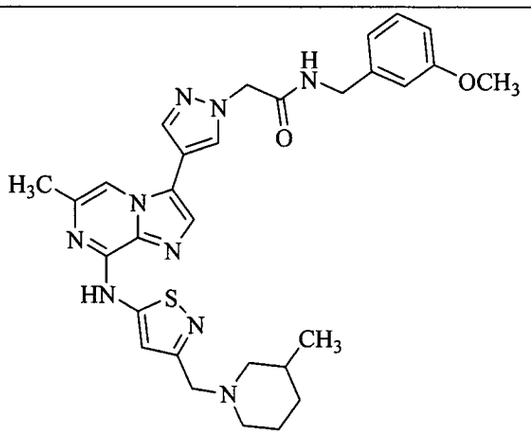
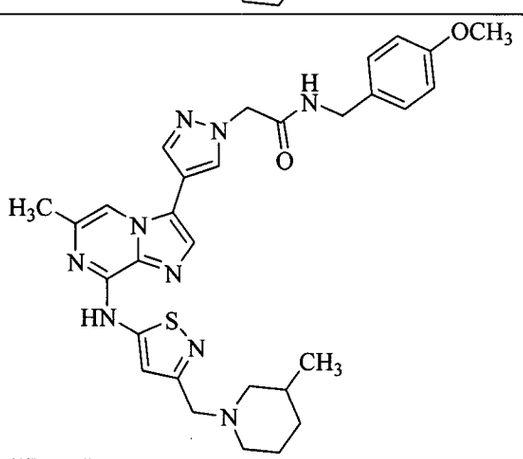


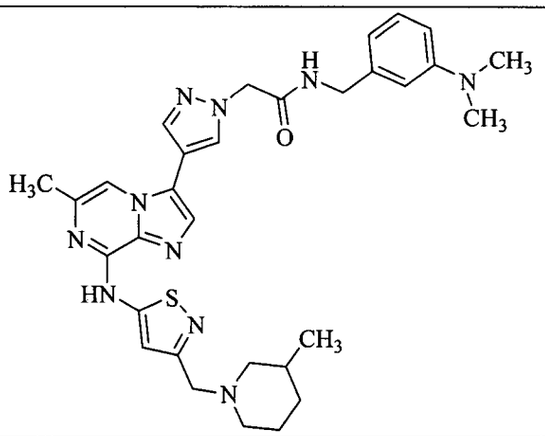
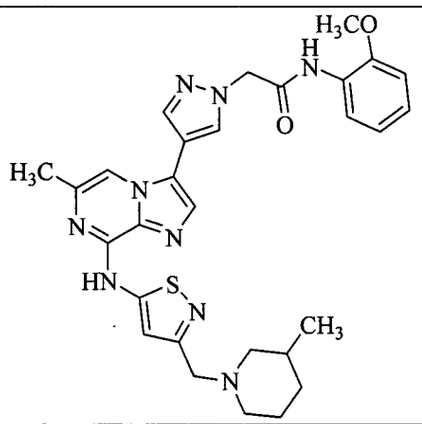
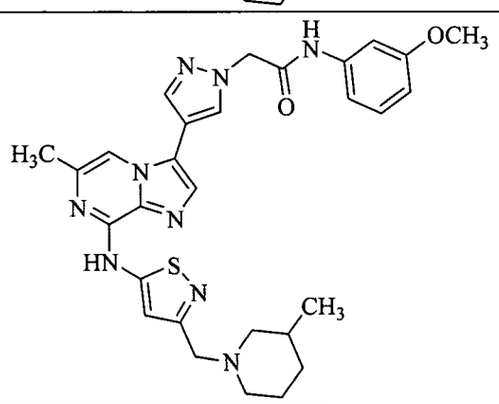
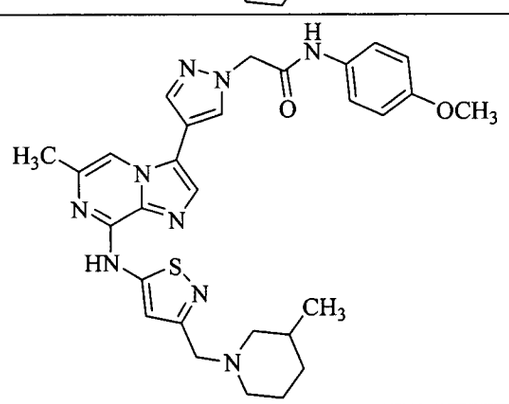
Una mezcla de ácido (1 equivalente), la respectiva amina (1,5 equivalentes), HATU (1,5 equivalentes) y diisopropiletilamina (3 equivalentes) en DMF anhidra (500 µL) se agitó a temperatura ambiente durante 2 horas. La reacción luego se concentró a presión reducida, se purificó por HPLC preparativa y la conversión en la sal de clorhidrato dio compuestos mostrados en la columna 2 de la Tabla 1(mostrada inmediatamente a continuación):

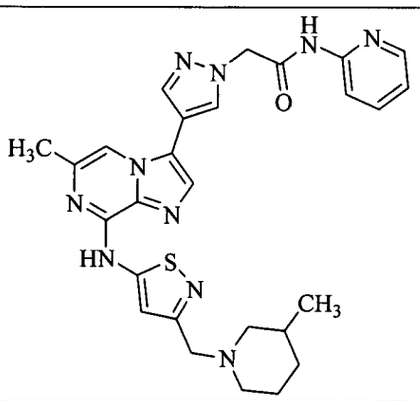
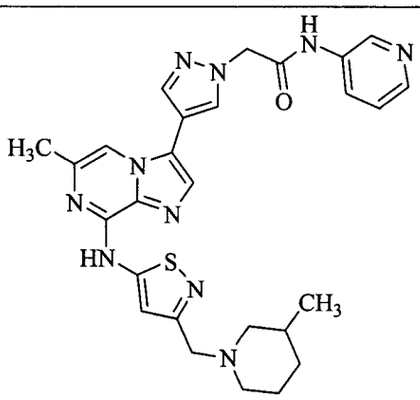
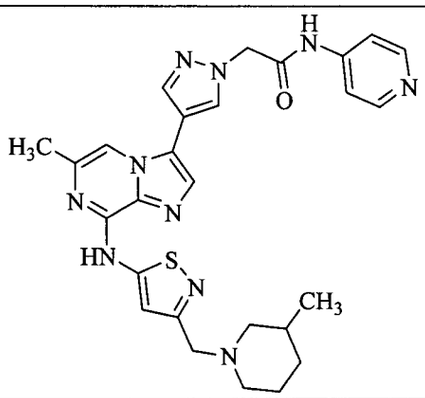
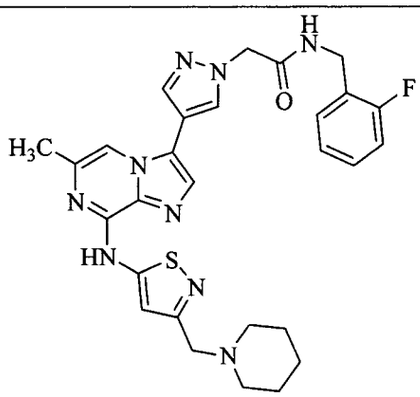
Tabla 1

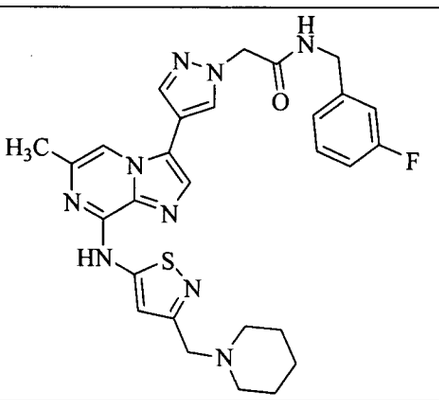
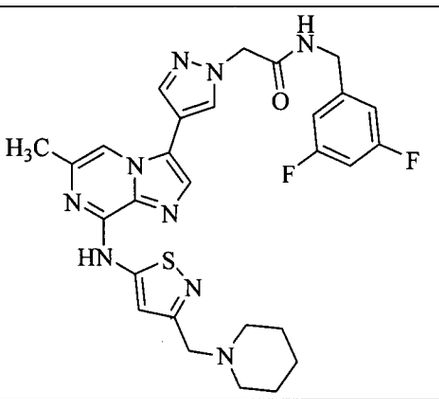
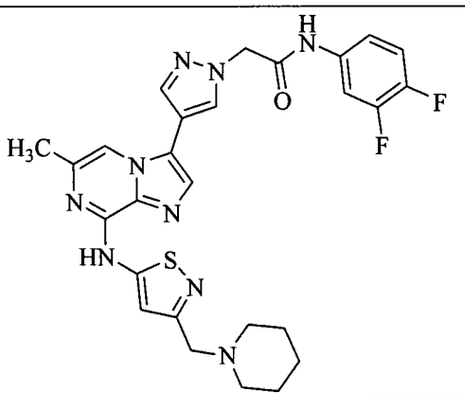
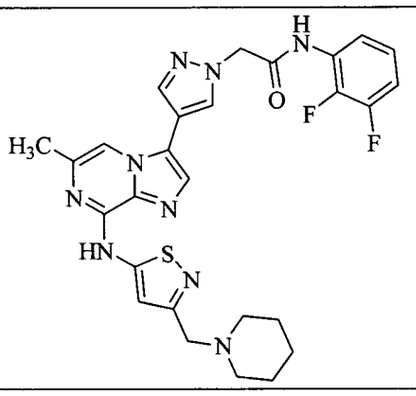
Ejemplo	Columna 2	PM	MS MH^+ m/z	HPLC t_R
6–1		556,2	557,4	3,51
6–2		556,2	557,2	3,48
6–3		556,2	557,3	3,48

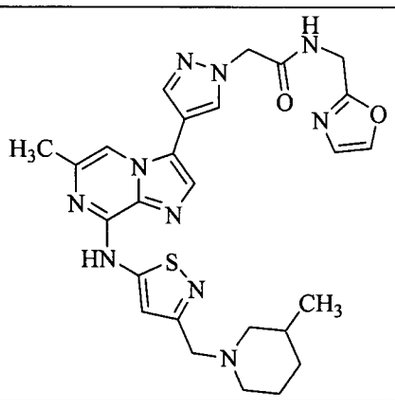
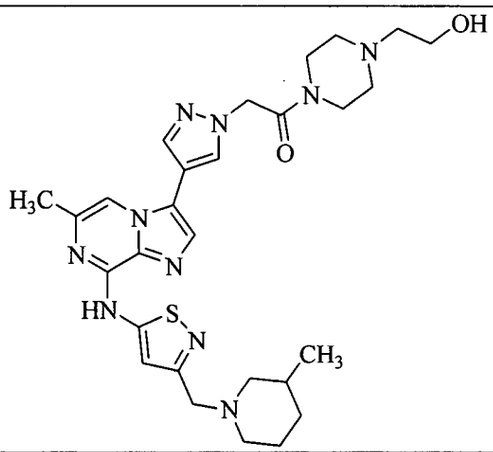
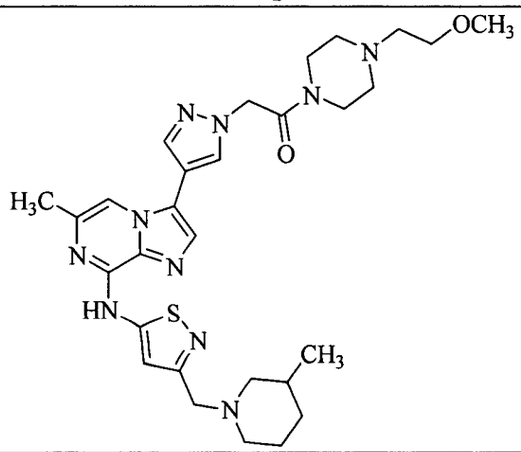
6–4		623,2	624,6	5,34
6–5		623,2	624,6	5,35
6–6		623,2	624,5	5,39

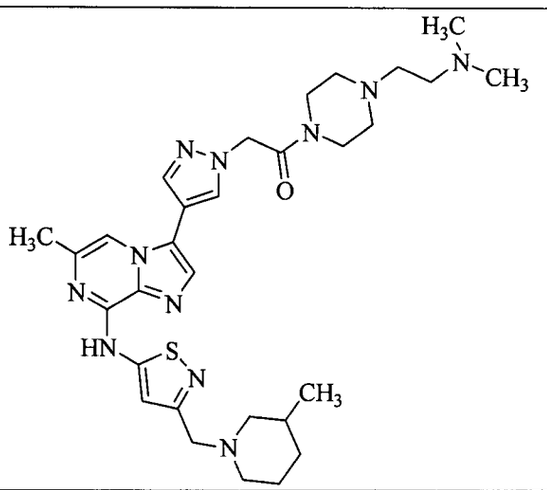
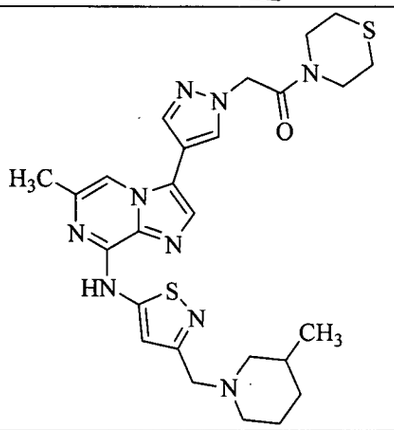
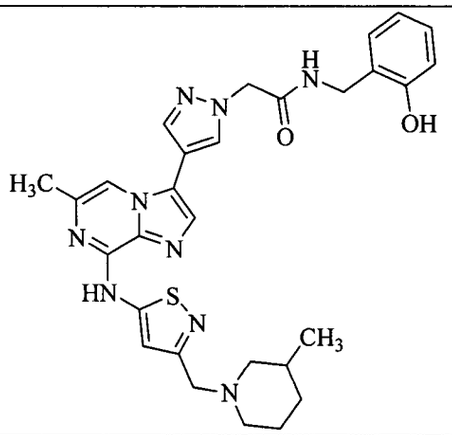
6–7		585,2	586,9	4,96
6–8		585,2	586,3	4,85
6–9		585,2	586,2	4,82

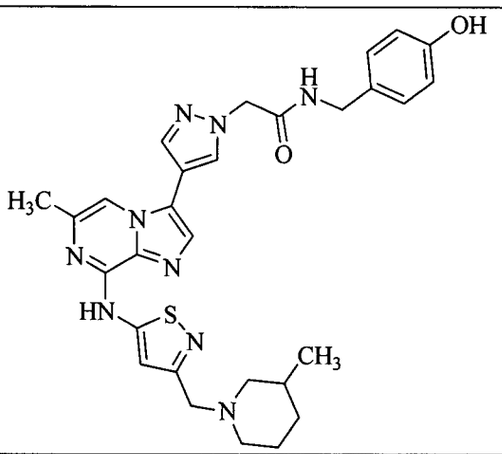
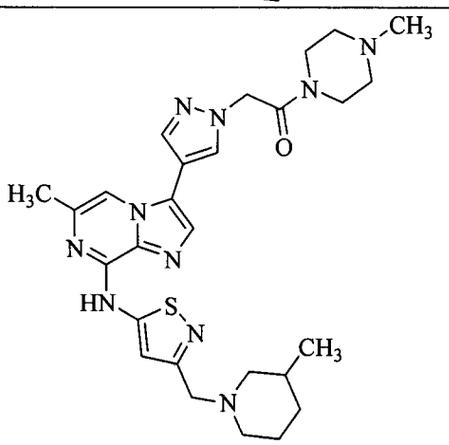
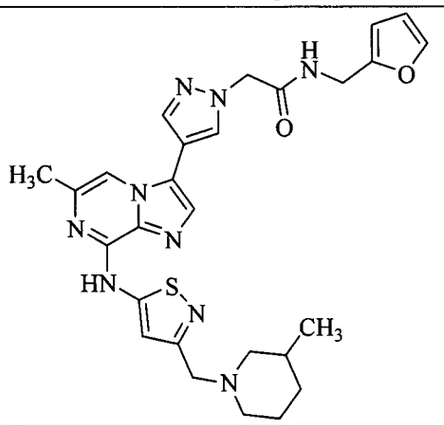
6–10		598,3	599,8	3,71
6–11		571,2	572,4	5,12
6–12		571,2	572,4	4,98
6–13		571,2	572,5	4,87

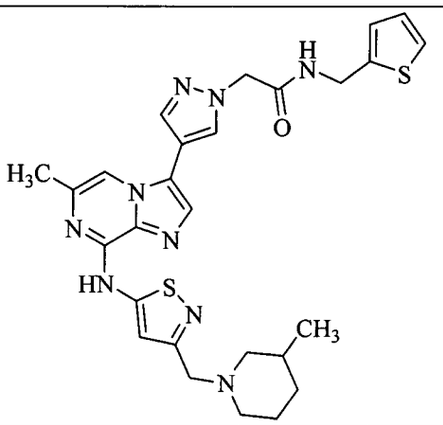
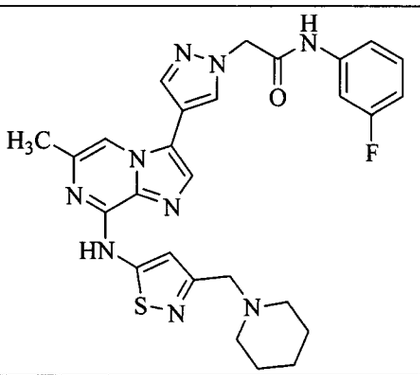
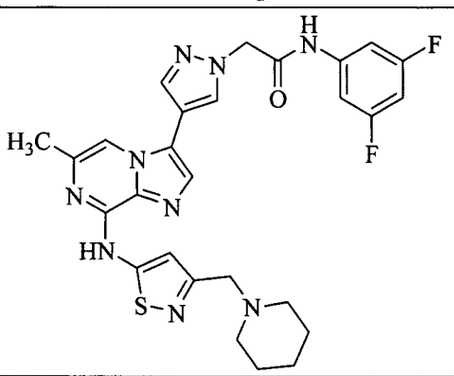
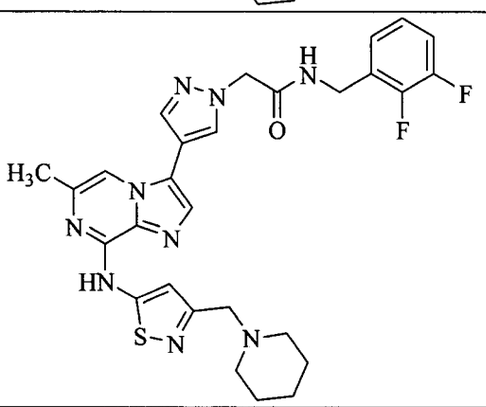
6–14		542,2	543,7	3,93
6–15		542,2	543,6	3,60
6–16		542,2	543,6	3,67
6–17		559,6	260,2	5,10

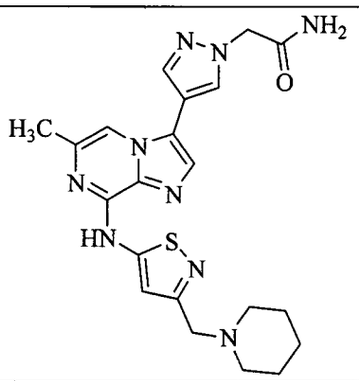
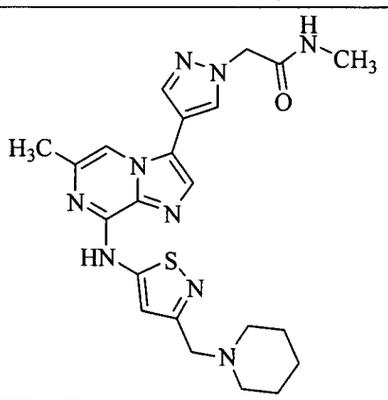
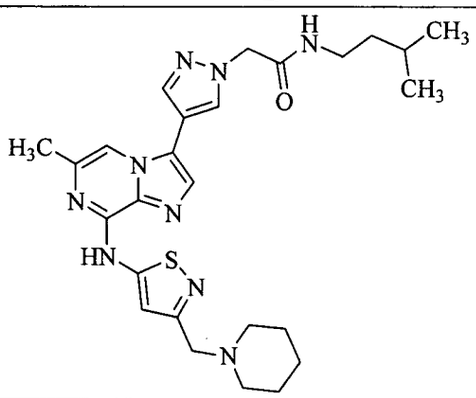
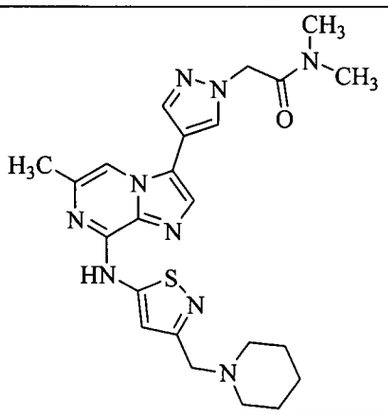
6–18		559,6	560,3	5,13
6–19		577,6	578,9	5,26
6–20		563,6	564,7	5,43
6–21		563,6	564,7	5,34

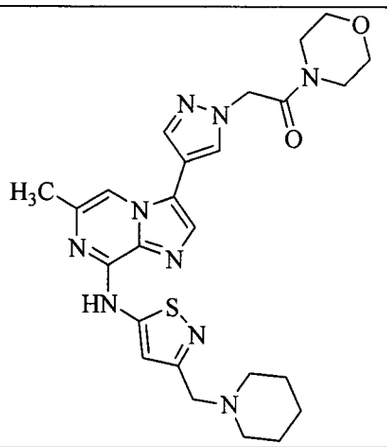
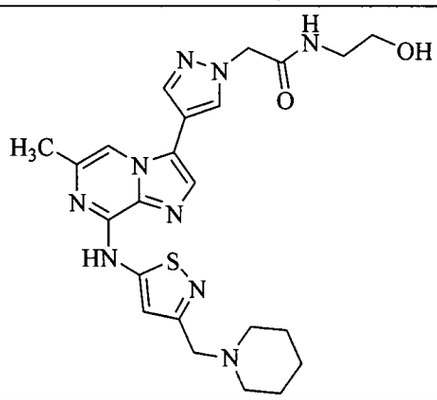
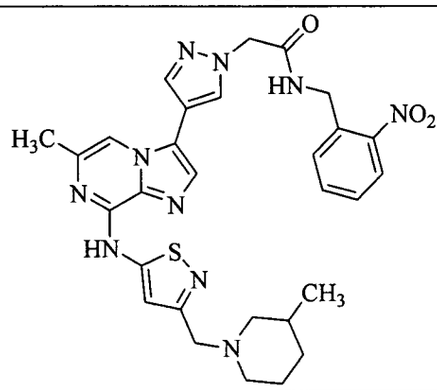
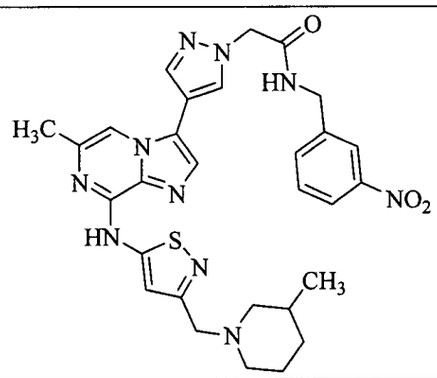
6–22		546,6	547,6	3,96
6–23		578,7	579,8	3,39
6–24		592,7	593,9	3,52

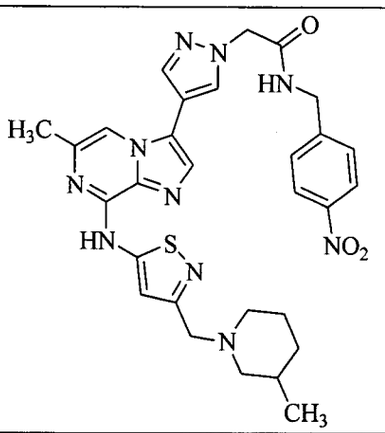
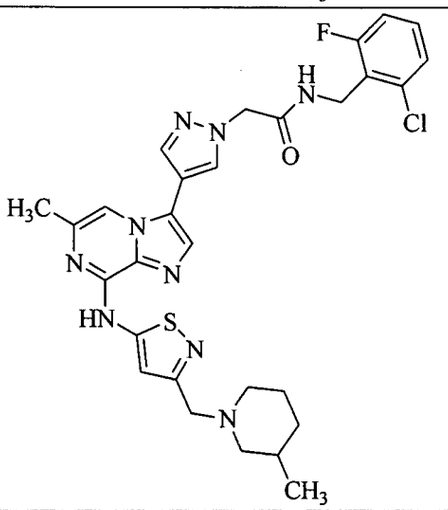
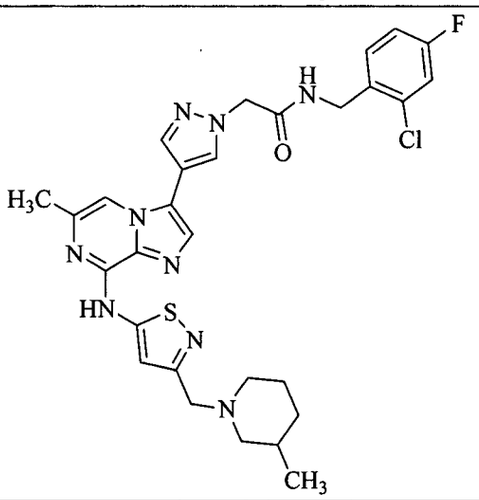
6–25		605,8	606,8	3,35
6–26		551,7	552,8	4,47
6–27		571,7	572,5	4,59

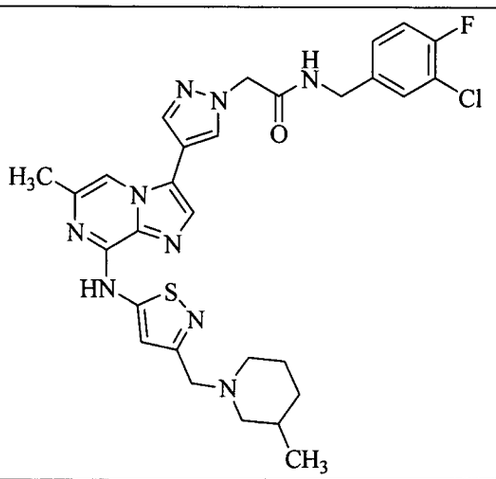
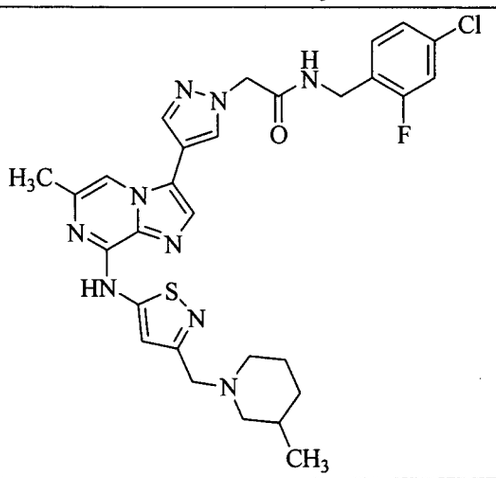
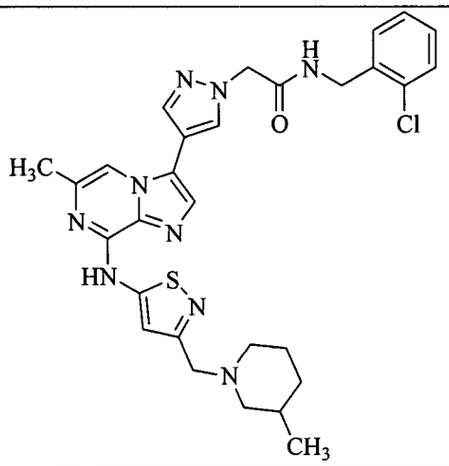
6–28		571,7	572,4	4,26
6–29		548,7	549,8	3,45
6–30		545,6	546,5	4,53

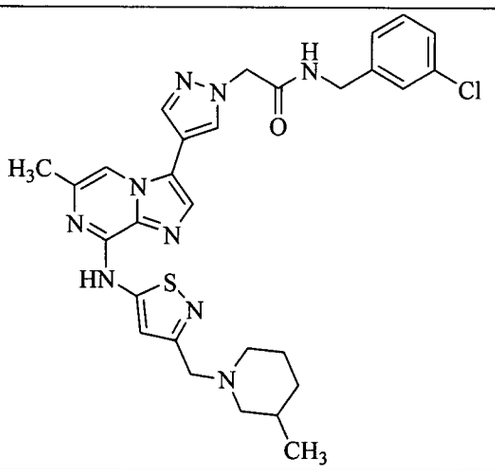
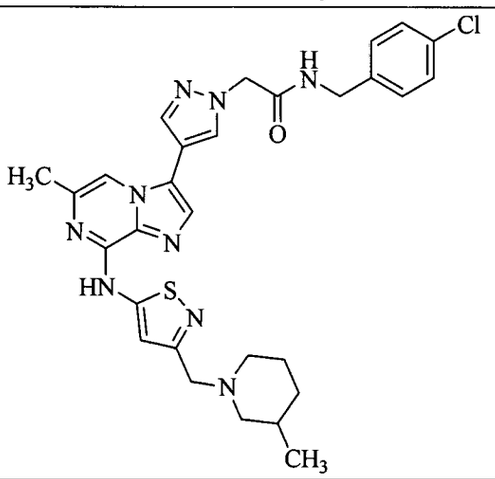
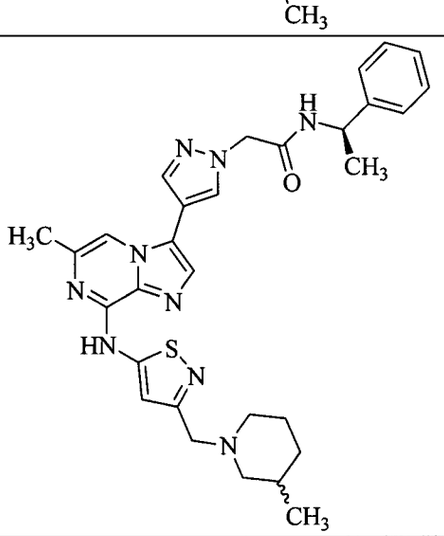
6–31		561,7	562,1	4,72
6–32		545,2	546,5	5,08
6–33		563,2	564,7	5,32
6–34		577,2	578,9	4,97

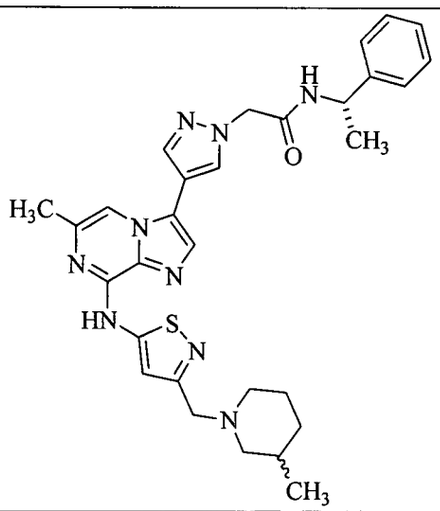
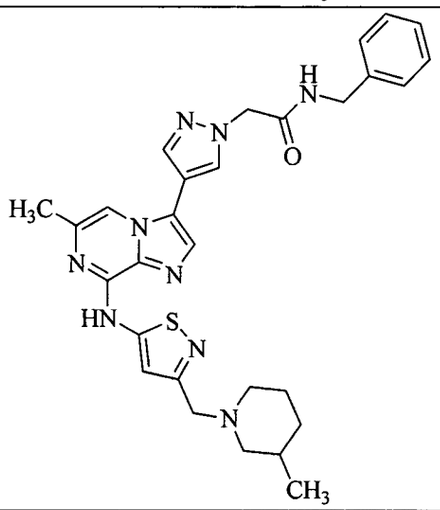
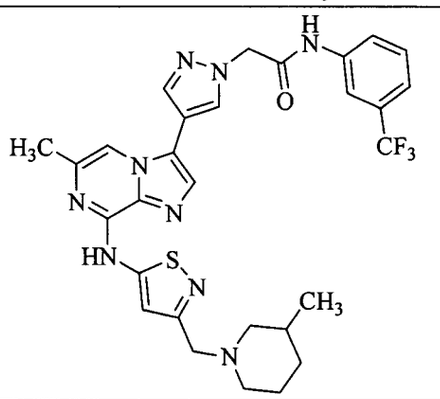
6–35		451,1	452,2	3,44
6–36		465,2	466,7	3,57
6–37		521,2	522,9	4,71
6–38		479,2	480,1	3,73

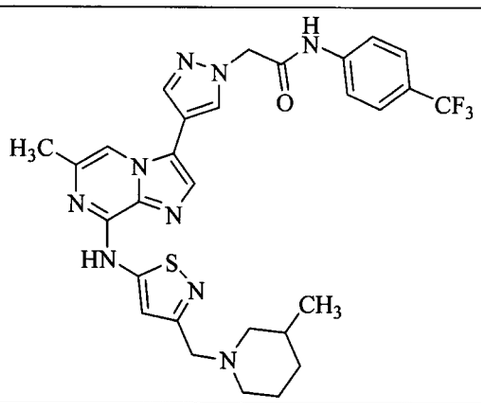
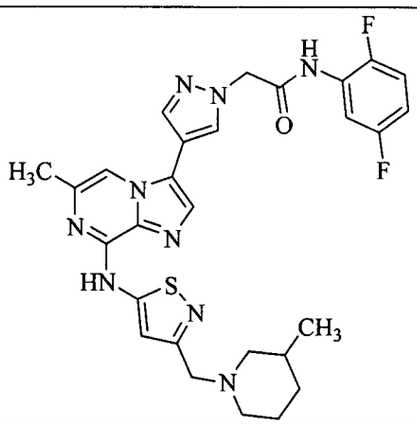
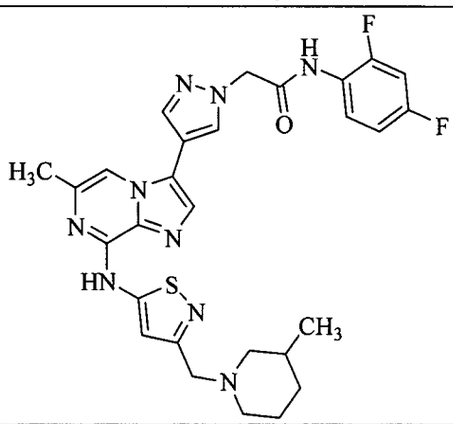
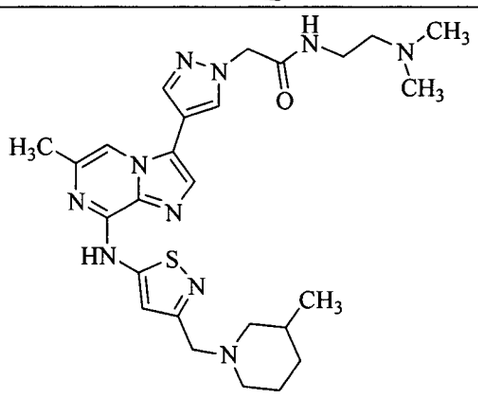
6–39		521,2	522,9	3,73
6–40		495,2	496,9	3,42
6–41		600,2	601,7	4,91
6–42		600,2	601,6	4,90

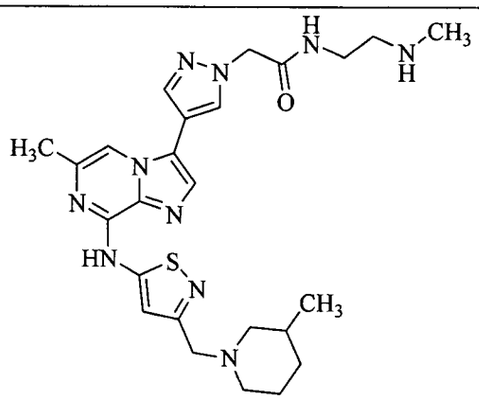
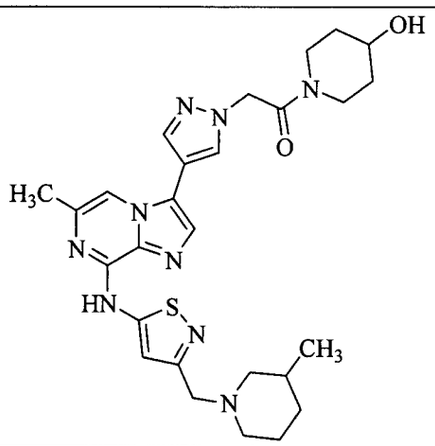
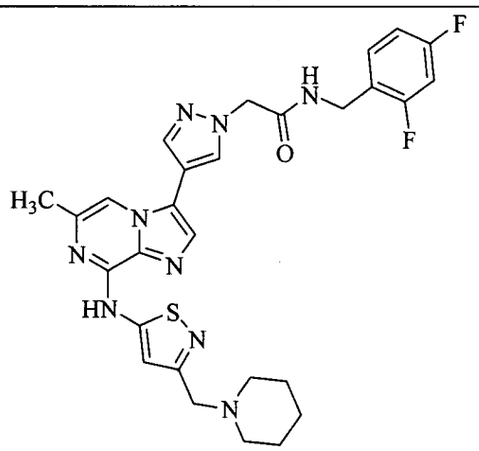
6–43		600,2	601,6	4,90
6–44		607,2	608,5	5,12
6–45		607,2	608,4	5,23

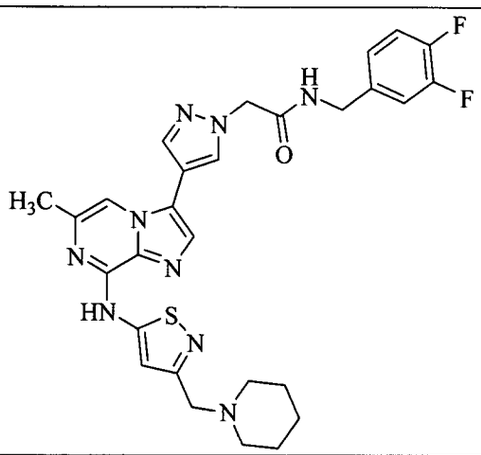
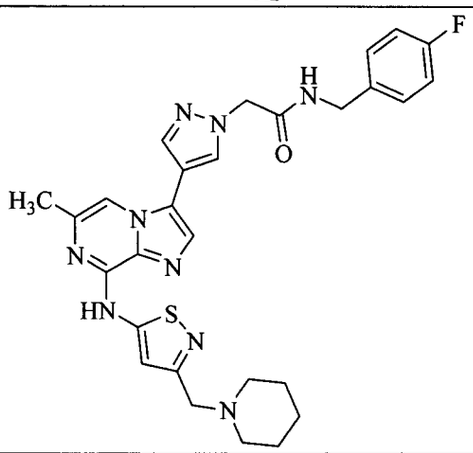
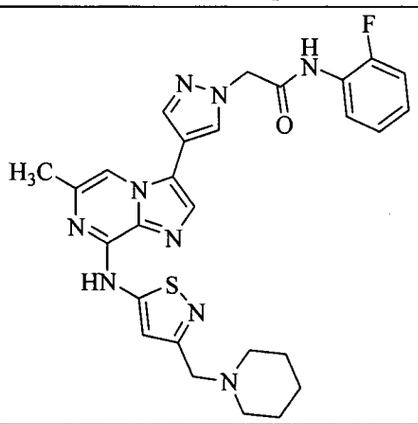
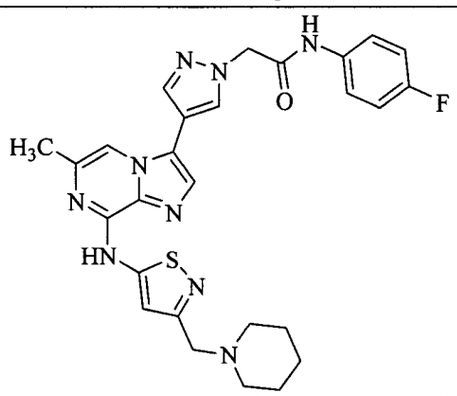
6–46		607,2	609,4	5,23
6–47		607,2	609,4	5,27
6–48		589,2	591,8	5,15

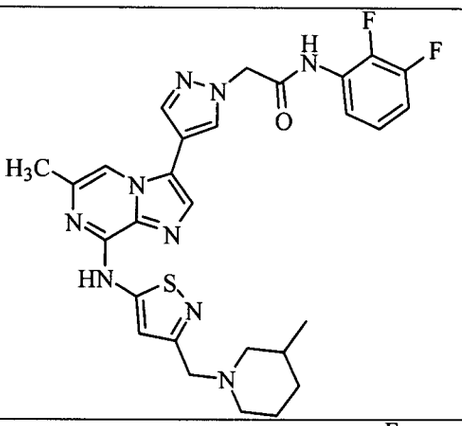
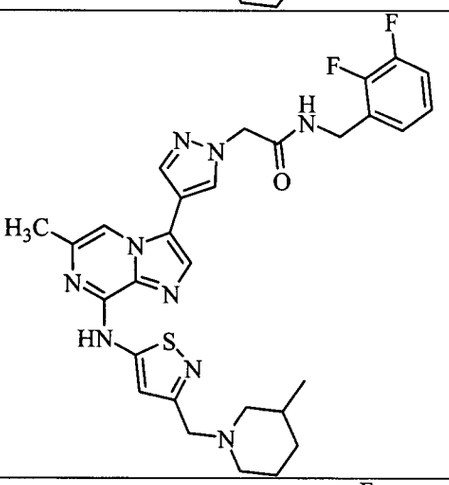
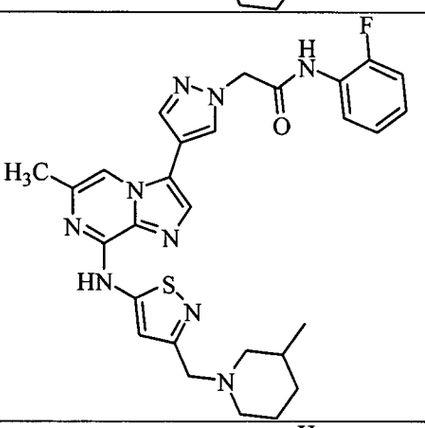
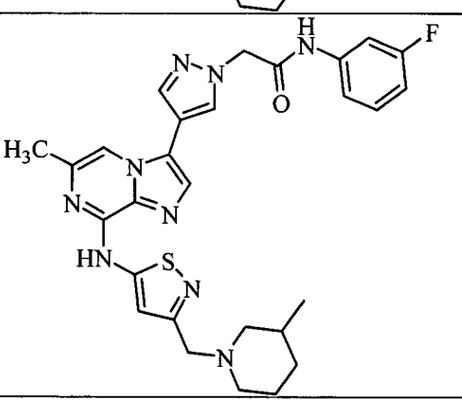
6–49		589,2	591,8	5,16
6–50		589,2	591,8	5,17
6–51		569,3	570,7	5,01

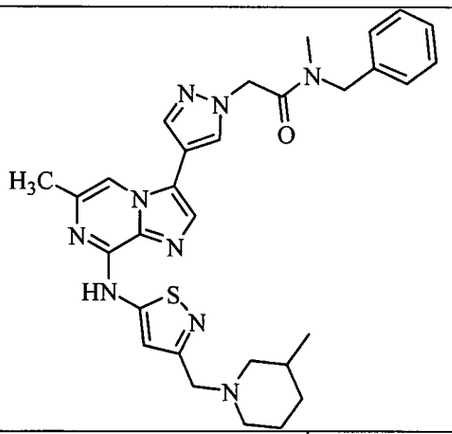
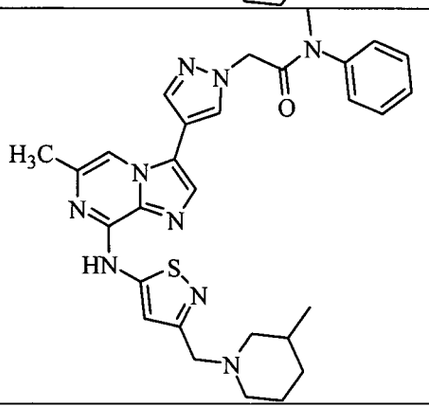
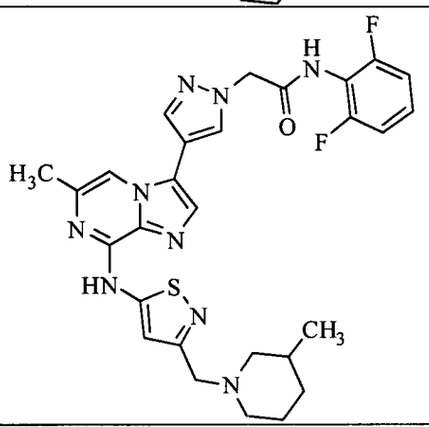
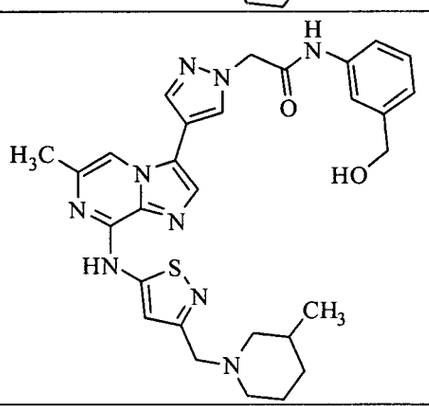
6–52		569,3	570,7	4,99
6–53		555,3	556,3	4,82
6–54		609,6	610,4	5,54

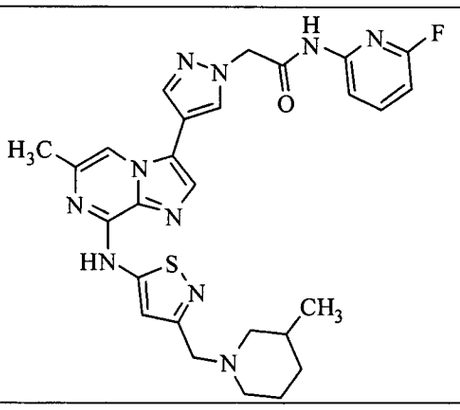
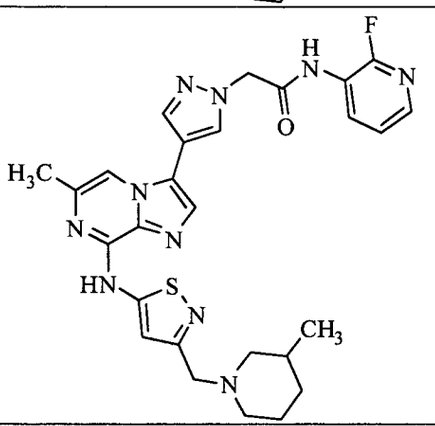
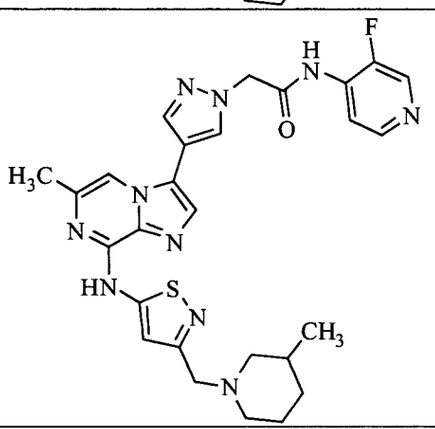
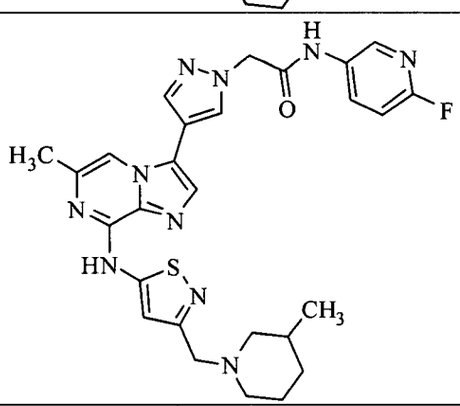
6–55		609,6	610,6	5,59
6–56		577,6	578,8	5,17
6–57		577,6	578,9	5,03
6–58		536,7	537,7	3,45

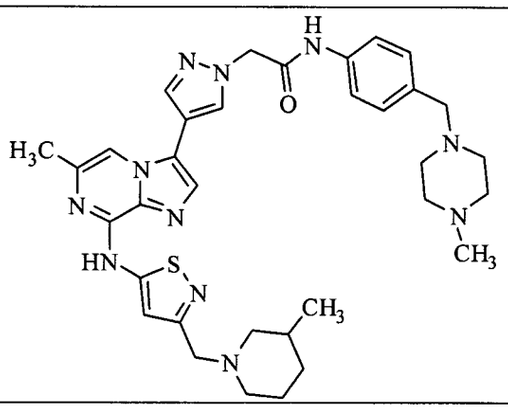
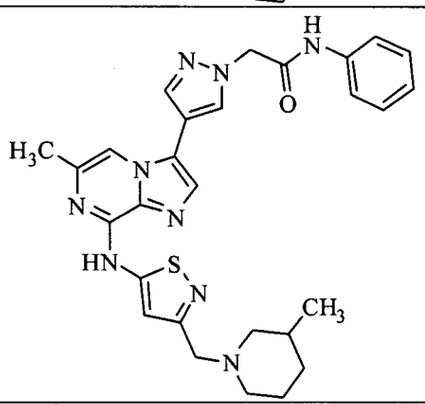
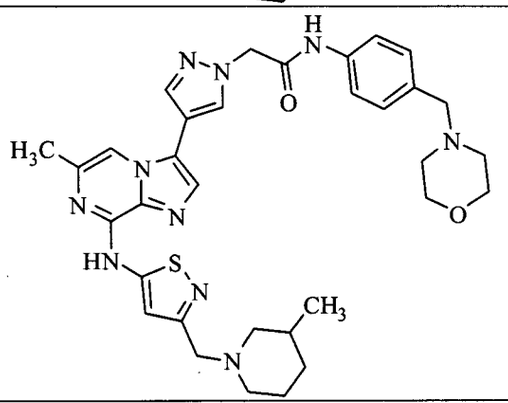
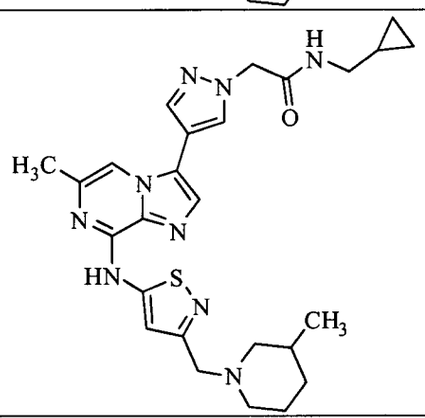
6–59		522,6	523,9	3,43
6–60		549,6	550,7	3,76
6–61		577,22	578,9	5,20

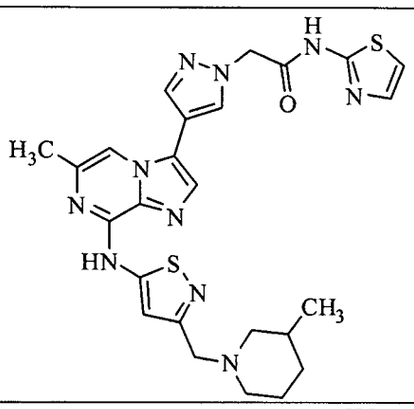
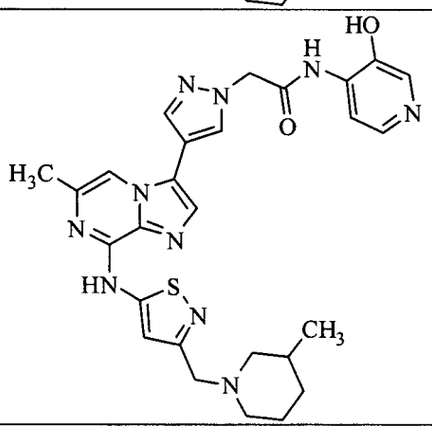
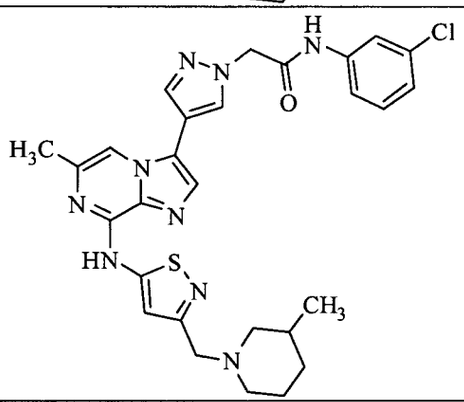
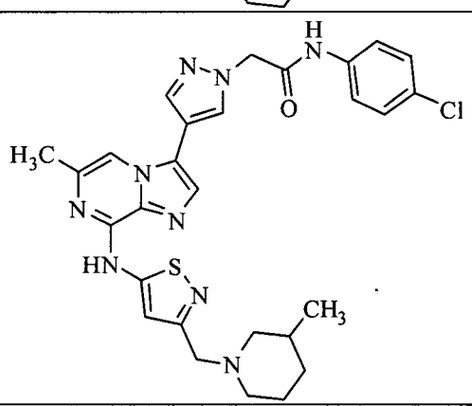
6–62		577,22	578,9	5,25
6–63		559,23	560,2	5,12
6–64		545,21	546,5	5,17
6–65		545,21	546,4	5,21

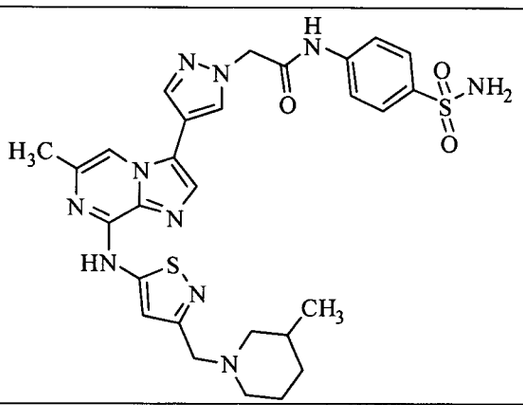
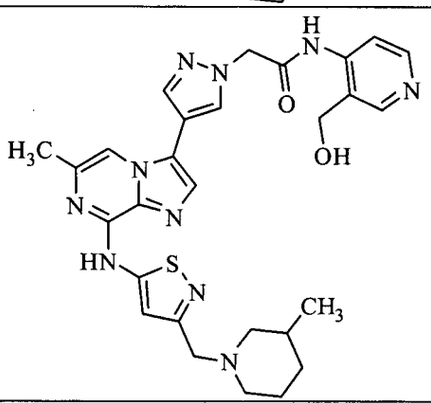
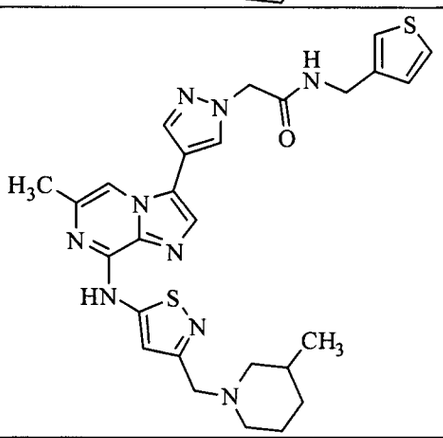
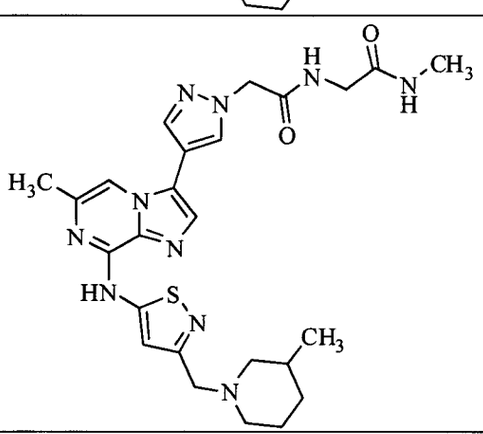
6–66		577,6	578,9	5,14
6–67		591,6	592,8	5,03
6–68		559,6	560,4	5,00
6–69		559,6	560,4	5,11

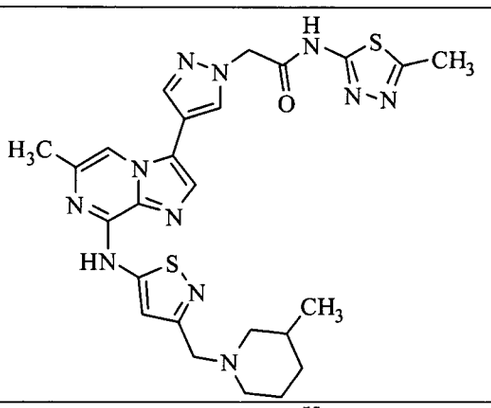
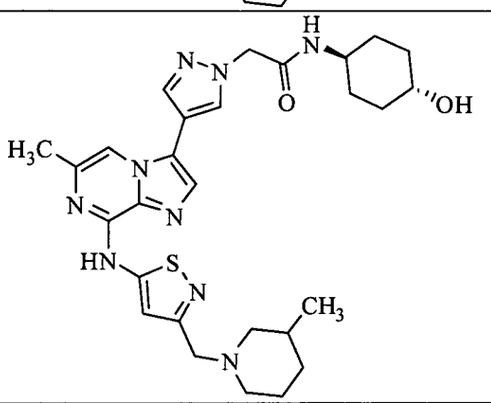
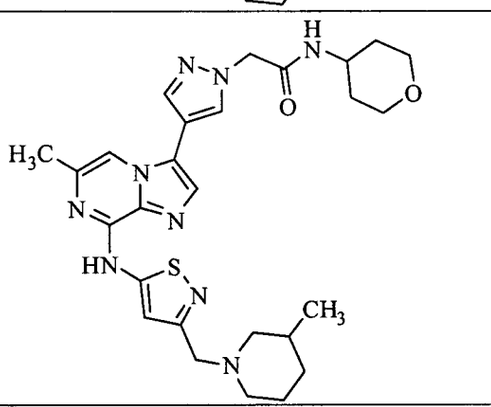
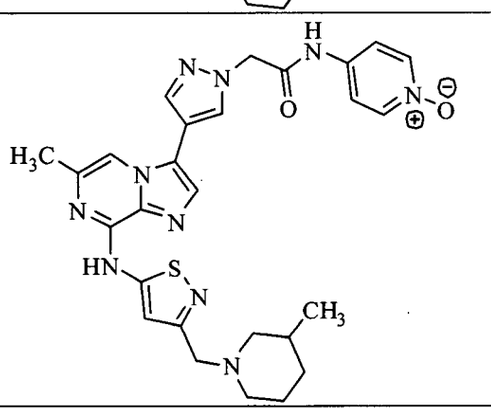
6–70		569,7	570,6	5,05
6–71		555,6	556,4	4,96
6–72		577,6	578,3	4,85
6–73		571,6	572,4	4,33

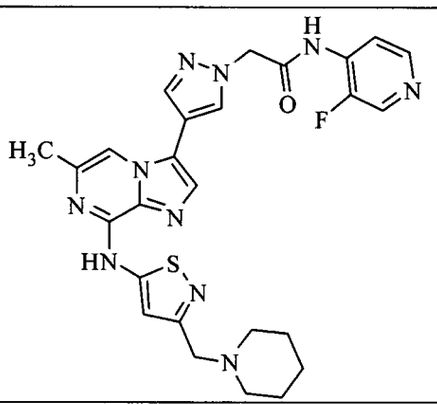
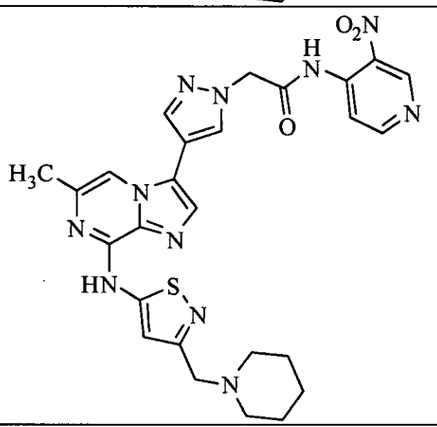
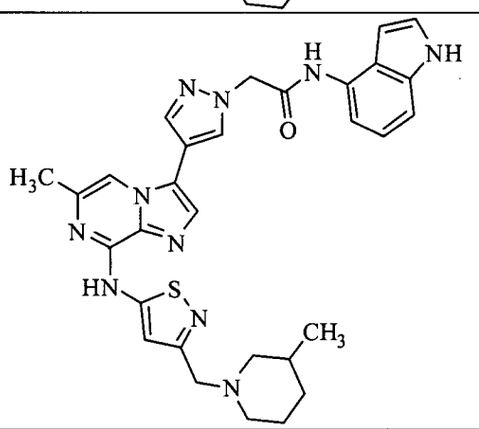
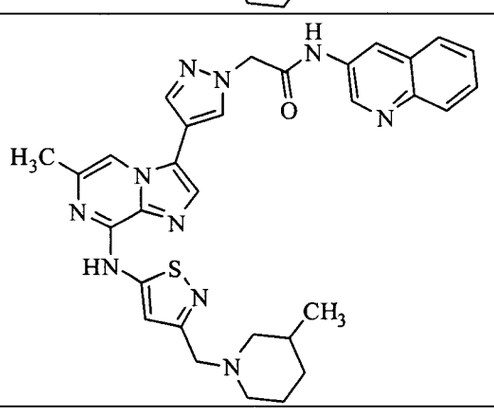
6–74		560,6	561,3	4,92
6–75		560,6	561,2	4,52
6–76		560,6	561,2	3,75
6–77		560,6	561,3	4,53

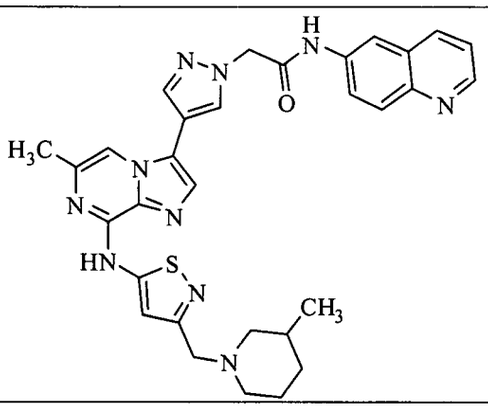
6–78		653,8	654,8	3,63
6–79		541,6	542,6	4,91
6–80		640,8	641,6	3,84
6–81		519,6	520,4	4,42

6–82		548,6	549,6	4,44
6–83		558,6	559,4	3,79
6–84		576,1	576,8	5,41
6–85		576,1	576,8	5,37

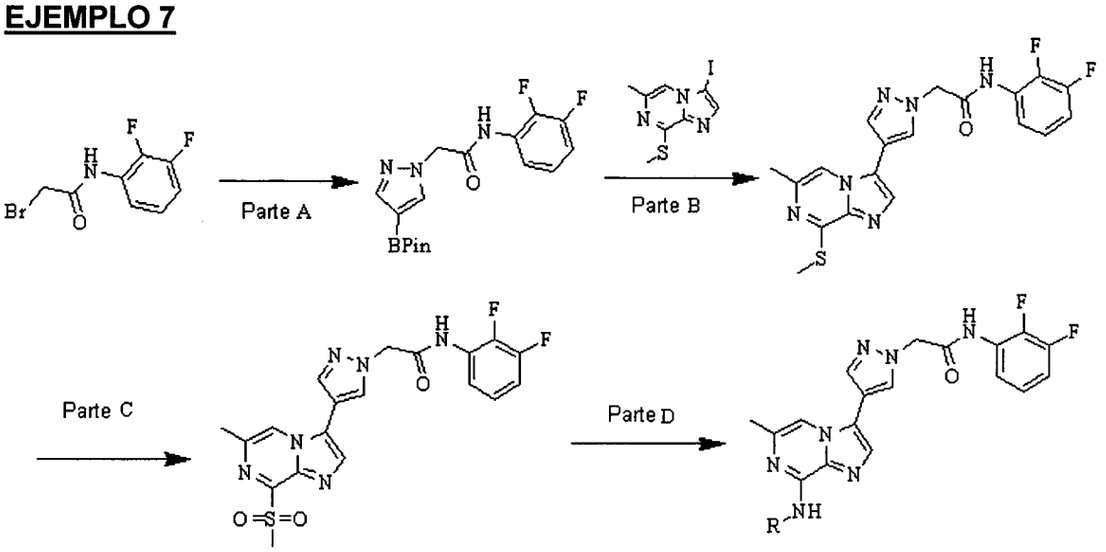
6–86		620,7	621,7	4,28
6–87		572,6	573,3	3,77
6–88		561,7	562,3	4,71
6–89		536,6	537,6	3,69

6–90		563,7	564,9	4,24
6–91		563,7	564,8	3,89
6–92		549,6	550,8	3,98
6–93		558,6	559,5	3,72

6–94		546,6	547,7	3,52
6–95		573,6	574,5	4,47
6–96		566,6	567,7	4,63
6–97		592,7	593,9	4,16

6–98		592,7	593,9	3,84

EJEMPLO 7



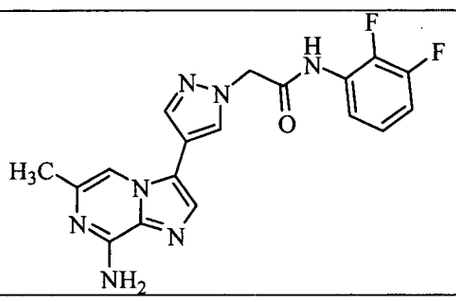
Parte A: A una solución de 4–(4,4,5,5–Tetrametil–1,3,2–dioxaborolan–2–il)–1H–pirazol (2,2 g, 11,32) y bromuro (2,83 g, 11,32 mmol) en DMA (5 mL) se añadió carbonato de potasio (1,9 g, 13,6 mmol). La mezcla se calentó a 60 ºC durante 20 h. A la mezcla de reacción se añadió cloruro de amonio semisaturado y acetato de etilo. La fase orgánica se lavó con agua (2x), salmuera y se secó (sulfato de sodio). La concentración y la purificación por cromatografía (50% acetato de etilo en hexanos) dio el compuesto del título en forma de un sólido de color amarillo pálido. (2,1 g, 51%). ^{1}H RMN (300 MHz, DMSO–d6) δ 10,3 (1H, br s), 7,95 (1H, s), 7,7–7,6 (1H, app t), 7,59 (1H, s), 7,1–7,2 (1H, m), 5,12 (s, 2H), 1,23 (s, 12H).

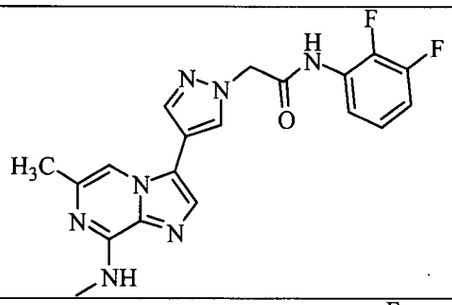
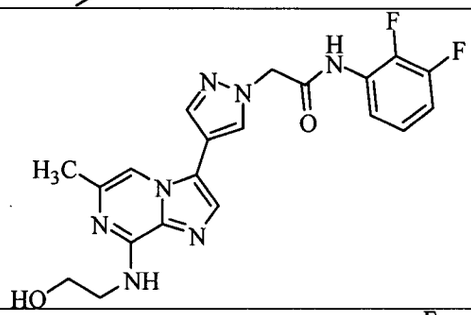
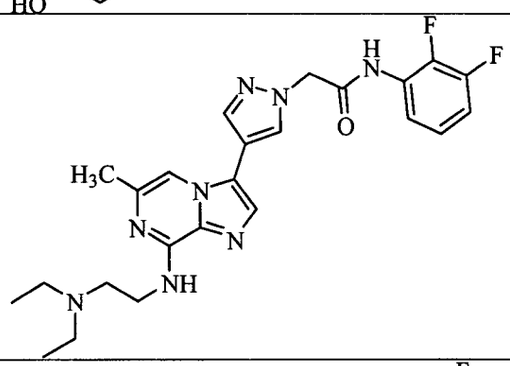
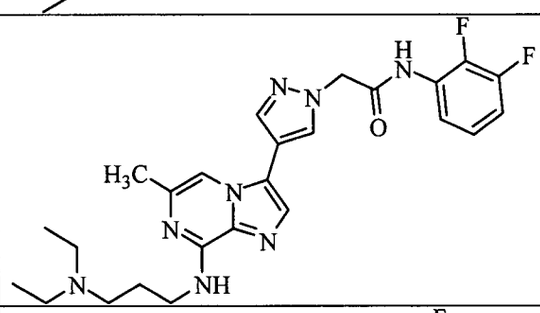
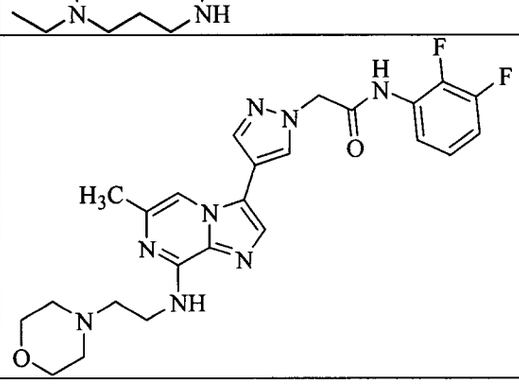
Parte B: Una mezcla de Ejemplo 1, Parte D (1,49 g), boronato del Ejemplo 7, Parte A (2,13 g), PdCl2(dppf) (0,398 g), fosfato de potasio (2,07 g), en DME (45 mL) y agua (5 mL) se calentó a 95 °C durante la noche. La reacción se dejó enfriar, se diluyó con acetato de etilo y se filtró a través de Celite. El filtrado se lavó con agua, salmuera y se secó (sulfato de sodio). La cromatografía dio el compuesto del título.

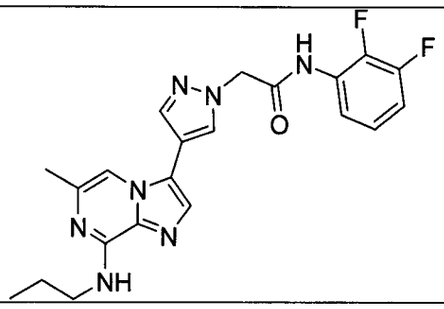
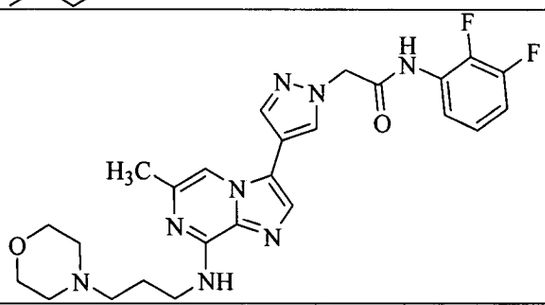
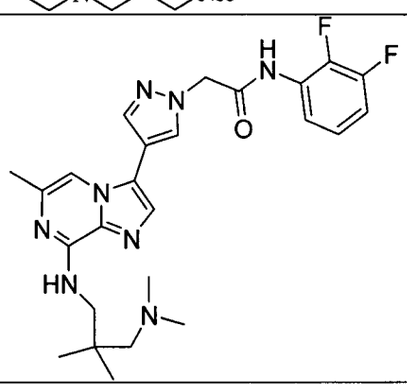
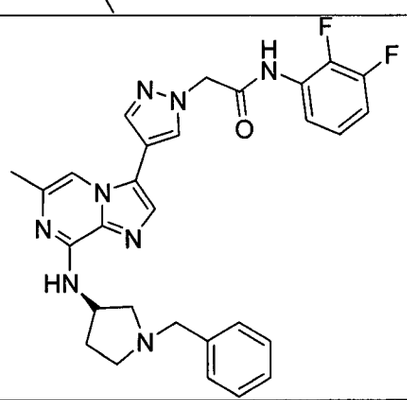
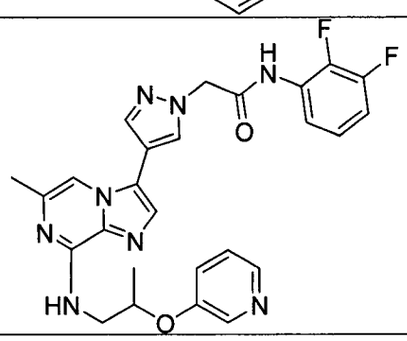
Parte C: Una solución del compuesto del Ejemplo 7, Parte B (260 mg) en THF (25 mL) a temperatura ambiente se añadió MCPBA (288 mg) en una porción. Después de 1 h a temperatura ambiente, se añadió acetato de etilo y se lavó con bicarbonato de sodio saturado (2x), salmuera y se secó (sulfato de sodio). La concentración dio el compuesto del título que se usó sin ulterior purificación.

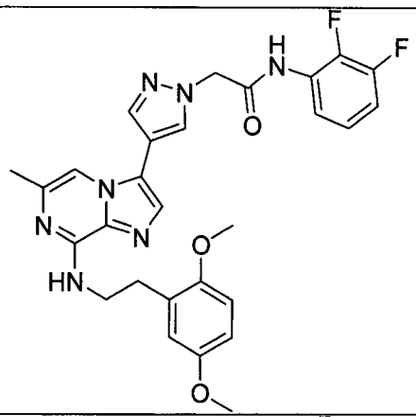
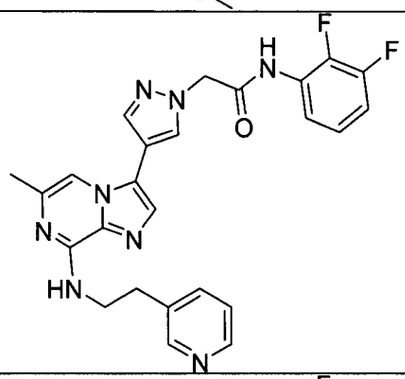
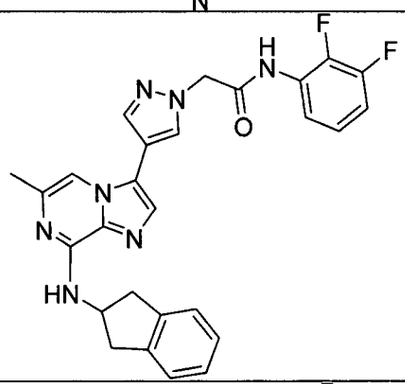
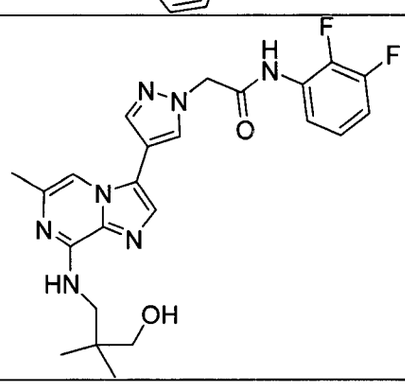
Parte D: Una solución del compuesto del Ejemplo 7, Parte C (1 equiv), amina (5 equiv), DIEA (5 equiv) en NMP se calentó a 50 °C durante la noche. La mezcla de reacción se concentró y se purificó por LC preparativa. Usando este procedimiento general, se prepararon los compuestos enumerados en la Tabla 2 (mostrada inmediatamente a continuación).

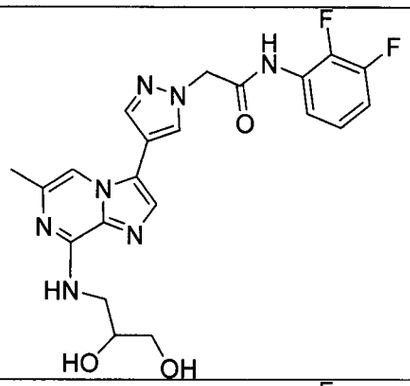
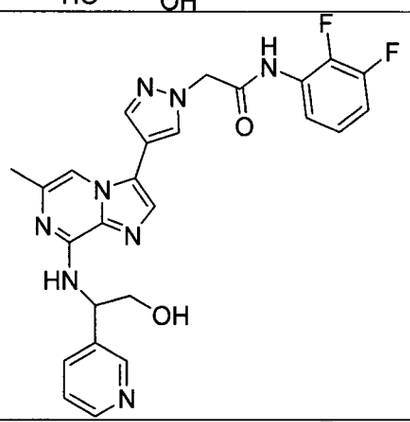
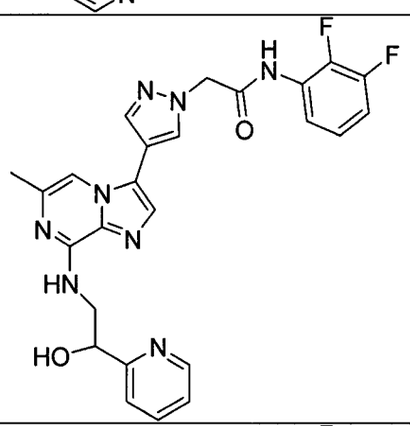
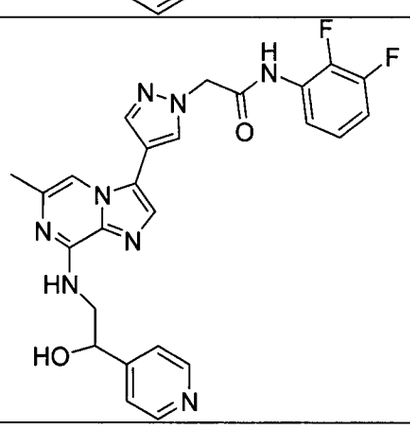
Tabla 2

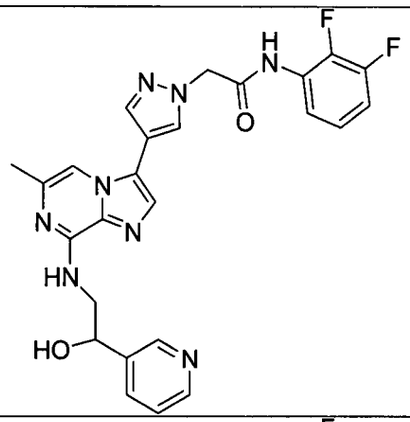
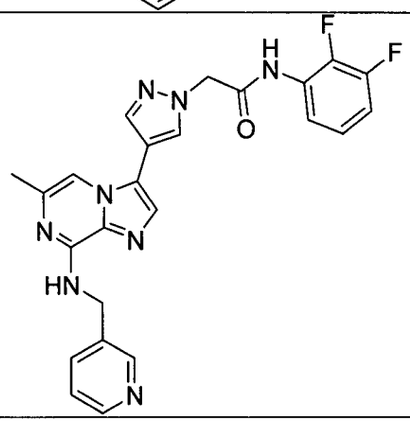
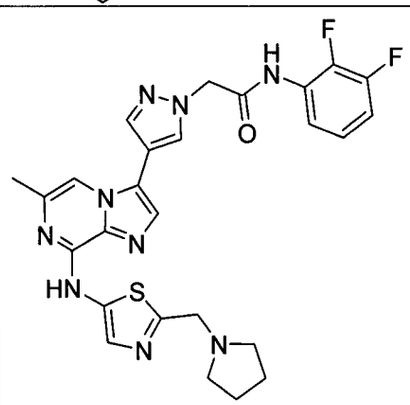
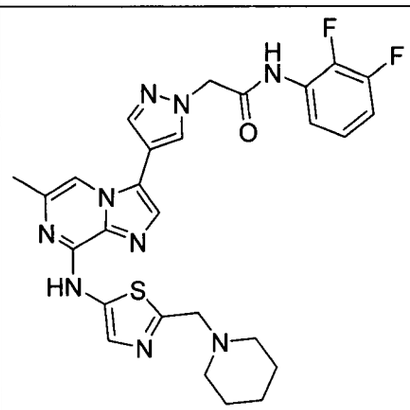
Ejemplo	columna 2	PM	MS MH^+ m/z	HPLC t_R
7–1		383,35	384,1	3,01

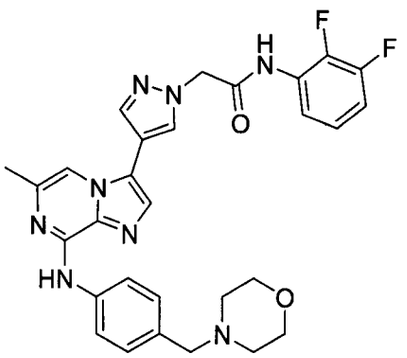
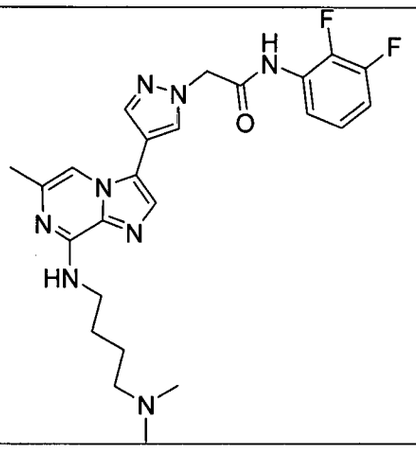
7–2		397,38	398,2	2,59
7–3		427,4	428,2	2,57
7–4		482,53	483,3	2,90
7–5		496,56	497,3	2,83
7–6		496,51	497,2	3,02

7–7		425,43	426,1	3,00
7–8		510,54	511,1	2,38
7–9		496,56	497,2	2,71
7–10		542,58	543,2	3,22
7–11		518,52	519,2	2,39

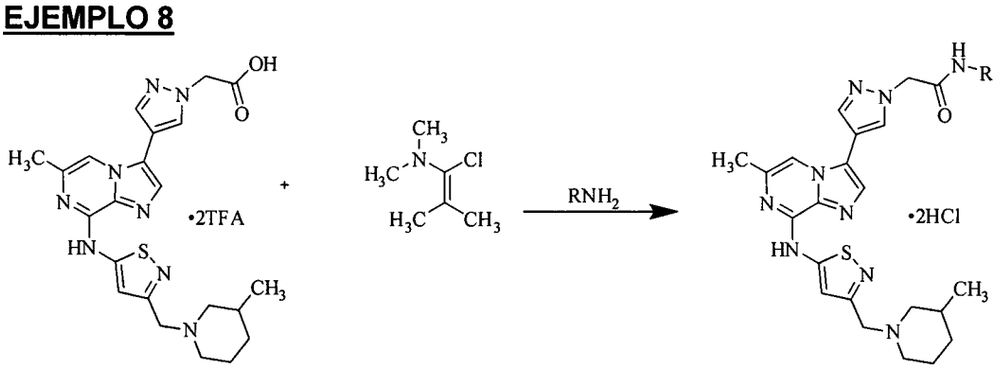
7–12		547,56	548,2	4,29
7–13		488,49	489,1	2,44
7–14		499,51	500,2	3,36
7–15		469,49	470,2	3,09

7–16		457,43	458,2	2,95
7–17		504,49	505,2	2,31
7–18		504,49	505,1	2,60
7–19		504,49	505,1	2,37

7–20		504,49	505,1	2,15
7–21		474,47	475,1	2,56
7–22		549,2	550,2	3,12
7–23		563,2	564,2	3,21

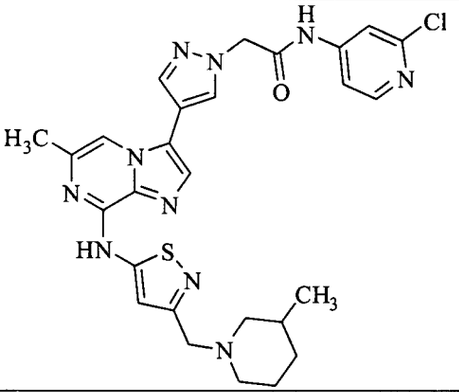
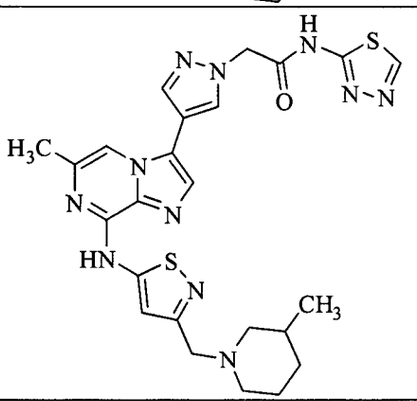
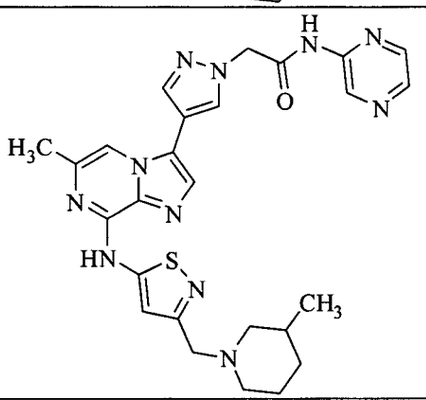
7–24		558,2	559,2	1,42
7–25		482,53	483,3	2,36

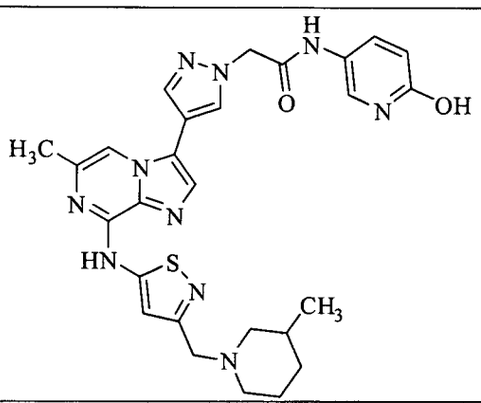
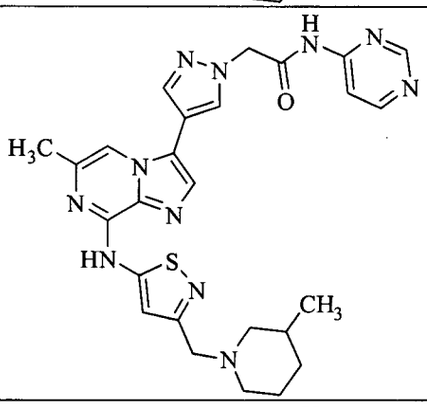
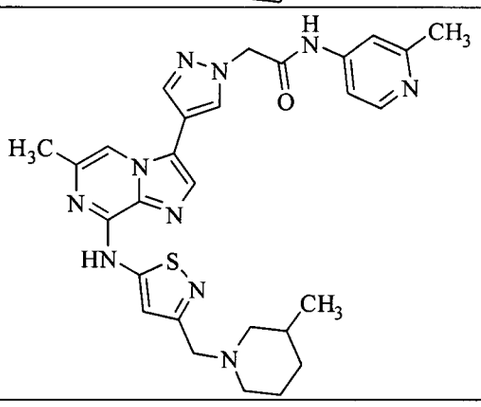
EJEMPLO 8



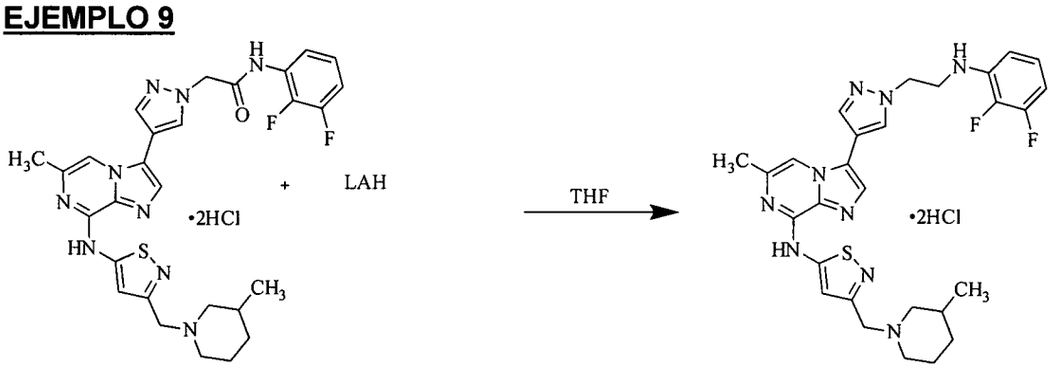
A una suspensión agitada de ácido carboxílico (1 equiv) en diclorometano a 0 °C se añadió 1–cloro–N,N–2–trimetil–1–propenilamina (5 equiv). Después de agitar durante 1 hora, se añadió la amina como una solución en diclorometano o piridina. Cuando la reacción pareció completa por el análisis de HPLC, la mezcla se concentró a presión reducida. La purificación por HPLC preparativa y la conversión en la sal de clorhidrato dio los compuestos enumerados en la Tabla 3 (mostrada inmediatamente a continuación).

Tabla 3

Ejemplo	columna 2	PM	MS MH^+ m/z	HPLC t_R
8–1		577,1	587,0	4,64
8–2		549,6	550,9	4,11
8–3		543,6	544,6	4,15

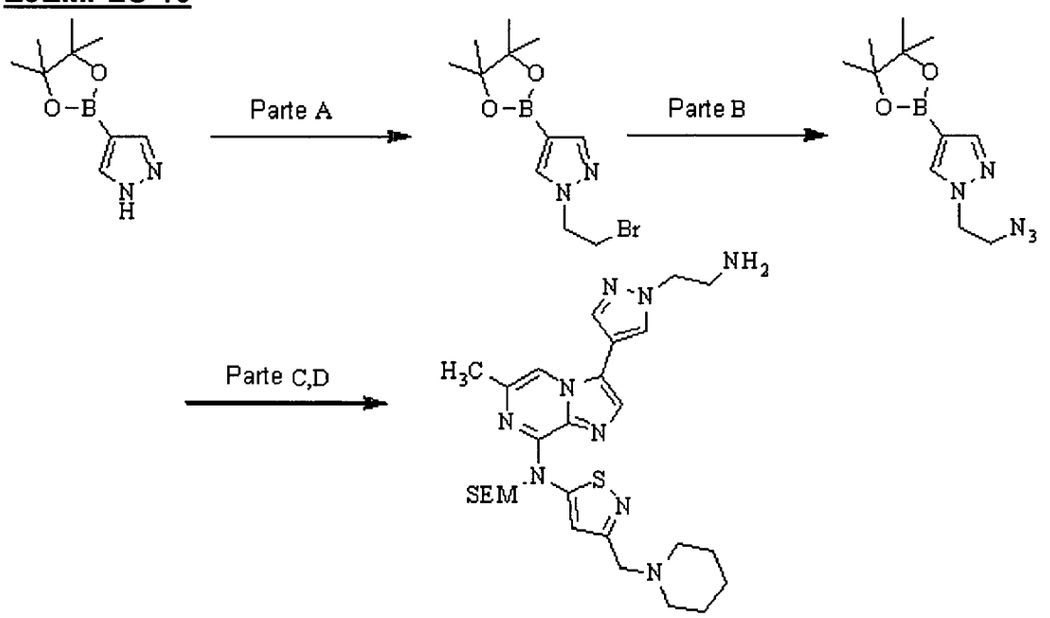
8–4		558,6	559,4	3,73
8–5		543,6	544,5	6,99
8–6		556,6	557,3	3,73

EJEMPLO 9



Se añadió hidruro de litio y aluminio (2 mg, 2,2 equiv) a una suspensión agitada de amida (14 mg, 1 equiv) en THF (1 mL) a temperatura ambiente. El análisis de HPLC después de 15 minutos no mostró material de partida, de modo que la reacción se neutralizó con metanol, se concentró a presión reducida, se purificó por HPLC preparativa y la conversión en la sal de clorhidrato dio el compuesto del título en forma de un sólido blanco 6,5 mg (47%)). ^{1}H RMN (300 MHz, DMSO–d_6) δ 12,3 (s, 1H), 10,1 (bs, 1H), 8,41 (s, 1H), 8,03 (s, 1H), 7,89 (m, 2H), 7,30 (s, 1H), 6,97 (m, 1H), 6,55 (m, 2H), 4,39 (m, 4H), 3,67 (m, 2H), 3,39 (m, 2H), 2,80 (m, 2H), 2,48 (s, 3H), 1,79 (m, 4H), 1,05 (m, 1H), 0,89 (m, 3H). HPLC t_R = 5,58 min (UV $_{254nm}$). Masa calculada para la fórmula $C_{28}H_{31}F_2N_9S$ 563,24; MH^+ observada (ESI MS) 564,8 (m/z).

EJEMPLO 10



Parte A: Se añadió hidróxido de potasio (1,45 g, 10,0 equiv) a una solución agitada de 4–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)–1H–pirazol (500 mg, 1,00 equiv) en DMSO (5 mL) a temperatura ambiente. Después de agitar durante 1 hora, se añadió 1,2–dibromoetano (9,69 g, 20,0 equiv). La reacción se agitó durante 16 horas en cuyo momento la TLC indicó que no quedaba más material

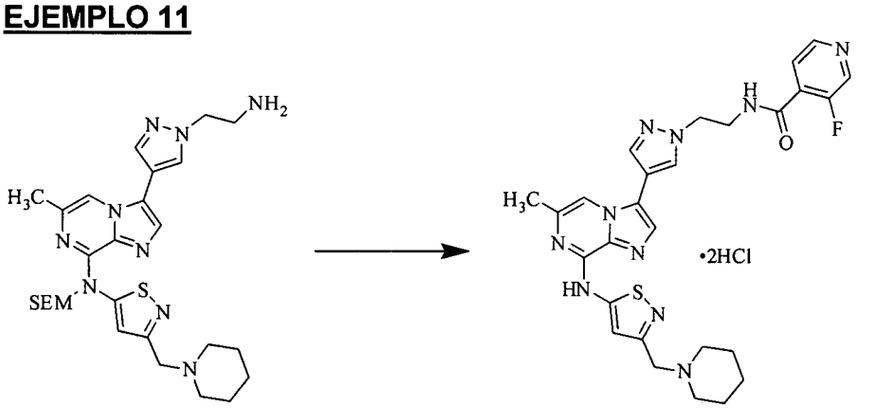
de partida, de modo que la reacción se neutralizó con agua (10 mL) y se extrajo con acetato de etilo (3 x 15 mL). Las sustancias orgánicas combinadas se lavaron con salmuera (20 mL), se secaron sobre sulfato de sodio, se filtraron, se concentraron a presión reducida y la purificación por cromatografía en gel de sílice (12 g de SiO_2, diclorometano a 5% de metanol en diclorometano) dio el boronato deseado en forma de un aceite amarillo 350 mg (45%).

Parte B: Una mezcla del boronato del Ejemplo 10 parte A (250 mg, 1,00 equiv), azida de sodio (108 mg, 2,00 equiv) y yoduro de sodio (124 mg, 1,00 equiv) en DMSO (2 mL) se agitó a 50 °C durante 2 horas en cuyo momento la TLC indicó que no quedaba más material de partida. La reacción se dejó enfriar hasta temperatura ambiente, luego se neutralizó con agua (8 mL) y se extrajo con acetato de etilo (3 x 15 mL). Las sustancias orgánicas combinadas se lavaron con salmuera (15 mL), se secaron sobre sulfato de sodio, se filtraron, se concentraron a presión reducida y la purificación por cromatografía en gel de sílice (12 g de SiO_2, diclorometano a 5% de metanol en diclorometano) dio el boronato deseado en forma de un sólido amarillo 170 mg (78%).

Parte C: A una mezcla de yoduro de arilo de la Parte B (315 mg, 1,00 equiv), $PdCl_2$(dppf) (39 mg, 0,10 equiv) y fosfato de potasio (228 mg, 2,00 equiv) bajo nitrógeno se añadió una solución del boronato de la Parte B (170 mg, 1,20 equiv) en 1,4–dioxano (1,5 mL), seguido de agua (0,15 mL). La mezcla se agitó a 90 °C durante 17 horas en cuyo momento la TLC indicó que no quedaba más material de partida. La reacción se dejó enfriar hasta temperatura ambiente, luego se diluyó con acetato de etilo (8 mL) y se lavó con salmuera (10 mL), se secó sobre sulfato de sodio, se filtró, se concentró a presión reducida y la purificación por cromatografía en gel de sílice (12 g de SiO_2, diclorometano a 5% de metanol en diclorometano) dio la azida deseada en forma de un sólido marrón 125 mg (39%).

Parte D: A una solución agitada de azida de la Parte C (125 mg, 1,00 equiv) en 1,4–dioxano (2 mL) y agua (0,2 mL) se añadió trifenilfosfina unida a poliestireno (84 mg, 1,20 equiv). La reacción se agitó a temperatura ambiente durante 3 días en cuyo momento la TLC indicó que no quedaba más material de partida. La mezcla se filtró, el licor madre se concentró a presión reducida y el residuo resultante se purificó por cromatografía en gel de sílice (12 g SiO_2, diclorometano a 10% de metanol en diclorometano) que dio como resultado la amina deseada en forma de un aceite marrón 77 mg (64%).

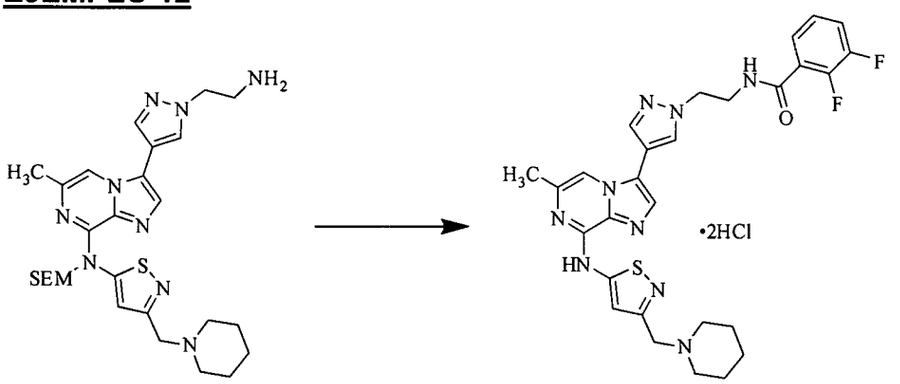
EJEMPLO 11



Se añadió N–metilmorfolina (14 mg, 2,00 equiv) a una mezcla agitada de carboxílico (14 mg, 1,50 equiv) y HATU (39 mg, 1,50 equiv) en DMF (0,5 mL). Después de 30 minutos, la amina del Ejemplo 10 (38,5 mg, 1,00 equiv) se añadió en forma de una solución en DMF (0,5 mL). La mezcla se agitó durante 5 horas en cuyo momento la HPLC indicó que no quedaba más material de partida. La mezcla se concentró y el residuo se disolvió en 1,4–dioxano (1 mL). Una solución en HCl en dioxano (1 mL, 4 M en dioxano) se añadió y la mezcla se sonicó durante 1,5 horas en cuyo momento la HPLC indicó que no quedaba más material de partida. La mezcla se concentró a presión reducida, se purificó por HPLC preparativa y la conversión en la sal de HCl dio el compuesto deseado en forma de un sólido amarillo 6 mg (14%). ^{1}H RMN (300 MHz, CD_3OD) δ 8,90 (m, 1H),

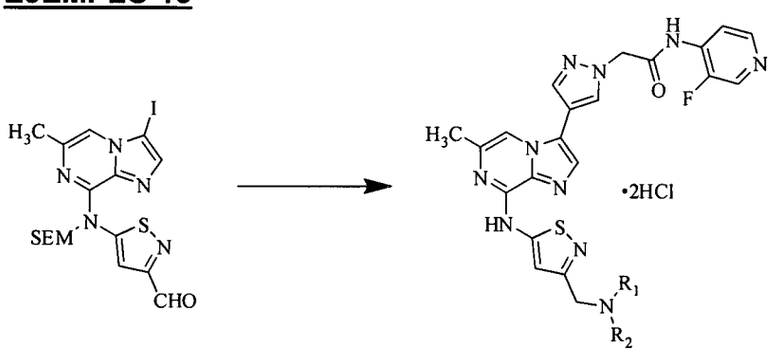
8,72 (m, 1H), 8,36 (s, 1H), 8,24 (s, 1H), 8,01(m, 3H), 7,32 (s, 1H), 4,58 (m, 2H), 4,42 (s, 2H), 3,94 (m, 2H), 3,60 (m, 2H), 3,09 (m, 2H), 2,61 (s, 3H), 1,81 (m, 6H), 1,55 (m, 2H). HPLC t_R = 3,97 min (UV $_{254nm}$). Masa calculada para la fórmula $C_{27}H_{29}FN_{10}OS$ 560,22; MH^+ observada (ESI MS) 561,3 (m/z).

EJEMPLO 12



A una solución agitada de amina del Ejemplo 10 (38,5 mg, 1,00 equiv) y trietilamina (14 mg, 2,00 equiv) en diclorometano (0,75 mL) se añadió cloruro de 2,3–difluorobenzoílo (13 mg, 1,10 equiv) gota a gota. El análisis de HPLC después de 4 horas no mostró material de partida, de modo que la reacción se neutralizó con bicarbonato de sodio acuoso saturado (2 mL) y luego se extrajo con diclorometano (3 x 1mL). Las sustancias orgánicas combinadas se concentraron y el residuo resultante se disolvió en 1,4–dioxano (1 mL) y se añadió una solución en HCl en dioxano (1 mL, 4 M en dioxano) y la mezcla se sonicó durante 1,5 horas en cuyo momento la HPLC indicó que no quedaba más material de partida. La mezcla se concentró a presión reducida, se purificó por HPLC preparativa y la conversión en la sal de HCl dio el compuesto deseado en forma de un sólido amarillo 5 mg (11%). ^{1}H RMN (300 MHz, CD_3OD) δ 8,34 (s, 1H), 8,21 (s, 1H), 8,06 (s, 1H), 7,92 (s, 1H), 7,44 (m, 2H), 7,36 (2, 1H), 7,20 (m, 1H), 4,56 (m, 2H), 4,41 (s, 2H), 3,92 (m, 2H), 3,59 (m, 2H), 3,08 (m, 2H), 2,59 (s, 3H), 1,78 (m, 6H). HPLC t_R = 4,61 min (UV $_{254nm}$). Masa calculada para formula $C_{28}H_{29}F_2N_9OS$ 577,22; MH^+ observada (ESI MS) 578,8 (m/z).

EJEMPLO 13

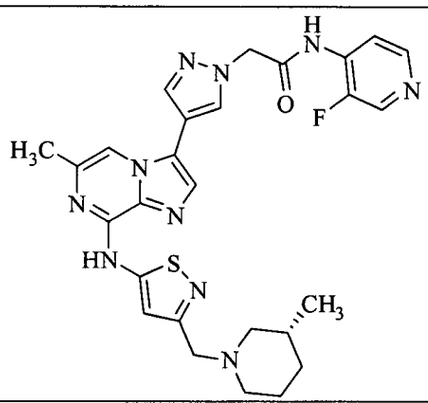
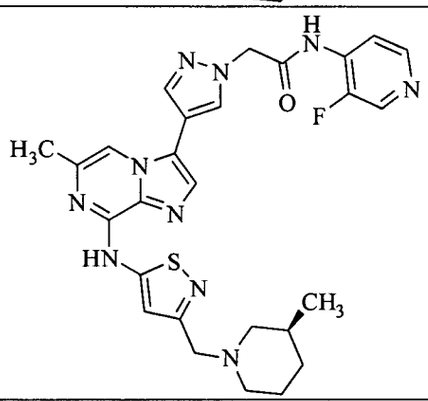
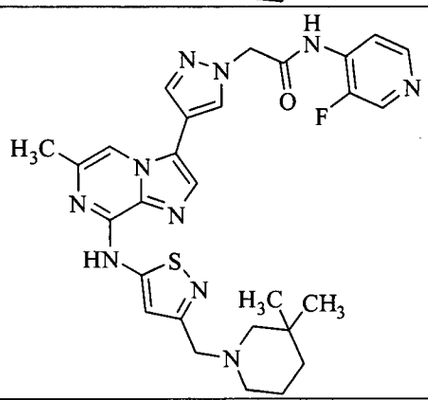
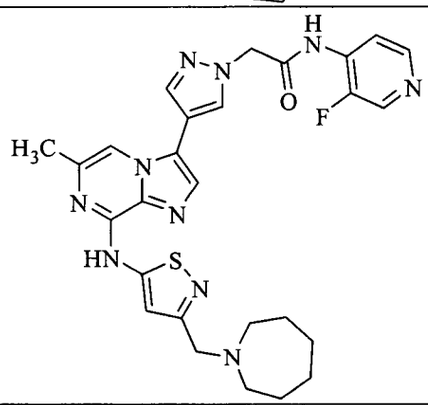


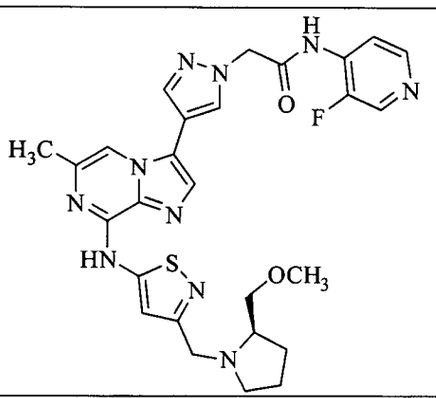
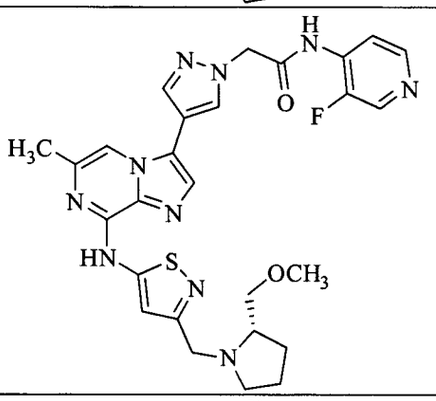
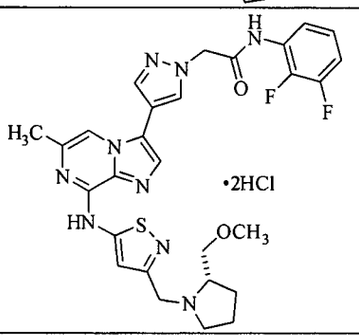
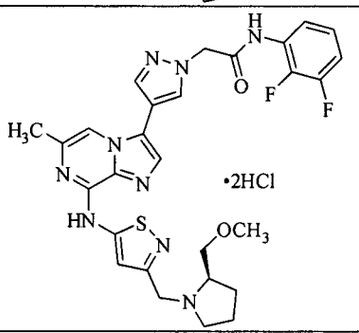
Se añadió triacetoxiborhidruro de sodio (1,50 equiv) a una mezcla agitada de aldehído (1,00 equiv), amina (1,20 equiv) y ácido acético (1,00 equiv) en 1,2–dicloroetano a temperatura ambiente. La mezcla se agitó hasta que no quedó más material de partida tal como se juzgó por TLC. La reacción luego se neutralizó con NaOH 1 N y se extrajo tres veces con cloroformo. Las sustancias orgánicas combinadas se secaron sobre sulfato de sodio, se filtraron y se concentraron. El residuo luego se añadió como una solución en dioxano (1 equiv) a una mezcla de boronato (1,50 equiv), $PdCl_2$(dppf) (0,10 equiv) y fosfato de potasio (2,00 equiv) bajo nitrógeno. Se añadió agua y la mezcla se agitó a 90 °C durante 17 horas en cuyo momento la HPLC indicó que no quedaba más material de partida. La reacción se dejó enfriar hasta temperatura ambiente, se diluyó con acetato de etilo, se lavó con agua, se secó sobre sulfato de sodio, se filtró, se concentró a presión reducida y la purificación por cromatografía en gel de sílice dio el producto acoplado. Este material se disolvió en 1,4–dioxano, se añadió HCl (4 N en dioxano) y la mezcla se sonicó hasta el momento en que la HPLC indicó que no quedaba más material de partida. La mezcla se concentró a presión reducida, se purificó por HPLC preparativa y la conversión en la sal de clorhidrato dio los compuestos del título como sólidos blancos en la Tabla 4 (mostrada inmediatamente a continuación):

Tabla 4

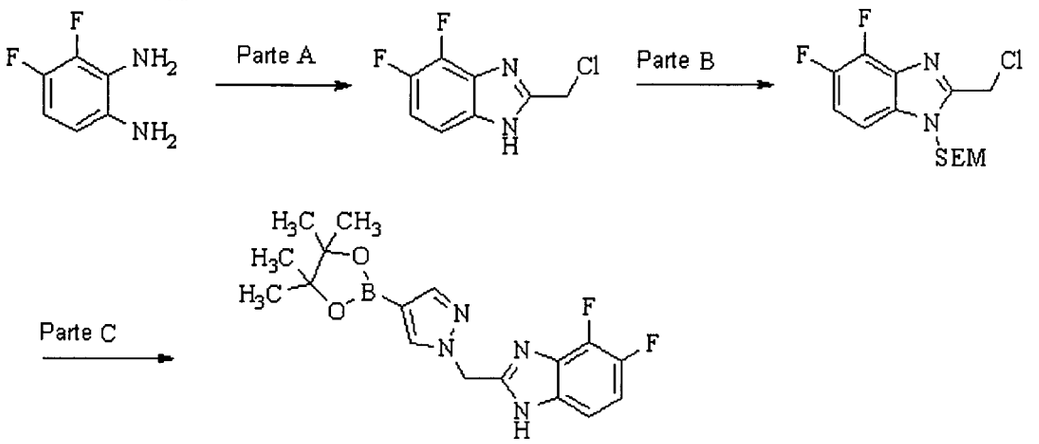
Ejemplo	Columna 2	PM	MS	HPLC

1003

			MH^+ m/z	t_R
13–1		560,6	561,4	3,75
13–2		560,6	561,3	3,78
13–3		574,6	575,6	3,97
13–4		560,6	561,4	3,76

13–5		576,6	578,2	3,63
13–6		576,6	578,2	3,62
13–7		593,7	594,7	5,13
13–8		593,7	594,7	5,15

EJEMPLO 14

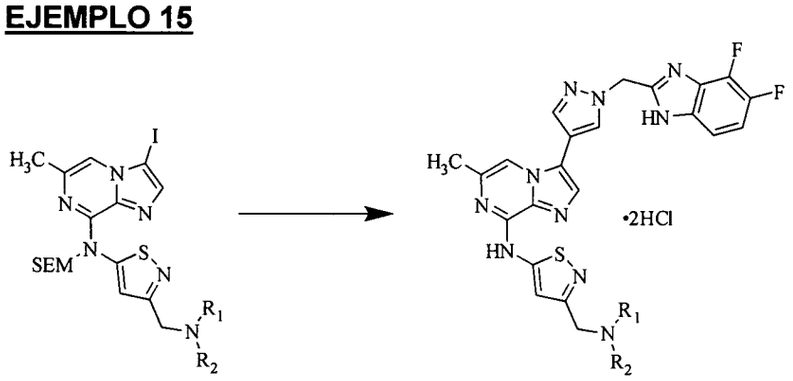


Parte A: Se añadió ácido cloroacético (5,11 g, 1,3 equiv) a una solución agitada de 2–amino–3,4–difluoroanilina (6,00 g, 1 equiv) en ácido clorhídrico 6 N (28 mL). Después de agitar durante 18 horas a 95 °C, la reacción se enfrió hasta temperatura ambiente, se alcalinizó con carbonato de potasio acuoso al 10% y se extrajo con acetato de etilo (850 mL). La capa orgánica se separó, se secó sobre sulfato de sodio, se filtró, se concentró a presión reducida y la purificación por cromatografía en gel de sílice (120 g SiO_2, hexanos a 60% de acetato de etilo en hexanos) dio el bencimidazol deseado en forma de un sólido rosado 6,24 g (74%).

Parte B: Una mezcla del bencimidazol del Ejemplo 14 parte A (4,18 g, 1,00 equiv), carbonato de potasio (8,53 g, 3,00 equiv) en DMF (50 mL) se agitó a temperatura ambiente durante 5 minutos en cuyo momento se añadió cloruro de 2–(trimetilsilil)etoximetilo (4,0 mL, 1,1 equiv). Después de agitar a temperatura ambiente durante 18 horas, la reacción se neutralizó con una solución acuosa saturada de bicarbonato de sodio (40 mL) y se concentró a presión reducida hasta formar un residuo. El residuo se diluyó con acetato de etilo (500 mL) y se lavó con agua (150 mL), se secó sobre sulfato de sodio, se filtró, se concentró a presión reducida y la purificación por cromatografía en gel de sílice (120 g SiO_2, hexanos a 50% de acetato de etilo en hexanos) dio el bencimidazol deseado en forma de un aceite marrón 3,11 g (45%).

Parte C: A una solución de 4–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)–1H–pirazol (1,65 g, 1 equiv), bencimidazol del Ejemplo 14 parte B (3,11 g, 1,1 equiv) en DMA (57 mL) se añadió carbonato de potasio (3,51 g, 3 equiv). La mezcla se calentó a 50 °C durante 18 horas. La mezcla de reacción se vertió en agua (250 mL), se extrajo con acetato de etilo (500 mL), la capa orgánica se lavó con salmuera (250 mL), se secó sobre sulfato de sodio, se filtró, se concentró a presión reducida y la purificación por cromatografía en gel de sílice (80 g SiO2, hexanos a 50% de acetato de etilo en hexanos) dio el boronato deseado en forma de un sólido blanquecino 2,67 g (64%).

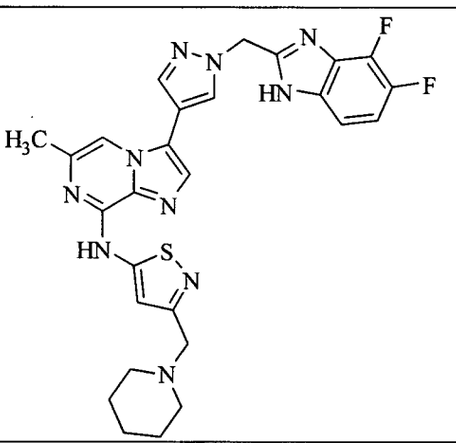
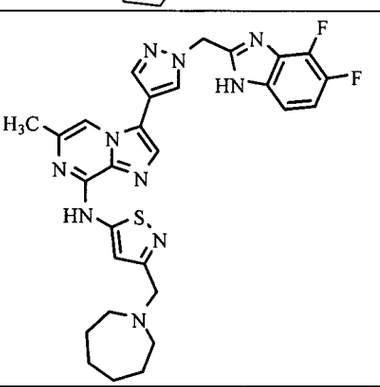
EJEMPLO 15



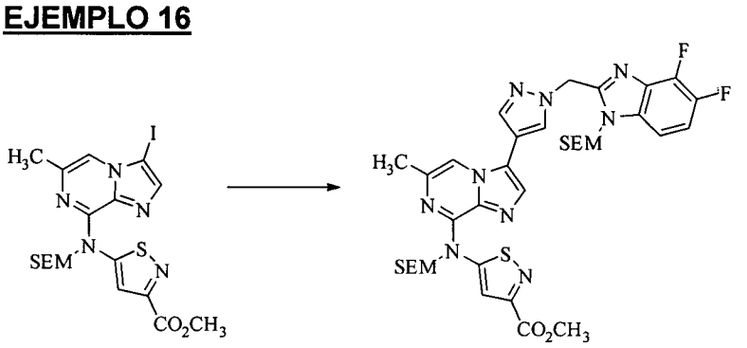
A una mezcla de yoduro de arilo (100 mg, 1,00 equiv), $PdCl_2(dppf)$ (12 mg, 0,10 equiv) y fosfato de potasio (71 mg, 2,00 equiv) bajo nitrógeno se añadió una solución del boronato del Ejemplo 14 parte C (123 mg, 1,20 equiv) en 1,4–dioxano (2,0 mL), seguido de agua (0,2 mL). La mezcla se agitó a 90 °C durante 18 horas en cuyo momento la TLC indicó que no quedaba más material de partida. La reacción se dejó enfriar hasta temperatura ambiente, luego se diluyó con acetato de etilo (100 mL) y se lavó con agua (30 mL), se secó sobre sulfato de sodio, se filtró, se concentró a presión reducida y la purificación por cromatografía en gel de sílice (12 g de SiO_2, diclorometano a 10% de metanol en diclorometano) dio el producto acoplado deseado. Este material se disolvió en 1,4–dioxano, se añadió HCl (4 N en dioxano) y la mezcla se sonicó hasta que la HPLC indicó que no quedaba más material de partida. La mezcla se concentró a presión reducida, se

purificó por HPLC preparativa y la conversión en la sal de clorhidrato dio los compuestos de ensayo como sólidos blanquecinos en la Tabla 5 (mostrada inmediatamente a continuación):

Tabla 5

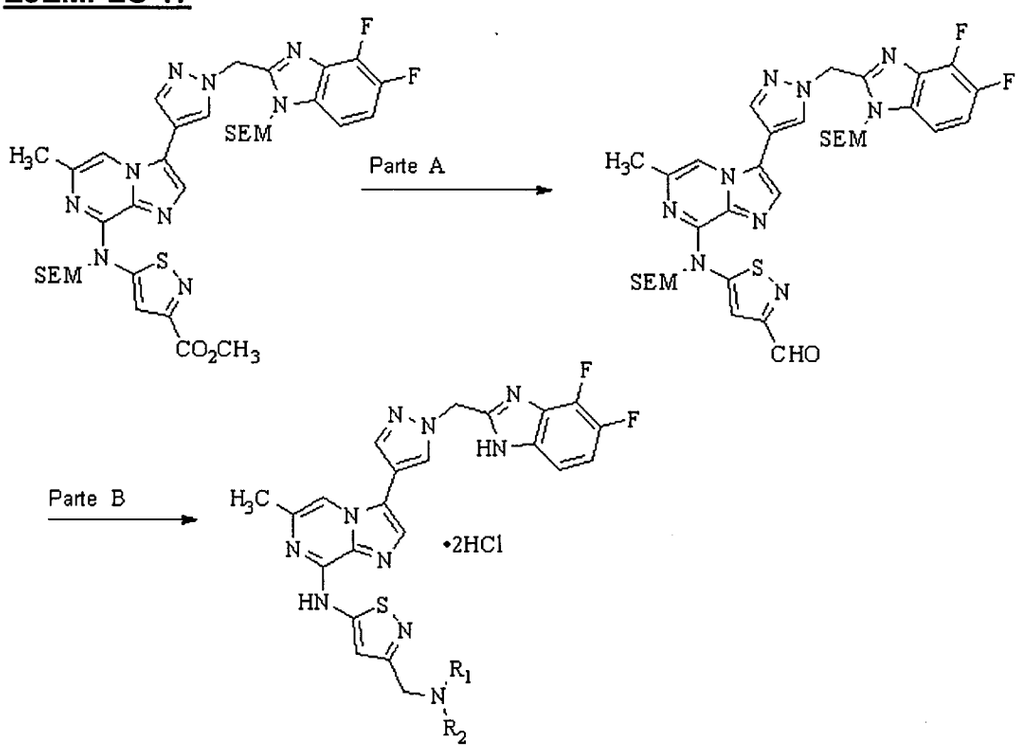
Ejemplo	Columna 2	PM	MS MH^+ m/z	HPLC t_R
15–1		560,2	561,2	4,74
15–2		574,2	575,7	4,99

EJEMPLO 16



A una mezcla de yoduro de arilo (2,15 g, 1,00 equiv), $PdCl_2$(dppf) (288 mg, 0,10 equiv) y fosfato de potasio (1,67 mg, 2,00 equiv) bajo nitrógeno se añadió una solución del boronato del Ejemplo 14 parte C (2,51 g, 1,20 equiv) en 1,4–dioxano (47 mL), seguido de agua (4,7 mL). La mezcla se agitó a 90 °C durante 3 horas en cuyo momento la TLC indicó que no quedaba más material de partida. La reacción se dejó enfriar hasta temperatura ambiente, luego se diluyó con acetato de etilo (700 mL) y se lavó con agua (250 mL), se secó sobre sulfato de sodio, se filtró, se concentró a presión reducida y la purificación por cromatografía en gel de sílice (120 g de SiO_2, hexanos a 100% de acetato de etilo) dio el producto acoplado deseado en forma de una espuma marrón 2,04 g (66%).

EJEMPLO 17

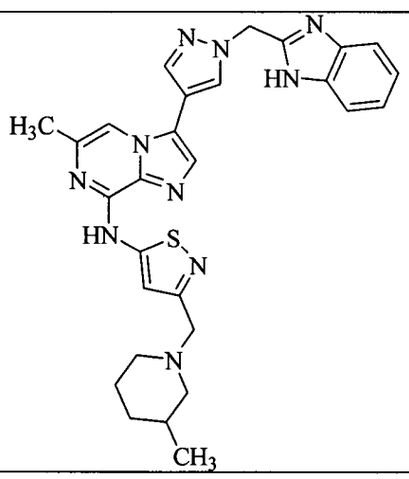


Parte A: A una solución agitada del producto acoplado del Ejemplo 16 (2,04 g, 1 equiv) en tetrahidrofurano (63 mL) a –78 °C se añadió DIBAL–H (1 M en diclorometano, 6,5 mL, 2,5 equiv) gota a gota. La mezcla se agitó a –78 °C durante 5 horas en cuyo momento la cromatografía en cada fina (30% de acetato de etilo/hexanos) indicó que la reacción estaba completa. La mezcla se vertió

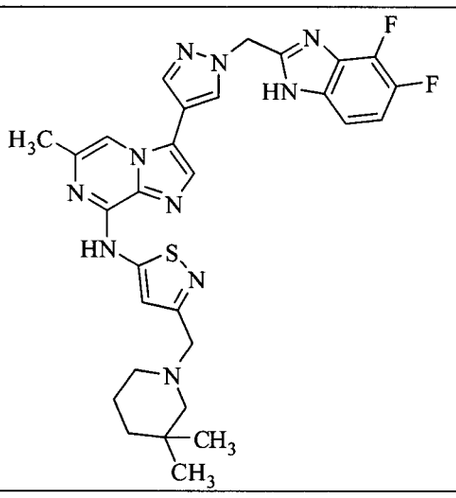
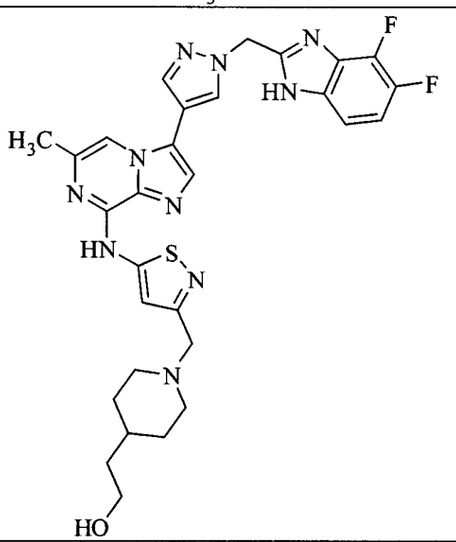
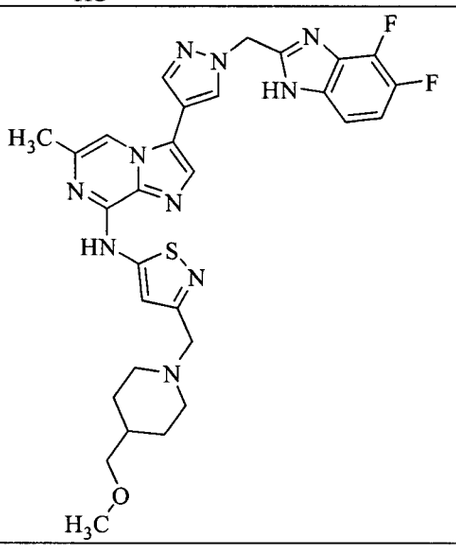
rápidamente en tartrato de potasio y sodio acuoso saturado agitado y se agitó a temperatura ambiente durante 14 horas. La mezcla se extrajo con acetato de etilo (500 mL), la capa orgánica se separó, se secó sobre sulfato de sodio, se filtró y se concentró a presión reducida dando el aldehído como una espuma marrón 1,96 g (100%).

Parte B: Se añadió triacetoxiborhidruo de sodio (1,50 equiv) a una mezcla agitada de aldehído (1,00 equiv), amina (1,20 equiv) y ácido acético (1,00 equiv) en 1,2–dicloroetano a temperatura ambiente. La mezcla se agitó hasta que no quedó más material de partida tal como se juzgó por medio de la TLC. La reacción luego se neutralizó con NaOH 1 N y se extrajo tres veces con cloroformo. Las sustancias orgánicas combinadas se secaron sobre sulfato de sodio, se filtraron y se concentraron. Este material se disolvió en 1,4–dioxano, se añadió HCl (4 N en dioxano) y la mezcla se sonicó hasta que la HPLC indicó que no quedaba más material de partida. La mezcla se concentró a presión reducida, se purificó por HPLC preparativa y la conversión en la sal de clorhidrato dio los compuestos del título en forma de sólidos blanquecinos en la Tabla 6 (mostrada inmediatamente a continuación):

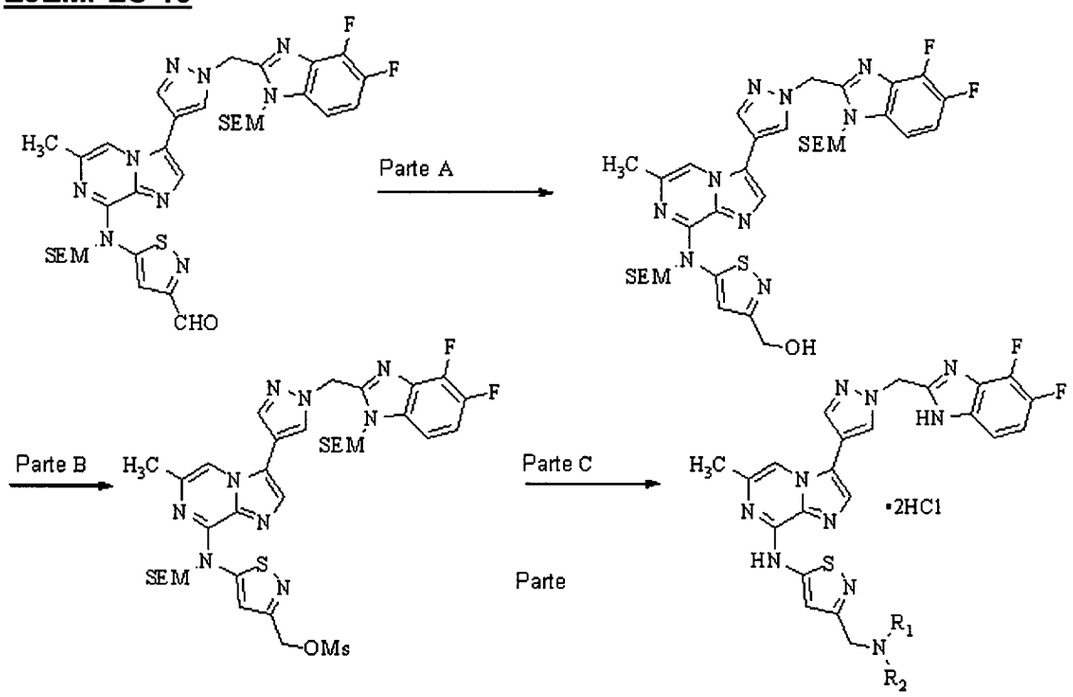
Tabla 6

Ejemplo	Columna 2	PM	MS MH^+ m/z	HPLC t_R
17–1		538,6	539,8	4,08

1010

17–2		588,23	589,1	4,84
17–3		604,2	605,9	4,35
17–4		604,2	605,2	4,38

EJEMPLO 18

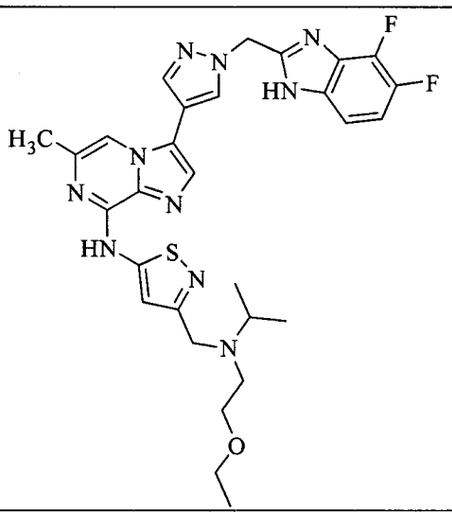


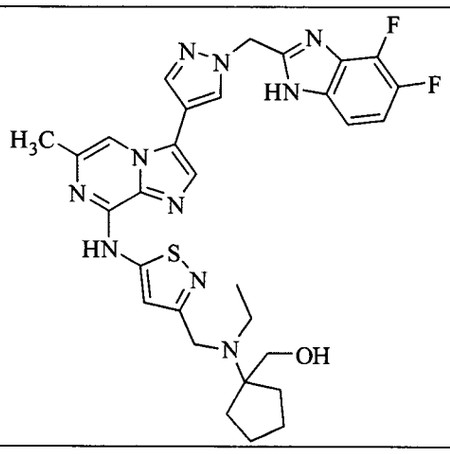
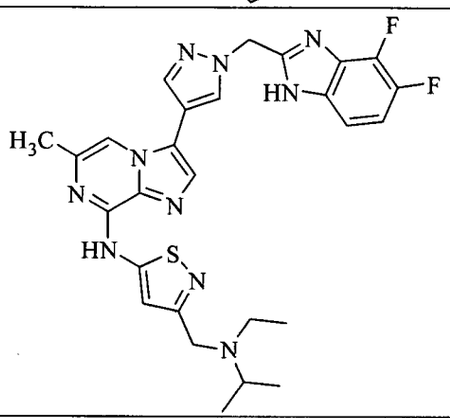
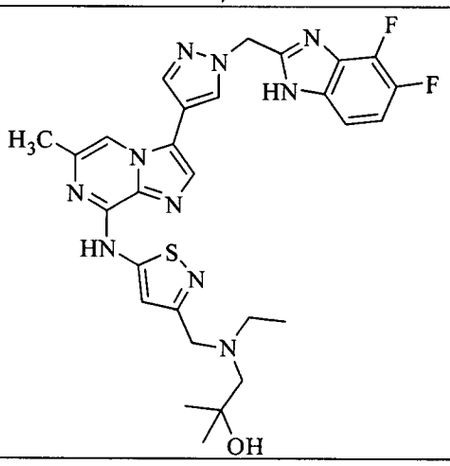
Parte A: Se añadió borhidruro de sodio (2,0 equiv) a una mezcla agitada de aldehído del Ejemplo 17 parte A (1,00 equiv) en ácido acético (5,7 mL) en 1,2–diclorometano (17 mL) a temperatura ambiente. La mezcla se agitó hasta que no quedó más material de partida tal como se juzgó por medio de TLC. La reacción luego se neutralizó con NaOH 2 N (11 mL) y una solución saturada de bicarbonato de sodio acuoso (35 mL). Después de agitar a temperatura ambiente durante 15 minutos, las fases se separaron y la capa orgánica se secó sobre sulfato de sodio, se filtró y se concentró a presión reducida para obtener el alcohol en forma de una espuma marrón 1,01 g (100%).

Parte B: Se añadió cloruro de metansulfonilo (2 equiv) a una solución agitada de alcohol del Ejemplo 18 parte A (1 equiv) y trietilamina (4 equiv) en THF (40 mL). Después de agitar a temperatura ambiente durante 30 minutos, la reacción se neutralizó con una solución acuosa saturada de cloruro de amonio (14 mL) y agua (14 mL), se extrajo con diclorometano (2×80 mL), se secó sobre sulfato de sodio, se filtró y se concentró a presión reducida dando el mesilato en forma de una espuma marrón 1,04 g (90%).

Parte C: A una solución agitada de mesilato del Ejemplo 18 parte B (1 equiv), amina (3 equiv), yoduro de sodio (0,5 equiv) en THF (1,0 mL) se añadió diisopropiletilamina (3 equiv) y la reacción se calentó hasta 60 °C durante 18 horas. La reacción se enfrió hasta temperatura ambiente, se diluyó con diclorometano (50 mL) y la capa orgánica se lavó con agua (30 mL), salmuera (30 mL), se secó sobre sulfato de sodio, se filtró y se concentró a presión reducida. Este material se disolvió en 1,4–dioxano, se añadió HCl (4 N en dioxano) y la mezcla se sonicó hasta que la HPLC indicó que no quedaba más material de partida. La mezcla se concentró a presión reducida, se purificó por HPLC preparativa y la conversión en la sal de clorhidrato dio los compuestos del título en forma de sólidos blanquecinos en la Tabla 7 (mostrada inmediatamente a continuación):

Tabla 7

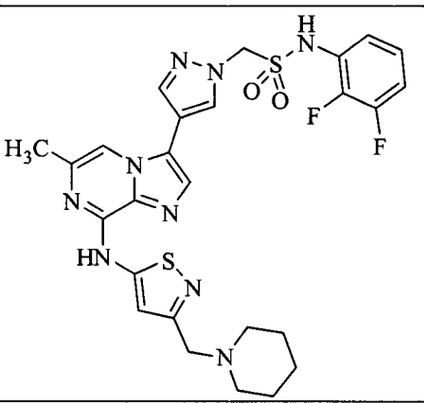
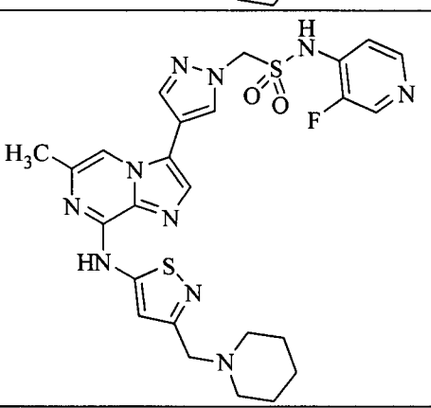
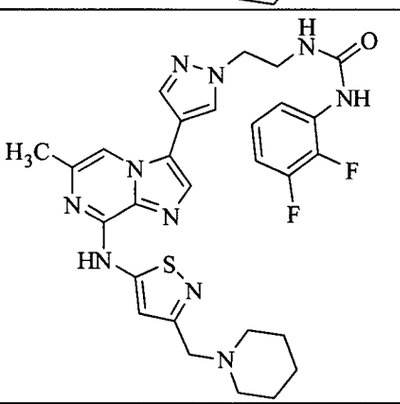
Ejemplo	Columna 2	PM	MS MH^+ m/z	HPLC t_R
18–1		606,2	607,1	4,95

18–2		618,2	619,9	4,67
18–3		562,2	563,5	4,48
18–4		592,2	593,5	4,37

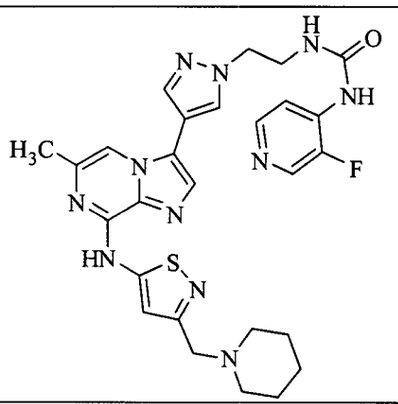
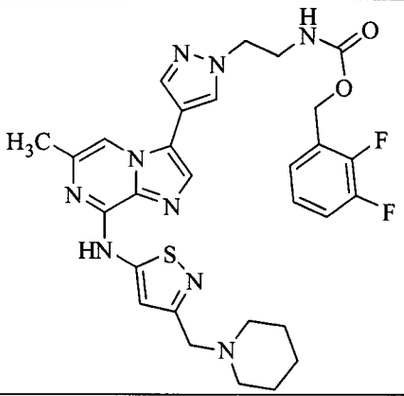
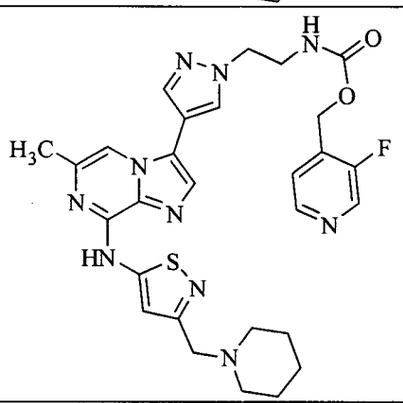
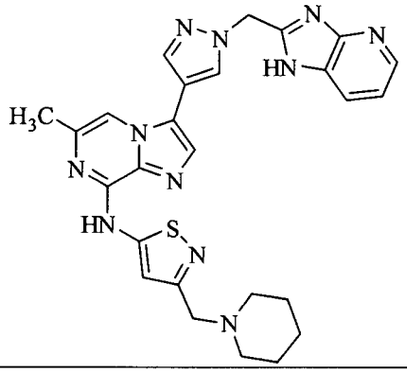
EJEMPLO 19

Los siguientes compuestos en la Tabla 8 (mostrada inmediatamente a continuación) se prepararon por medio de un método similar al método descrito en el Ejemplo 18.

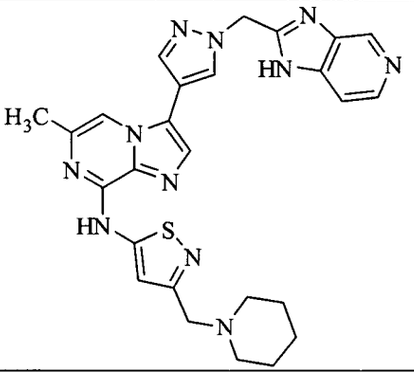
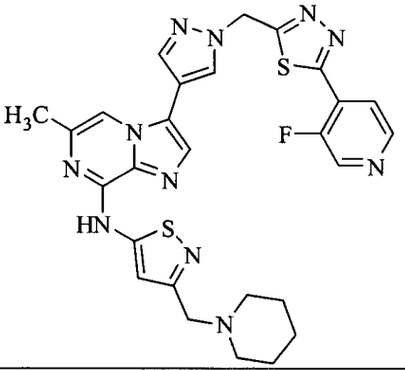
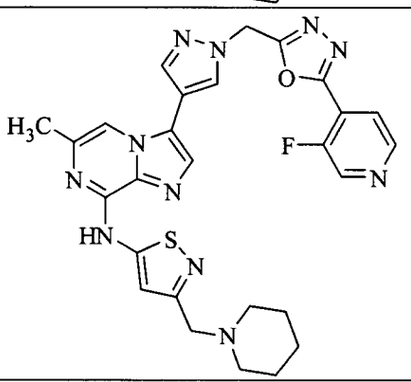
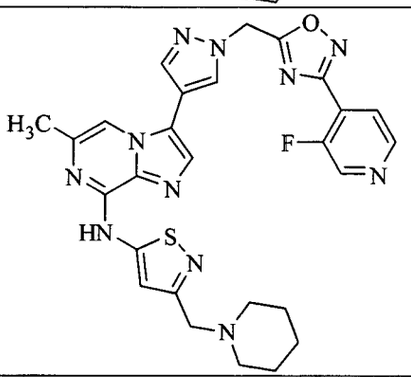
Tabla 8

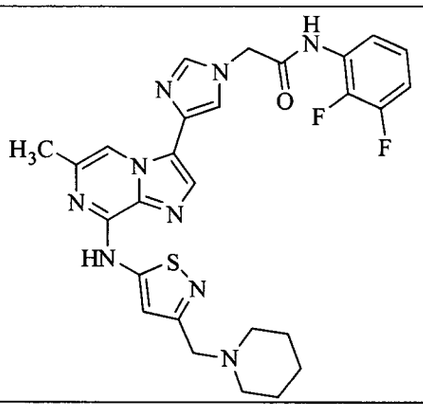
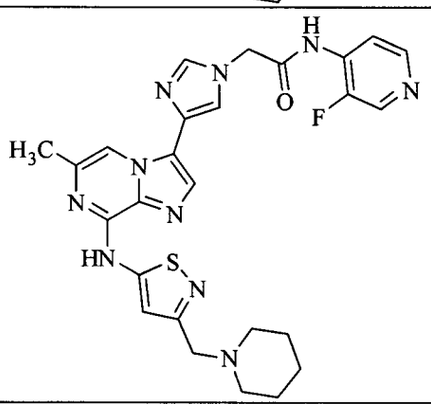
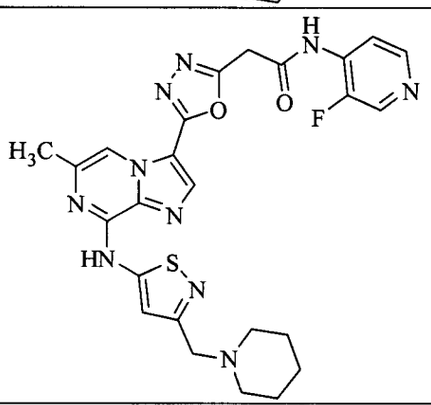
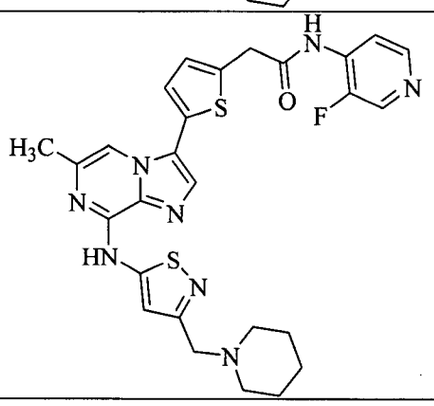
Ejemplo	Columna 2	PM	MS MH^+ m/z	HPLC t_R
19–1		599,1		
19–2		582,1		
19–3		592,2		

1015

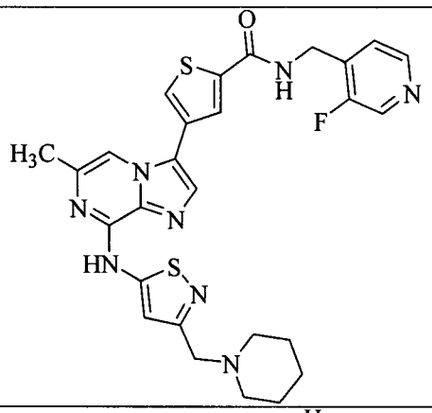
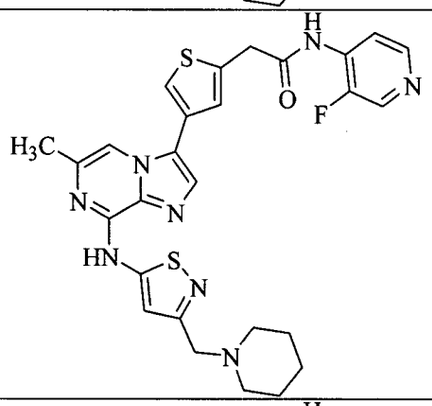
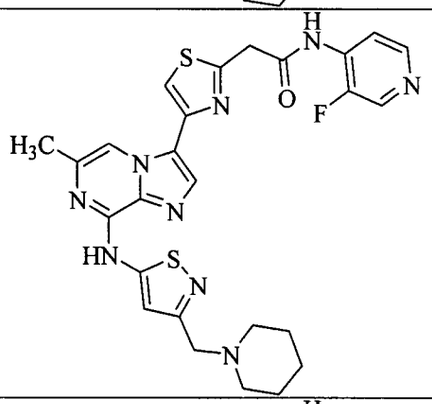
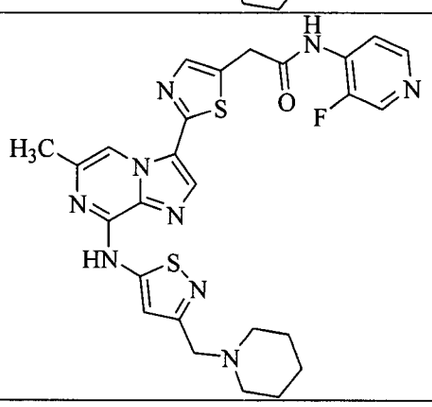
19–4		575,2		
19–5		607,2		
19–6		590,6		
19–7		525,2		

1016

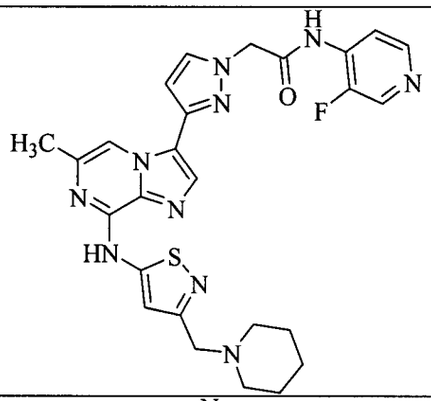
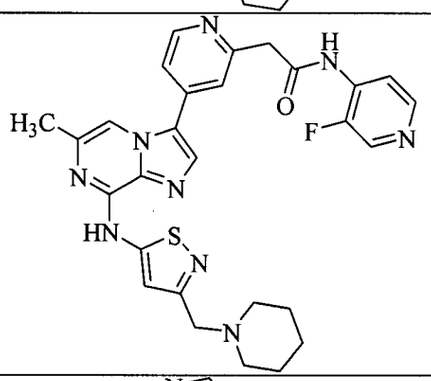
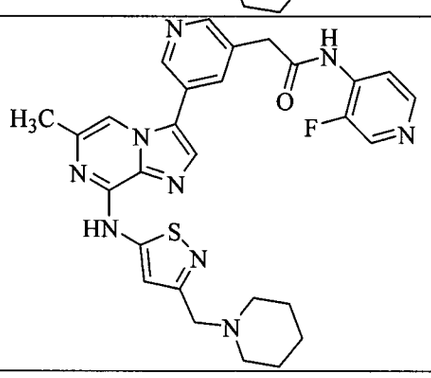
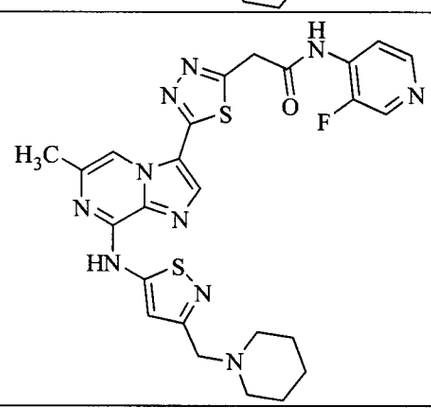
19–8		525,2		
19–9		587,1		
19–10		571,2		
19–11		571,2		

19–12		563,2		
19–13		546,2		
19–14		548,1		
19–15				

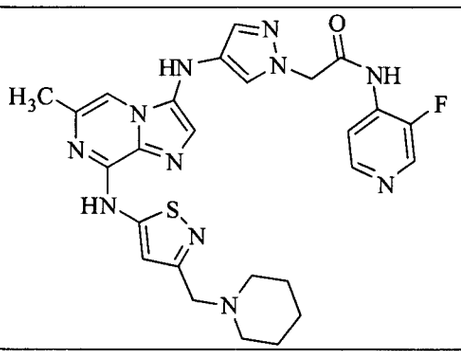
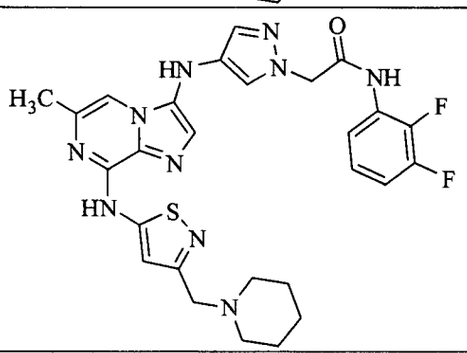
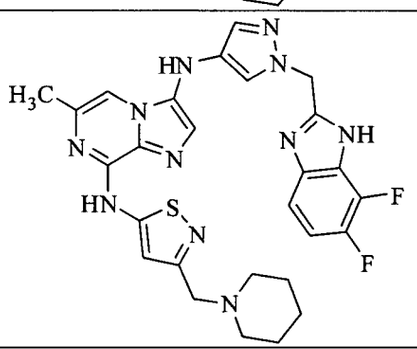
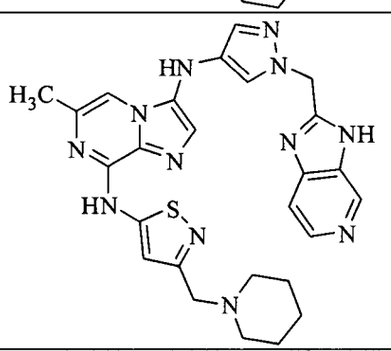
1018

19–17				
19–16				
19–17				
19–18				

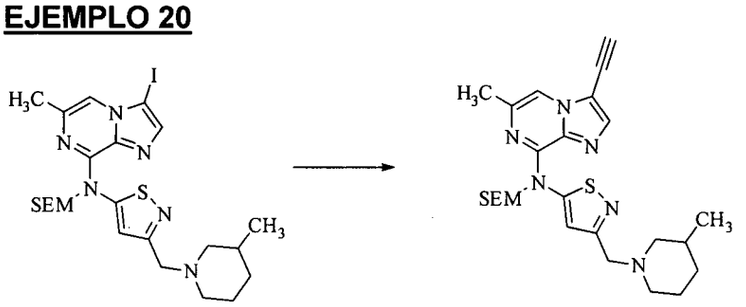
1019

19–19				
19–20				
19–21				
19–22		564,1		

1020

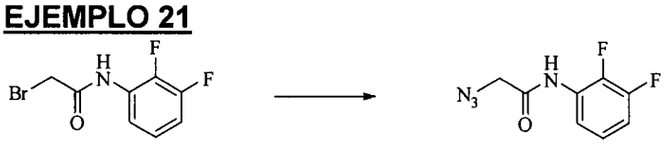
19–23		561,6		
19–24		578,6		
19–25		575,6		
19–26		540,6		

EJEMPLO 20



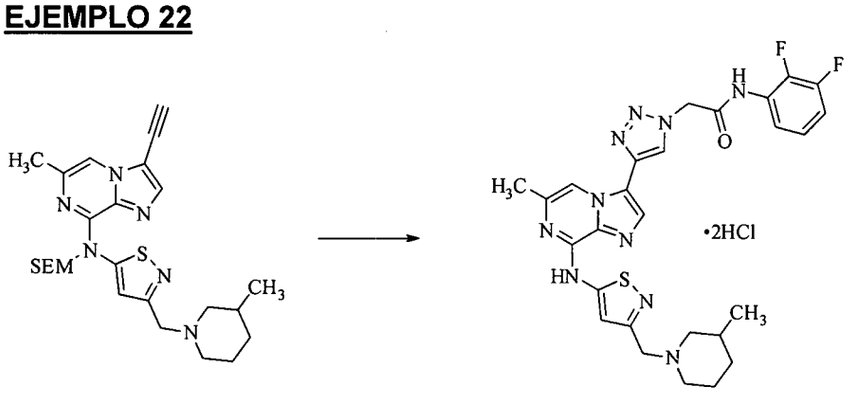
Una solución de trimetilsililacetileno (46 mg, 0,46 mmol) en trietilamina (0,5 mL) se añadió a una mezcla inundada con nitrógeno de yoduro (136 mg, 0,23 mmol), trifenilfosfina de paladio (0) (26 mg, 0,02 mmol) y yoduro de cobre (I) (8,6 mg, 0,4 mmol). La reacción se agitó a temperatura ambiente durante 12 horas, luego se diluyó con acetato de etilo (25 mL). Los contenidos de la reacción se pasaron a través de Celite, se concentraron y se colocaron en una columna (SiO_2; 12 g; 10% a 50% de acetato de etilo en hexanos) que dio el intermediario acoplado deseado. El intermediario se disolvió en metanol (8 mL), luego se trató con carbonato de potasio (790 mg). La reacción se agitó a temperatura ambiente durante 72 horas, luego se diluyó con cloruro de metileno (50 mL). La capa orgánica se lavó con bicarbonato de sodio acuoso saturado (50 mL), se secó (sulfato de sodio), se filtró y se concentró hasta sequedad. El residuo resultante se colocó en una columna flash (SiO_2; 4 g; 10% a 50% de acetato de etilo en hexanos) para obtener el compuesto del título en forma de un sólido blanco 19 mg (17%). ^{1}H RMN (300 MHz, $CDCl_3$) δ 7,91 (s, 1H), 7,82 (s, 1H), 7,31 (s, 1H), 6,67 (s, 2H), 3,91 (s, 1H), 3,81 (t, *J* = 6,4 Hz, 2H), 3,71 (s, 2H), 3,03–2,87 (m, 2H), 2,66 (s, 3H), 2,19–1,99 (m, 2H), 1,85–1,63 (m, 5H), 1,01 (t, *J* = 6,4 Hz, 2H), 0,93 (d, *J* = 5,6 Hz, 3H), 0,00 (s, 9H).

EJEMPLO 21



Se añadió azida de sodio (116 mg, 1,79 mmol) a una solución de bromuro (408 mg, 1,63 mmol) en dimetilformamida (30 mL). La mezcla de reacción luego se calentó hasta 60 °C y se agitó durante 12 horas. Después de completar, la reacción se enfrió hasta temperatura ambiente y el solvente se eliminó al vacío. El residuo resultante se extrajo en acetato de etilo (75 mL), luego se lavó con bicarbonato de sodio (50 mL), agua (50 mL) y salmuera (50 mL). La capa orgánica luego se secó (sulfato de sodio), se filtró y se concentró hasta sequedad. El sólido resultante se colocó en una columna flash (SiO_2; 12 g; 10% a 50% de acetato de etilo en hexanos) para dar el compuesto del título en forma de un sólido blanco 240 mg (69%). ^{1}H RMN (300 MHz, $CDCl_3$) δ 8,28 (br s, 1H), 8,12–7,96 (m, 1H), 7,16–7,02 (m, 1H), 7,01–6,87 (m, 1H), 4,20 (s, 2H).

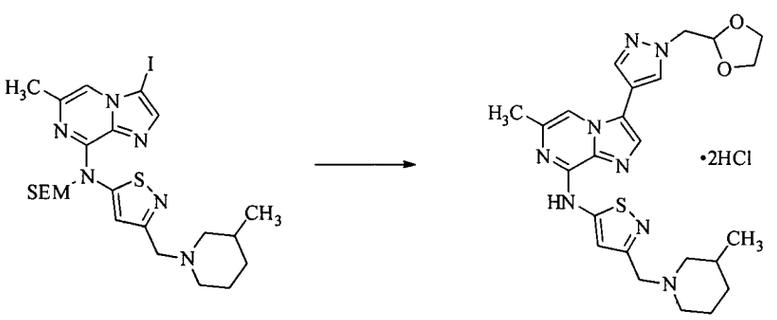
EJEMPLO 22



Se añadió cobre en polvo (5 mg, 0,08 mmol) a una solución de alquino (19 mg, 0,04 mmol) del Ejemplo 21 y azida (16 mg, 0,08 mmol) del Ejemplo 22 en alcohol *t*–butílico (0,3 mL) y agua (0,6 mL). La reacción se agitó a temperatura ambiente durante 72 horas, luego se diluyó con acetato de etilo (100 mL). La capa orgánica se lavó con agua (100 mL) y salmuera (100 mL), luego se secó (sulfato de sodio), se filtró y se concentró. El residuo resultante se colocó en una columna flash (SiO_2; 4 g; 0% a 10% de metanol en cloruro de metileno) para obtener el intermediario acoplado. El intermediario deseado luego se disolvió en dioxano (2 mL) y se trató con HCl 4 N en dioxano (2 mL). La reacción se sonicó a temperatura ambiente durante 1 hora. El solvente se eliminó y el residuo se

purificó por HPLC preparativa (95:5 a 5:95 de agua/acetonitrilo con 0,1% de ácido trifluoroacético). Las fracciones se recogieron y se secaron y el residuo se trató con HCl 0,2 N y se liofilizaron para obtener el compuesto del título en forma de un sólido blanco 6,9 mg (28%). ^{1}H RMN (300 MHz, CD_3OD) δ 8,65 (s, 1H), 8,58 (s, 1H), 8,13 (s, 1H), 7,77–7,70 (m, 1H), 7,21 (s, 1H), 7,17–7,04 (m, 2H), 5,59 (s, 2H), 4,38 (s, 2H), 3,71–3,46 (m, 2H), 3,13–3,09 (m, 1H), 2,79–2,63 (m, 1H), 2,58 (s, 3H), 2,06–1,74 (m, 4H), 1,32–1,11 (m, 1H), 1,00 (d, *J* = 6,4 Hz, 3H). HPLC t_R = 5,45 min (UV $_{254nm}$). Masa calculada para la fórmula $C_{27}H_{28}F_2N_{10}OS$ 578,2; MH^+ observada (ESI MS) 579,8 (m/z).

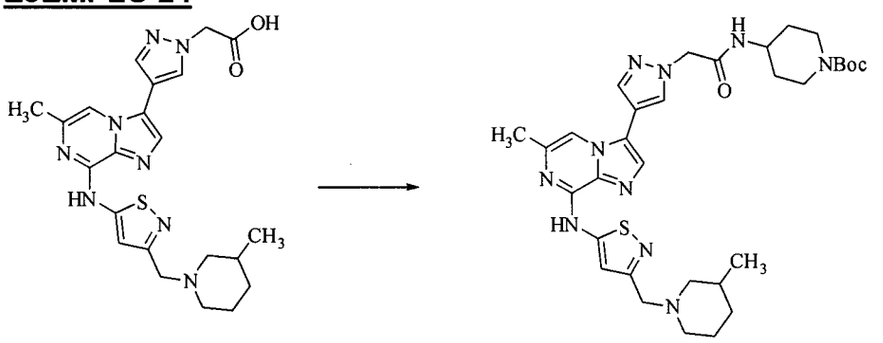
EJEMPLO 23



El Ejemplo 24 se preparó de una manera similar a la del Ejemplo 15. ^{1}H RMN (300 MHz, CD_3OD) δ 8,30 (s, 1H), 8,21 (s, 1H), 8,03 (s, 1H), 8,00 (s, 1H), 7,35 (s, 1H), 5,31–5,22 (m, 1H), 4,49–4,37 (m, 4H), 3,91 (s, 4H), 3,69–3,46 (m, 2H), 3,10–2,91 (m, 1H), 2,80–2,66 (m, 1H), 2,63 (s, 3H), 2,07–1,74 (m. 4H), 1,39–1,12 (m, 1H), 1,00 (d, *J* = 6,5 Hz, 3H). HPLC t_R = 7,36 min (UV $_{254nm}$). Masa calculada para la fórmula $C_{24}H_{30}N_8O_2S$ 494,2; MH^+ observada (ESI MS) 495,8 (m/z).

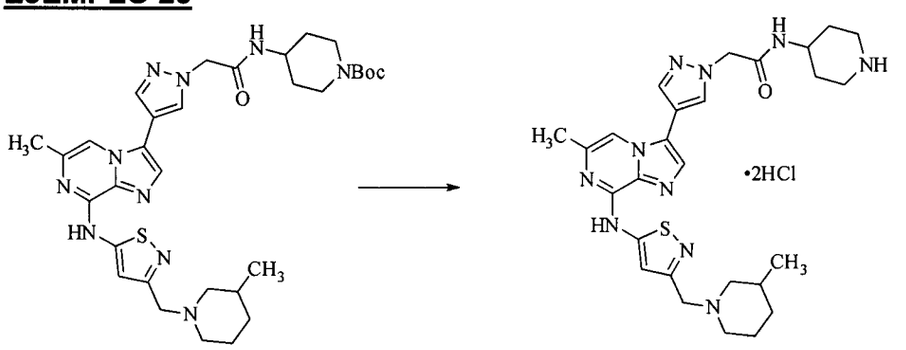
1024

EJEMPLO 24



El Ejemplo 25 se preparó de una manera similar a la del Ejemplo 6. ^{1}H RMN (300 MHz, CD_3OD) δ 8,20 (s, 1H), 7,94 (s, 1H), 7,85 (s, 1H), 7,77 (s, 1H), 7,18 (s, 1H), 4,98 (s, 2H), 4,37 (br s, 2H), 4,17–3,81 (m, 2H), 3,71–3,40 (m, 2H), 3,20–3,05 (m, 1H), 3,03–2,84 (m, 2H), 2,79–2,62 (m, 1H), 2,52 (s, 3H), 2,06–1,97 (m, 4H), 1,97–1,69 (m, 5H), 1,46 (s, 9H), 1,32–1,14 (m, 1H), 1,00 (d, *J* = 6,4 Hz, 3H).

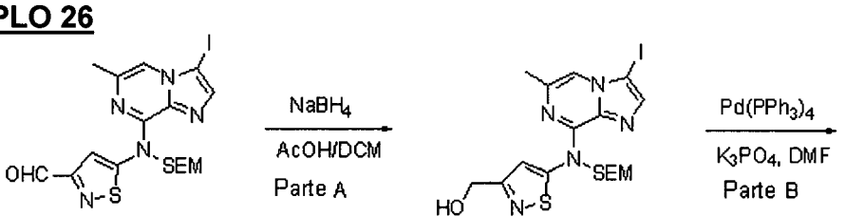
EJEMPLO 25

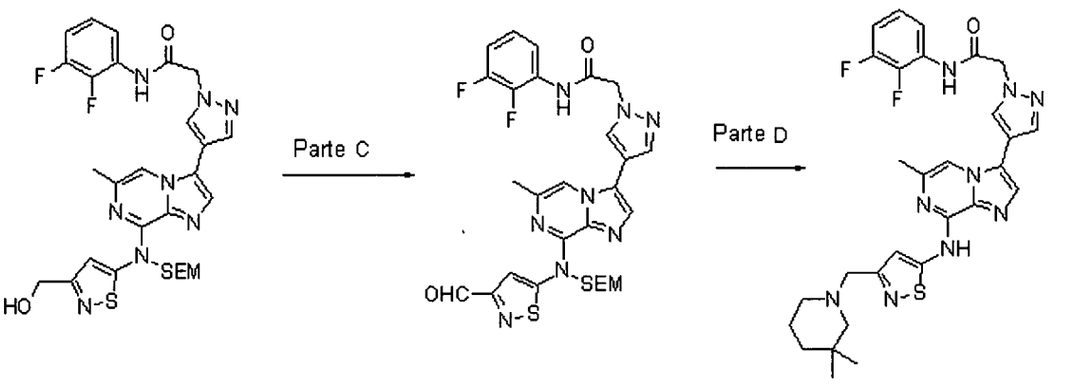


Se añadió ácido trifluoroacético (2 mL) a una solución de amida (20 mg, 0,02 mmol) en cloruro de metileno (2 mL). La reacción se dejó bajo agitación a temperatura ambiente durante 2 horas. El solvente se eliminó y el residuo resultante se colocó en una HPLC preparativa (95:5 a 40:60 de agua/acetonitrilo con 0,1% de ácido trifluoroacético). Las fracciones recogidas se concentraron, luego se trataron con HCl 0,2 N y se liofilizaron para obtener el compuesto del título en forma de un sólido blanco 3,2 mg (23%). ^{1}H RMN (300 MHz, CD_3OD) δ 8,23 (s, 1H), 7,96 (s, 1H), 7,91 (s, 1H), 7,85 (s, 1H), 7,21 (s, 1H), 5,00 (s, 2H), 4,39 (br s, 2H), 4,09–3,93 (m, 1H), 3,68–3,39 (m, 4H), 3,20–3,04 (m, 2H), 3,04–

2,89 (m, 1H), 2,79–2,63 (m, 1H), 2,51 (s, 3H), 2,24–2,09 (m, 2H), 2,05–1,67 (m, 6H), 1,32–1,12 (m, 1H), 1,01 (d, J = 6,4 Hz, 3H). HPLC t_R = 3,47 min (UV $_{254nm}$). Masa calculada para la fórmula $C_{27}H_{36}N_{10}OS$ 548,3; MH^+ observada (ESI MS) 549,9 (m/z).

EJEMPLO 26





Parte A: A una solución de yoduro (390 mg, 0,757 mmol) en 10 mL de CH_2Cl_2 se añadieron 8 mL de AcOH. Luego se agregó $NaBH_4$ (57 mg, 1,51 mmol) en una porción. La reacción se agitó a temperatura ambiente durante 15 min. Se diluyó con 100 mL de CH_2Cl_2 y se neutralizó con NaOH 5 N (ac.). A la mezcla se añadieron 100 ml de $NaHCO_3$ acuoso saturado. La mezcla resultante se agitó a temperatura ambiente durante 30 min. La capa orgánica se aisló. Se secó sobre Na_2SO_4 anhidro y luego se concentró. El residuo se purificó por cromatografía flash eluyendo con 60% de EtOAc/ CH_2Cl_2 para dar 390 mg del compuesto del título. ^1H RMN (400 MHz, $CDCl_3$) δ 7,72 (s, 1H), 7,60 (s, 1H), 7,13 (s, 1H), 6,58 (brs, 2H), 4,78 (s, 2H), 3,72 (t, 2H), 2,60 (s, 3H), 0,95 (t, 2H), –0,10 (s, 9H).

1036

Parte B: A una mezcla de alcohol de la Parte A (80 mg, 0,15 mmol), boronato del Ejemplo 7, Parte A (84 mg, 0,23 mmol) y $Pd(PPh_3)_4$ (17,8 mg, 0,015 mmol) se añadieron 2 mL de DMF seguido de solución acuosa 3 M de K_3PO_4 (0,21 mL, 0,63 mmol). La mezcla de reacción se calentó a 65 °C durante 18 h. Se diluyó con 30 mL de EtOAc y se lavó con solución acuosa 1 N de NH_4Cl (20 mL x 2). La capa orgánica se concentró al vacío. El residuo se purificó por cromatografía flash eluyendo con 4% de MeOH/CH_2Cl_2 para dar 68 m g de **5**. ^1H RMN (400 MHz, $CDCl_3$) δ 8,90 (brs, 1H), 8,02–8,12 (m, 1H), 8,00 (s, 1H), 7,87 (s, 1H), 7,68 (s, 1H), 7,57 (s, 1H), 7,15 (s, 1H), 6,90–7,13 (m, 2H), 6,65 (brs, 2H), 5,09 (s, 2H), 4,75–4,81 (m, 2H), 3,77 (t, 2H), 2,80 (brs, 1H), 2,60 (s, 3H), 0,95 (t, 2H), –0,10 (s, 9H).

Parte C: A una solución de alcohol de la Parte B (31 mg, 0,049 mmol) en 1,5 mL de THF, se añadieron 3 µL de agua seguido de peryodinano de Dess–Martin (64 mg, 0,15 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 30 min. Se diluyó con 5 mL de THF. La mezcla se filtró. El filtrado se diluyó con 20 mL de CH_2Cl_2 y se lavó con 10 mL de solución acuosa saturada de $NaHCO_3$. Se secó sobre Na_2SO_4 anhidro y luego se concentró para dar 30 mg del compuesto del título que se usó en posteriores reacciones sin ulterior purificación.

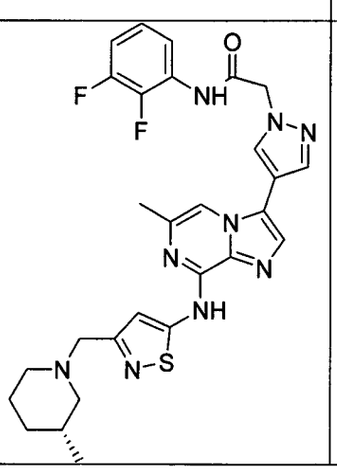
Parte D: Una solución de aldehído (12 mg, 0,019 mmol), 3,3–dimetilpiperidina (22 mg, 0,19 mmol) en 1 mL de CH_2Cl_2 se agitó a temperatura ambiente durante 30 min. A la solución se añadió $NaBH_4$ (3,6 mg, 0,096 mmol) seguido de 0,3 mL de MeOH. La reacción se agitó a temperatura ambiente durante 1 h. Se diluyó con 10 mL de CH_2Cl_2 y 10 mL de solución acuosa saturada de $NaHCO_3$. La mezcla resultante se agitó durante 1 h. La capa orgánica se separó y se concentró al vacío. El residuo se purificó por cromatografía flash eluyendo con NH_4OH (ac.)/MeOH/ CH_2Cl_2 (1:10:190) para dar 10 mg del

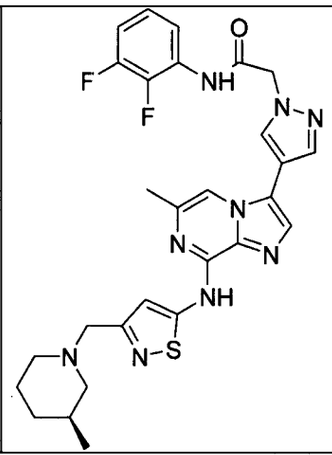
compuesto del título protegido con SEM. A una solución del material protegido con SEM (10 mg, 0,014 mmol) en 2 mL de THF calentado a 80 °C se añadieron 0,2 mL de HCl 4 N en dioxano. La reacción se agitó a 80 °C durante 1,5 h. Se enfrió hasta temperatura ambiente y luego se añadieron 8 mL de éter. El sólido se recogió por filtración y se lavó con éter para dar 8,7 mg del compuesto del título. ^{1}H RMN (400 MHz, CD_3OD) δ 8,38 (s, 1H), 8,15 (s, 1H), 8,08 (s, 1H), 8,02 (s, 1H), 7,72–7,81 (m, 1H), 7,27 (s, 1H), 7,03–7,20 (m, 2H), 5,30 (s, 2H), 4,35–4,60 (m, 2H), 3,55–3,65 (d, 1H), 3,00–3,10 (m, 1H), 2,80–2,90 (d, 1H), 2,60 (s, 3H), 1,81–2,10 (m, 2H), 1,40–1,69 (m, 2H), 1,20 (s, 3H), 1,00 (s, 3H). HPLC–MS t_R = 2,96 min (UV $_{254nm}$). Masa calculada para la fórmula $C_{29}H_{31}F_2N_9OS$ 591,2; MH^+ observada (LCMS) 592,3 (m/z).

EJEMPLO 27

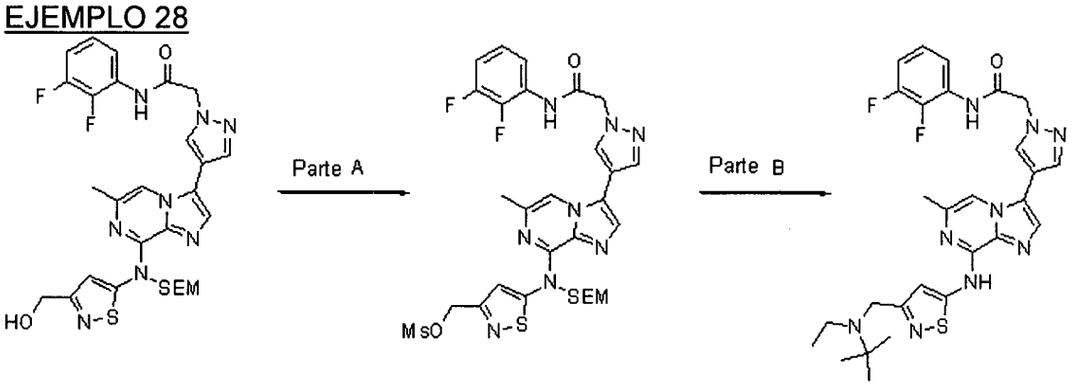
Esencialmente por medio del mismo procedimiento que el establecido en el Ejemplo 26, pero sólo reemplazando la 3,3–dimetilpiperidina con otras aminas respectivas en la Parte A, se prepararon los compuestos mostrados en la columna 2 de la Tabla 9 (mostrada inmediatamente a continuación).

TABLA 9

Ejemplo	Columna 2	PM	LCMS MH^+ m/z	HPLC MS t_R
9–1		577,2	578,3	2,87

9–2		577,2	578,3	2,87

EJEMPLO 28

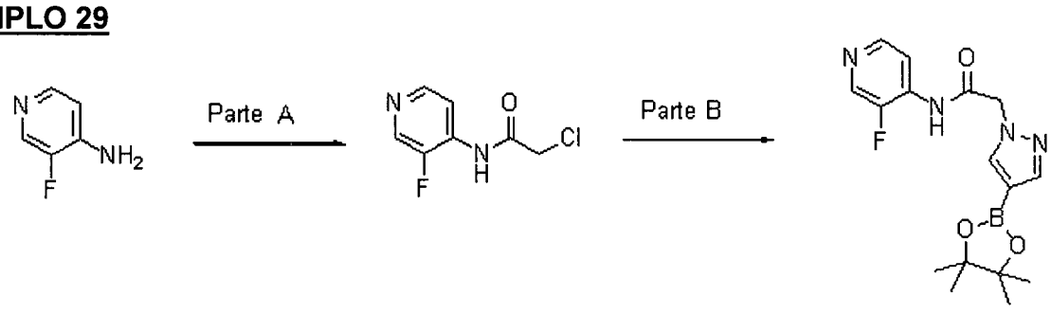


Parte A: A una solución de alcohol del Ejemplo 26, Parte B (30 mg, 0,047 mmol) en 1,5 mL de THF, se añadió trietilamina (9,5 mg, 0,094 mmol) seguido de cloruro de metansulfonilo (7,3 µL, 0,094 mmol). La reacción se agitó a temperatura ambiente durante 20 min. Se diluyó con 10 mL de CH_2Cl_2, se lavó con 5 mL de HCl acuoso 1 N. La capa orgánica se secó sobre Na_2SO_4 anhidro. El solvente se eliminó para dar 31 mg del compuesto del título en forma de un material crudo que se usó en la posterior reacción sin ulterior purificación.

Parte B: Una mezcla de mesilato de la Parte A (9,6 mg, 0,014 mmol), N,N–dietilisopropilamina (6,0 mg, 0,068 mmol) y NaI (4,1 mg, 0,027 mmol) en 1 mL de THF se agitó a 60 °C durante 3 h. Se diluyó con 10 mL de CH_2Cl_2 y se lavó con agua. La capa orgánica se concentró al vacío. El residuo se purificó por cromatografía flash eluyendo con NH_4OH (ac.)/MeOH/CH_2Cl_2 (1:10:190) para dar

8 mg de *N*–(2,3–difluoro–fenil)–2–(4–{8–[{3–[(etil–isopropil–amino)–metil]–isotiazol–5–il}–(2–trimetilsilanil–etoximetil)–amino]–6–metil–imidazo[1,2–a]pirazin–3–il}–pirazol–1–il)–acetamida. A una solución de *N*–(2,3–difluoro–fenil)–2–(4–{8–[{3–[(etil–isopropil–amino)–metil]–isotiazol–5–il}–(2–trimetilsilanil–etoximetil)–amino]–6–metil–imidazo[1,2–a]pirazin–3–il}–pirazol–1–il)–acetamida (8,0 mg, 0,011 mmol) en 2 mL de THF calentada a 80 °C se añadieron 0,2 mL de HCl 4 N en dioxano. La reacción se agitó a 80 °C durante 1,5 h. Se enfrió hasta temperatura ambiente y luego se añadieron 8 mL de éter. El sólido se recogió por filtración y se lavó con éter para dar 5,8 mg del compuesto del título. ^{1}H RMN (400 MHz, CD_3OD) δ 8,35 (s, 1H), 7,95–8,10 (m, 3H), 7,70–7,82 (m, 1H), 7,25 (s, 1H), 7,00–7,20 (m, 2H), 5,30 (s, 2H), 4,30–4,60 (m, 2H), 3,75–3,85 (m, 1H), 2,60 (s, 3H), 1,30–1,50 (m, 9H). HPLC–MS t_R = 2,80 min (UV $_{254nm}$). Masa calculada para la fórmula $C_{27}H_{29}F_2N_9OS$ 565,2; MH^+ observada (LCMS) 566,3 (m/z).

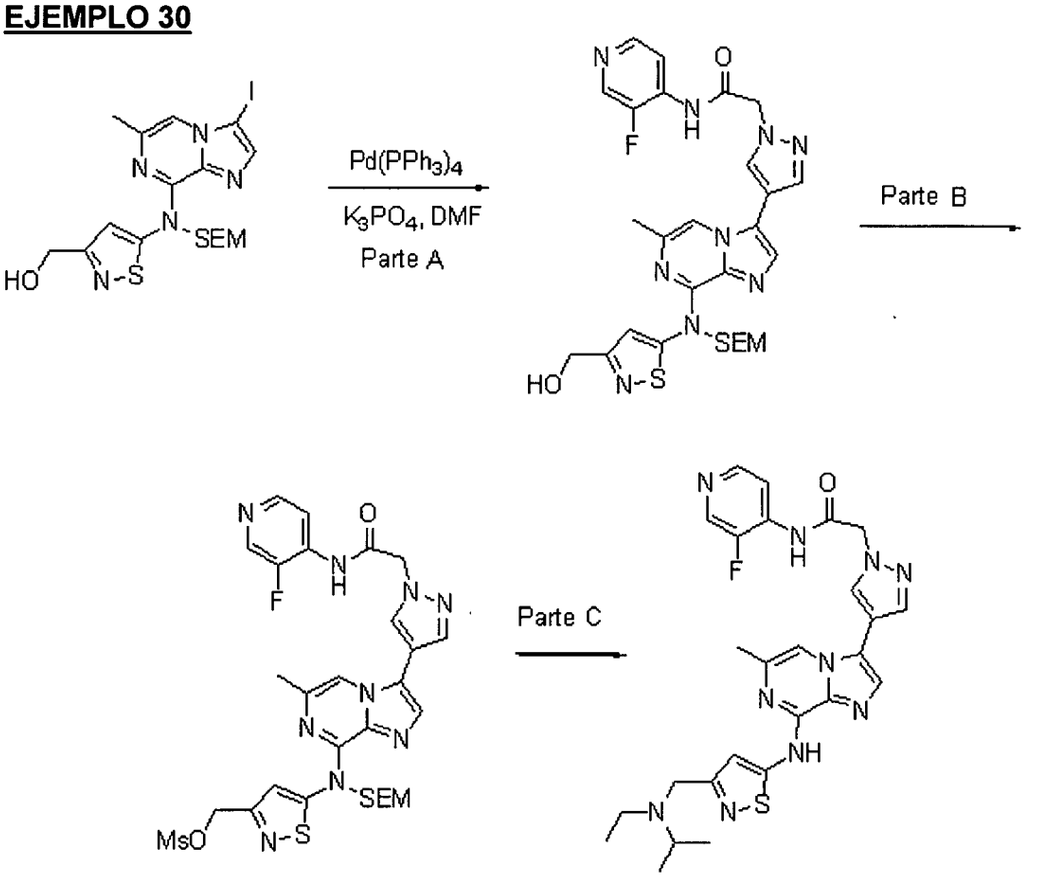
EJEMPLO 29



Parte A: A una solución de 4–amino–3–fluoropiridina (560 mg, 5,0 mmol) y Et_3N (760 mg, 7,5 mmol) en 20 mL de THF, se añadió cloruro de cloroacetilo (622 mg, 5,5 mmol). La reacción se agitó a temperatura ambiente y se controló por cromatografía en capa fina. Se añadió más cloruro de cloroacetilo hasta que se consumiera la 4–amino–3–fluoropiridina. Se neutralizó por adición de 20 mL de $NaHCO_3$ acuoso saturado. La mezcla se diluyó con 150 mL de CH_2Cl_2. La capa orgánica se concentró y se purificó por cromatografía flash eluyendo con 35% de $EtOAc/CH_2Cl_2$ para dar 850 mg del compuesto del título. RMN (400 MHz, $CDCl_3$) δ 8,62 (brs, 1H), 8,41 (d, 1H), 8,33 (d, 1H), 8,26 (t, 1H), 4,20 (s, 2H).

Parte B: Una mezcla de la amida de la Parte A (106 mg, 0,55 mmol) y Cs_2CO_3 (326 mg, 1,0 mmol) en 2 mL de DMSO se calentó a 100 °C durante 5 min. A la mezcla se añadió éster pinacólico del ácido 4–pirazolborónico (94 mg, 0,50 mmol). La reacción se agitó a 100 °C durante 20 min. Se enfrió hasta temperatura ambiente y se diluyó con 30 mL de CH_2Cl_2. La mezcla se lavó con agua. La capa orgánica se concentró y se purificó por columna rápida eluyendo con 2% de MeOH/EtOAc para dar 52 mg del compuesto del título. RMN (400 MHz, $CDCl_3$) δ 9,30 (brs, 1H), 8,33 (d, 1H), 8,20–8,30 (m, 2H), 7,93 (s, 1H), 7,75 (s, 1H), 4,90 (s, 2H), 1,24 (s, 12H).

EJEMPLO 30



Parte A: A una mezcla de yoduro (43 mg, 0,083 mmol), boronato del Ejemplo 29, Parte B (43 mg, 0,124 mmol) y $Pd(PPh_3)_4$ (14 mg, 0,012 mmol) en un vial, se añadieron 1,1 mL de DMF, seguido de la adición de 0,11 mL de solución

acuosa 3 M de K_3PO_4 (0,33 mmol). El vial se selló y se agitó a 65 °C durante la noche. Se diluyó con 30 mL de EtOAc y se lavó con agua. Se concentró y se purificó por cromatografía flash eluyendo con 7% de MeOH/DCM para dar 24 mg del compuesto del título. RMN (400 MHz, $CDCl_3$) δ 9,25 (brs, 1H), 8,25–8,43 (m, 3H), 7,95 (s, 1H), 7,80 (s, 1H), 7,61 (s, 1H), 7,50 (s, 1H), 7,09 (s, 1H), 6,60 (s, 2H), 5,05 (s, 2H), 4,72 (s, 2H), 3,70 (t, 2H), 2,75 (brs, 1H), 2,48 (s, 3H), 0,90 (t, 2H), –0,14 (s, 9H).

Parte B: A una solución de alcohol de la Parte A (102 mg, 0,17 mmol) en 5 mL de THF, se añadió NEt_3 (0,094 mL, 0,67 mmol), seguido de cloruro de metansulfonilo (0,029 mL, 0,37 mmol). La reacción se agitó a temperatura ambiente durante 15 min. Se controló por cromatografía en capa fina y se halló que el alcohol de partida no se había consumido totalmente. Se añadió cloruro de metansulfonilo adicional (0,0035 mL, 0,039 mmol). Se continuó agitando durante 5 min. Se neutralizó por adición de 2 mL de NH_4Cl saturado (ac.) y 2 mL de agua. La capa orgánica se recogió. La capa acuosa se extrajo con CH_2Cl_2 (10 mL X 3) hasta que no quedara más producto deseado en la capa acuosa. Las sustancias orgánicas combinadas luego se purificaron por cromatografía flash eluyendo con MeOH/CH_2Cl_2 (1:10) para dar 63,3 mg del compuesto del título en forma de un sólido de color amarillo claro. ^{1}H RMN (400 MHz, DMSO–d_6) δ 10,75 (s, 1H), 8,60 (d, 1H), 8,51 (s, 1H), 8,36 (d, 1H), 8,20 (t, 1H), 8,10 (s, 2H), 7,96 (s, 1H), 7,38 (s, 1H), 6,70 (brs, 2H), 5,34 (s, 2H), 5,28 (s, 2H), 3,68 (t, 2H), 3,28 (s, 3H), 2,54 (s, 3H), 0,85 (t, 2H), –0,10 (s, 9H).

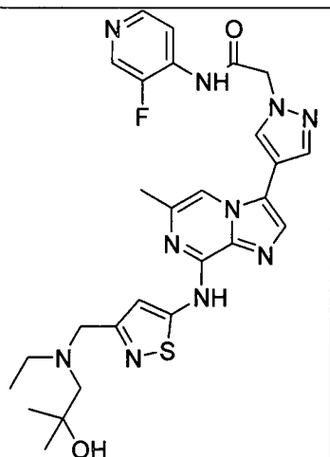
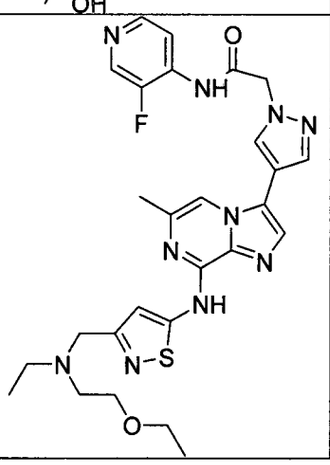
Parte C: Una mezcla de mesilato de la Parte B (24,7 mg, 0,036 mmol), N,N–dietilisopropilamina (7,8 mg, 0,089 mmol) y NaI (1 mg, 0,007 mmol) en 1,5 mL de THF se agitó a 80 °C durante 4 h. Se diluyó con 10 mL de CH_2Cl_2 y se lavó con agua y salmuera. Se secó sobre Na_2SO_4 anhidro. La capa orgánica se concentró al vacío. El residuo se purificó por cromatografía flash eluyendo con

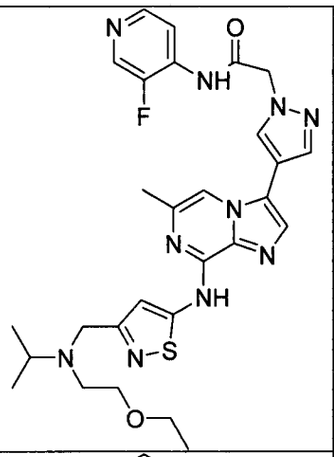
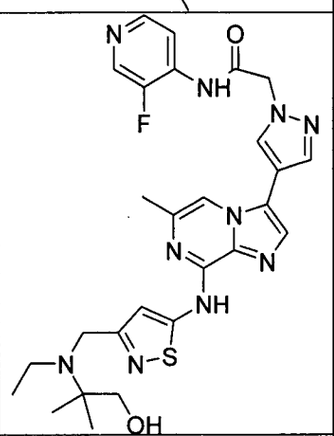
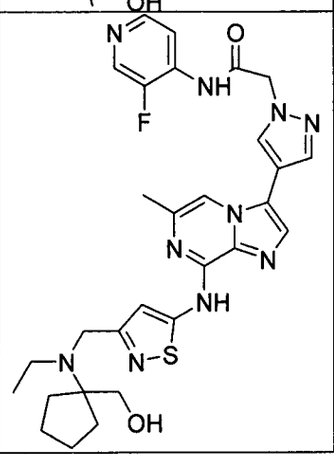
NH_3 7 N en $MeOH/CH_2Cl_2$ (1:30) para dar 11,5 mg de 2–(4–{8–[{3–[(etil–isopropil–amino)–metil]–isotiazol–5–il}–(2–trimetilsilanil–etoximetil)–amino]–6–metil–imidazo[1,2–a]pirazin–3–il}–pirazol–1–il)–*N*–(3–fluoro–piridin–4–il)–acetamida. RMN (400 MHz, $CDCl_3$) δ 9,36 (brs, 1H), 8,30–8,48 (m, 3H), 8,02 (s, 1H), 7,85 (s, 1H), 7,66 (s, 1H), 7,55 (s, 1H), 7,30 (s, 1H), 6,62 (s, 2H), 3,60–3,85 (m, 4H), 2,96–3,15 (brs, 3H), 2,40–2,68 (m, 5H), 0,90–1,20 (m, 12H), 0,00 (s, 9H). A una solución de 2–(4–{8–[{3–[(etil–isopropil–amino)–metil]–isotiazol–5–il}–(2–trimetilsilanil–etoximetil)–amino]–6–metil–imidazo[1,2–a]pirazin–3–il}–pirazol–1–il)–*N*–(3–fluoro–piridin–4–il)–acetamida (11,5 mg, 0,0169 mmol) en 0,4 mL de THF calentada a 80 °C se añadieron 0,4 mL de HCl 4 N en dioxano. La reacción se agitó a 80 °C durante 1 h. Se enfrió hasta temperatura ambiente y luego se añadieron 8 mL de éter. El sólido se recogió por filtración y se lavó con éter para dar 10 mg del compuesto del título. HPLC–MS t_R = 2,18 min (UV $_{254nm}$). Masa calculada para la fórmula $C_{26}H_{29}FN_{10}OS$ 548,2; MH^+ observada (LCMS) 549,3 (m/z).

EJEMPLO 31

Esencialmente por el mismo procedimiento establecido en el Ejemplo 30, pero sólo reemplazando la etilisopropilamina con otras aminas respectivas en la Parte C, se prepararon los compuestos mostrados en la columna 2 de la Tabla 10 (mostrada inmediatamente a continuación).

TABLA 10

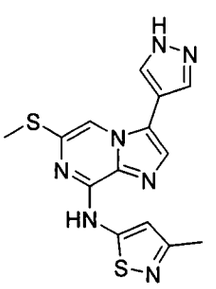
Ejemplo	Columna 2	PM	LCMS MH^+ m/z	HPLC MS t_R
17–1		578,7	579,3	2,17
17–2		578,7	579,3	2,28

17–3		592,7	593,3	2,23
17–4		578,7	579,3	2,28
17–5		604,7	605,3	2,40

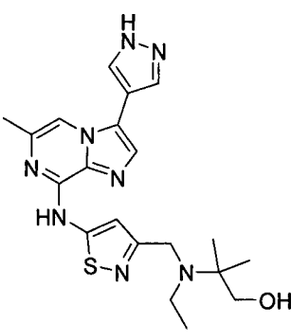
EJEMPLOS

Las células asincrónicas requieren 24 horas de exposición a inhibidores de Aurora quinasa (tales como 250 nM de VX–680 o 1000 nM de COMPUESTO X (el compuesto X se describe en el documento WO 2008/057512, presentado el 6 de noviembre de 2007, Ejemplo 4–3 y reivindicación 70, Ejemplo 4–3 y reivindicación

70 y se muestra más abajo y está representado en la fórmula H y Tabla 2, columna 2, fila 17 de la presentes solicitud) o 25 nM del COMPUESTO Z (el compuesto Z se describe en el documento PCT US2008/007295, presentado el 11 de junio de 2008, Ejemplo 76–2 y reivindicación 25, fila 7, columna 4 y está representado en la Tabla 13, el compuesto 76–2 de la presente solicitud)) para inducir la endorreduplicación (contenido de ADN >4N) o muerte celular. Por ejemplo, se trataron células cancerosas de colon HCT–116 con 1000 nM de COMPUESTO X o 25 nM de COMPUESTO Z durante los tiempos indicados, momentos en los cuales se lavó la droga y se reemplazó con medios nuevos, ver Figura 1 y Figura 8, respectivamente. Las células se analizaron por FACS después de un total de 72 horas. Las exposiciones menores a 24 horas eran insuficientes para inducir la endorreduplicación (contenido de ADN >4N), mientras que la exposición de la droga durante 24, 48 ó 72 horas dio como resultado la acumulación de células que se sometieron a endorreduplicación. Se encontraron similares hallazgos en células de colon HT29, de mama MCF–7 y T47D, de pulmón NCI–460 y A549, de próstata PC_3, DU145, LNCAp, de ovario A2780, SKOV3, PA1, TOV112D y ES2.



el compuesto X



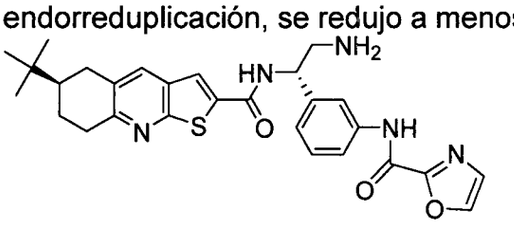
el compuesto Z

Una vez analizadas las células asincrónicas por medio de FACS a las 24 horas, la exposición de 24 horas a un inhibidor de Aurora quinasa (como 250 nM

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de VX–680 o 1000 nM de COMPUESTO X) fue suficiente para inducir la endorreduplicación. Sin embargo, un menor tiempo de exposición fue insuficiente para inducir la endorreduplicación. Por ejemplo, las células cancerosas de colon HCT–116 se trataron con 1000 nM de COMPUESTO X o 25 nM de COMPUESTO Z durante los tiempos indicados, momentos en los cuales la droga se lavó y se reemplazó por nuevos medios, ver Figura 2 y Figura 9, respectivamente. Se analizaron células por medio de FACS después de un total de 24 horas. Las exposiciones menores de 24 horas fueron insuficientes para inducir la endorreduplicación (contenido de ADN >4N), mientras que la exposición de la droga durante 24 horas enteras dio como resultado la acumulación de células que se sometieron a endorreduplicación.

De modo interesante, después de un pretratamiento de 16 horas con taxanos (taxol o taxotere) o inhibidores de KSP, ispinesib SB–715992 o el COMPUESTO A (el compuesto A es un inhibidor de KSP descrito en el documento WO 2006/098.961 presentado el 7 de marzo de 2006, Ejemplo 263, reivindicación 51 y el compuesto A, mostrado más abajo, está representado en la presente solicitud en la fórmula B y Tabla 1, columna 2, fila 7). Después del pretratamiento de células cancerosas de colon HCT–116 con taxano o un inhibidor de KSP descritos con anterioridad, el tiempo de exposición al inhibidor de Aurora quinasa, el compuesto X o Z requerido para inducir la endorreduplicación, se redujo a menos de 4–horas.



compuesto A

Por ejemplo, se trataron células cancerosas de colon HCT–116 durante 16 horas con DMSO (Figura 3) o 5 nM de taxotere y luego se expusieron a DMSO o 1000 nM de COMPUESTO X o 25 nM de COMPUESTO Z durante 4, 8 y 24 horas. Después de 4 u 8 horas, el COMPUESTO X o el COMPUESTO Z se lavaron y se añadió nuevo medio a las células. Las células se recolectaron después de 24 horas y se analizaron por medio de FACS (ver Figura 4 y Figura 11, respectivamente). Después del pretratamiento con DMSO, el DMSO no tuvo efecto sobre la distribución del ciclo celular. El pretratamiento con DMSO seguido de COMPUESTO X o COMPUESTO Z indujo la endorreduplicación, pero sólo cuando la exposición del COMPUESTO X o COMPUESTO Z fue de 24 horas, fue similar a los resultados de la Figura 2. El pretratamiento con taxotere (rotulado en 0 horas), las células se acumularon en mitosis (ADN 4 N). COn el paso del tiempo, cuando se liberaron en DMSO, las células fueron a mitosis. El taxotere seguido de COMPUESTO X o COMPUESTO Z indujo la endorreduplicación. La endorreduplicación se observó incluso cuando la exposición al COMPUESTO X o COMPUESTO Z fue un poco menor de 4 horas. Un similar acortamiento del tiempo requerido para un inhibidor de Aurora quinasa que se ha de exponer a células a fin de inducir endorreduplicación se observó después del pretratamiento con 5 nM de taxol o 10–50 nM de inhibidores de KSP.

Sin embargo, después de un pretratamiento de 16 horas con nocodazol para incrustación, el tiempo requerido para un inhibidor de Aurora (como 250 nM de VX–680 o 1000 nM de COMPUESTO X o COMPUESTO Z) para inducir endorreduplicación no se había reducido. Por ejemplo, se trataron células cancerosas de colon HCT–116 durante 16 horas con 0,4 µg/ml de nocodazol, ver Figura 5 y luego se expusieron a DMSO o 1000 nM de COMPUESTO X o COMPUESTO Z durante 4, 8 ó 24 horas. Después de 4 u 8 horas, el COMPUESTO X o el COMPUESTO Z se lavaron y se añadieron nuevos medios a

las células. Las células se recogieron después de 24 horas y se analizaron por medio de FACS. Después del pretratamiento con nocodazol (rotulados en 0 horas), las células se acumularon en mitosis (ADN 4 N). Con el paso del tiempo, cuando se liberaron en DMSO, las células pasaron por mitosis. El nocodazol seguido de una exposición de 24 horas al COMPUESTO X o al COMPUESTO Z indujo endorreduplicación, sin embargo, una exposición de 4 u 8 horas al COMPUESTO X o al COMPUESTO Z fue insuficiente para inducir endorreduplicación.

Para seguir explorando la combinación con taxotere, analizamos el tratamiento simultáneo con un inhibidor de Aurora quinasa, el compuesto X o el COMPUESTO Z. Cuando se administra el inhibidor de Aurora quinasa al mismo momento que taxotere, una exposición de 4 horas no es suficiente y se necesita una exposición de 24 horas para inducir endorreduplicación. Por ejemplo, las células cancerosas de colon HCT–116 no pretratadas se trataron con 5 nM de taxotere más DMSO o 1000 nM de COMPUESTO X o COMPUESTO Z juntos durante 4, 8 ó 24 horas. En el momento indicado, los medios se retiraron y se reemplazaron con nuevos medios y se añadió taxotere en estas células. Las células se recolectaron después de 24 horas y se analizaron por FACS, ver Figura 6 o Figura 12, respectivamente. Estos datos sugieren que el tratamiento concurrente no era suficiente para reducir el tiempo de exposición requerido para un inhibidor de Aurora quinasa para inducir endorreduplicación.

Los inhibidores individuales de Aurora quinasa requieren de un tiempo de exposición de la droga de 24 horas para inducir endorreduplicación en células asincrónicas. Un pretratamiento de 16 horas con un taxano o un inhibidor de KSP fue suficiente para reducir el tiempo requerido para un inhibidor de Aurora quinasa para inducir endorreduplicación, pero el pretratamiento con otros agentes antimitóticos ensayados (nocodazol y vincristina) no dieron como resultado la

misma reducción en el tiempo de exposición requerido. Los inhibidores de la Aurora quinasa (tales como VX–680 y COMPUESTO X y COMPUESTO Z) son capaces de inhibir la fosforilación de Histona H3 (en serina–10) estimulada por taxanos, inhibidor de KSP y nocodazol. En consecuencia, esto no explica la diferencia. Hallamos que los inhibidores de la Aurora quinasa aceleraron la salida de la mitosis, tal como se midió con un marcador fos–MPM2, en respuesta a la detención inducida por taxano y KSP, pero no a una detención con nocodazol. Este efecto se vio con inhibidores duales de Aurora A/B tales como VX–680, COMPUESTO X, COMPUESTO Z y AT9283, así como con el inhibidor selectivo de Aurora B AZD1152.

La aceleración de taxano, pero no nocodazol, confirma los informes publicados de hallazgos similares. Morrow et al. (*Journal of Cell Science* 2005; 118: 3639) y Ditchfield et al. (*Journal of Cell Biology* 2003; 161: 267) mostraron que el inhibidor de Aurora quinasa ZM4477439 abrogó una detención mitótica inducida por taxol, pero no por nocodazol. El primero grupo sugirió que esto fue causado por la salida acelerada de la detención inducida por taxol. Hauf et al (*Journal of Cell Biology* 2003; 161: 281) demostraron que la hesperadina, un inhibidor no selectivo de Aurora quinasa, causó la detención de las células con taxol o monastrol (un inhibidor de KSP) para entrar en la anafase en menos de 1 hora, mientras que las células en nocodazol quedaron detenidas durante 3–5 horas. De modo similar, Carvalho et al (*Journal of Cell Science* 2003; 116: 2987) mostraron células agotadas de sobrevivir (un regulador de Aurora B) por siARN detenido en mitosis en presencia de nocodazol pero no taxol.

Nuestros datos sugieren que se podrían necesitar exposiciones clínicamente más cortas de células cancerosas a inhibidores de Aurora quinasa si se sigue un tratamiento con taxano. El tratamiento ideal de células cancerosas

con un inhibidor de Aurora quinasa debería seguir un tratamiento de células cancerosas con agentes antimitóticos tales como taxanos.

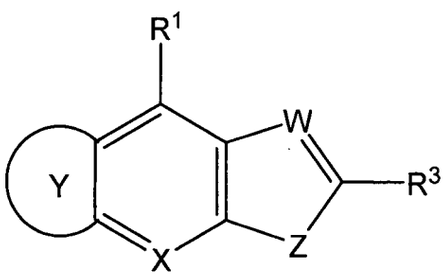
La anterior descripción no pretende detallar todas las modificaciones y variaciones de la invención. Será apreciado por los especialistas en el arte que se pueden hacer cambios a las formas de realización descritas con anterioridad sin apartarse del concepto de la invención. Se entiende, en consecuencia, que la invención no está limitada a las formas de realización particulares descritas con anterioridad, pero pretende cubrir las modificaciones que están dentro del espíritu y el alcance de la invención, tal como se define por el texto de las siguientes reivindicaciones.

REIVINDICACIONES

Habiendo así especialmente descrito y determinado la naturaleza de la presente invención y la forma como la misma ha de ser llevada a la práctica, se declara reivindicar como de propiedad y derecho exclusivo:

1. Una composición farmacéutica para tratar o mejorar cáncer, que comprende en combinación (a) al menos un agente antimitótico seleccionado del grupo que consiste en un taxano, paclitaxel, docetaxel, un inhibidor de Cenp–E, abraxano, epotilona, monastrol, un inhibidor de KSP, ispinesib y un compuesto de las fórmulas A–D mostradas en los puntos a–d que figuran más abajo:

a. Un compuesto representado por la fórmula estructural A:



fórmula A

o una de sus sales, solvatos o ésteres farmacéuticamente aceptables, en donde:

el anillo Y es un arilo de 5 ó 6 miembros o un heteroarilo de 5 ó 6 miembros fusionado tal como se indica en la fórmula A, en donde en dichos arilo y heteroarilo cada carbono del anillo sustituible está sustituido, de modo independiente, con R^2 y cada nitrógeno del anillo sustituible está sustituido, de modo independiente, con R^6;

W es N o $C(R^{12})$;

X es N o N–óxido;

Z es S, S(=O) o $S(=O)_2$;

R^1 es H, alquilo, alcoxi, hidroxi, halo, –CN, $–S(O)_m–$alquilo, $–C(O)NR^9R^{10}$, $–(CR^9R^{10})_{1–6}OH$ o $–NR^4(CR^9R^{10})_{1–2}OR^9$;

cada R^2 está seleccionado, de modo independiente, del grupo que consiste en H, halo, alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo, heteroaralquilo, $–(CR^{10}R^{11})_{0–6}–OR^7$, $–C(O)R^4$, $–C(S)R^4$, $–C(O)OR^7$, $–C(S)OR^7$, $–OC(O)R^7$, $–OC(S)R^7$, $–C(O)NR^4R^5$, $–C(S)NR^4R^5$, $–C(O)NR^4OR^7$, $–C(S)NR^4OR^7$, $–C(O)NR^7NR^4R^5$, $–C(S)NR^7NR^4R^5$, $–C(S)NR^4OR^7$, $–C(O)SR^7$, $–NR^4R^5$, $–NR^4C(O)R^5$, $–NR^4C(S)R^5$, $–NR^4C(O)OR^7$, $–NR^4C(S)OR^7$, $–OC(O)NR^4R^5$, $–OC(S)NR^4R^5$, $–NR^4C(O)NR^4R^5$, $–NR^4C(S)NR^4R^5$, $–NR^4C(O)NR^4OR^7$, $–NR^4C(S)NR^4OR^7$, $–(CR^{10}R^{11})_{0–6}SR^7$, SO_2R^7, $–S(O)_{1–2}NR^4R^5$, $–N(R^7)SO_2R^7$, $–S(O)_{1–2}NR^5OR^7$, –CN, $–OCF_3$, $–SCF_3$, $–C(=NR^7)NR^4$, $–C(O)NR^7(CH_2)_{1–10}NR^4R^5$, $–C(O)NR^7(CH_2)_{1–10}OR^7$, $–C(S)NR^7(CH_2)_{1–10}NR^4R^5$, $–C(S)NR^7(CH_2)_{1–10}OR^7$, haloalquilo y alquilsililo, en donde cada uno de dichos alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo o heteroaralquilo está opcionalmente sustituido, de modo independiente, con 1–5 restos R^9;

cada R^3 está seleccionado, de modo independiente, del grupo que consiste en H, halo, alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo, heteroaralquilo, $–(CR^{10}R^{11})_{0–6}–OR^7$, $–C(O)R^4$, $–C(S)R^4$, $–C(O)OR^7$, $–C(S)OR^7$, $–OC(O)R^7$, $–OC(S)R^7$, $–C(O)NR^4R^5$, $–C(S)NR^4R^5$, $–C(O)NR^4OR^7$, $–C(S)NR^4OR^7$, $–C(O)NR^7NR^4R^5$, $–C(S)NR^7NR^4R^5$, $–C(S)NR^4OR^7$, $–C(O)SR^7$, $–NR^4R^5$, $–NR^4C(O)R^5$, $–NR^4C(S)R^5$, $–NR^4C(O)OR^7$, $–NR^4C(S)OR^7$, $–OC(O)NR^4R^5$, $–OC(S)NR^4R^5$, $–NR^4C(O)NR^4R^5$, $–NR^4C(S)NR^4R^5$, $–NR^4C(O)NR^4OR^7$, $–NR^4C(S)NR^4OR^7$, $–(CR^{10}R^{11})_{0–6}SR^7$, SO_2R^7, $–S(O)_{1–2}NR^4R^5$, $–N(R^7)SO_2R^7$, $–S(O)_{1–2}NR^5OR^7$, –CN, $–OCF_3$, $–SCF_3$, $–C(=NR^7)NR^4R^5$, $–C(O)NR^7(CH_2)_{1–10}NR^4R^5$,

$-C(O)NR^7(CH_2)_{1-10}OR^7$, $-C(S)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(S)NR^7(CH_2)_{1-10}OR^7$, haloalquilo y alquilsililo, en donde cada uno de dichos alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo o heteroaralquilo está opcionalmente sustituido, de modo independiente, con 1–5 restos R^9;

cada R^4 y R^5 está seleccionado, de modo independiente, del grupo que consiste en H, alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo, heteroaralquilo, $-OR^7$, $-C(O)R^7$ y $-C(O)OR^7$, en donde cada uno de dichos alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo o heteroaralquilo está opcionalmente sustituido con 1–4 restos R^8;

o R^4 y R^5, cuando están unidos al mismo átomo de nitrógeno, se toman opcionalmente juntos con el átomo de nitrógeno al que están unidos para formar un anillo heterocíclico de 3–6 miembros que tiene 0–2 heteroátomos adicionales seleccionados de N, O o S;

cada R^6 está seleccionado, de modo independiente, del grupo que consiste en H, alquilo, arilo, aralquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, heteroarilo, heteroaralquilo, $-(CH_2)_{1-6}CF_3$, $-C(O)R^7$, $-C(O)OR^7$ y $-SO_2R^7$;

cada R^7 está seleccionado, de modo independiente, del grupo que consiste en H, alquilo, arilo, aralquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, heteroarilo y heteroaralquilo, en donde cada miembro de R^7 excepto H está opcionalmente sustituido con 1–4 restos R^8;

cada R^8 está seleccionado, de modo independiente, del grupo que consiste en halo, alquilo, cicloalquilo, heterociclilo, arilo, heteroarilo, $-NO_2$, $-OR^{10}$, $-$(alquil C_1–C_6)$-OR^{10}$, $-CN$, $-NR^{10}R^{11}$, $-C(O)R^{10}$, $-C(O)OR^{10}$, $-C(O)NR^{10}R^{11}$, $-CF_3$, $-OCF_3$, $-CF_2CF_3$, $-C(=NOH)R^{10}$, $-N(R^{10})C(O)R^{11}$,

$-C(=NR^{10})NR^{10}R^{11}$ y $-NR^{10}C(O)OR^{11}$, en donde cada uno de dichos alquilo, cicloalquilo, heterociclilo, arilo y heteroarilo está opcionalmente sustituido, de modo independiente, con 1–3 restos seleccionados del grupo que consiste en halo, alquilo, cicloalquilo, heterociclilo, arilo, heteroarilo, $-NO_2$, $-OR^{10}$, –(alquil C_1–C_6)–OR^{10}, –CN, $-NR^{10}R^{11}$, $-C(O)OR^{10}$, $-C(O)NR^{10}R^{11}$, $-CF^3$, $-OCF_3$, $-NR^{10}C(O)OR^{11}$ y $-NR^{10}C(O)R^{40}$;

o dos grupos R^8, cuando están unidos al mismo átomo de carbono, se toman opcionalmente juntos con el átomo de carbono al que están unidos para formar un grupo C=O o un grupo C=S;

cada R^9 está seleccionado, de modo independiente, del grupo que consiste en H, alquilo, alcoxi, OH, CN, halo, $-(CR^{10}R^{11})_{0-4}NR^4R^5$, haloalquilo, hidroxialquilo, alcoxialquilo, $-C(O)NR^4R^5$, $-C(O)OR^7$, $-OC(O)NR^4R^5$, $-NR^4C(O)R^5$ y $-NR^4C(O)NR^4R^5$;

cada R^{10} es, de modo independiente, H o alquilo; o R^9 y R^{10}, cuando están unidos al mismo átomo de nitrógeno, se toman opcionalmente juntos con el átomo de nitrógeno al que están unidos para formar un anillo heterocíclico de 3–6 miembros que tiene 0–2 heteroátomos adicionales seleccionados de N, O o S;

cada R^{11} es, de modo independiente, H o alquilo; o R^{10} y R^{11}, cuando están unidos al mismo átomo de nitrógeno, se toman opcionalmente juntos con el átomo de nitrógeno al que están unidos para formar un anillo heterocíclico de 3–6 miembros que tiene 0–2 heteroátomos adicionales seleccionados de N, O o S;

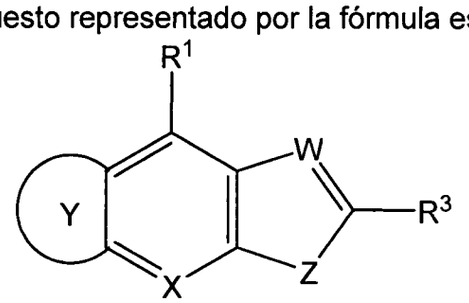
cada R^{12} está seleccionado, de modo independiente, del grupo que consiste en H, halo, alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo, heteroaralquilo, $-(CR^{10}R^{11})_{0-6}-OR^7$, $-C(O)R^4$, $-C(S)R^4$, $-C(O)OR^7$, $-C(S)OR^7$, $-OC(O)R^7$, $-OC(S)R^7$,

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$-C(O)NR^4R^5$, $-C(S)NR^4R^5$, $-C(O)NR^4OR^7$, $-C(S)NR^4OR^7$, $-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, $-CN$, $-OCF_3$, $-SCF_3$, $-C(=NR^7)NR^4$, $-C(O)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}OR^7$, $-C(S)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(S)NR^7(CH_2)_{1-10}OR^7$, haloalquilo y alquilsililo, en donde cada uno de dichos alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo o heteroaralquilo está opcionalmente sustituido, de modo independiente, con 1–5 restos R^9; y

R^{40} está seleccionado del grupo que consiste en cicloalquilo, heterociclilo, arilo y heteroarilo, en donde cada uno de dichos cicloalquilo, heterociclilo, arilo y heteroarilo está opcionalmente sustituidos, de modo independiente, con 1–3 restos seleccionados, de modo independiente, del grupo que consiste en –CN, –OH, halo, alquilo, haloalquilo, alcoxi y $-NR^{10}R^{11}$;

b. Un compuesto representado por la fórmula estructural B:



fórmula B

o una de sus sales, solvatos o ésteres farmacéuticamente aceptables, en donde:

el anillo Y es un anillo de 5 a 7 miembros seleccionado del grupo que consiste en cicloalquilo, cicloalquenilo, heterociclilo o heterociclenilo fusionado tal como se indica en la fórmula B, en donde en cada uno de dichos anillos de 5 a 7

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miembros, cada carbono del anillo sustituible está sustituido, de modo independiente, con 1–2 restos R^2 y cada heteroátomo del anillo sustituible está sustituido, de modo independiente, con R^6;

W es N o $C(R^{12})$;

X es N o N–óxido;

Z es S, S(=O) o $S(=O)_2$;

R^1 es H, alquilo, alcoxi, hidroxi, halo, –CN, $–S(O)_m–$alquilo, $–C(O)NR^9R^{10}$, $–(CR^9R^{10})_{1–6}OH$ o $–NR^4(CR^9R^{10})_{1–2}OR^9$; en donde m es 0 a 2;

cada R^2 está seleccionado, de modo independiente, del grupo que consiste en H, halo, alquilo, cicloalquilo, alquilsililo, cicloalquenilo, heterociclilo, heterociclenilo, arilo, heteroarilo, $–(CR^{10}R^{11})_{0–6}–OR^7$, $–C(O)R^4$, $–C(S)R^4$, $–C(O)OR^7$, $–C(S)OR^7$, $–OC(O)R^7$, $–OC(S)R^7$, $–C(O)NR^4R^5$, $–C(S)NR^4R^5$, $–C(O)NR^4OR^7$, $–C(S)NR^4OR^7$, $–C(O)NR^7NR^4R^5$, $–C(S)NR^7NR^4R^5$, $–C(S)NR^4OR^7$, $–C(O)SR^7$, $–NR^4R^5$, $–NR^4C(O)R^5$, $–NR^4C(S)R^5$, $–NR^4C(O)OR^7$, $–NR^4C(S)OR^7$, $–OC(O)NR^4R^5$, $–OC(S)NR^4R^5$, $–NR^4C(O)NR^4R^5$, $–NR^4C(S)NR^4R^5$, $–NR^4C(O)NR^4OR^7$, $–NR^4C(S)NR^4OR^7$, $–(CR^{10}R^{11})_{0–6}SR^7$, SO_2R^7, $–S(O)_{1–2}NR^4R^5$, $–N(R^7)SO_2R^7$, $–S(O)_{1–2}NR^5OR^7$, –CN, $–OCF_3$, $–SCF_3$, $–C(=NR^7)NR^4$, $–C(O)NR^7(CH_2)_{1–10}NR^4R^5$, $–C(O)NR^7(CH_2)_{1–10}OR^7$, $–C(S)NR^7(CH_2)_{1–10}NR^4R^5$ y $–C(S)NR^7(CH_2)_{1–10}OR^7$, en donde cada uno de dichos alquilo, cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, arilo y heteroarilo está opcionalmente sustituido, de modo independiente, con 1–5 restos R^9;

o dos grupos R^2 en el mismo átomo de carbono se toman opcionalmente juntos con el átomo de carbono al que están unidos para formar un grupo C=O, un grupo C=S o un grupo etilendioxi;

R^3 está seleccionado, de modo independiente, del grupo que consiste en H, halo, alquilo, cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, arilo, heteroarilo, $–(CR^{10}R^{11})_{0–6}–OR^7$, $–C(O)R^4$, $–C(S)R^4$, $–C(O)OR^7$, $–C(S)OR^7$,

$-OC(O)R^7$, $-OC(S)R^7$, $-C(O)NR^4R^5$, $-C(S)NR^4R^5$, $-C(O)NR^4OR^7$, $-C(S)NR^4OR^7$, $-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, $-CN$, $-C(=NR^7)NR^4R^5$, $-C(O)N(R^7)-(CR^{40}R^{41})_{1-5}-C(=NR^7)NR^4R^5$, $-C(O)N(R^7)(CR^{40}R^{41})_{1-5}-NR^4R^5$, $-C(O)N(R^7)(CR^{40}R^{41})_{1-5}-C(O)-NR^4R^5$, $-C(O)N(R^7)(CR^{40}R^{41})_{1-5}-OR^7$, $-C(S)NR^7(CH_2)_{1-5}NR^4R^5$ y $-C(S)NR^7(CH_2)_{1-5}OR^7$, en donde cada uno de dichos alquilo, cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, arilo y heteroarilo está opcionalmente sustituido, de modo independiente, con 1–5 restos R^9;

cada uno de R^4 y R^5 está seleccionado, de modo independiente, del grupo que consiste en H, alquilo, cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, arilo, heteroarilo,
$-OR^7$, $-C(O)R^7$ y $-C(O)OR^7$, en donde cada uno de dichos alquilo, cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, arilo y heteroarilo está opcionalmente sustituido con 1–4 restos R^8;

o R^4 y R^5, cuando están unidos al mismo átomo de nitrógeno, se toman opcionalmente juntos con el átomo de nitrógeno al que están unidos para formar un anillo heterocíclico de 3–6 miembros que tiene 0–2 heteroátomos adicionales seleccionados de N, O o S;

cada R^6 está seleccionado, de modo independiente, del grupo que consiste en H, alquilo, arilo, aralquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, heteroarilo, heteroaralquilo, $-(CH_2)_{1-6}CF_3$, $-C(O)R^7$, $-C(O)OR^7$ y $-SO_2R^7$;

cada R^7 está seleccionado, de modo independiente, del grupo que consiste en H, alquilo, arilo, aralquilo, cicloalquilo, cicloalquilalquilo, heterociclilo,

heterociclilalquilo, heteroarilo y heteroaralquilo, en donde cada miembro de R^7 excepto H está opcionalmente sustituido con 1–4 restos R^8;

cada R^8 está seleccionado, de modo independiente, del grupo que consiste en halo, alquilo, cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, arilo, heteroarilo, $-NO_2$, $-OR^{10}$, –(alquil C_1–C_6)–OR^{10}, –CN, $-NR^{10}R^{11}$, $-C(O)R^{10}$, $-C(O)OR^{10}$, $-C(O)NR^{10}R^{11}$, $-CF_3$, $-OCF_3$, $-CF_2CF_3$, $-C(=NOH)R^{10}$, $-N(R^{10})C(O)R^{11}$, $-C(=NR^{10})NR^{10}R^{11}$ y $-NR^{10}C(O)OR^{11}$; en donde cada uno de dichos alquilo, cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, arilo y heteroarilo está opcionalmente sustituido, de modo independiente, con 1–4 restos R^{42}; en donde cuando cada uno de dichos cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, arilo y heteroarilo contienen dos radicales en átomos de carbono adyacentes en cualquier parte dentro de dichos cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, arilo y heteroarilo, dichos radicales se pueden formar, opcional e independientemente en cualquier aparición, junto con los átomos de carbono a los que están unidos para formar un anillo carbocíclico o heterocíclico de cinco o seis miembros;

o dos grupos R^8, cuando están unidos al mismo carbono, se toman opcionalmente juntos con el átomo de carbono al que están unidos para formar un grupo C=O o un grupo C=S;

cada R^9 está seleccionado, de modo independiente, del grupo que consiste en H, alquilo, alcoxi, OH, CN, halo, $-(CR^{10}R^{11})_{0-4}NR^4R^5$, haloalquilo, hidroxialquilo, alcoxialquilo, $-C(O)NR^4R^5$, $-C(O)OR^7$, $-OC(O)NR^4R^5$, $-NR^4C(O)R^5$ y $-NR^4C(O)NR^4R^5$;

cada R^{10} es, de modo independiente, H o alquilo; o R^9 y R^{10}, cuando están unidos al mismo átomo de nitrógeno, se toman opcionalmente juntos con el átomo de nitrógeno al que están unidos para formar un anillo heterocíclico de 3–6 miembros que tiene 0–2 heteroátomos adicionales seleccionados de N, O o S;

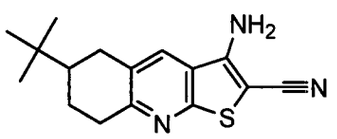
cada R^{11} es, de modo independiente, H, alquilo, cicloalquilo, cicloalquenilo, arilo, heterociclilo, heterociclenilo o heteroarilo; o R^{10} y R^{11}, cuando están unidos al mismo átomo de nitrógeno, se toman opcionalmente juntos con el átomo de nitrógeno al que están unidos para formar un anillo heterocíclico de 3–6 miembros que tiene 0–2 heteroátomos adicionales seleccionados de N, O o S; en donde cada uno de dichos R^{11} alquilo, cicloalquilo, cicloalquenilo, arilo, heterociclilo, heterociclenilo y heteroarilo está opcionalmente sustituido, de modo independiente, con 1–3 restos seleccionados del grupo que consiste en –CN, –OH, $-NH_2$, –N(H)alquilo, $-N(alquilo)_2$, halo, haloalquilo, CF_3, alquilo, hidroxialquilo, alcoxi, arilo, ariloxi y heteroarilo;

cada R^{12} está seleccionado, de modo independiente, del grupo que consiste en H, halo, alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo, heteroaralquilo, $-(CR^{10}R^{11})_{0-6}-OR^7$, $-C(O)R^4$, $-C(S)R^4$, $-C(O)OR^7$, $-C(S)OR^7$, $-OC(O)R^7$, $-OC(S)R^7$, $-C(O)NR^4R^5$, $-C(S)NR^4R^5$, $-C(O)NR^4OR^7$, $-C(S)NR^4OR^7$, $-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, –CN, $-OCF_3$, $-SCF_3$, $-C(=NR^7)NR^4$, $-C(O)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}OR^7$, $-C(S)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(S)NR^7(CH_2)_{1-10}OR^7$, haloalquilo y alquilsililo, en donde cada uno de dichos alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo o heteroaralquilo está opcionalmente sustituido, de modo independiente, con 1–5 restos R^9;

R^{40} y R^{41} pueden ser iguales o diferentes, en donde cada uno está seleccionado, de modo independiente, del grupo que consiste en H, alquilo, arilo, heteroarilo, heterociclilo, heterociclenilo, cicloalquilo y cicloalquenilo;

cada R^{42} está seleccionado, de modo independiente, del grupo que consiste en halo, alquilo, cicloalquilo, heterociclilo, arilo, heteroarilo, $-NO_2$, $-OR^{10}$, $-$(alquil C_1–C_6)$-OR^{10}$, $-CN$, $-NR^{10}R^{11}$, $-C(O)R^{10}$, $-C(O)OR^{10}$, $-C(O)NR^{10}R^{11}$, $-CF_3$, $-OCF_3$, $-N(R^{10})C(O)R^{11}$ y $-NR^{10}C(O)OR^{11}$;

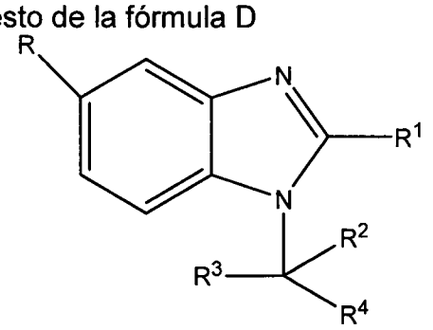
con la condición de que, cuando W es $C(R^{12})$, R^{12} y R^3 se tomen opcionalmente juntos con los dos átomos de carbono del anillo a los que están unidos para formar un anillo de 6 miembros seleccionado del grupo que consiste en cicloalquenilo, arilo, heteroarilo, heterociclilo y heterociclenilo, en donde dicho anillo de 6 miembros está opcionalmente sustituido con 1–3 restos seleccionados, de modo independiente, de oxo, tioxo, $-OR^{11}$, $-NR^{10}R^{11}$, $-C(O)R^{11}$, $-C(O)OR^{11}$, $-C(O)N(R^{10})(R^{11})$ o $-N(R^{10})C(O)R^{11}$;

c. 

fórmula C

o una de sus sales, solvatos o ésteres farmacéuticamente aceptables; y

d. Un compuesto de la fórmula D



fórmula D

o una de sus sales, solvatos o ésteres farmacéuticamente aceptables, en donde:

R está seleccionado del grupo que consiste en H, alquilo, ciano, haloalquilo, halo, —SH, –S–alquilo, –S–haloalquilo, $-S(=O)_2$alquilo, $-S(=O)_2OH$, $-S(=O)_2NH_2$, $-S(=O)_2NH$(alquilo), $S(=O)_2NH$(cicloalquilo),

$-S(=O)_2N(alquilo)_2$, $-S(=O)_2$heterociclilo, $-S(=O)_2$heteroarilo, cicloalquilo, arilo, heterociclilo, heteroarilo, –NHC(=O)alquilo, $-C(=O)NH_2$, –C(=O)NH(alquilo), –C(=O)NH(cicloalquilo), $-C(=O)N(alquilo)_2$, –C(=O)OH, –C(=O)Oalquilo, –C(=O)heterociclilo, –C(=O)NH(arilo), en donde cuando cada uno de dichos cicloalquilo, arilo, heterociclilo, heteroarilo y las porciones de "heterociclilo" y "arilo" de dichos grupos R tiene dos sustituyentes en átomos de carbono adyacentes, dichos sustituyentes se pueden tomar opcionalmente juntos con los átomos de carbono a los que están unidos para formar un anillo cicloalquilo, arilo, heterociclilo, heterociclenilo o heteroarilo de cinco o seis miembros; en donde cada uno de los R antes mencionados alquilo, arilo, cicloalquilo, heterociclilo y heteroarilo y las porciones de "alquilo", "cicloalquilo", "heterociclilo" y "arilo" de dichos grupos R, opcionalmente con dichos anillo arilo, heterociclilo, heterociclenilo o heteroarilo de cinco o seis miembros, está opcionalmente sustituido con 1–3 sustituyentes seleccionados, de modo independiente, del grupo que consiste en alquilo, alquenilo, alquinilo, hidroxilo, ciano, halo, haloalquilo, haloalcoxi, –C(O)OH, –C(=O)Oalquilo y $-C(O)NH_2$;

R^1 está seleccionado del grupo que consiste en alquilo, heterociclilo, –C(=O)arilo, $-NH_2$, –NH(alquilo), –NH(cicloalquilo), –N(alquil)(cicloalquilo), –NH(heterociclilo), –N(alquil)(heterociclilo), $N(alquilo)_2$, –NH(arilo), –N(alquil)(arilo), $-N(arilo)_2$, –NH(heteroarilo), –N(alquil)(heteroarilo), –NHC(=O)–alquilo, –N(alquil)C(=O)–alquilo, –NHC(=O)Oalquilo, –N(alquil)C(=O)O–alquilo, en donde cada uno de los alquilo, heterociclilo antes mencionados y las porciones de "alquilo", "cicloalquilo", "arilo" y "heteroarilo" de dichos grupos R^1 está opcionalmente sustituido con 1–3 sustituyentes seleccionados, de modo independiente, del grupo que consiste en halo, heterociclilo, arilo, heteroarilo, haloalquilo, haloalcoxi,

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ariloxi, ciano, –SH, –S–alquilo, –S–haloalquilo, $–S(=O)_2$alquilo, $–S(=O)_2OH$, $–S(=O)_2NH_2$, $–S(=O)_2$NH(alquilo), $S(=O)_2$NH(cicloalquilo), $–S(=O)_2N$(alquilo)$_2$, $–S(=O)_2$heterociclilo, $–S(=O)_2$heteroarilo, hidroxi, alquilo, alquenilo, alquinilo, $–NH_2$, –NH(alquilo), $–N(alquilo)_2$, alcoxi, –NHC(=O)alquilo, –C(=O)H, –C(=O)alquilo, –C(=O)arilo, –C(=O)heteroarilo, –C(=O)Oalquilo, $–C(=O)NH_2$, –C(O)NHalquilo, $–C(=O)N(alquilo)_2$; en donde cuando cada uno de dichos heterociclilo, arilo y heteroarilo tiene dos sustituyentes en átomos de carbono adyacentes, dichos sustituyentes se pueden tomar opcionalmente juntos con los átomos de carbono a los que están unidos para formar un anillo arilo, heterociclilo, heterociclenilo o heteroarilo de cinco a seis miembros;

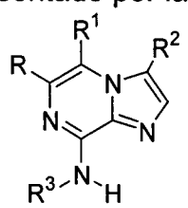
R^2 y R^3 son, de modo independiente, H o alquilo o $–C(R^2)(R^3)–$ está ausente;

R^4 está seleccionado del grupo que consiste en alquilo, cicloalquilo, heterociclilo, arilo y heteroarilo, en donde cuando cada uno de dichos cicloalquilo, heterociclilo, arilo y heteroarilo tiene dos sustituyentes en átomos de carbono adyacentes, dichos sustituyentes se pueden tomar opcionalmente juntos con los átomos de carbono a los que están unidos para formar un anillo arilo, heterociclilo, heterociclenilo o heteroarilo de cinco a seis miembros; en donde cada uno de los R^4 antes mencionados alquilo, cicloalquilo, heterociclilo, arilo y heteroarilo, opcionalmente con dichos anillos arilo, heterociclilo, heterociclenilo o heteroarilo de cinco a seis miembros está opcionalmente sustituido con 1–3 sustituyentes seleccionados, de modo independiente, del grupo que consiste en ciano, halo, haloalquilo, alquilo, alcoxi, hidroxilo, haloalcoxi, cicloalquilo, heterociclilo, arilo, heteroarilo, $–S(=O)_2$alquilo, $–S(=O)_2NH_2$,

$-S(=O)_2NH$(alquilo), $-S(=O)_2N$(alquilo)$_2$, –S–alquilo, –S–haloalquilo, $-C(=O)OH$, $-NH_2$, –NH(alquilo), –N(alquilo)$_2$ y $-C(=O)O$alquilo;

y (b) uno o varios de un segundo compuesto, en donde dicho segundo compuesto es un inhibidor de aurora quinasa seleccionado del grupo que consiste en compuestos representados por las fórmulas E–K mostrados más abajo en los puntos e–k:

e. Un compuesto representado por la fórmula estructural E:



fórmula E

o una de sus sales, solvatos, ésteres o profármacos farmacéuticamente aceptables, en donde:

R es H, CN, $-NR^5R^6$, cicloalquilo, cicloalquenilo, heterociclenilo, heteroarilo, $-C(O)NR^5R^6$, $-N(R^5)C(O)R^6$, heterociclilo, heteroarilo sustituido con $(CH_2)_{1-3}NR^5R^6$, alquilo no sustituido o alquilo sustituido con uno o varios restos que pueden ser iguales o diferentes, donde cada resto está seleccionado, de modo independiente, del grupo que consiste en $-OR^5$, heterociclilo, $-N(R^5)C(O)N(R^5R^6)$, $-N(R^5)-C(O)OR^6$, $-(CH_2)_{1-3}-N(R^5R^6)$ y $-NR^5R^6$;

R^1 es H, halo, arilo o heteroarilo, en donde cada uno de dichos arilo y heteroarilo pueden no estar sustituidos o pueden estar sustituidos con uno o varios restos que pueden ser iguales o diferentes donde cada resto está seleccionado, de modo independiente, del grupo que consiste en halo, alquilo, alquenilo, alquinilo, cicloalquilo, arilo, heteroarilo, heterociclilo, $-CH_2OR^5$, $-C(O)NR^5R^6$, $-C(O)OH$, $-C(O)NH_2$,

$-NR^5R^6$ (en donde R^5 y R^6, junto con el N de dicho $-NR^5R^6$, forman un anillo heterociclilo), $-S(O)R^5$, $-S(O_2)R^5$, –CN, –CHO, $-SR^5$, $-C(O)OR^5$,

$-C(O)R^5$ y $-OR^5$;

R^2 es H, halo, arilo, arilalquilo o heteroarilo, en donde cada uno de dichos arilo, arilalquilo y heteroarilo puede no estar sustituido o puede estar opcionalmente sustituido, de modo independiente, con uno o varios restos que pueden ser iguales o diferentes donde cada resto está seleccionado, de modo independiente, del grupo que consiste en halo, amida, alquilo, alquenilo, alquinilo, cicloalquilo, arilo, $-C(O)OH$, $-C(O)NH_2$, $-NR^5R^6$ (en donde R^5 y R^6, junto con el N de dicho $-NR^5R^6$, forman un anillo heterociclilo), –CN, arilalquilo, $-CH_2OR^5$, $-S(O)R^5$, $-S(O_2)R^5$, –CN, –CHO, $-SR^5$, $-C(O)OR^5$, $-C(O)R^5$, heteroarilo y heterociclilo;

R^3 es H, alquilo, cicloalquilo, heterociclilo, arilo o heteroarilo, en donde:

– dicho alquilo mostrado con anterioridad para R^3 puede no estar sustituido o puede estar sustituido con uno o varios restos que pueden ser iguales o diferentes donde cada resto está seleccionado, de modo independiente, del grupo que consiste en $-OR^5$, alcoxi, heteroarilo y $-NR^5R^6$;

– dicho arilo mostrado con anterioridad para R^3 puede no estar sustituido o puede estar opcionalmente sustituido u opcionalmente fusionado con halo, heteroarilo, heterociclilo, cicloalquilo o heteroarilalquilo, en donde cada uno de dichos heteroarilo, heterociclilo, cicloalquilo y heteroarilalquilo puede no estar sustituido o puede estar opcionalmente sustituido, de modo independiente, con uno o varios restos que pueden ser iguales o diferentes, donde cada resto está seleccionado, de modo independiente, de alquilo, $-OR^5$, $-N(R^5R^6)$ y $-S(O_2)R^5$; y

– dicho heteroarilo mostrado con anterioridad para R^3 puede no estar sustituido o puede estar opcionalmente sustituido u opcionalmente

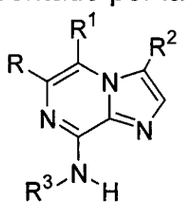
fusionado con uno o varios restos que pueden ser iguales o diferentes con donde cada resto está seleccionado, de modo independiente, del grupo que consiste en halo, amino, alcoxicarbonilo, $-OR^5$, alquilo, –CHO, – NR^5R^6, $-S(O_2)N(R^5R^6)$, $-C(O)N(R^5R^6)$, $-SR^5$, alquenilo, alquinilo, cicloalquilo, arilo, heteroarilo, heterociclenilo y heterociclilo;

R^5 es H, alquilo, aminoalquilo, arilo, heteroarilo, heterociclilo o cicloalquilo; y

R^6 es H, alquilo, arilo, arilalquilo, heteroarilo, heterociclilo o cicloalquilo;

también en donde en cualquier $-NR^5R^6$ en la fórmula I, dichos R^5 y R^6 pueden estar opcionalmente unidos junto con el N de dicho $-NR^5R^6$ para formar un anillo cíclico;

f. Un compuesto representado por la fórmula estructural:

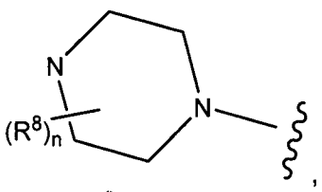
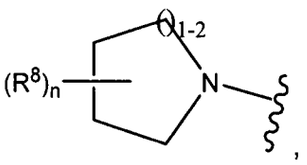
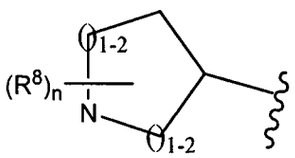
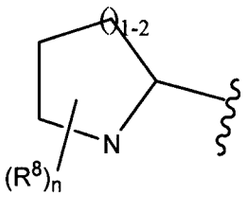


fórmula F

o una de sus sales, solvatos, ésteres o profármacos farmacéuticamente aceptables, en donde:

R está seleccionado del grupo que consiste en H, halógeno, arilo, heteroarilo, cicloalquilo, arilalquilo, heterociclilo, heterociclilalquilo, alquenilo, alquinilo,

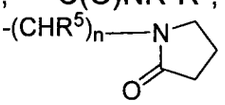
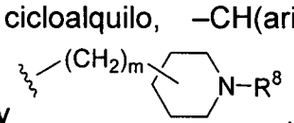
$-C(O)R^7$,


,

,

y


en donde cada uno de dichos arilo, heteroarilo, cicloalquilo, arilalquilo, alquenilo, heterociclilo y los restos de heterociclilo cuyas estructuras se muestran inmediatamente antes para R pueden no estar sustituidas o pueden estar opcionalmente sustituidas, de modo independiente, con uno o varios restos que pueden ser iguales o diferentes, donde cada resto está seleccionado, de modo independiente, del grupo que consiste en halógeno, alquilo, cicloalquilo, CF_3, CN, $-OCF_3$, $-OR^6$, $-C(O)R^7$, $-NR^5R^6$, $-C(O_2)R^6$, $-C(O)NR^5R^6$, $-(CHR^5)_nOR^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^6$;

R^1 es H, halógeno o alquilo;

R^2 es alquilo;

R^3 está seleccionado del grupo que consiste en H, arilo, heteroarilo, heterociclilo, $-(CHR^5)_n$–arilo, $-(CHR^5)_n$–heteroarilo, $-(CHR^5)_n-OR^6$, $-S(O_2)R^6$, $-C(O)R^6$, $-S(O_2)NR^5R^6$, $-C(O)OR^6$, $-C(O)NR^5R^6$, cicloalquilo, $-CH(arilo)_2$, $-(CH_2)_m-NR^8$, $-(CHR^5)_n-CH(arilo)_2$,  y  , en donde cada uno de dichos arilo, heteroarilo y heterociclilo puede estar sustituido u opcionalmente sustituido con uno o varios restos que pueden ser iguales o diferentes, donde cada resto está seleccionado, de modo independiente, del grupo que consiste en halógeno, alquilo, arilo, cicloalquilo, CF_3, CN, $-OCF_3$, $-OR^5$, $-NR^5R^6$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^6$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^6$;

R^5 es H o alquilo;

R^6 está seleccionado del grupo que consiste en H, alquilo, arilo, heteroarilo, arilalquilo y heteroarilalquilo, en donde cada uno de dichos alquilo, heteroarilalquilo, arilo, heteroarilo y arilalquilo puede no estar sustituido o puede estar opcionalmente sustituido con uno o varios restos que pueden ser iguales o diferentes, donde cada resto está seleccionado, de modo independiente, del grupo que consiste en halógeno, alquilo, arilo, cicloalquilo, CF_3, OCF_3, CN, $-OR^5$, $-NR^5R^6$, $-CH_2OR^5$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^6$;

R^7 está seleccionado del grupo que consiste en alquilo, arilo, heteroarilo, arilalquilo y heteroarilalquilo, en donde cada uno de dichos alquilo, heteroarilalquilo, arilo, heteroarilo y arilalquilo puede no estar sustituido o puede estar opcionalmente sustituido con uno o varios restos que pueden ser iguales o diferentes, donde cada resto está seleccionado, de modo independiente, del grupo que consiste en halógeno, alquilo, arilo, cicloalquilo, CF_3, OCF_3, CN, $-OR^5$, $-NR^5R^6$, $-CH_2OR^5$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^6$;

R^8 está seleccionado del grupo que consiste en R^6, $-C(O)NR^5R^6$, $-S(O_2)NR^5R^6$, $-C(O)R^7$, $-C(O_2)R^6$, $-S(O_2)R^7$ y $-(CH_2)$–arilo;

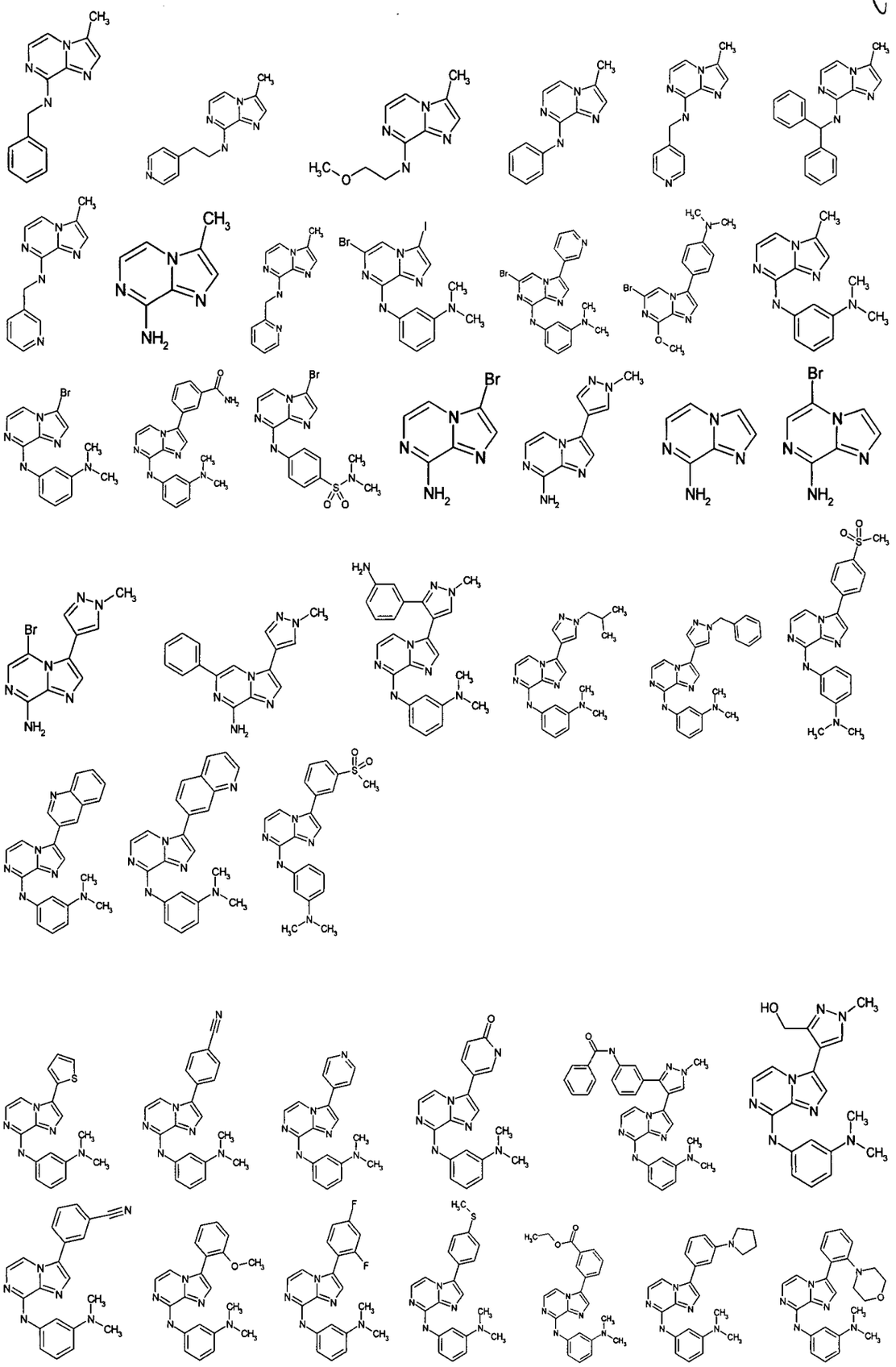
R^9 está seleccionado del grupo que consiste en halógeno, CN, NR^5R^6, $-C(O_2)R^6$, $-C(O)NR^5R^6$, $-OR^6$, $-C(O)R^7$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^6$;

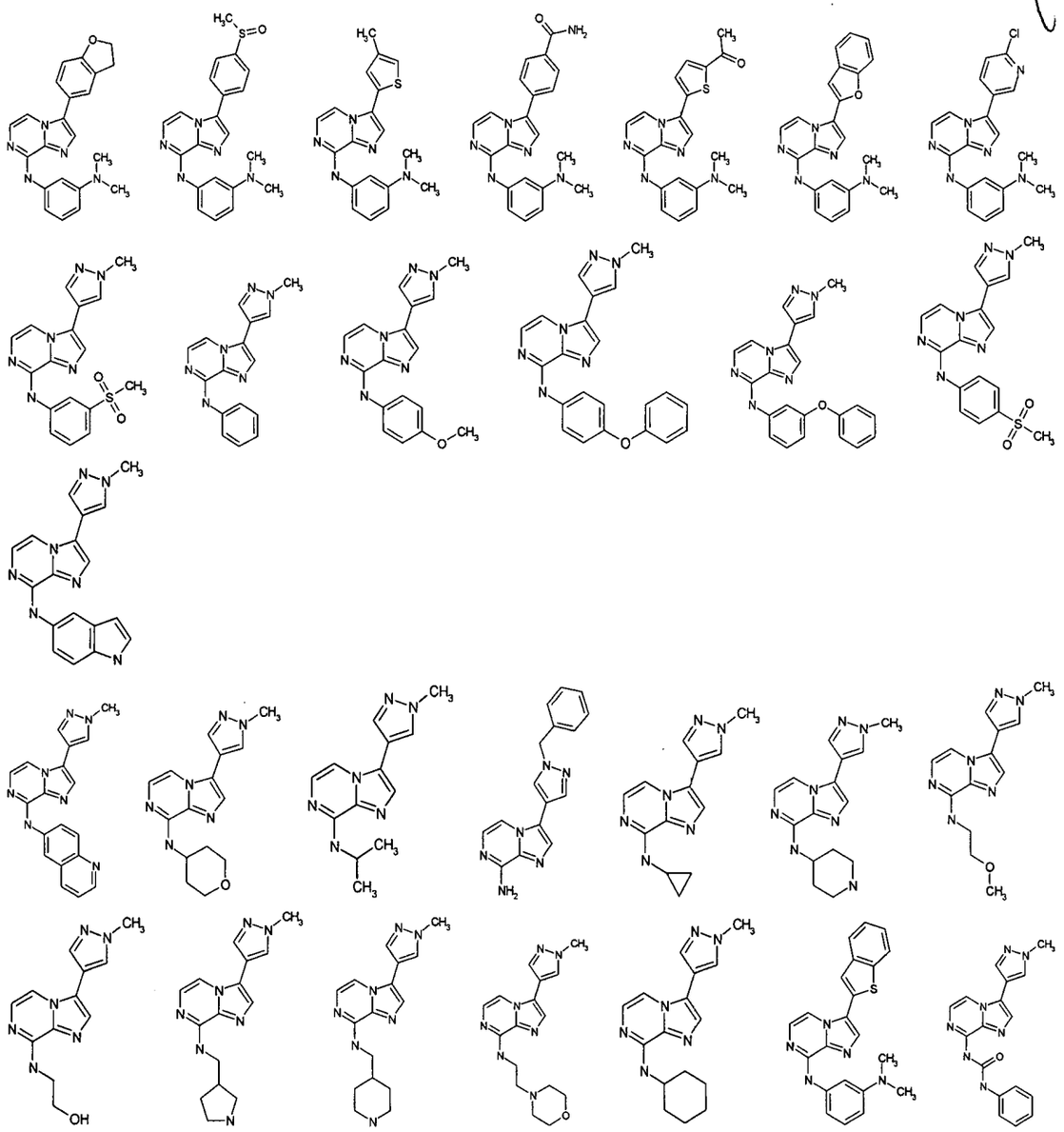
m es 0 a 4;

n es 1–4; y

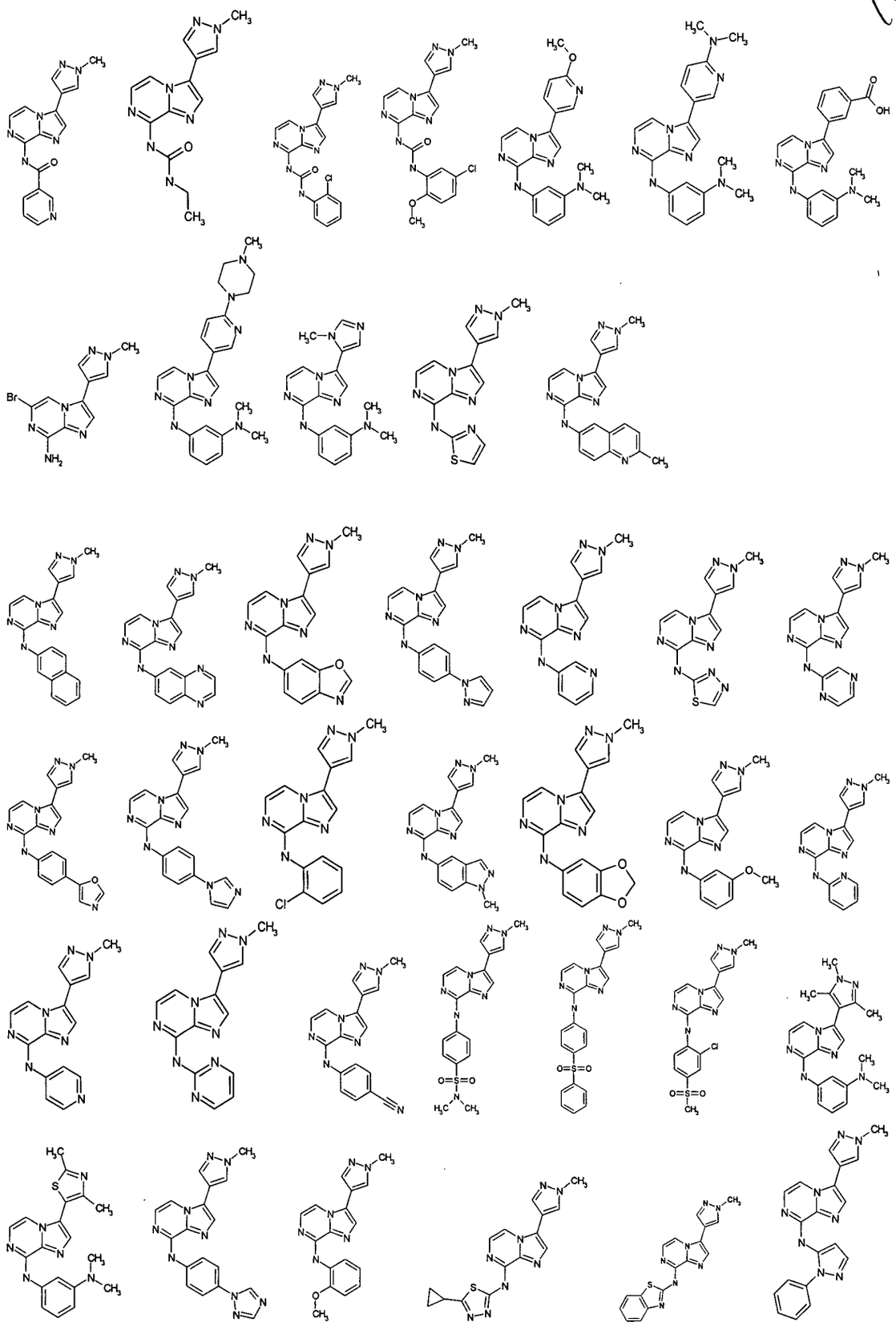
p es 0–3;

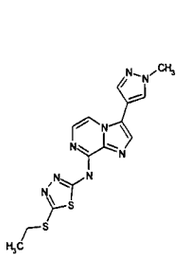
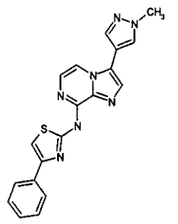
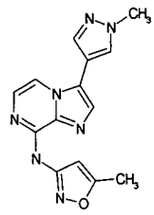
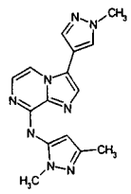
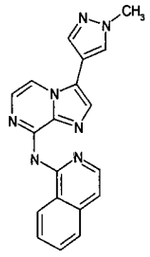
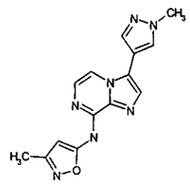
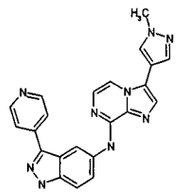
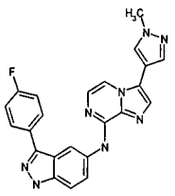
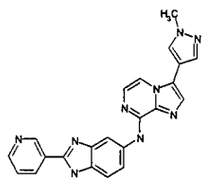
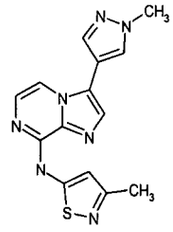
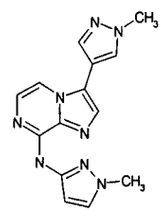
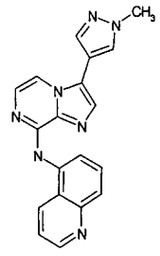
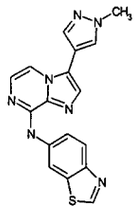
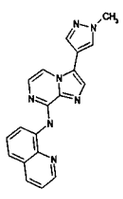
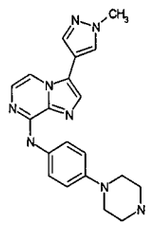
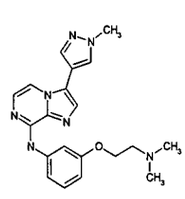
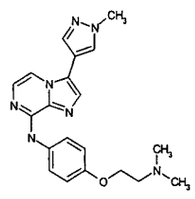
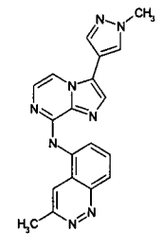
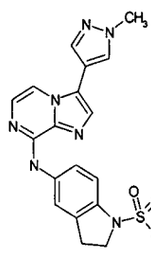
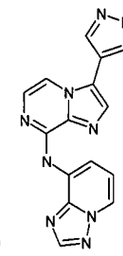
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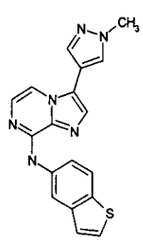
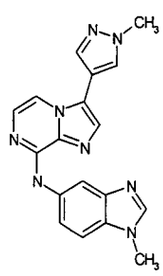
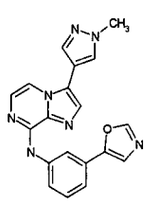
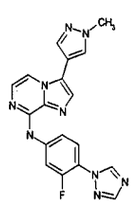
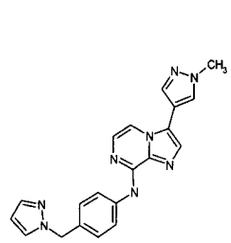
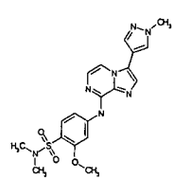
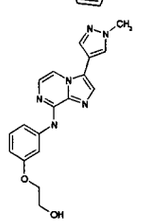
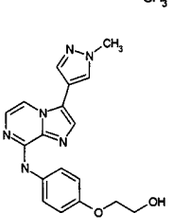
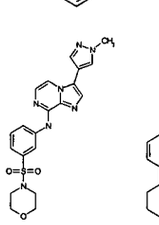
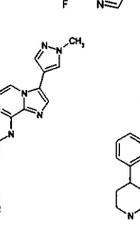
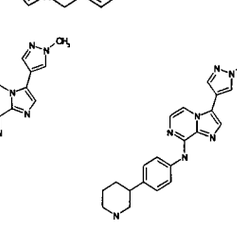
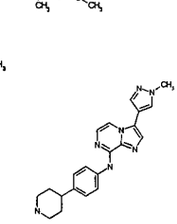


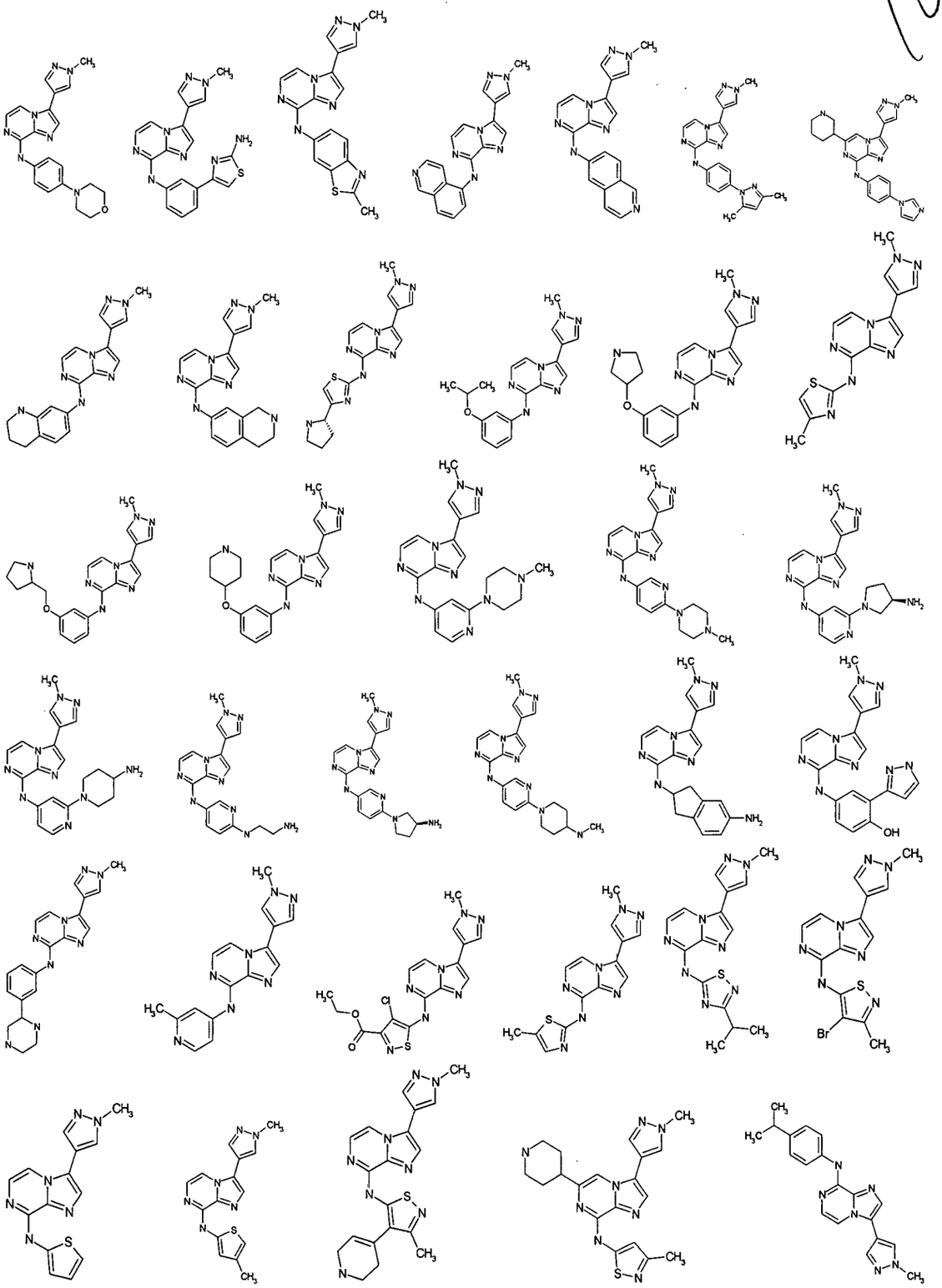


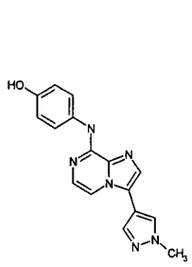
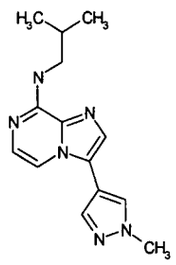
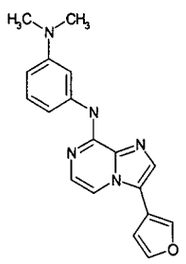
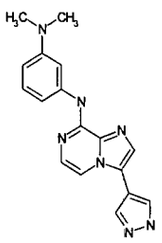
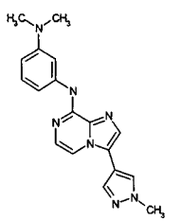
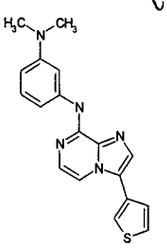
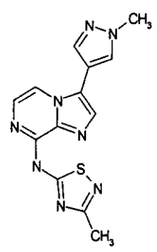
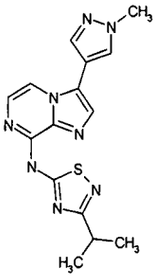
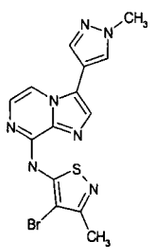
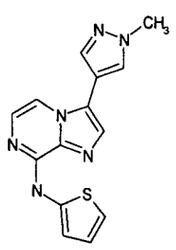
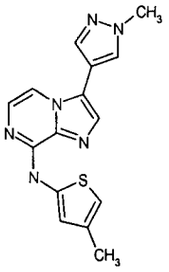
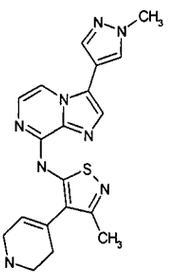
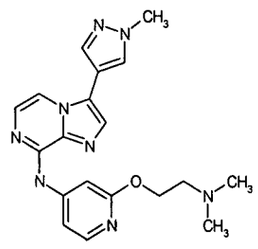
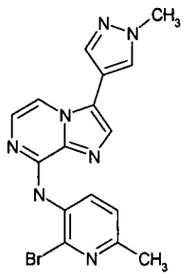
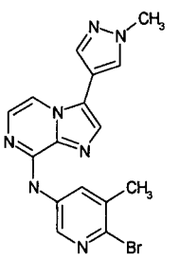
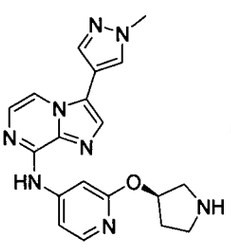
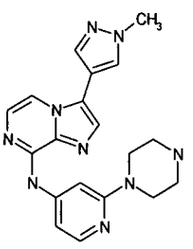
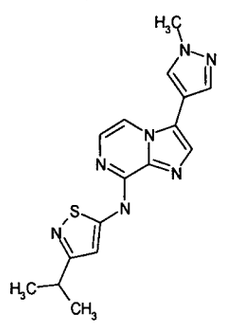
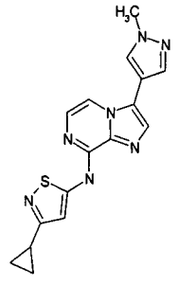
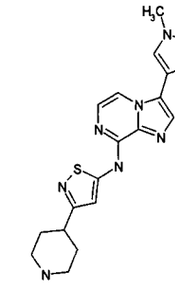
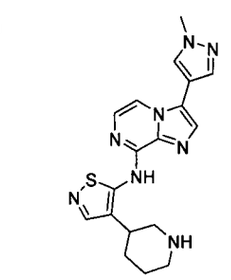
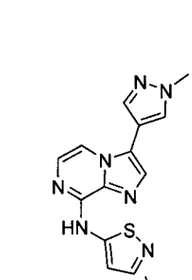
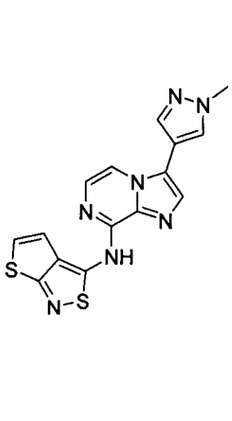
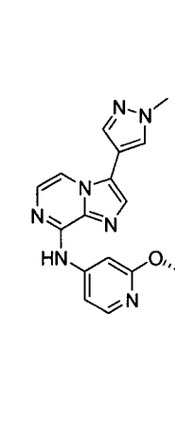
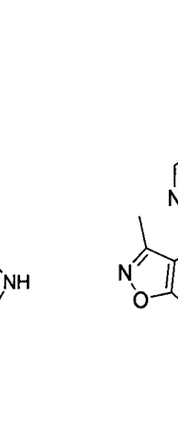
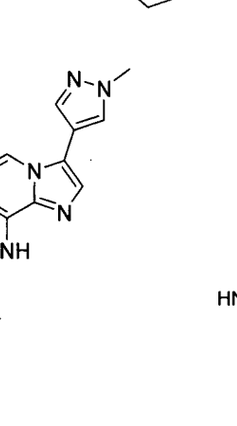
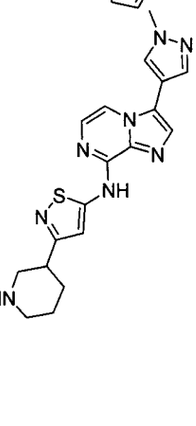
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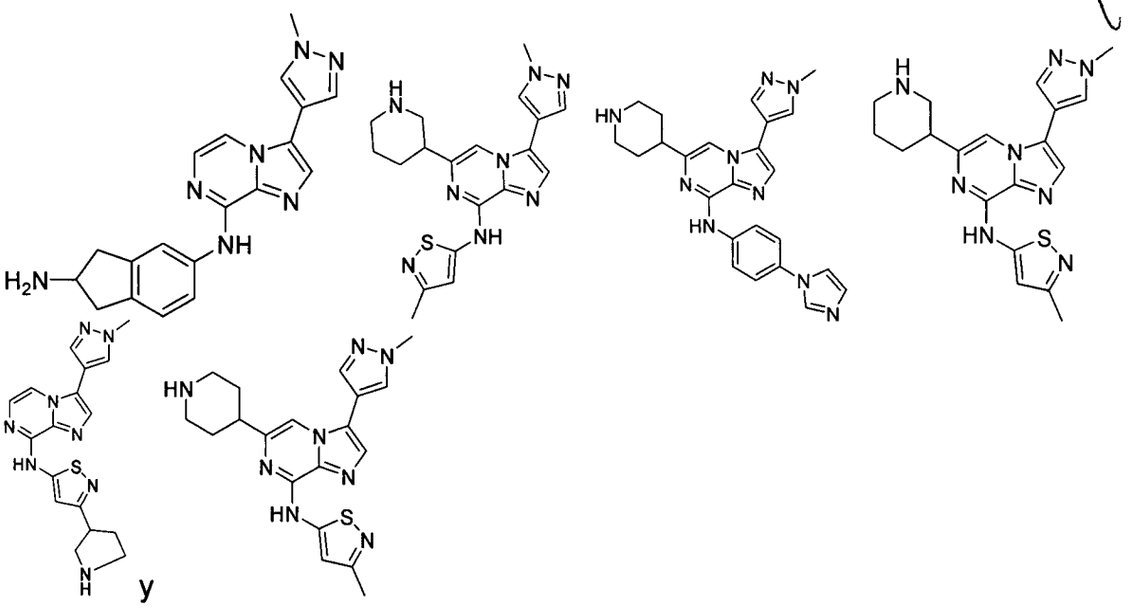




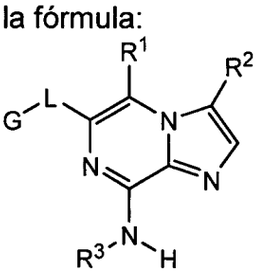






























y

o una de sus sales, solvatos, ésteres o profármacos farmacéuticamente aceptables;

h. Un compuesto de la fórmula:



fórmula H

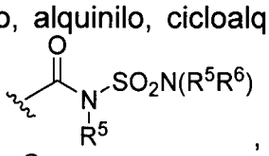
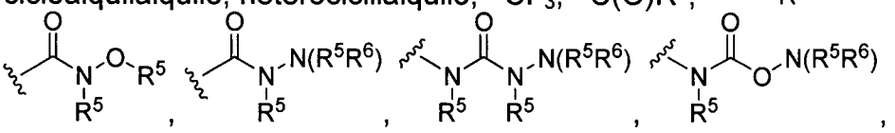
o una de sus sales, solvatos, ésteres o profármacos farmacéuticamente aceptables, en donde:

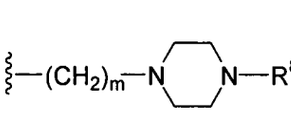
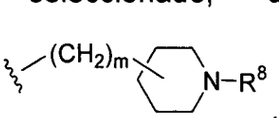
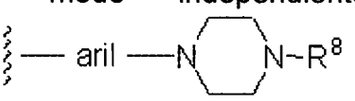
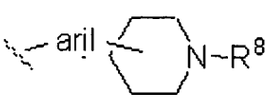
L está seleccionado del grupo que consiste en S, S(O) y $S(O_2)$;

G es alquilo, alquenilo, cicloalquilo, cicloalquenilo, arilo, heteroarilo, heterociclenilo o heterociclilo, en donde cada uno de dichos alquilo, alquenilo, cicloalquilo, cicloalquenilo, arilo, heteroarilo, heterociclenilo o heterociclilo puede no estar sustituido o puede estar opcionalmente sustituido, de modo independiente, con uno o varios restos que están seleccionados, de modo independiente, del grupo que consiste en $-OR^5$, halo, $-CN$, $-C(O)NR^5R^6$, $-N(H)-C(O)R^5$,$-N(H)-C(O)-NR^5R^6$, $-S(O_2)NR^5R^6$, $-NR^5R^6$, $-C(O)R^5$, –

$C(O_2)R^5$, $-SR^5$, $-S(O)R^5$, $-S(O_2)R^5$;

R^1 es H, halo, alquilo, arilo o heteroarilo, en donde cada uno de dichos alquilo, arilo y heteroarilo puede no estar sustituido o puede estar sustituido con uno o varios restos que pueden ser iguales o diferentes donde cada resto está seleccionado, de modo independiente, del grupo que consiste en halo, alquilo, alquenilo, alquinilo, cicloalquilo, arilo, heteroarilo, heterociclilo, $-C(O)NR^5R^6$ y $-OR^5$;

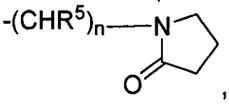
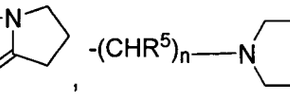
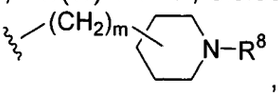
R^2 está seleccionado del grupo que consiste en H, R^9, alquilo, arilo, arilalquilo, heteroarilo, heteroarilalquilo, heterociclilo, alquenilo, alquinilo, cicloalquilo, cicloalquilalquilo, heterociclilalquilo, $-CF_3$, $-C(O)R^7$,  ,  ,

alquilo sustituido con 1–6 grupos R^9 que pueden ser iguales o diferentes estando cada R^9 seleccionado, de modo independiente,  ,  ,  y  ,

en donde cada uno de dichos arilo, heteroarilo, cicloalquilo, arilalquilo y heterociclilo antes mencionados puede no estar sustituido o puede estar opcionalmente sustituido, de modo independiente, con uno o varios restos que pueden ser iguales o diferentes, donde cada resto está seleccionado, de modo independiente, del grupo que consiste en halo, alquilo, alquenilo, alquinilo, cicloalquilo, arilo, heteroarilo, heterociclilo, CF_3, CN, $-OCF_3$, $-OR^6$, $-C(O)R^7$, $-NR^5R^6$, $-C(O_2)R^6$,

$-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$,

$-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^6$;

R^3 está seleccionado del grupo que consiste en H, alquilo, arilo, heteroarilo, heterociclilo, aralquilo, heteroarilalquilo, cicloalquilalquilo, heterociclilalquilo,  ,  , $-(CHR^5)_n-OR^6$, $-S(O_2)R^6$, $-C(O)R^6$, $-S(O_2)NR^5R^6$, $-C(O)OR^6$, $-C(O)NR^5R^6$, cicloalquilo, $-CH(arilo)_2$, $-CH(heteroarilo)_2$, $-(CH_2)_m-NR^8$ y  , en donde cada uno de dichos alquilo, arilo, heteroarilo y heterociclilo puede estar sustituido u opcionalmente sustituido con uno o varios restos que pueden ser iguales o diferentes, donde cada resto está seleccionado, de modo independiente, del grupo que consiste en halo, alquilo, arilo, cicloalquilo, CF_3, CN, $-OCF_3$, $-OR^5$, $-NR^5R^6$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^6$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^6$;

R^5 es H, alquilo, arilo, heteroarilo, heterociclilo o cicloalquilo; y

R^6 está seleccionado del grupo que consiste en H, alquilo, arilo, heteroarilo, arilalquilo y heteroarilalquilo, en donde cada uno de dichos alquilo, heteroarilalquilo, arilo, heteroarilo y arilalquilo puede no estar sustituido o puede estar opcionalmente sustituido con uno o varios restos que pueden ser iguales o diferentes, donde cada resto está seleccionado, de modo independiente, del grupo que consiste en halógeno, alquilo, arilo, cicloalquilo, CF_3, OCF_3, CN, $-OR^5$, $-NR^5R^6$, $-CH_2OR^5$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^6$;

R^7 está seleccionado del grupo que consiste en alquilo, arilo, heteroarilo, arilalquilo y heteroarilalquilo, en donde cada uno de dichos alquilo, heteroarilalquilo, arilo, heteroarilo y arilalquilo puede no estar sustituido o puede estar opcionalmente sustituido con uno o varios restos que pueden ser iguales o diferentes, donde cada resto está seleccionado, de modo

independiente, del grupo que consiste en halógeno, alquilo, arilo, cicloalquilo, CF_3, OCF_3, CN, $-OR^5$, $-NR^5R^6$, $-CH_2OR^5$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^6$;

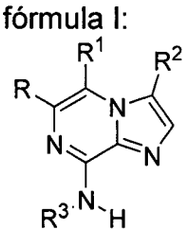
R^8 está seleccionado del grupo que consiste en R^6, $-C(O)NR^5R^6$, $-S(O_2)NR^5R^6$, $-C(O)R^7$, $-C(O_2)R^6$, $-S(O_2)R^7$ y $-(CH_2)$–arilo;

R^9 está seleccionado del grupo que consiste en halógeno, CN, NR^5R^6, $-C(O_2)R^6$, $-C(O)NR^5R^6$, $-OR^6$, $-C(O)R^7$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$and $-N(R^5)C(O)NR^5R^6$;

m es 0 a 4; y

p es 0–3;

i. Un compuesto de la fórmula I:



fórmula I

o una de sus sales, solvatos, ésteres o profármacos farmacéuticamente aceptables, en donde:

R es H, CN, $-NR^5R^6$, cicloalquilo, cicloalquenilo, heterociclenilo, heteroarilo, $-C(O)NR^5R^6$, $-N(R^5)C(O)R^6$, heterociclilo, heteroarilo sustituido con $(CH_2)_{1-3}$ NR^5R^6, alquilo no sustituido o alquilo sustituido con uno o varios restos que pueden ser iguales o diferentes donde cada resto está seleccionado, de modo independiente, del grupo que consiste en $-OR^5$, heterociclilo, $-N(R^5)C(O)N(R^5R^6)$, $-N(R^5)$–$C(O)OR^6$, $-(CH_2)_{1-3}$–$N(R^5R^6)$ y $-NR^5R^6$;

R^1 es H, halo, arilo o heteroarilo, en donde cada uno de dichos arilo y heteroarilo pueden no estar sustituidos o pueden estar sustituidos con uno o varios restos que pueden ser iguales o diferentes donde cada resto está

seleccionado, de modo independiente, del grupo que consiste en halo, alquilo, alquenilo, alquinilo, cicloalquilo, arilo, heteroarilo, heterociclilo, $-CH_2OR^5$, $-C(O)NR^5R^6$, $-C(O)OH$, $-C(O)NH_2$, $-NR^5R^6$ (en donde R^5 y R^6, junto con el N de dicho $-NR^5R^6$, forman un anillo heterociclilo), $-S(O)R^5$, $-S(O_2)R^5$, $-CN$, $-CHO$, $-SR^5$, $-C(O)OR^5$, $-C(O)R^5$ y $-OR^5$;

R^2 es H, halo, arilo, arilalquilo o heteroarilo, en donde cada uno de dichos arilo, arilalquilo y heteroarilo puede no estar sustituido o puede estar opcionalmente sustituido, de modo independiente, con uno o varios restos que pueden ser iguales o diferentes donde cada resto está seleccionado, de modo independiente, del grupo que consiste en halo, amida, alquilo, alquenilo, alquinilo, cicloalquilo, arilo, $-C(O)OH$, $-C(O)NH_2$, $-NR^5R^6$ (en donde R^5 y R^6, junto con el N de dicho $-NR^5R^6$, forman un anillo heterociclilo), $-CN$, arilalquilo, $-CH_2OR^5$, $-S(O)R^5$, $-S(O_2)R^5$, $-CN$, $-CHO$, $-SR^5$, $-C(O)OR^5$, $-C(O)R^5$, heteroarilo y heterociclilo;

R^3 es heterociclil–$(CR^7R^8)_n$–X, heterociclenil–$(CR^7R^8)_n$–X, heteroaril–$(CR^7R^8)_n$–X o aril–$(CR^7R^8)_n$–X, en donde cada uno de los restos de heterociclilo, heterociclenilo, heteroarilo o arilo de dicho R^3 puede no estar sustituido o puede estar sustituido con uno o varios restos seleccionados, de modo independiente, del grupo que consiste en $-CONR^5R^6$, $-OR^5$ y alquilo,

n es 1–6,

X es seleccionado del grupo que consiste en $-NR^5R^6$, $-OR^5$, $-SO-R^5$, $-SR^5$, SO_2R^5, heteroarilo, heterociclilo y arilo, en donde dicho heteroarilo o arilo puede no estar sustituido o puede estar sustituido con uno o varios restos seleccionados, de modo independiente, del grupo que consiste en –O–alquilo, alquilo, halo o NR^5R^6;

R^7 y R^8 son cada uno, de modo independiente, hidrógeno, alquilo, heterociclilo, arilo, heteroarilo o cicloalquilo;

R^5 está seleccionado del grupo que consiste en hidrógeno, alquilo, alquenilo, alcoxialquilo, –alquil–S–alquilo, aminoalquilo, arilo, heteroarilo, heterociclenilo, heterocicloalquilo, cicloalquilo, ciclenilo, heterociclilalcoxilo, –S–alquilheterociclilo, heterociclilo, heterociclenilo, alquilN(alquilo)$_2$, alquilNH(alquilo), alquilN(alquenilo)$_2$, –alquilN(alcoxilo)$_2$, –alquil–SH, hidroxialquilo, trihaloalquilo, dihaloalquilo, monohaloalquilo, en donde cada uno de dichos alquilo, alquenilo, alcoxialquilo, –alquil–S–alquilo, aminoalquilo, arilo, heteroarilo, heterociclenilo, heterocicloalquilo, cicloalquilo, ciclenilo, heterociclilalcoxilo, –S–alquilheterociclilo, heterociclilo, heterociclenilo, alquilN(alquilo)$_2$, alquilNH(alquilo), alquilN(alquenilo)$_2$, –alquilN(alcoxilo)$_2$, –alquil–SH, hidroxialquilo, trihaloalquilo, dihaloalquilo, monohaloalquilo puede no estar sustituido o puede estar sustituido con uno o varios restos seleccionados, de modo independiente, del grupo que consiste en alquilo, alquenilo, arilo, ciclenilo, cicloalquilo, arilalquilo, ciclenilalquilo, cicloalquilalquilo, heteroarilo, heterociclenilo, heterociclilo, heteroarilalquilo, heterociclenilalquilo, heterocicloalquilalquilo, alcoxialquilo, –alquil–S–alquilo, –alquilSH, alcoxilo, –S–alquilo, hidroxialquilo y aminoalquilo;

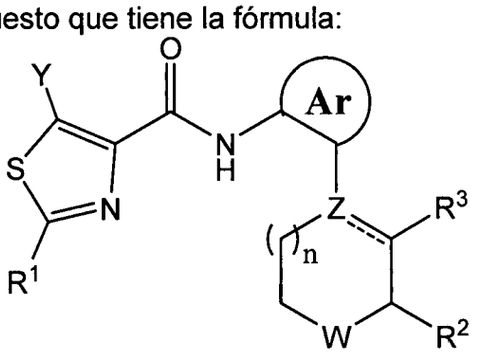
R^6 está seleccionado del grupo que consiste en hidrógeno, alquilo, alquenilo, arilo, ciclenilo, cicloalquilo, arilalquilo, ciclenilalquilo, cicloalquilalquilo, heteroarilo, heterociclenilo, heterociclilo, heteroarilalquilo, heterociclenilalquilo, heterocicloalquilalquilo, alcoxialquilo, –alquil–S–alquilo, –alquilSH, alcoxilo, –S–alquilo,

hidroxialquilo, aminoalquilo, –alquil–OC(O)alquilo, –alquilOC(O)cicloalquilo, –alquilOC(O)arilo, –alquilOC(O)aralquilo, –alquilOC(O)NR^5arilo, –alquilOC(O)NR^5alquilo, –alquilOC(O)NR^5heterociclilo, –alquilOC(O)NR^5heteroarilo, alquilOC(O)NR^5cicloalquilo, –alquilOC(O)heterociclilo, alquilC(O)OH, alquilC(O)Oalquilo, –alquilC(O)Ocicloalquilo, –alquilC(O)Oarilo, –alquilC(O)Oaralquilo, –alquilC(O)ONR^5arilo, –alquilC(O)ONR^5alquilo, –alquilC(O)ONR^5heterociclilo, –alquilC(O)ONR^5heteroaril –alquilC(O)ONR^5cicloalquilo, –alquilC(O)Oheterociclilo, alquilC(O)OH y alquilC(O)Oalquilo, en donde cada uno de dichos arilo, ciclenilo, cicloalquilo, arilalquilo, ciclenilalquilo, cicloalquilalquilo, heteroarilo, heterociclenilo, heterociclilo, heteroarilalquilo, heterociclenilalquilo, heterocicloalquilalquilo, –alquil–OC(O)alquilo, –alquilOC(O)cicloalquilo, –alquilOC(O)arilo, –alquilOC(O)aralquilo, –alquilOC(O)NR^5arilo, –alquilOC(O)NR^5alquilo, –alquilOC(O)NR^5heterociclilo, –alquilOC(O)NR^5heteroarilo, alquilOC(O)NR^5cicloalquilo, –alquilOC(O)heterociclilo, alquilC(O)OH, alquilC(O)Oalquilo, –alquilC(O)Ocicloalquilo, –alquilC(O)Oarilo, –alquilC(O)Oaralquilo, –alquilC(O)ONR^5arilo, –alquilC(O)ONR^5alquilo, –alquilC(O)ONR^5heterociclilo, –alquilC(O)ONR^5heteroaril –alquilC(O)ONR^5cicloalquilo, –alquilC(O)Oheterociclilo, alquilC(O)OH y alquilC(O)Oalquilo puede no estar sustituido o puede estar sustituido con uno o varios restos seleccionados, de modo independiente, del grupo que consiste en alquilo, alquenilo, arilo, ciclenilo, cicloalquilo, arilalquilo, ciclenilalquilo, cicloalquilalquilo, heteroarilo, heterociclenilo,

heterociclilo, heteroarilalquilo, heterociclenilalquilo, heterocicloalquilalquilo, alcoxialquilo, –alquil–S–alquilo, –alquilSH, alcoxilo, –S–alquilo, hidroxialquilo, aminoalquilo, amino, aminodialquilo, aminocicloalquilo, halo, trihaloalquilo, dihaloalquilo y monohaloalquilo;

también en donde en cualquier $-NR^5R^6$ en la fórmula I, dichos R^5 y R^6 pueden estar opcionalmente unidos junto con el N de dicho $-NR^5R^6$ para formar un anillo cíclico o anillo cíclico en puente, en donde cada uno de dicho anillo cíclico o anillo cíclico en puente pueden no estar sustituidos o pueden estar sustituidos con uno o varios restos, que pueden ser iguales o diferentes seleccionados, de modo independiente, del grupo que consiste en hidroxilo, –SH, alquilo, alquenilo, hidroxialquilo, –alquil–SH, alcoxilo, –S–alquilo, $-CO_2-$alquilo, $-CO_2-$alquenilo, arilalquilo, ciclenilalquilo, cicloalquilalquilo, heteroarilalquilo, heterociclenilalquilo, heterocicloalquilalquilo, heteroarilo, arilo, ciclenilo, cicloalquilo, espiroheterociclilo, espiroheterociclenilo, espiroheteroarilo, espirociclilo, espirociclenilo, espiroarilo, alcoxialquilo, –alquil–S–alquilo, heterociclilo, heterociclenilo, halo, trihaloalquilo, dihaloalquilo, CN y monohaloalquilo.

j. Un compuesto que tiene la fórmula:



(J)

o una de sus sales, solvatos, ésteres, prodrogas o estereoisómeros farmacéuticamente aceptables, en donde las líneas punteadas indican un enlace opcional y adicional y en donde:

R^1 es heteroarilo con contenido de nitrógeno, heterociclilo con contenido de nitrógeno, heteroarilo benzofusionado con contenido de nitrógeno o heterociclilo benzofusionado con contenido de nitrógeno, en donde R^1 está unido con el resto del compuesto de la fórmula (I) a través de un átomo de nitrógeno del anillo y en donde uno o varios átomos de carbono del anillo de un grupo heteroarilo con contenido de nitrógeno, heterociclilo con contenido de nitrógeno, heteroarilo benzofusionado con contenido de nitrógeno o heterociclilo benzofusionado con contenido de nitrógeno puede estar sustituido con hasta 5 sustituyentes, que pueden ser iguales o diferentes y están seleccionados, de modo independiente, de alquilo, arilo, halo, –OH, –O–alquilo, –O–arilo, $-N(R^8)_2$, $-CF_3$, $-NO_2$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)N(R^8)_2$, $-OC(O)R^8$ o $-NHC(O)R^8$;

R^2 es –H, –alquilo, $-NH_2$ o $-CH_2NH_2$;

R^3 es –H, –alquilo, $-NH_2$ o $-CH_2NH_2$;

cada aparición de R^4 es, de modo independiente, –H, –alquilo, $-NH_2$, –OH, –alquilen–OH, $-CH_2NH_2$, $-C(O)R^5$, $-C(O)NH_2$, –C(O)NH–alquilo, $-C(O)N(alquilo)_2$, $-NHC(O)R^6$ o $-NHS(O)_2R^6$;

R^5 es –H, –alquilo, –arilo, –heteroarilo, –NHOH;

R^6 es –H, –alquilo o $-CF_3$;

R^7 es –H, –OH, –alquilo C_1–C_6, –O–(alquilo C_1–C_6) o $-CF_3$;

R^8 es –H, alquilo, arilo, heterociclilo, heteroarilo o cicloalquilo;

Ar es –arileno– o –heteroarileno–, en donde el arileno o heteroarileno está unido a través de 2 de sus átomos de carbono del anillo adyacentes y en donde el –arileno– o –heteroarileno– pueden estar sustituidos con hasta 4 sustituyentes,

que pueden ser iguales o diferentes y están seleccionados, de modo independiente, de –halo, alquilo, alcoxi, ariloxi, $–SR^8$, $–S(O)R^8$, $–S(O)_2R^8$, $–C(O)R^8$, $–C(O)OR^8$, $–C(O)N(R^8)_2$, $–NHC(O)R^8$, $–CF_3$, –CN o NO_2 y de modo tal que, cuando Ar es tetrahidronaftileno, R^1 y R^2 no puedan ser ambos hidrógeno

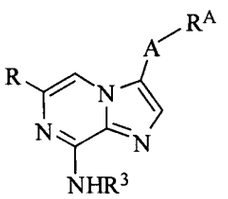
W es –NH– o $–C(R^4)_2–$, en donde ambos grupos R^4 y el átomo de carbono al que están unidos se pueden combinar para formar un grupo heterociclilo o heteroarilo de cinco a siete miembros;

Y es –H, –halo, –alquilo o –CN;

Z es $–CR^7–$ o –N–, cuando el enlace adicional opcional está ausente y –C– cuando el enlace adicional opcional está presente;

n es un número entero que va de 0 a 2; y

(k) Un compuesto de la fórmula K:



fórmula K

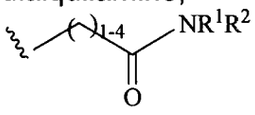
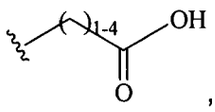
o una de sus sales, solvatos, ésteres, prodrogas o estereoisómeros farmacéuticamente aceptables, en donde:

R es H, halo o alquilo;

R^3 es heteroaril–X, en donde X es heterociclilalquilo–, en donde dicho heterociclilo puede no estar sustituido o puede estar opcionalmente sustituido con 1–4 restos alquilo;

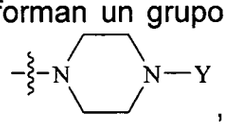
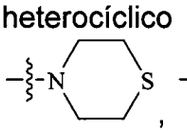
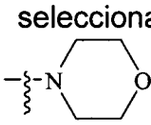
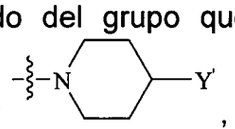
A es –arilo–, –heteroarilo–, $–N(R^1)–$arilo– o $–N(R^1)–$heteroarilo– , en donde cada uno de dichos arilo y heteroarilo puede no estar sustituido, de modo independiente, o puede estar opcionalmente sustituido con uno o varios sustituyentes, que pueden ser iguales o diferentes, donde cada sustituyente está seleccionado, de modo independiente, del grupo que consiste en alquilo, $–NO_2$,

halo, hidroxi, trihaloalquilo, alcoxi y dialquilamino;

R^A es $-(CH_2)_{1-4}$–heteroarilo,  o  , en donde dicho heteroarilo puede estar opcionalmente fusionado con un arilo, en donde cada uno de dichos arilo y heteroarilo puede estar opcionalmente sustituido, de modo independiente, con uno o varios restos donde cada resto está seleccionado, de modo independiente, del grupo que consiste en trihaloalquilo, $-NO_2$, halo, hidroxialquilo, alcoxialquilo y dialquilamino;

R^1 es H o alquilo;

R^2 es H, hidroxialquilo–, arilalquilo–, heteroarilo, arilo, heteroarilalquilo–, alquilo, dialquilaminoalquilo–, alquilaminoalquilo–, cicloalquilalquilo–, cicloalquilo, heterociclilalquilo– o heterociclilo, en donde dichos arilo y arilo de arilalquilo puede no estar sustituido o puede estar sustituido con uno o varios restos seleccionados, de modo independiente, del grupo que consiste en trihaloalquilo, $-NO_2$, halo, hidroxialquilo, alcoxialquilo, dialquilamino y heterociclilalquilo–, en donde dicho heterociclilalquilo puede no estar sustituido o puede estar sustituido con alquilo o $-SO_2NH_2$; dichos heteroarilo y heteroarilo de heteroarilalquilo pueden no estar sustituidos o pueden estar sustituidos con uno o varios restos, donde cada resto está seleccionado, de modo independiente, del grupo que consiste en hidroxialquilo, alcoxi, alquilo, halo, hidroxilo y $-NO_2$; y dicho cicloalquilo no está sustituido o está sustituido con hidroxilo; o

R^1 y R^2 junto con N al que cada uno está unido, forman un grupo heterocíclico seleccionado del grupo que consiste en  ,  ,  y  , en donde

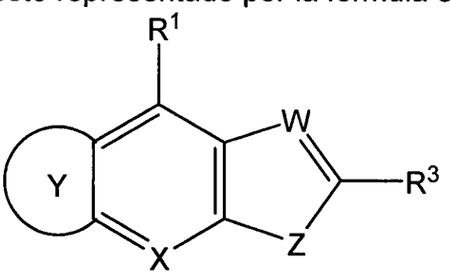
Y es alcoxialquilo, hidroxialquilo, dialquilaminoalquilo o alquilo, también en donde

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Y' es hidroxilo.

2. Un método de tratamiento o mejora del cáncer que comprende la administración secuencial a un mamífero que necesita de dicho tratamiento de una cantidad de al menos un primer compuesto, en donde dicho primer compuesto es un agente antimitótico seleccionado del grupo que consiste en un taxano, paclitaxel, docetaxel, un inhibidor de Cenp–E, abraxano, epotilona, monastrol, un inhibidor de KSP, ispinesib y un compuesto de las fórmulas A–D mostradas en los puntos a–d que figuran más abajo:

a. Un compuesto representado por la fórmula estructural A:



fórmula A

o una de sus sales, solvatos o ésteres farmacéuticamente aceptables, en donde:

el anillo Y es un arilo de 5 ó 6 miembros o un heteroarilo de 5 ó 6 miembros fusionado tal como se indica en la fórmula A, en donde en dichos arilo y heteroarilo cada carbono del anillo sustituible está sustituido, de modo independiente, con R^2 y cada nitrógeno del anillo sustituible está sustituido, de modo independiente, con R^6;

W es N o $C(R^{12})$;

X es N o N–óxido;

Z es S, S(=O) o $S(=O)_2$;

R^1 es H, alquilo, alcoxi, hidroxi, halo, –CN, $–S(O)_m$–alquilo, $–C(O)NR^9R^{10}$, $–(CR^9R^{10})_{1–6}OH$ o $–NR^4(CR^9R^{10})_{1–2}OR^9$;

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cada R^2 está seleccionado, de modo independiente, del grupo que consiste en H, halo, alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo, heteroaralquilo, $-(CR^{10}R^{11})_{0-6}-OR^7$, $-C(O)R^4$, $-C(S)R^4$, $-C(O)OR^7$, $-C(S)OR^7$, $-OC(O)R^7$, $-OC(S)R^7$, $-C(O)NR^4R^5$, $-C(S)NR^4R^5$, $-C(O)NR^4OR^7$, $-C(S)NR^4OR^7$, $-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, $-CN$, $-OCF_3$, $-SCF_3$, $-C(=NR^7)NR^4$, $-C(O)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}OR^7$, $-C(S)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(S)NR^7(CH_2)_{1-10}OR^7$, haloalquilo y alquilsililo, en donde cada uno de dichos alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo o heteroaralquilo está opcionalmente sustituido, de modo independiente, con 1–5 restos R^9;

cada R^3 está seleccionado, de modo independiente, del grupo que consiste en H, halo, alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo, heteroaralquilo, $-(CR^{10}R^{11})_{0-6}-OR^7$, $-C(O)R^4$, $-C(S)R^4$, $-C(O)OR^7$, $-C(S)OR^7$, $-OC(O)R^7$, $-OC(S)R^7$, $-C(O)NR^4R^5$, $-C(S)NR^4R^5$, $-C(O)NR^4OR^7$, $-C(S)NR^4OR^7$, $-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, $-CN$, $-OCF_3$, $-SCF_3$, $-C(=NR^7)NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}OR^7$, $-C(S)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(S)NR^7(CH_2)_{1-10}OR^7$, haloalquilo y alquilsililo, en donde cada uno de

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dichos alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo o heteroaralquilo está opcionalmente sustituido, de modo independiente, con 1–5 r estos R^9;

cada R^4 y R^5 está seleccionado, de modo independiente, del grupo que consiste en H, alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo, heteroaralquilo, $-OR^7$, $-C(O)R^7$ y $-C(O)OR^7$, en donde cada uno de dichos alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo o heteroaralquilo está opcionalmente sustituido con 1–4 restos R^8;

o R^4 y R^5, cuando están unidos al mismo átomo de nitrógeno, se toman opcionalmente juntos con el átomo de nitrógeno al que están unidos para formar un anillo heterocíclico de 3–6 miembros que tiene 0–2 heteroátomos adicionales seleccionados de N, O o S;

cada R^6 está seleccionado, de modo independiente, del grupo que consiste en H, alquilo, arilo, aralquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, heteroarilo, heteroaralquilo, $-(CH_2)_{1-6}CF_3$, $-C(O)R^7$, $-C(O)OR^7$ y $-SO_2R^7$;

cada R^7 está seleccionado, de modo independiente, del grupo que consiste en H, alquilo, arilo, aralquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, heteroarilo y heteroaralquilo, en donde cada miembro de R^7 excepto H está opcionalmente sustituido con 1–4 restos R^8;

cada R^8 está seleccionado, de modo independiente, del grupo que consiste en halo, alquilo, cicloalquilo, heterociclilo, arilo, heteroarilo, $-NO_2$, $-OR^{10}$, $-$(alquil C_1–C_6)$-OR^{10}$, $-CN$, $-NR^{10}R^{11}$, $-C(O)R^{10}$, $-C(O)OR^{10}$, $-C(O)NR^{10}R^{11}$, $-CF_3$, $-OCF_3$, $-CF_2CF_3$, $-C(=NOH)R^{10}$, $-N(R^{10})C(O)R^{11}$, $-C(=NR^{10})NR^{10}R^{11}$ y $-NR^{10}C(O)OR^{11}$, en donde cada uno de dichos alquilo, cicloalquilo, heterociclilo, arilo y heteroarilo está opcionalmente

sustituido, de modo independiente, con 1–3 restos seleccionados del grupo que consiste en halo, alquilo, cicloalquilo, heterociclilo, arilo, heteroarilo, $-NO_2$, $-OR^{10}$, –(alquil C_1–C_6)–OR^{10}, –CN, $-NR^{10}R^{11}$, $-C(O)OR^{10}$, $-C(O)NR^{10}R^{11}$, $-CF^3$, $-OCF_3$, $-NR^{10}C(O)OR^{11}$ y $-NR^{10}C(O)R^{40}$;

o dos grupos R^8, cuando están unidos al mismo átomo de carbono, se toman opcionalmente juntos con el átomo de carbono al que están unidos para formar un grupo C=O o un grupo C=S;

cada R^9 está seleccionado, de modo independiente, del grupo que consiste en H, alquilo, alcoxi, OH, CN, halo, $-(CR^{10}R^{11})_{0-4}NR^4R^5$, haloalquilo, hidroxialquilo, alcoxialquilo, $-C(O)NR^4R^5$, $-C(O)OR^7$, $-OC(O)NR^4R^5$, $-NR^4C(O)R^5$ y $-NR^4C(O)NR^4R^5$;

cada R^{10} es, de modo independiente, H o alquilo; o R^9 y R^{10}, cuando están unidos al mismo átomo de nitrógeno, se toman opcionalmente juntos con el átomo de nitrógeno al que están unidos para formar un anillo heterocíclico de 3–6 miembros que tiene 0–2 heteroátomos adicionales seleccionados de N, O o S;

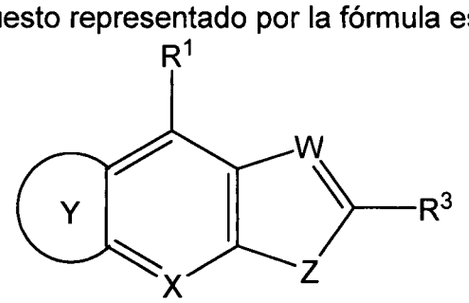
cada R^{11} es, de modo independiente, H o alquilo; o R^{10} y R^{11}, cuando están unidos al mismo átomo de nitrógeno, se toman opcionalmente juntos con el átomo de nitrógeno al que están unidos para formar un anillo heterocíclico de 3–6 miembros que tiene 0–2 heteroátomos adicionales seleccionados de N, O o S;

cada R^{12} está seleccionado, de modo independiente, del grupo que consiste en H, halo, alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo, heteroaralquilo, $-(CR^{10}R^{11})_{0-6}$ $-OR^7$, $-C(O)R^4$, $-C(S)R^4$, $-C(O)OR^7$, $-C(S)OR^7$, $-OC(O)R^7$, $-OC(S)R^7$, $-C(O)NR^4R^5$, $-C(S)NR^4R^5$, $-C(O)NR^4OR^7$, $-C(S)NR^4OR^7$,

$-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, $-CN$, $-OCF_3$, $-SCF_3$, $-C(=NR^7)NR^4$, $-C(O)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}OR^7$, $-C(S)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(S)NR^7(CH_2)_{1-10}OR^7$, haloalquilo y alquilsililo, en donde cada uno de dichos alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo o heteroaralquilo está opcionalmente sustituido, de modo independiente, con 1–5 restos R^9; y

R^{40} está seleccionado del grupo que consiste en cicloalquilo, heterociclilo, arilo y heteroarilo, en donde cada uno de dichos cicloalquilo, heterociclilo, arilo y heteroarilo está opcionalmente sustituidos, de modo independiente, con 1–3 restos seleccionados, de modo independiente, del grupo que consiste en –CN, –OH, halo, alquilo, haloalquilo, alcoxi y $-NR^{10}R^{11}$;

b. Un compuesto representado por la fórmula estructural B:



fórmula B

o una de sus sales, solvatos o ésteres farmacéuticamente aceptables, en donde:

el anillo Y es un anillo de 5 a 7 miembros seleccionado del grupo que consiste en cicloalquilo, cicloalquenilo, heterociclilo o heterociclenilo fusionado tal como se indica en la fórmula B, en donde en cada uno de dichos anillos de 5 a 7 miembros, cada carbono del anillo sustituible está sustituido, de modo

independiente, con 1–2 restos R^2 y cada heteroátomo del anillo sustituible está sustituido, de modo independiente, con R^6;

W es N o $C(R^{12})$;

X es N o N–óxido;

Z es S, S(=O) o $S(=O)_2$;

R^1 es H, alquilo, alcoxi, hidroxi, halo, –CN, $–S(O)_m–$alquilo, $–C(O)NR^9R^{10}$, $–(CR^9R^{10})_{1–6}OH$ o $–NR^4(CR^9R^{10})_{1–2}OR^9$; en donde m es 0 a 2;

cada R^2 está seleccionado, de modo independiente, del grupo que consiste en H, halo, alquilo, cicloalquilo, alquilsililo, cicloalquenilo, heterociclilo, heterociclenilo, arilo, heteroarilo, $–(CR^{10}R^{11})_{0–6}–OR^7$, $–C(O)R^4$, $–C(S)R^4$, $–C(O)OR^7$, $–C(S)OR^7$, $–OC(O)R^7$, $–OC(S)R^7$, $–C(O)NR^4R^5$, $–C(S)NR^4R^5$, $–C(O)NR^4OR^7$, $–C(S)NR^4OR^7$, $–C(O)NR^7NR^4R^5$, $–C(S)NR^7NR^4R^5$, $–C(S)NR^4OR^7$, $–C(O)SR^7$, $–NR^4R^5$, $–NR^4C(O)R^5$, $–NR^4C(S)R^5$, $–NR^4C(O)OR^7$, $–NR^4C(S)OR^7$, $–OC(O)NR^4R^5$, $–OC(S)NR^4R^5$, $–NR^4C(O)NR^4R^5$, $–NR^4C(S)NR^4R^5$, $–NR^4C(O)NR^4OR^7$, $–NR^4C(S)NR^4OR^7$, $–(CR^{10}R^{11})_{0–6}SR^7$, SO_2R^7, $–S(O)_{1–2}NR^4R^5$, $–N(R^7)SO_2R^7$, $–S(O)_{1–2}NR^5OR^7$, –CN, $–OCF_3$, $–SCF_3$, $–C(=NR^7)NR^4$, $–C(O)NR^7(CH_2)_{1–10}NR^4R^5$, $–C(O)NR^7(CH_2)_{1–10}OR^7$, $–C(S)NR^7(CH_2)_{1–10}NR^4R^5$ y $–C(S)NR^7(CH_2)_{1–10}OR^7$, en donde cada uno de dichos alquilo, cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, arilo y heteroarilo está opcionalmente sustituido, de modo independiente, con 1–5 restos R^9;

o dos grupos R^2 en el mismo átomo de carbono se toman opcionalmente juntos con el átomo de carbono al que están unidos para formar un grupo C=O, un grupo C=S o un grupo etilendioxi;

R^3 está seleccionado, de modo independiente, del grupo que consiste en H, halo, alquilo, cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, arilo, heteroarilo, $–(CR^{10}R^{11})_{0–6}–OR^7$, $–C(O)R^4$, $–C(S)R^4$, $–C(O)OR^7$, $–C(S)OR^7$, $–OC(O)R^7$, $–OC(S)R^7$, $–C(O)NR^4R^5$, $–C(S)NR^4R^5$, $–C(O)NR^4OR^7$, $–C(S)NR^4OR^7$,

$C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, $-CN$, $-C(=NR^7)NR^4R^5$, $-C(O)N(R^7)-(CR^{40}R^{41})_{1-5}-C(=NR^7)NR^4R^5$, $-C(O)N(R^7)(CR^{40}R^{41})_{1-5}-NR^4R^5$, $-C(O)N(R^7)(CR^{40}R^{41})_{1-5}-C(O)-NR^4R^5$, $-C(O)N(R^7)(CR^{40}R^{41})_{1-5}-OR^7$, $-C(S)NR^7(CH_2)_{1-5}NR^4R^5$ y $-C(S)NR^7(CH_2)_{1-5}OR^7$, en donde cada uno de dichos alquilo, cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, arilo y heteroarilo está opcionalmente sustituido, de modo independiente, con 1–5 restos R^9;

cada uno de R^4 y R^5 está seleccionado, de modo independiente, del grupo que consiste en H, alquilo, cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, arilo, heteroarilo, $-OR^7$, $-C(O)R^7$ y $-C(O)OR^7$, en donde cada uno de dichos alquilo, cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, arilo y heteroarilo, está opcionalmente sustituido con 1–4 restos R^8;

o R^4 y R^5, cuando están unidos al mismo átomo de nitrógeno, se toman opcionalmente juntos con el átomo de nitrógeno al que están unidos para formar un anillo heterocíclico de 3–6 miembros que tiene 0–2 heteroátomos adicionales seleccionados de N, O o S;

cada R^6 está seleccionado, de modo independiente, del grupo que consiste en H, alquilo, arilo, aralquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, heteroarilo, heteroaralquilo, $-(CH_2)_{1-6}CF_3$, $-C(O)R^7$, $-C(O)OR^7$ y $-SO_2R^7$;

cada R^7 está seleccionado, de modo independiente, del grupo que consiste en H, alquilo, arilo, aralquilo, cicloalquilo, cicloalquilalquilo, heterociclilo,

heterociclilalquilo, heteroarilo y heteroaralquilo, en donde cada miembro de R^7 excepto H está opcionalmente sustituido con 1–4 restos R^8;

cada R^8 está seleccionado, de modo independiente, del grupo que consiste en halo, alquilo, cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, arilo, heteroarilo, $-NO_2$, $-OR^{10}$, –(alquil C_1–C_6)–OR^{10}, –CN, $-NR^{10}R^{11}$, $-C(O)R^{10}$, $-C(O)OR^{10}$, $-C(O)NR^{10}R^{11}$, $-CF_3$, $-OCF_3$, $-CF_2CF_3$, $-C(=NOH)R^{10}$, $-N(R^{10})C(O)R^{11}$, $-C(=NR^{10})NR^{10}R^{11}$ y $-NR^{10}C(O)OR^{11}$; en donde cada uno de dichos alquilo, cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, arilo y heteroarilo está opcionalmente sustituido, de modo independiente, con 1–4 restos R^{42}; en donde cuando cada uno de dichos cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, arilo y heteroarilo contienen dos radicales en átomos de carbono adyacentes en cualquier parte dentro de dichos cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, arilo y heteroarilo, dichos radicales se pueden formar, opcional e independientemente en cualquier aparición, junto con los átomos de carbono a los que están unidos para formar un anillo carbocíclico o heterocíclico de cinco o seis miembros;

o dos grupos R^8, cuando están unidos al mismo carbono, se toman opcionalmente juntos con el átomo de carbono al que están unidos para formar un grupo C=O o un grupo C=S;

cada R^9 está seleccionado, de modo independiente, del grupo que consiste en H, alquilo, alcoxi, OH, CN, halo, $-(CR^{10}R^{11})_{0-4}NR^4R^5$, haloalquilo, hidroxialquilo, alcoxialquilo, $-C(O)NR^4R^5$, $-C(O)OR^7$, $-OC(O)NR^4R^5$, $-NR^4C(O)R^5$ y $-NR^4C(O)NR^4R^5$;

cada R^{10} es, de modo independiente, H o alquilo; o R^9 y R^{10}, cuando están unidos al mismo átomo de nitrógeno, se toman opcionalmente juntos con el átomo de nitrógeno al que están unidos para formar un anillo heterocíclico de 3–6 miembros que tiene 0–2 heteroátomos adicionales seleccionados de N, O o S;

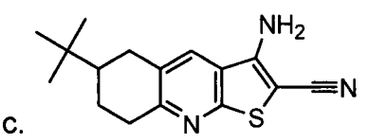
cada R^{11} es, de modo independiente, H, alquilo, cicloalquilo, cicloalquenilo, arilo, heterociclilo, heterociclenilo o heteroarilo; o R^{10} y R^{11}, cuando están unidos al mismo átomo de nitrógeno, se toman opcionalmente juntos con el átomo de nitrógeno al que están unidos para formar un anillo heterocíclico de 3–6 miembros que tiene 0–2 heteroátomos adicionales seleccionados de N, O o S; en donde cada uno de dicho R^{11} alquilo, cicloalquilo, cicloalquenilo, arilo, heterociclilo, heterociclenilo y heteroarilo está opcionalmente sustituido, de modo independiente, con 1–3 restos seleccionados del grupo que consiste en –CN, –OH, $–NH_2$, –N(H)alquilo, $–N(alquilo)_2$, halo, haloalquilo, CF_3, alquilo, hidroxialquilo, alcoxi, arilo, ariloxi y heteroarilo;

cada R^{12} está seleccionado, de modo independiente, del grupo que consiste en H, halo, alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo, heteroaralquilo, $–(CR^{10}R^{11})_{0–6}–OR^7$, $–C(O)R^4$, $–C(S)R^4$, $–C(O)OR^7$, $–C(S)OR^7$, $–OC(O)R^7$, $–OC(S)R^7$, $–C(O)NR^4R^5$, $–C(S)NR^4R^5$, $–C(O)NR^4OR^7$, $–C(S)NR^4OR^7$, $–C(O)NR^7NR^4R^5$, $–C(S)NR^7NR^4R^5$, $–C(S)NR^4OR^7$, $–C(O)SR^7$, $–NR^4R^5$, $–NR^4C(O)R^5$, $–NR^4C(S)R^5$, $–NR^4C(O)OR^7$, $–NR^4C(S)OR^7$, $–OC(O)NR^4R^5$, $–OC(S)NR^4R^5$, $–NR^4C(O)NR^4R^5$, $–NR^4C(S)NR^4R^5$, $–NR^4C(O)NR^4OR^7$, $–NR^4C(S)NR^4OR^7$, $–(CR^{10}R^{11})_{0–6}SR^7$, SO_2R^7, $–S(O)_{1–2}NR^4R^5$, $–N(R^7)SO_2R^7$, $–S(O)_{1–2}NR^5OR^7$, –CN, $–OCF_3$, $–SCF_3$, $–C(=NR^7)NR^4$, $–C(O)NR^7(CH_2)_{1–10}NR^4R^5$, $–C(O)NR^7(CH_2)_{1–10}OR^7$, $–C(S)NR^7(CH_2)_{1–10}NR^4R^5$, $–C(S)NR^7(CH_2)_{1–10}OR^7$, haloalquilo y alquilsililo, en donde cada uno de dichos alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo o heteroaralquilo está opcionalmente sustituido, de modo independiente, con 1–5 restos R^9;

R^{40} y R^{41} pueden ser iguales o diferentes, en donde cada uno está seleccionado, de modo independiente, del grupo que consiste en H, alquilo, arilo, heteroarilo, heterociclilo, heterociclenilo, cicloalquilo y cicloalquenilo;

cada R^{42} está seleccionado, de modo independiente, del grupo que consiste en halo, alquilo, cicloalquilo, heterociclilo, arilo, heteroarilo, $-NO_2$, $-OR^{10}$, $-$(alquil C_1–C_6)$-OR^{10}$, $-CN$, $-NR^{10}R^{11}$, $-C(O)R^{10}$, $-C(O)OR^{10}$, $-C(O)NR^{10}R^{11}$, $-CF_3$, $-OCF_3$, $-N(R^{10})C(O)R^{11}$ y $-NR^{10}C(O)OR^{11}$;

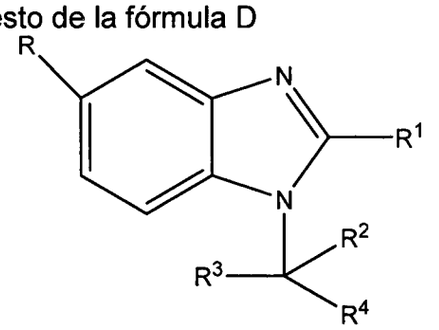
con la condición de que, cuando W es $C(R^{12})$, R^{12} y R^3 se tomen opcionalmente juntos con los dos átomos de carbono del anillo a los que están unidos para formar un anillo de 6 miembros seleccionado del grupo que consiste en cicloalquenilo, arilo, heteroarilo, heterociclilo y heterociclenilo, en donde dicho anillo de 6 miembros está opcionalmente sustituido con 1–3 restos seleccionados, de modo independiente, de oxo, tioxo, $-OR^{11}$, $-NR^{10}R^{11}$, $-C(O)R^{11}$, $-C(O)OR^{11}$, $-C(O)N(R^{10})(R^{11})$ o $-N(R^{10})C(O)R^{11}$;

c. 

fórmula C

o una de sus sales, solvatos o ésteres farmacéuticamente aceptables; y

d. Un compuesto de la fórmula D



fórmula D

o una de sus sales, solvatos o ésteres farmacéuticamente aceptables, en donde:

R está seleccionado del grupo que consiste en H, alquilo, ciano, haloalquilo, halo, —SH, –S–alquilo, –S–haloalquilo, $-S(=O)_2$alquilo,

$-S(=O)_2OH$, $-S(=O)_2NH_2$, $-S(=O)_2NH$(alquilo), $S(=O)_2NH$(cicloalquilo), $-S(=O)_2N$(alquilo)$_2$, $-S(=O)_2$heterociclilo, $-S(=O)_2$heteroarilo, cicloalquilo, arilo, heterociclilo, heteroarilo, $-NHC(=O)$alquilo, $-C(=O)NH_2$, $-C(=O)NH$(alquilo), $-C(=O)NH$(cicloalquilo), $-C(=O)N$(alquilo)$_2$, $-C(=O)OH$, $-C(=O)O$alquilo, $-C(=O)$heterociclilo, $-C(=O)NH$(arilo), en donde cuando cada uno de dichos cicloalquilo, arilo, heterociclilo, heteroarilo y las porciones de "heterociclilo" y "arilo" de dichos grupos R tiene dos sustituyentes en átomos de carbono adyacentes, dichos sustituyentes se pueden tomar opcionalmente juntos con los átomos de carbono a los que están unidos para formar un anillo cicloalquilo, arilo, heterociclilo, heterociclenilo o heteroarilo de cinco o seis miembros; en donde cada uno de los R antes mencionados alquilo, arilo, cicloalquilo, heterociclilo y heteroarilo y las porciones de "alquilo", "cicloalquilo", "heterociclilo" y "arilo" de dichos grupos R, opcionalmente con dichos anillo arilo, heterociclilo, heterociclenilo o heteroarilo de cinco o seis miembros, está opcionalmente sustituido con 1–3 sustituyentes seleccionados, de modo independiente, del grupo que consiste en alquilo, alquenilo, alquinilo, hidroxilo, ciano, halo, haloalquilo, haloalcoxi, $-C(O)OH$, $-C(=O)O$alquilo y $-C(O)NH_2$;

R^1 está seleccionado del grupo que consiste en alquilo, heterociclilo, $-C(=O)$arilo, $-NH_2$, $-NH$(alquilo), $-NH$(cicloalquilo), $-N$(alquil)(cicloalquilo), $-NH$(heterociclilo), $-N$(alquil)(heterociclilo), N(alquilo)$_2$, $-NH$(arilo), $-N$(alquil)(arilo), $-N$(arilo)$_2$, $-NH$(heteroarilo), $-N$(alquil)(heteroarilo), $-NHC(=O)-$alquilo, $-N$(alquil)$C(=O)-$alquilo, $-NHC(=O)O$alquilo, $-N$(alquil)$C(=O)O-$alquilo, en donde cada uno de los alquilo, heterociclilo antes mencionados y las porciones de "alquilo", "cicloalquilo", "arilo" y "heteroarilo" de dichos grupos R^1 está opcionalmente sustituido con 1–3

sustituyentes seleccionados, de modo independiente, del grupo que consiste en halo, heterociclilo, arilo, heteroarilo, haloalquilo, haloalcoxi, ariloxi, ciano, –SH, –S–alquilo, –S–haloalquilo, $-S(=O)_2$alquilo, $-S(=O)_2OH$, $-S(=O)_2NH_2$, $-S(=O)_2NH$(alquilo), $S(=O)_2NH$(cicloalquilo), $-S(=O)_2N$(alquilo)$_2$, $-S(=O)_2$heterociclilo, $-S(=O)_2$heteroarilo, hidroxi, alquilo, alquenilo, alquinilo, $-NH_2$, –NH(alquilo), –N(alquilo)$_2$, alcoxi, –NHC(=O)alquilo, –C(=O)H, –C(=O)alquilo, –C(=O)arilo, –C(=O)heteroarilo, –C(=O)Oalquilo, $-C(=O)NH_2$, –C(O)NHalquilo, $-C(=O)N$(alquilo)$_2$; en donde cuando cada uno de dichos heterociclilo, arilo y heteroarilo tiene dos sustituyentes en átomos de carbono adyacentes, dichos sustituyentes se pueden tomar opcionalmente juntos con los átomos de carbono a los que están unidos para formar un anillo arilo, heterociclilo, heterociclenilo o heteroarilo de cinco a seis miembros;

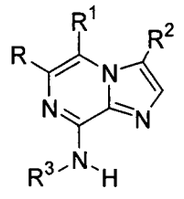
R^2 y R^3 son, de modo independiente, H o alquilo o $-C(R^2)(R^3)-$ está ausente;

R^4 está seleccionado del grupo que consiste en alquilo, cicloalquilo, heterociclilo, arilo y heteroarilo, en donde cuando cada uno de dichos cicloalquilo, heterociclilo, arilo y heteroarilo tiene dos sustituyentes en átomos de carbono adyacentes, dichos sustituyentes se pueden tomar opcionalmente juntos con los átomos de carbono a los que están unidos para formar un anillo arilo, heterociclilo, heterociclenilo o heteroarilo de cinco a seis miembros; en donde cada uno de los R^4 antes mencionados alquilo, cicloalquilo, heterociclilo, arilo y heteroarilo, opcionalmente con dichos anillos arilo, heterociclilo, heterociclenilo o heteroarilo de cinco a seis miembros está opcionalmente sustituido con 1–3 sustituyentes seleccionados, de modo independiente, del grupo que consiste en ciano, halo, haloalquilo, alquilo, alcoxi, hidroxilo, haloalcoxi, cicloalquilo,

heterociclilo, arilo, heteroarilo, $-S(=O)_2$alquilo, $-S(=O)_2NH_2$, $-S(=O)_2NH$(alquilo), $-S(=O)_2N$(alquilo)$_2$, –S–alquilo, –S–haloalquilo, $-C(=O)OH$, $-NH_2$, –NH(alquilo), $-N$(alquilo)$_2$ y $-C(=O)O$alquilo;

seguido de la administración de uno o varios de un segundo compuesto, en donde dicho segundo compuesto es un inhibidor de aurora quinasa seleccionado del grupo que consiste en compuestos representados por las fórmulas E–K mostrados más abajo en los puntos e–k:

e. Un compuesto representado por la fórmula estructural E:



fórmula E

o una de sus sales, solvatos, ésteres o profármacos farmacéuticamente aceptables, en donde:

R es H, CN, $-NR^5R^6$, cicloalquilo, cicloalquenilo, heterociclenilo, heteroarilo, $-C(O)NR^5R^6$, $-N(R^5)C(O)R^6$, heterociclilo, heteroarilo sustituido con $(CH_2)_{1-3}NR^5R^6$, alquilo no sustituido o alquilo sustituido con uno o varios restos que pueden ser iguales o diferentes donde cada resto está seleccionado, de modo independiente, del grupo que consiste en $-OR^5$, heterociclilo, $-N(R^5)C(O)N(R^5R^6)$, $-N(R^5)-C(O)OR^6$, $-(CH_2)_{1-3}-N(R^5R^6)$ y $-NR^5R^6$;

R^1 es H, halo, arilo o heteroarilo, en donde cada uno de dichos arilo y heteroarilo pueden no estar sustituidos o pueden estar sustituidos con uno o varios restos que pueden ser iguales o diferentes donde cada resto está seleccionado, de modo independiente, del grupo que consiste en halo, alquilo, alquenilo, alquinilo, cicloalquilo, arilo, heteroarilo, heterociclilo, $-CH_2OR^5$, $-C(O)NR^5R^6$, $-C(O)OH$, $-C(O)NH_2$, $-NR^5R^6$ (en donde R^5 y R^6, junto con el N de dicho $-NR^5R^6$, forman un anillo heterociclilo), $-S(O)R^5$,

$-S(O_2)R^5$, –CN, –CHO, $-SR^5$, $-C(O)OR^5$, $-C(O)R^5$ y $-OR^5$;

R^2 es H, halo, arilo, arilalquilo o heteroarilo, en donde cada uno de dichos arilo, arilalquilo y heteroarilo puede no estar sustituido o puede estar opcionalmente sustituido, de modo independiente, con uno o varios restos que pueden ser iguales o diferentes donde cada resto está seleccionado, de modo independiente, del grupo que consiste en halo, amida, alquilo, alquenilo, alquinilo, cicloalquilo, arilo, $-C(O)OH$, $-C(O)NH_2$, $-NR^5R^6$ (en donde R^5 y R^6, junto con el N de dicho $-NR^5R^6$, forman un anillo heterociclilo), –CN, arilalquilo, $-CH_2OR^5$, $-S(O)R^5$, $-S(O_2)R^5$, –CN, –CHO, $-SR^5$, $-C(O)OR^5$, $-C(O)R^5$, heteroarilo y heterociclilo;

R^3 es H, alquilo, cicloalquilo, heterociclilo, arilo o heteroarilo, en donde:

– dicho alquilo mostrado con anterioridad para R^3 puede no estar sustituido o puede estar sustituido con uno o varios restos que pueden ser iguales o diferentes donde cada resto está seleccionado, de modo independiente, del grupo que consiste en $-OR^5$, alcoxi, heteroarilo y $-NR^5R^6$;

– dicho arilo mostrado con anterioridad para R^3 puede no estar sustituido o puede estar opcionalmente sustituido u opcionalmente fusionado, con halo, heteroarilo, heterociclilo, cicloalquilo o heteroarilalquilo, en donde cada uno de dichos heteroarilo, heterociclilo, cicloalquilo y heteroarilalquilo puede no estar sustituido o puede estar opcionalmente sustituido, de modo independiente, con uno o varios restos que pueden ser iguales o diferentes donde cada resto está seleccionado, de modo independiente, de alquilo, $-OR^5$, $-N(R^5R^6)$ y $-S(O_2)R^5$; y

– dicho heteroarilo mostrado con anterioridad para R^3 puede no estar sustituido o puede estar opcionalmente sustituido u opcionalmente

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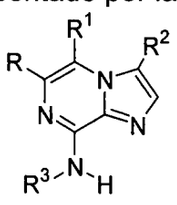
fusionado con uno o varios restos que pueden ser iguales o diferentes con donde cada resto está seleccionado, de modo independiente, del grupo que consiste en halo, amino, alcoxicarbonilo, $-OR^5$, alquilo, –CHO, $-NR^5R^6$, $-S(O_2)N(R^5R^6)$, $-C(O)N(R^5R^6)$, $-SR^5$, alquenilo, alquinilo, cicloalquilo, arilo, heteroarilo, heterociclenilo, y heterociclilo;

R^5 es H, alquilo, aminoalquilo, arilo, heteroarilo, heterociclilo o cicloalquilo; y

R^6 es H, alquilo, arilo, arilalquilo, heteroarilo, heterociclilo o cicloalquilo;

también en donde en cualquier $-NR^5R^6$ en la fórmula I, dichos R^5 y R^6 pueden estar opcionalmente unidos junto con el N de dicho $-NR^5R^6$ para formar un anillo cíclico;

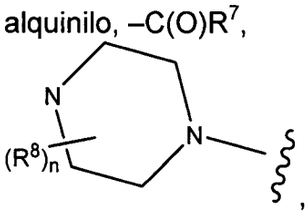
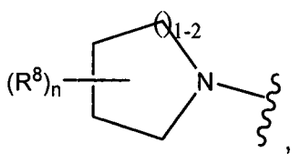
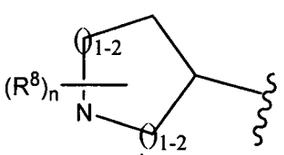
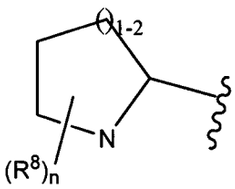
f. Un compuesto representado por la fórmula estructural:



fórmula F

o una de sus sales, solvatos, ésteres o profármacos farmacéuticamente aceptables, en donde:

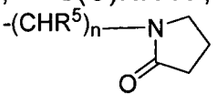
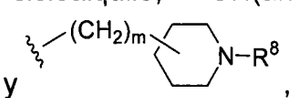
R está seleccionado del grupo que consiste en H, halógeno, arilo, heteroarilo, cicloalquilo, arilalquilo, heterociclilo, heterociclilalquilo, alquenilo, alquinilo, $-C(O)R^7$,


,

,

y


en donde cada uno de dichos arilo, heteroarilo, cicloalquilo, arilalquilo, alquenilo, heterociclilo y los restos de heterociclilo cuyas estructuras se muestran inmediatamente antes para R pueden no estar sustituidas o pueden estar opcionalmente sustituidas, de modo independiente, con uno o varios restos que pueden ser iguales o diferentes, donde cada resto está seleccionado, de modo independiente, del grupo que consiste en halógeno, alquilo, cicloalquilo, CF_3, CN, $-OCF_3$, $-OR^6$, $-C(O)R^7$, $-NR^5R^6$, $-C(O_2)R^6$, $-C(O)NR^5R^6$, $-(CHR^5)_nOR^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^6$;

R^1 es H, halógeno o alquilo;

R^2 es alquilo;

R^3 está seleccionado del grupo que consiste en H, arilo, heteroarilo, heterociclilo, $-(CHR^5)_n$–arilo, – $(CHR^5)_n$–heteroarilo, $-(CHR^5)_n-OR^6$, $-S(O_2)R^6$, $-C(O)R^6$, $-S(O_2)NR^5R^6$, $-C(O)OR^6$, $-C(O)NR^5R^6$, cicloalquilo, $-CH(arilo)_2$, $-(CH_2)_m-NR^8$, $-(CHR^5)_n-CH(arilo)_2$,  y  , en donde cada uno de dichos arilo, heteroarilo y heterociclilo puede estar sustituido u opcionalmente sustituido con uno o varios restos que pueden ser iguales o diferentes, donde cada resto está seleccionado, de modo independiente, del grupo que consiste en halógeno, alquilo, arilo, cicloalquilo, CF_3, CN, $-OCF_3$, $-OR^5$, $-NR^5R^6$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^6$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^6$;

R^5 es H o alquilo;

R^6 está seleccionado del grupo que consiste en H, alquilo, arilo, heteroarilo, arilalquilo y heteroarilalquilo, en donde cada uno de dichos alquilo, heteroarilalquilo, arilo, heteroarilo y arilalquilo puede no estar sustituido o puede estar opcionalmente sustituido con uno o varios restos que pueden ser iguales o diferentes, donde cada resto está seleccionado, de modo independiente, del grupo que consiste en halógeno, alquilo, arilo, cicloalquilo, CF_3, OCF_3, CN, $-OR^5$,

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$-NR^5R^6$, $-CH_2OR^5$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^6$;

R^7 está seleccionado del grupo que consiste en alquilo, arilo, heteroarilo, arilalquilo y heteroarilalquilo, en donde cada uno de dichos alquilo, heteroarilalquilo, arilo, heteroarilo y arilalquilo puede no estar sustituido o puede estar opcionalmente sustituido con uno o varios restos que pueden ser iguales o diferentes, donde cada resto está seleccionado, de modo independiente, del grupo que consiste en halógeno, alquilo, arilo, cicloalquilo, CF_3, OCF_3, CN, $-OR^5$, $-NR^5R^6$, $-CH_2OR^5$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^6$;

R^8 está seleccionado del grupo que consiste en R^6, $-C(O)NR^5R^6$, $-S(O_2)NR^5R^6$, $-C(O)R^7$, $-C(O_2)R^6$, $-S(O_2)R^7$ y $-(CH_2)$–arilo;

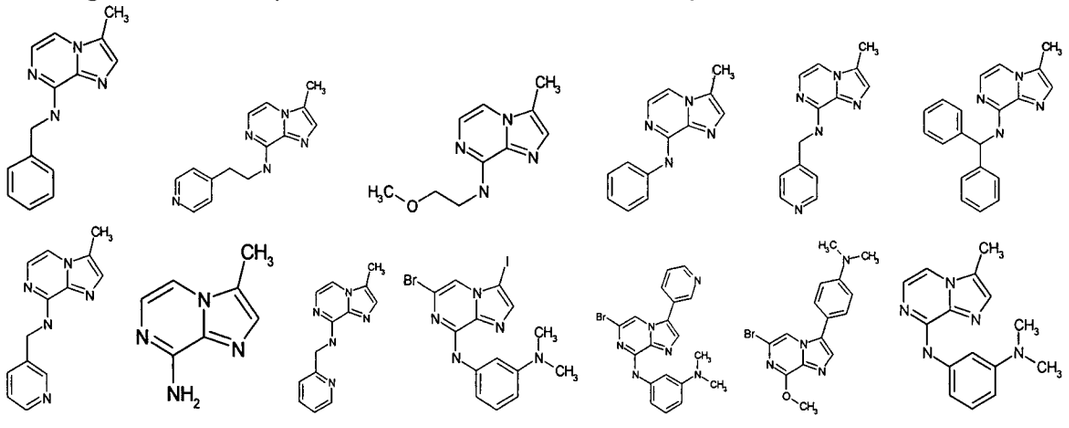
R^9 está seleccionado del grupo que consiste en halógeno, CN, NR^5R^6, $-C(O_2)R^6$, $-C(O)NR^5R^6$, $-OR^6$, $-C(O)R^7$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$and $-N(R^5)C(O)NR^5R^6$;

m es 0 a 4;

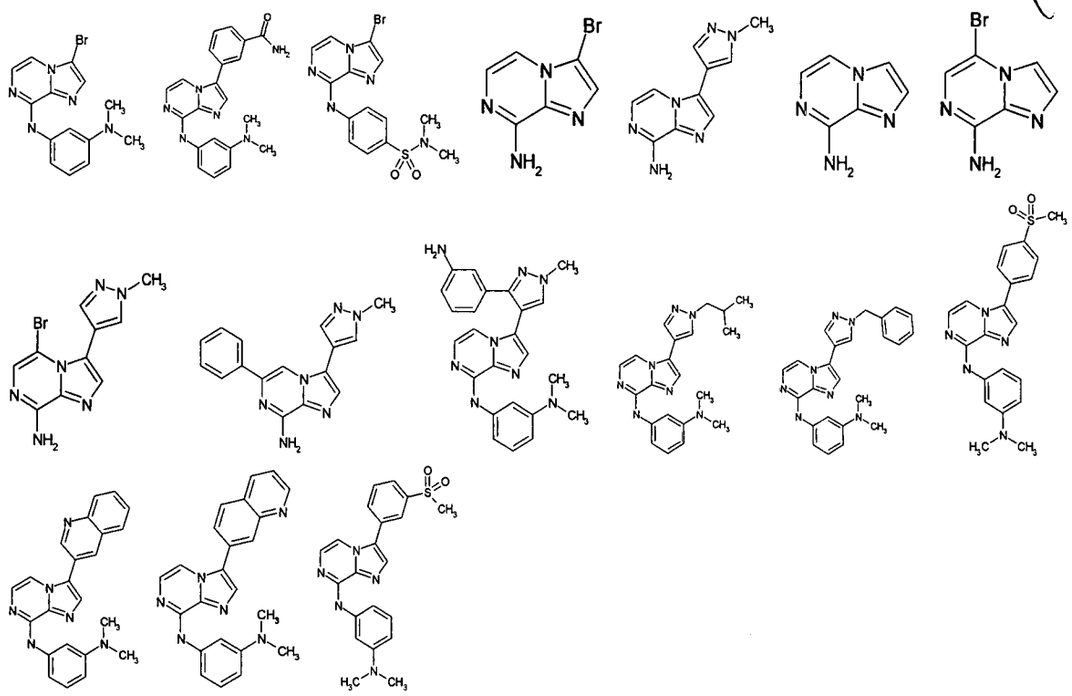
n es 1–4; y

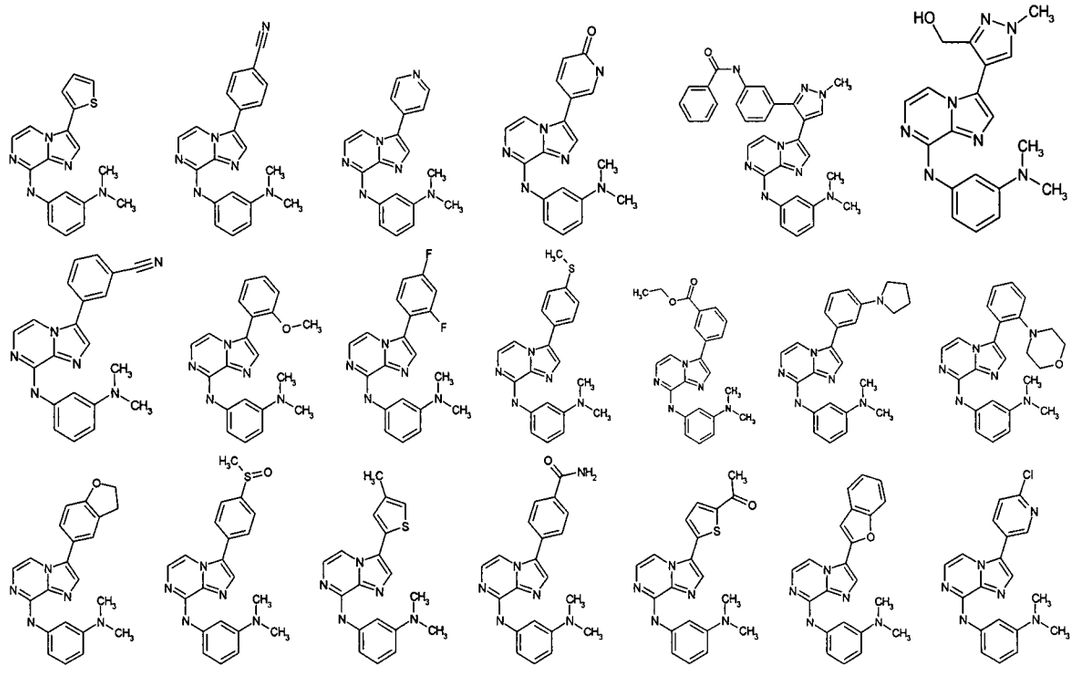
p es 0–3;

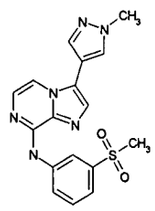
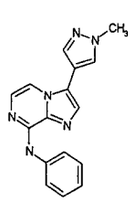
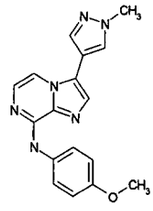
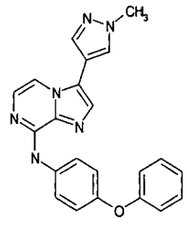
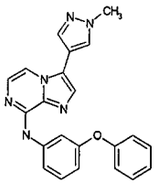
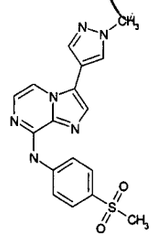
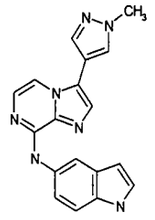
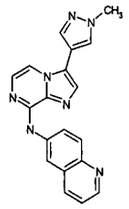
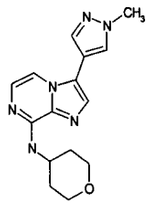
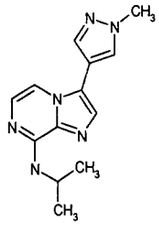
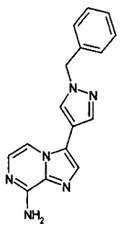
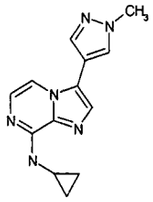
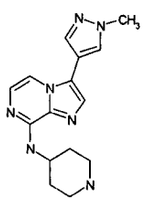
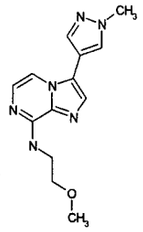
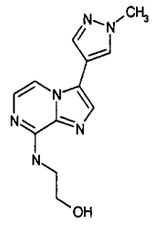
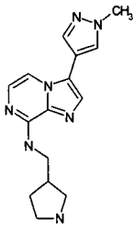
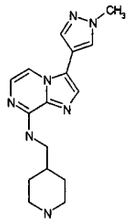
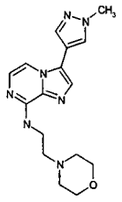
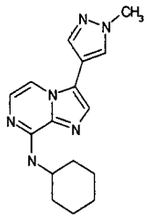
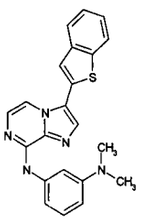
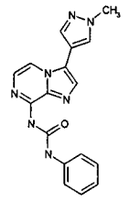
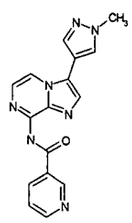
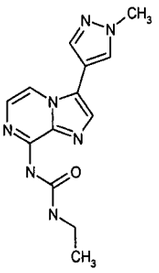
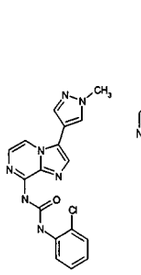
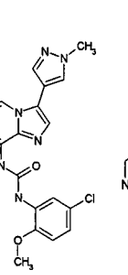
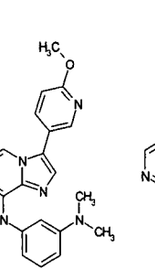
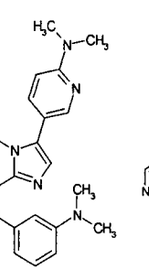
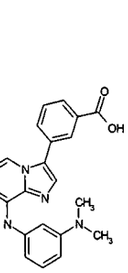
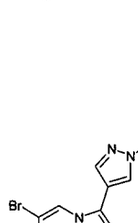
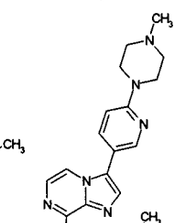
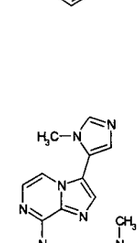
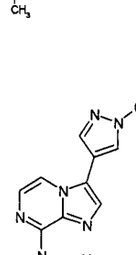
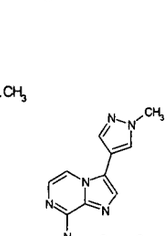
g. Un compuesto seleccionado de los compuestos de las fórmulas:

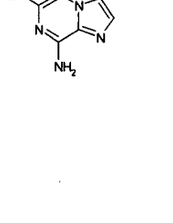
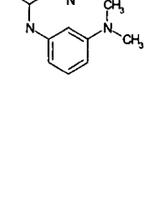
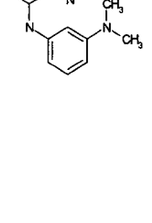


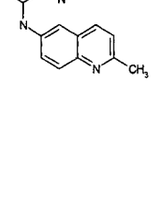
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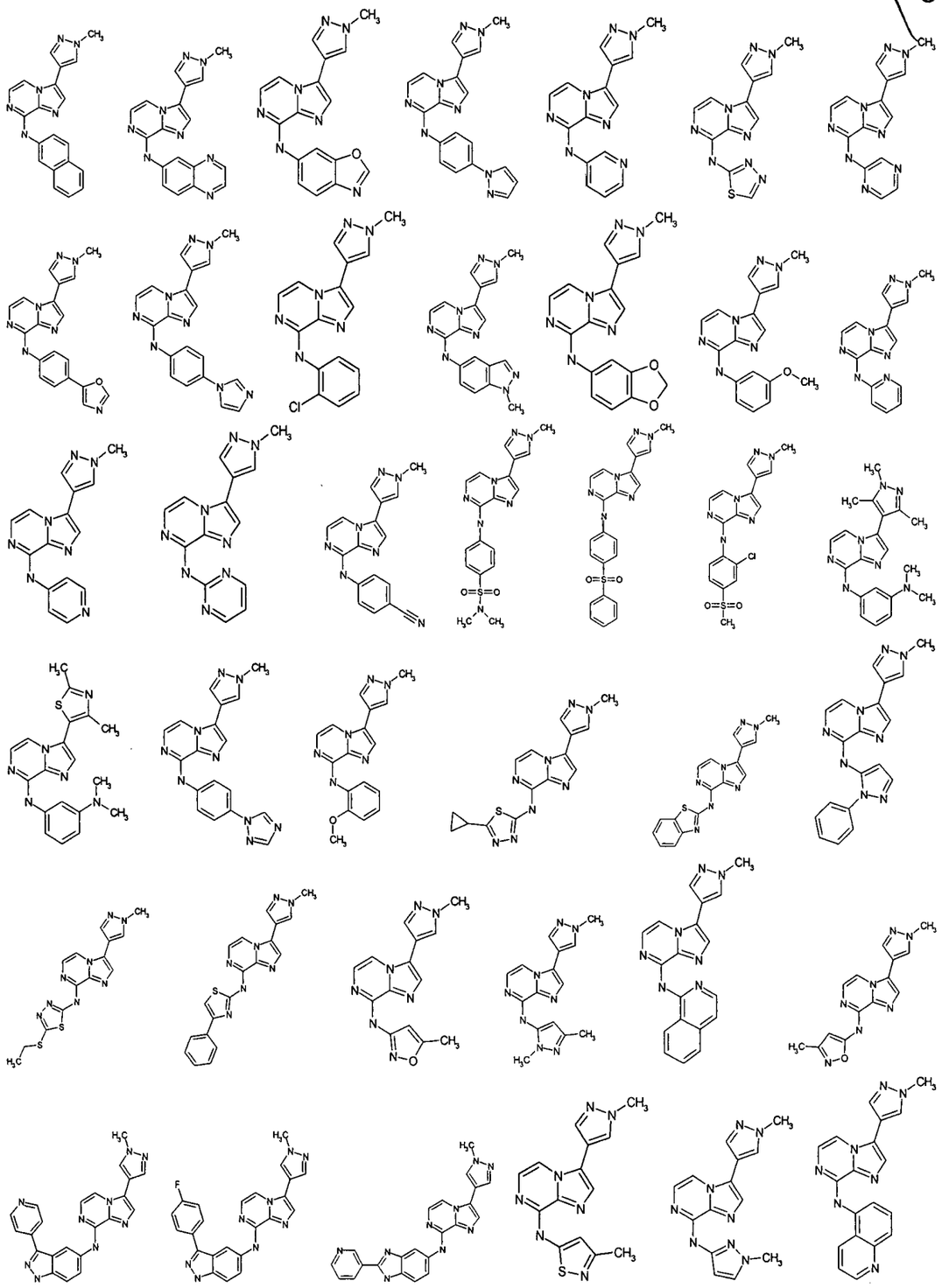


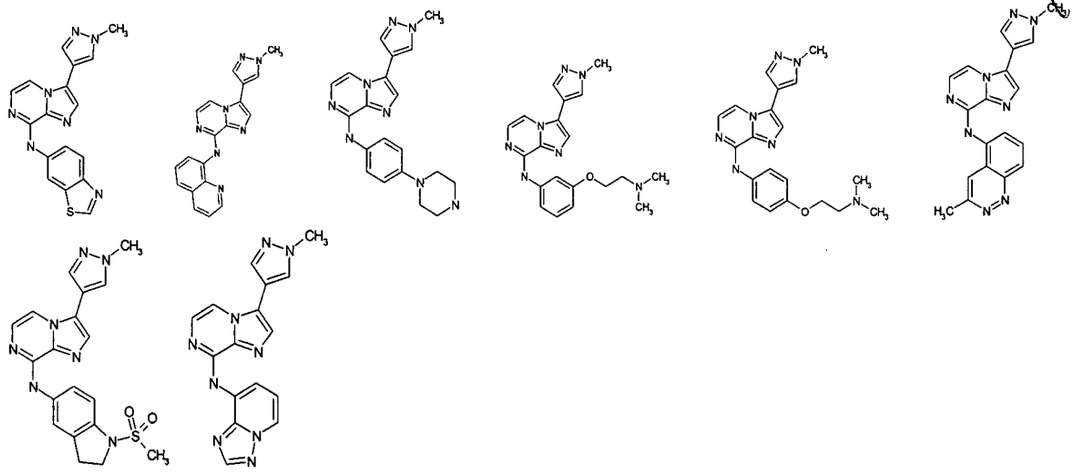


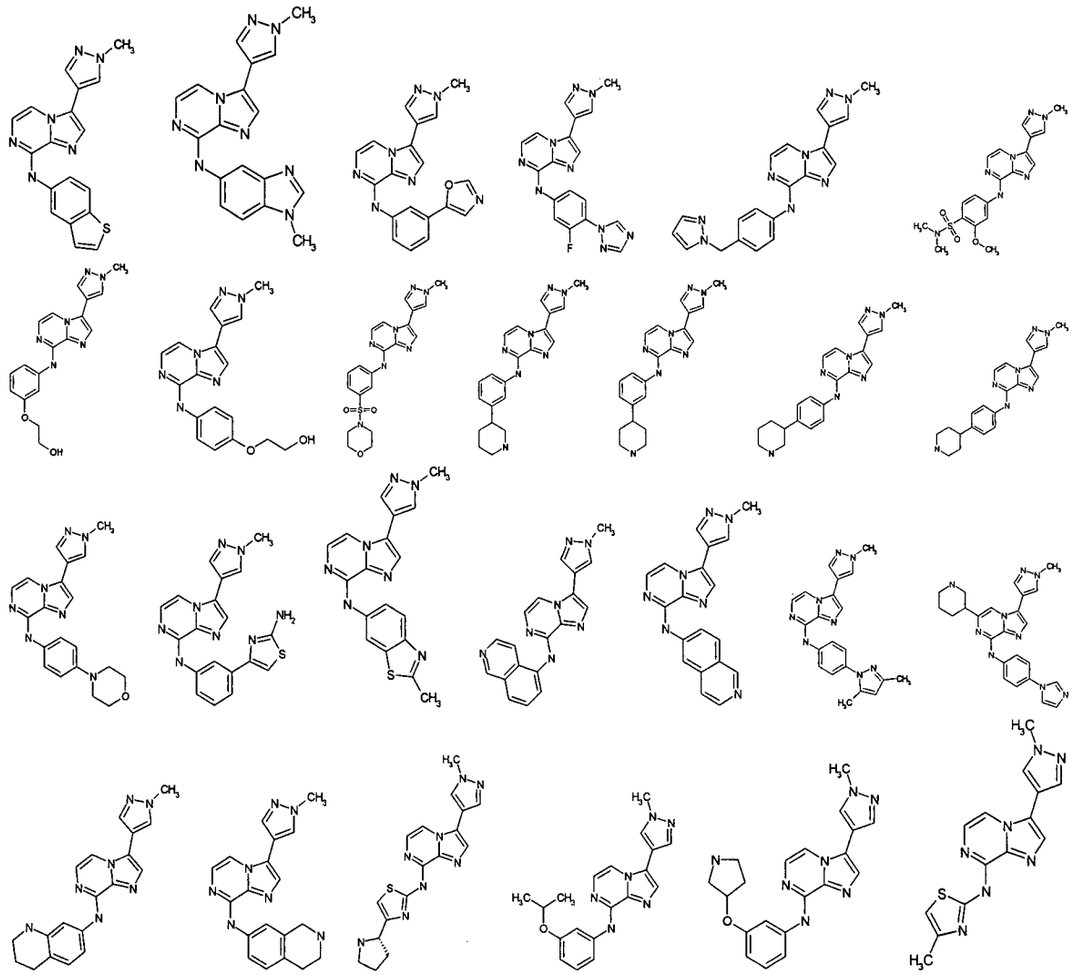


































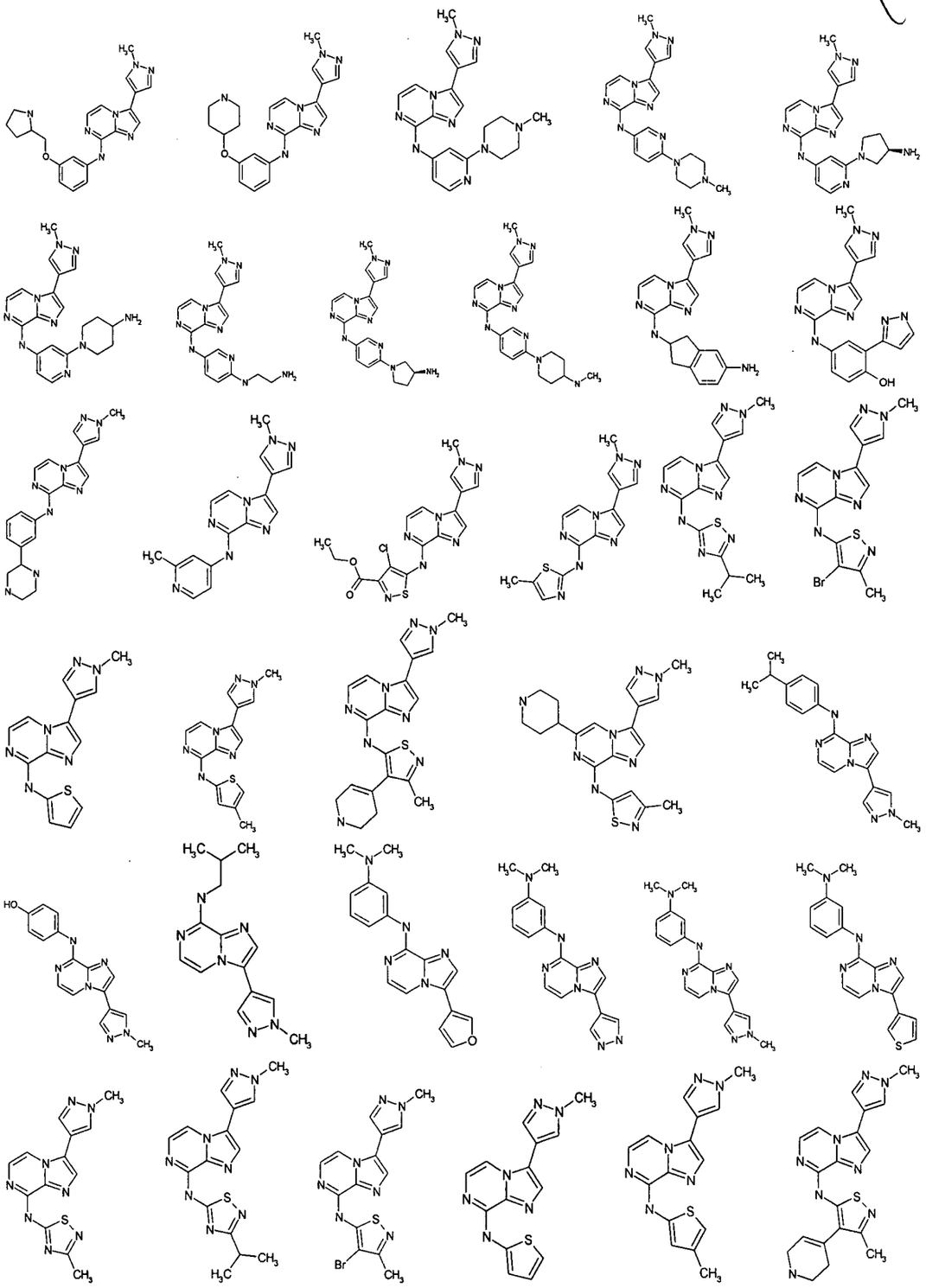




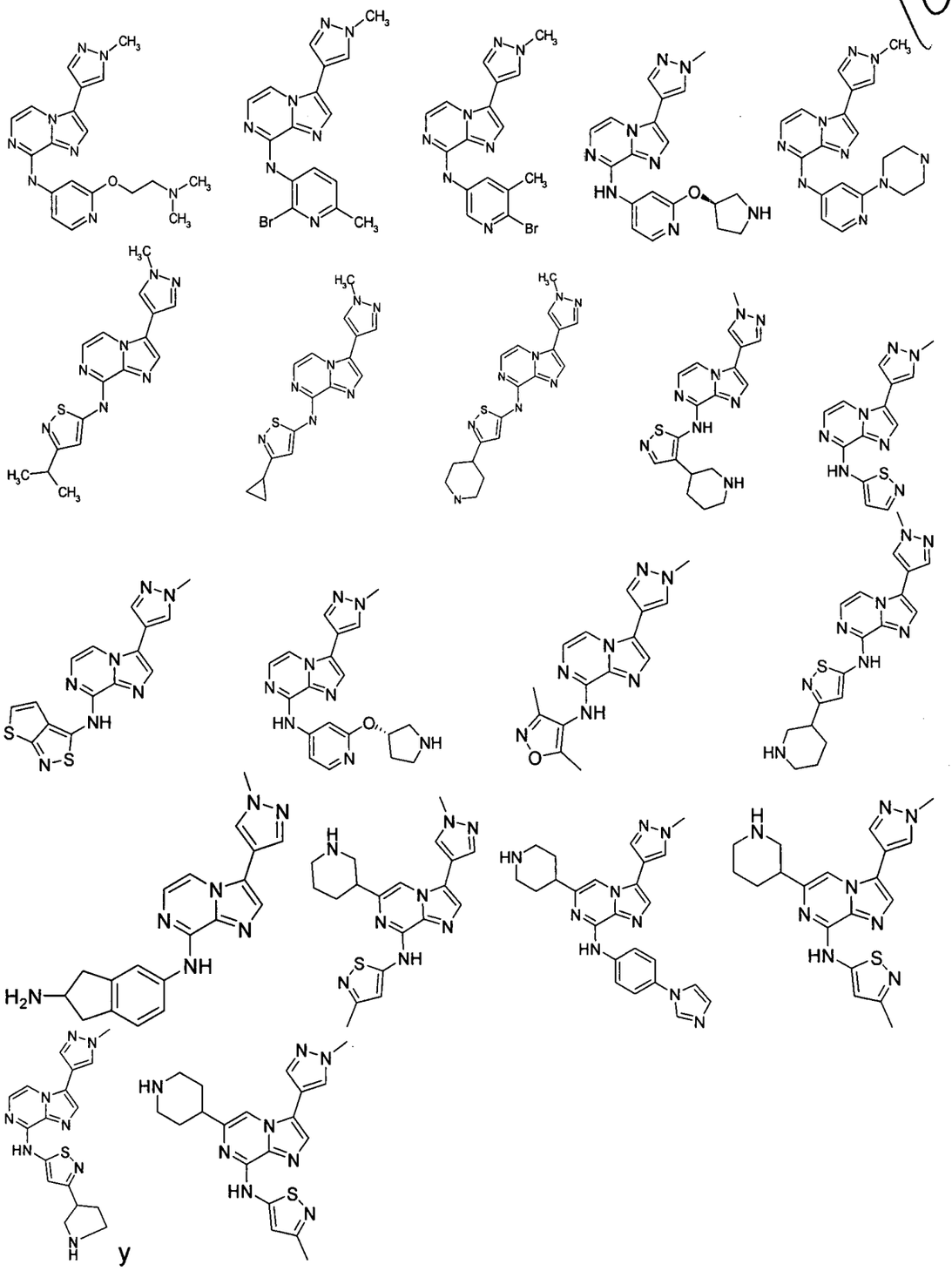








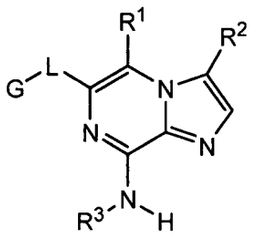




y

o una de sus sales, solvatos, ésteres o profármacos farmacéuticamente aceptables;

h. Un compuesto de la fórmula:



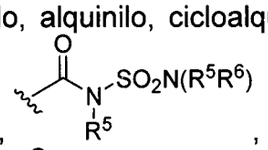
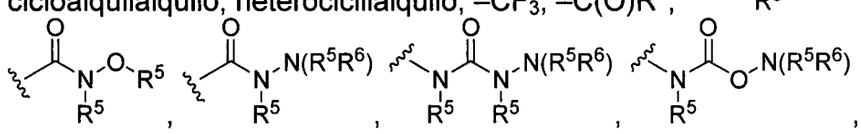
fórmula H

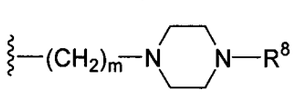
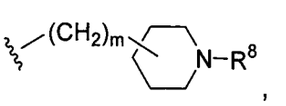
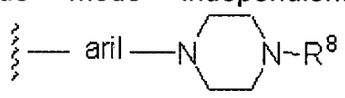
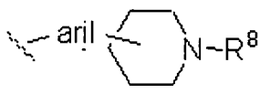
o una de sus sales, solvatos, ésteres o profármacos farmacéuticamente aceptables, en donde:

L está seleccionado del grupo que consiste en S, S(O) y $S(O_2)$;

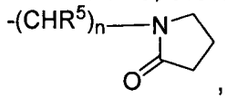
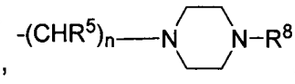
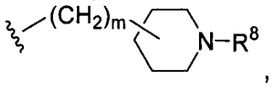
G es alquilo, alquenilo, cicloalquilo, cicloalquenilo, arilo, heteroarilo, heterociclenilo o heterociclilo, en donde cada uno de dichos alquilo, alquenilo, cicloalquilo, cicloalquenilo, arilo, heteroarilo, heterociclenilo o heterociclilo puede no estar sustituido o puede estar opcionalmente sustituido, de modo independiente, con uno o varios restos que están seleccionados, de modo independiente, del grupo que consiste en $-OR^5$, halo, $-CN$, $-C(O)NR^5R^6$, $-N(H)-C(O)R^5$,$-N(H)-C(O)-NR^5R^6$, $-S(O_2)NR^5R^6$, $-NR^5R^6$, $-C(O)R^5$, $-C(O_2)R^5$, $-SR^5$, $-S(O)R^5$, $-S(O_2)R^5$;

R^1 es H, halo, alquilo, arilo o heteroarilo, en donde cada uno de dichos alquilo, arilo y heteroarilo puede no estar sustituido o puede estar sustituido con uno o varios restos que pueden ser iguales o diferentes donde cada resto está seleccionado, de modo independiente, del grupo que consiste en halo, alquilo, alquenilo, alquinilo, cicloalquilo, arilo, heteroarilo, heterociclilo, $-C(O)NR^5R^6$ y $-OR^5$;

R^2 está seleccionado del grupo que consiste en H, R^9, alquilo, arilo, arilalquilo, heteroarilo, heteroarilalquilo, heterociclilo, alquenilo, alquinilo, cicloalquilo, cicloalquilalquilo, heterociclilalquilo, $-CF_3$, $-C(O)R^7$,  , 

alquilo sustituido con 1–6 R^9 que pueden ser iguales o diferentes, en donde cada R^9 está seleccionado, de modo independiente,  ,  ,  y  ,

en donde cada uno de dichos arilo, heteroarilo, cicloalquilo, arilalquilo y heterociclilo antes mencionados puede no estar sustituido o puede estar opcionalmente sustituido, de modo independiente, con uno o varios restos que pueden ser iguales o diferentes, donde cada resto está seleccionado, de modo independiente, del grupo que consiste en halo, alquilo, alquenilo, alquinilo, cicloalquilo, arilo, heteroarilo, heterociclilo, CF_3, CN, $-OCF_3$, $-OR^6$, $-C(O)R^7$, $-NR^5R^6$, $-C(O_2)R^6$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^6$;

R^3 está seleccionado del grupo que consiste en H, alquilo, arilo, heteroarilo, heterociclilo, aralquilo, heteroarilalquilo, cicloalquilalquilo, heterociclilalquilo,  ,  , $-(CHR^5)_n-OR^6$, $-S(O_2)R^6$, $-C(O)R^6$, $-S(O_2)NR^5R^6$, $-C(O)OR^6$, $-C(O)NR^5R^6$, cicloalquilo, $-CH(arilo)_2$, $-CH(heteroarilo)_2$, $-(CH_2)_m-NR^8$ y  , en donde cada uno de dichos alquilo, arilo, heteroarilo y heterociclilo puede estar sustituido u opcionalmente sustituido con uno o varios restos que pueden ser iguales o diferentes, donde cada resto está seleccionado, de modo independiente, del grupo que consiste en halo, alquilo, arilo, cicloalquilo, CF_3, CN, $-OCF_3$, $-OR^5$, $-NR^5R^6$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^6$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^6$;

R^5 es H, alquilo, arilo, heteroarilo, heterociclilo o cicloalquilo; y

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R^6 está seleccionado del grupo que consiste en H, alquilo, arilo, heteroarilo, arilalquilo y heteroarilalquilo, en donde cada uno de dichos alquilo, heteroarilalquilo, arilo, heteroarilo y arilalquilo puede no estar sustituido o puede estar opcionalmente sustituido con uno o varios restos que pueden ser iguales o diferentes, donde cada resto está seleccionado, de modo independiente, del grupo que consiste en halógeno, alquilo, arilo, cicloalquilo, CF_3, OCF_3, CN, $-OR^5$, $-NR^5R^6$, $-CH_2OR^5$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^6$;

R^7 está seleccionado del grupo que consiste en alquilo, arilo, heteroarilo, arilalquilo y heteroarilalquilo, en donde cada uno de dichos alquilo, heteroarilalquilo, arilo, heteroarilo y arilalquilo puede no estar sustituido o puede estar opcionalmente sustituido con uno o varios restos que pueden ser iguales o diferentes, donde cada resto está seleccionado, de modo independiente, del grupo que consiste en halógeno, alquilo, arilo, cicloalquilo, CF_3, OCF_3, CN, $-OR^5$, $-NR^5R^6$, $-CH_2OR^5$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^6$;

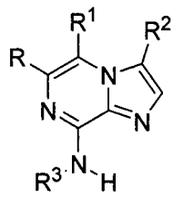
R^8 está seleccionado del grupo que consiste en R^6, $-C(O)NR^5R^6$, $-S(O_2)NR^5R^6$, $-C(O)R^7$, $-C(O_2)R^6$, $-S(O_2)R^7$ y $-(CH_2)$–arilo;

R^9 está seleccionado del grupo que consiste en halógeno, CN, NR^5R^6, $-C(O_2)R^6$, $-C(O)NR^5R^6$, $-OR^6$, $-C(O)R^7$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^6$;

m es 0 a 4; y

p es 0–3;

i. Un compuesto de la fórmula I:



fórmula I

o una de sus sales, solvatos, ésteres o profármacos farmacéuticamente aceptables, en donde:

R es H, CN, $-NR^5R^6$, cicloalquilo, cicloalquenilo, heterociclenilo, heteroarilo, $-C(O)NR^5R^6$, $-N(R^5)C(O)R^6$, heterociclilo, heteroarilo sustituido con $(CH_2)_{1-3}NR^5R^6$, alquilo no sustituido o alquilo sustituido con uno o varios restos que pueden ser iguales o diferentes donde cada resto está seleccionado, de modo independiente, del grupo que consiste en $-OR^5$, heterociclilo, $-N(R^5)C(O)N(R^5R^6)$, $-N(R^5)-C(O)OR^6$, $-(CH_2)_{1-3}-N(R^5R^6)$ y $-NR^5R^6$;

R^1 es H, halo, arilo o heteroarilo, en donde cada uno de dichos arilo y heteroarilo pueden no estar sustituidos o pueden estar sustituidos con uno o varios restos que pueden ser iguales o diferentes donde cada resto está seleccionado, de modo independiente, del grupo que consiste en halo, alquilo, alquenilo, alquinilo, cicloalquilo, arilo, heteroarilo, heterociclilo, $-CH_2OR^5$, $-C(O)NR^5R^6$, $-C(O)OH$, $-C(O)NH_2$, $-NR^5R^6$ (en donde R^5 y R^6, junto con el N de dicho $-NR^5R^6$, forman un anillo heterociclilo), $-S(O)R^5$, $-S(O_2)R^5$, $-CN$, $-CHO$, $-SR^5$, $-C(O)OR^5$, $-C(O)R^5$ y $-OR^5$;

R^2 es H, halo, arilo, arilalquilo o heteroarilo, en donde cada uno de dichos arilo, arilalquilo y heteroarilo puede no estar sustituido o puede estar opcionalmente sustituido, de modo independiente, con uno o varios restos que pueden ser iguales o diferentes donde cada resto está seleccionado, de modo independiente, del grupo que consiste en halo, amida, alquilo,

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alquenilo, alquinilo, cicloalquilo, arilo, –C(O)OH, –$C(O)NH_2$, –NR^5R^6 (en donde R^5 y R^6, junto con el N de dicho –NR^5R^6, forman un anillo heterociclilo), –CN, arilalquilo, –CH_2OR^5, –$S(O)R^5$, –$S(O_2)R^5$, –CN, –CHO, –SR^5, –$C(O)OR^5$, –$C(O)R^5$, heteroarilo y heterociclilo;

R^3 es heterociclil–$(CR^7R^8)_n$–X, heterociclenil–$(CR^7R^8)_n$–X, heteroaril–$(CR^7R^8)_n$–X o aril–$(CR^7R^8)_n$–X, en donde cada uno de los restos de heterociclilo, heterociclenilo, heteroarilo o arilo de dicho R^3 puede no estar sustituido o puede estar sustituido con uno o varios restos seleccionados, de modo independiente, del grupo que consiste en –$CONR^5R^6$, –OR^5 y alquilo,

n es 1–6,

X está seleccionado del grupo que consiste en –NR^5R^6, –OR^5, –SO–R^5 y –SR^5,

R^7 y R^8 son cada uno, de modo independiente, hidrógeno o alquilo;

R^5 está seleccionado del grupo que consiste en hidrógeno, alquilo, alquenilo, alcoxialquilo, –alquil–S–alquilo, aminoalquilo, arilo, heteroarilo, heterociclenilo, heterocicloalquilo, cicloalquilo, cicloalquenilo, heterociclilalcoxilo, –S–alquilheterociclilo, heterociclilo, heterociclenilo, alquilN$(alquilo)_2$, alquilNH(alquilo), alquilN$(alquenilo)_2$, –alquilN$(alcoxilo)_2$, –alquil–SH y hidroxialquilo, en donde each de said arilo, heteroarilo, heterociclenilo, heterocicloalquilo, cicloalquilo, cicloalquenilo, heterociclilalcoxilo, –S–alquilheterociclilo, heterociclilo, heterociclenilo puede no estar sustituido o puede estar sustituido con uno o varios restos seleccionados, de modo independiente, del grupo que consiste en alquilo, alquilo, alquenilo, arilo, cicloalquenilo, cicloalquilo, arilalquilo, cicloalquenilalquilo, cicloalquilalquilo, heteroarilo, heterociclenilo, heterociclilo, heteroarilalquilo, heterociclenilalquilo,

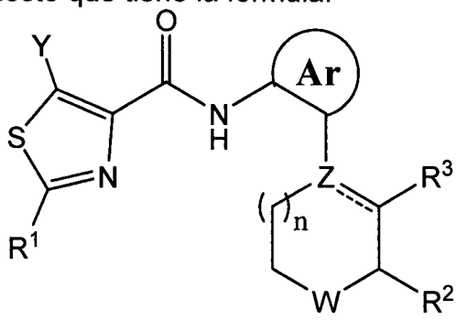
heterocicloalquilalquilo, alcoxialquilo, –alquil–S–alquilo, –alquilSH, alcoxilo, –S–alquilo, hidroxialquilo y aminoalquilo;

R^6 está seleccionado del grupo que consiste en hidrógeno, alquilo, alquenilo, arilo, cicloalquenilo, cicloalquilo, arilalquilo, cicloalquenilalquilo, cicloalquilalquilo, heteroarilo, heterociclenilo, heterociclilo, heteroarilalquilo, heterociclenilalquilo, heterocicloalquilalquilo, alcoxialquilo, –alquil–S–alquilo, –alquilSH, alcoxilo, –S–alquilo, hidroxialquilo y aminoalquilo, en donde cada uno de dichos arilo, cicloalquenilo, cicloalquilo, arilalquilo, cicloalquenilalquilo, cicloalquilalquilo, heteroarilo, heterociclenilo, heterociclilo, heteroarilalquilo, heterociclenilalquilo, heterocicloalquilalquilo puede no estar sustituido o puede estar sustituido con uno o varios restos seleccionados, de modo independiente, del grupo que consiste en alquilo, alquilo, alquenilo, arilo, cicloalquenilo, cicloalquilo, arilalquilo, cicloalquenilalquilo, cicloalquilalquilo, heteroarilo, heterociclenilo, heterociclilo, heteroarilalquilo, heterociclenilalquilo, heterocicloalquilalquilo, alcoxialquilo, –alquil–S–alquilo, –alquilSH, alcoxilo, –S–alquilo, hidroxialquilo y aminoalquilo;

también en donde en cualquier $–NR^5R^6$ en la fórmula I, dichos R^5 y R^6 pueden estar opcionalmente unidos junto con el N de dicho $–NR^5R^6$ para formar un anillo cíclico o anillo cíclico en puente, en donde cada uno de dicho anillo cíclico o anillo cíclico en puente, pueden no estar sustituidos o pueden estar sustituidos con uno o varios restos, que pueden ser iguales o diferentes seleccionados, de modo independiente, del grupo que consiste en hidroxilo, –SH, alquilo, alquenilo, hidroxialquilo, –alquil–SH, alcoxilo, –S–alquilo, $–CO_2–$

alquilo, $-CO_2-$alquenilo, arilalquilo, cicloalquenilalquilo, cicloalquilalquilo, heteroarilalquilo, heterociclenilalquilo, heterocicloalquilalquilo, heteroarilo, arilo, cicloalquenilo, cicloalquilo, espiroheterociclilo, espiroheterociclenilo, espiroheteroarilo, espirociclilo, espirociclenilo, espiroarilo, alcoxialquilo, –alquil–S–alquilo, heterociclilo y heterociclenilo;

j. Un compuesto que tiene la fórmula:



(J)

o una de sus sales, solvatos, ésteres, prodrogas o estereoisómeros farmacéuticamente aceptables, en donde las líneas punteadas indican un enlace opcional y adicional y en donde:

R^1 es heteroarilo con contenido de nitrógeno, heterociclilo con contenido de nitrógeno, heteroarilo benzofusionado con contenido de nitrógeno o heterociclilo benzofusionado con contenido de nitrógeno, en donde R^1 está unido con el resto del compuesto de la fórmula (I) a través de un átomo de nitrógeno del anillo y en donde uno o varios átomos de carbono del anillo de un grupo heteroarilo con contenido de nitrógeno, heterociclilo con contenido de nitrógeno, heteroarilo benzofusionado con contenido de nitrógeno o heterociclilo benzofusionado con contenido de nitrógeno puede estar sustituido con hasta 5 sustituyentes, que pueden ser iguales o diferentes y están seleccionados, de modo independiente,

de alquilo, arilo, halo, –OH, –O–alquilo, –O–arilo, $–N(R^8)_2$, $–CF_3$, $–NO_2$, $–C(O)R^8$, $–C(O)OR^8$, $–C(O)N(R^8)_2$, $–OC(O)R^8$ o $–NHC(O)R^8$;

R^2 es –H, –alquilo, $–NH_2$ o $–CH_2NH_2$;

R^3 es –H, –alquilo, $–NH_2$ o $–CH_2NH_2$;

cada aparición de R^4 es, de modo independiente, –H, –alquilo, $–NH_2$, –OH, –alquilen–OH, $–CH_2NH_2$, $–C(O)R^5$, $–C(O)NH_2$, –C(O)NH–alquilo, $–C(O)N(alquilo)_2$, $–NHC(O)R^6$ o $–NHS(O)_2R^6$;

R^5 es –H, –alquilo, –arilo, –heteroarilo, –NHOH;

R^6 es –H, –alquilo o $–CF_3$;

R^7 es –H, –OH, –alquilo C_1–C_6, –O–(alquilo C_1–C_6) o $–CF_3$;

R^8 es –H, alquilo, arilo, heterociclilo, heteroarilo o cicloalquilo;

Ar es –arileno– o –heteroarileno–, en donde el arileno o heteroarileno está unido a través de 2 de sus átomos de carbono del anillo adyacentes y en donde el –arileno– o –heteroarileno– pueden estar sustituidos con hasta 4 sustituyentes, que pueden ser iguales o diferentes y están seleccionados, de modo independiente, de –halo, alquilo, alcoxi, ariloxi, $–SR^8$, $–S(O)R^8$, $–S(O)_2R^8$, $–C(O)R^8$, $–C(O)OR^8$, $–C(O)N(R^8)_2$, $–NHC(O)R^8$, $–CF_3$, –CN o NO_2 y de modo tal que, cuando Ar es tetrahidronaftileno, R^1 y R^2 no puedan ser ambos hidrógeno

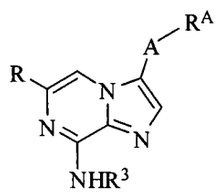
W es –NH– o $–C(R^4)_2–$, en donde ambos grupos R^4 y el átomo de carbono al que están unidos se pueden combinar para formar un grupo heterociclilo o heteroarilo de cinco a siete miembros;

Y es –H, –halo, –alquilo o –CN;

Z es $–CR^7–$ o –N–, cuando el enlace adicional opcional está ausente y –C– cuando el enlace adicional opcional está presente;

n es un número entero que va de 0 a 2; y

(k) Un compuesto de la fórmula K:



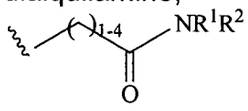
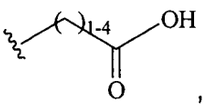
fórmula K

o una de sus sales, solvatos, ésteres, prodrogas o estereoisómeros farmacéuticamente aceptables, en donde:

R es H, halo o alquilo;

R^3 es heteroaril–X, en donde X es heterociclilalquilo–, en donde dicho heterociclilo puede no estar sustituido o puede estar opcionalmente sustituido con 1–4 restos alquilo;

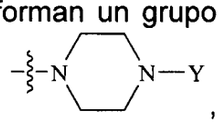
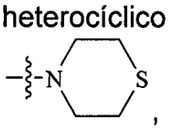
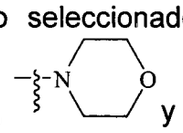
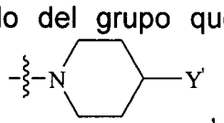
A es –arilo– , –heteroarilo–, –N(R^1)–arilo– o –N(R^1)–heteroarilo– , en donde cada uno de dichos arilo y heteroarilo puede no estar sustituido, de modo independiente, o puede estar opcionalmente sustituido con uno o varios sustituyentes que pueden ser iguales o diferentes, donde cada sustituyente está seleccionado, de modo independiente, del grupo que consiste en alquilo, $–NO_2$, halo, hidroxi, trihaloalquilo, alcoxi y dialquilamino;

R^A es $–(CH_2)_{1–4}$–heteroarilo,  o  , en donde dicho heteroarilo puede estar opcionalmente fusionado con un arilo, en donde cada uno de dichos arilo y heteroarilo puede estar opcionalmente sustituido, de modo independiente, con uno o varios restos donde cada resto está seleccionado, de modo independiente, del grupo que consiste en trihaloalquilo, $–NO_2$, halo, hidroxialquilo, alcoxialquilo y dialquilamino;

R^1 es H o alquilo;

R^2 es H, hidroxialquilo–, arilalquilo–, heteroarilo, arilo, heteroarilalquilo–, alquilo, dialquilaminoalquilo–, alquilaminoalquilo–, cicloalquilalquilo–, cicloalquilo, heterociclilalquilo– o heterociclilo, en donde dichos arilo y arilo de arilalquilo puede no estar sustituido o puede estar sustituido con uno o

varios restos seleccionados, de modo independiente, del grupo que consiste en trihaloalquilo, $-NO_2$, halo, hidroxialquilo, alcoxialquilo, dialquilamino y heterociclilalquilo–, en donde dicho heterociclilalquilo puede no estar sustituido o puede estar sustituido con alquilo o $-SO_2NH_2$; dichos heteroarilo y heteroarilo de heteroarilalquilo pueden no estar sustituidos o pueden estar sustituidos con uno o varios restos, donde cada resto está seleccionado, de modo independiente, del grupo que consiste en hidroxialquilo, alcoxi, alquilo, halo, hidroxilo y $-NO_2$; y dicho cicloalquilo no está sustituido o está sustituido con hidroxilo; o

R^1 y R^2 junto con N al que cada uno está unido, forman un grupo heterocíclico seleccionado del grupo que consiste en  ,  ,  y  , en donde

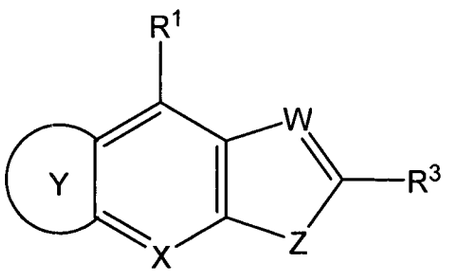
Y es alcoxialquilo, hidroxialquilo, dialquilaminoalquilo o alquilo, también en donde

Y' es hidroxilo;

en donde las cantidades del primer compuesto y del segundo compuesto dan como resultado un efecto terapéutico.

3. Un método de inducción de la endorreduplicación en células cancerosas, que comprende el pretratamiento de células cancerosas con al menos un agente antimitótico, en donde dicho agente antimitótico está seleccionado del grupo que consiste en un taxano, paclitaxel, docetaxel, un inhibidor de Cenp–E, abraxano, epotilona, monastrol y un inhibidor de KSP, ispinesib y compuestos de las fórmulas A–D mostradas en los puntos a–d que figuran más abajo:

a. Un compuesto representado por la fórmula estructural A:



fórmula A

o una de sus sales, solvatos o ésteres farmacéuticamente aceptables, en donde:

el anillo Y es un arilo de 5 ó 6 miembros o un heteroarilo de 5 ó 6 miembros fusionado tal como se indica en la fórmula A, en donde en dichos arilo y heteroarilo cada carbono del anillo sustituible está sustituido, de modo independiente, con R^2 y cada nitrógeno del anillo sustituible está sustituido, de modo independiente, con R^6;

W es N o $C(R^{12})$;

X es N o N–óxido;

Z es S, S(=O) o $S(=O)_2$;

R^1 es H, alquilo, alcoxi, hidroxi, halo, –CN, $–S(O)_m–$alquilo, $–C(O)NR^9R^{10}$, $–(CR^9R^{10})_{1–6}OH$ o $–NR^4(CR^9R^{10})_{1–2}OR^9$;

cada R^2 está seleccionado, de modo independiente, del grupo que consiste en H, halo, alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo, heteroaralquilo, $–(CR^{10}R^{11})_{0–6}–OR^7$, $–C(O)R^4$, $–C(S)R^4$, $–C(O)OR^7$, $–C(S)OR^7$, $–OC(O)R^7$, $–OC(S)R^7$, $–C(O)NR^4R^5$, $–C(S)NR^4R^5$, $–C(O)NR^4OR^7$, $–C(S)NR^4OR^7$, $–C(O)NR^7NR^4R^5$, $–C(S)NR^7NR^4R^5$, $–C(S)NR^4OR^7$, $–C(O)SR^7$, $–NR^4R^5$, $–NR^4C(O)R^5$, $–NR^4C(S)R^5$, $–NR^4C(O)OR^7$, $–NR^4C(S)OR^7$, $–OC(O)NR^4R^5$, $–OC(S)NR^4R^5$, $–NR^4C(O)NR^4R^5$, $–NR^4C(S)NR^4R^5$, $–NR^4C(O)NR^4OR^7$, $–NR^4C(S)NR^4OR^7$, $–(CR^{10}R^{11})_{0–6}SR^7$, SO_2R^7, $–S(O)_{1–2}NR^4R^5$, $–N(R^7)SO_2R^7$, $–S(O)_{1–2}NR^5OR^7$, –CN, $–OCF_3$, $–SCF_3$, $–C(=NR^7)NR^4$,

$-C(O)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}OR^7$, $-C(S)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(S)NR^7(CH_2)_{1-10}OR^7$, haloalquilo y alquilsililo, en donde cada uno de dichos alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo o heteroaralquilo está opcionalmente sustituido, de modo independiente, con 1–5 restos R^9;

cada R^3 está seleccionado, de modo independiente, del grupo que consiste en H, halo, alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo, heteroaralquilo, $-(CR^{10}R^{11})_{0-6}-OR^7$, $-C(O)R^4$, $-C(S)R^4$, $-C(O)OR^7$, $-C(S)OR^7$, $-OC(O)R^7$, $-OC(S)R^7$, $-C(O)NR^4R^5$, $-C(S)NR^4R^5$, $-C(O)NR^4OR^7$, $-C(S)NR^4OR^7$, $-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, $-CN$, $-OCF_3$, $-SCF_3$, $-C(=NR^7)NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}OR^7$, $-C(S)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(S)NR^7(CH_2)_{1-10}OR^7$, haloalquilo y alquilsililo, en donde cada uno de dichos alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo o heteroaralquilo está opcionalmente sustituido, de modo independiente, con 1–5 restos R^9;

cada R^4 y R^5 está seleccionado, de modo independiente, del grupo que consiste en H, alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo, heteroaralquilo, $-OR^7$, $-C(O)R^7$ y $-C(O)OR^7$, en donde cada uno de dichos alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo o heteroaralquilo está opcionalmente sustituido con 1–4 restos R^8;

o R^4 y R^5, cuando están unidos al mismo átomo de nitrógeno, se toman opcionalmente juntos con el átomo de nitrógeno al que están unidos para formar un anillo heterocíclico de 3–6 miembros que tiene 0–2 heteroátomos adicionales seleccionados de N, O o S;

cada R^6 está seleccionado, de modo independiente, del grupo que consiste en H, alquilo, arilo, aralquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, heteroarilo, heteroaralquilo, $-(CH_2)_{1-6}CF_3$, $-C(O)R^7$, $-C(O)OR^7$ y $-SO_2R^7$;

cada R^7 está seleccionado, de modo independiente, del grupo que consiste en H, alquilo, arilo, aralquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, heteroarilo y heteroaralquilo, en donde cada miembro de R^7 excepto H está opcionalmente sustituido con 1–4 restos R^8;

cada R^8 está seleccionado, de modo independiente, del grupo que consiste en halo, alquilo, cicloalquilo, heterociclilo, arilo, heteroarilo, $-NO_2$, $-OR^{10}$, –(alquil C_1–C_6)–OR^{10}, –CN, $-NR^{10}R^{11}$, $-C(O)R^{10}$, $-C(O)OR^{10}$, $-C(O)NR^{10}R^{11}$, $-CF_3$, $-OCF_3$, $-CF_2CF_3$, $-C(=NOH)R^{10}$, $-N(R^{10})C(O)R^{11}$, $-C(=NR^{10})NR^{10}R^{11}$ y $-NR^{10}C(O)OR^{11}$, en donde cada uno de dichos alquilo, cicloalquilo, heterociclilo, arilo y heteroarilo está opcionalmente sustituido, de modo independiente, con 1–3 restos seleccionados del grupo que consiste en halo, alquilo, cicloalquilo, heterociclilo, arilo, heteroarilo, $-NO_2$, $-OR^{10}$, –(alquil C_1–C_6)–OR^{10}, –CN, $-NR^{10}R^{11}$, $-C(O)OR^{10}$, $-C(O)NR^{10}R^{11}$, $-CF^3$, $-OCF_3$, $-NR^{10}C(O)OR^{11}$ y $-NR^{10}C(O)R^{40}$;

o dos grupos R^8, cuando están unidos al mismo átomo de carbono, se toman opcionalmente juntos con el átomo de carbono al que están unidos para formar un grupo C=O o un grupo C=S;

cada R^9 está seleccionado, de modo independiente, del grupo que consiste en H, alquilo, alcoxi, OH, CN, halo, $-(CR^{10}R^{11})_{0-4}NR^4R^5$, haloalquilo, hidroxialquilo, alcoxialquilo, $-C(O)NR^4R^5$, $-C(O)OR^7$, $-OC(O)NR^4R^5$, $-NR^4C(O)R^5$ y $-NR^4C(O)NR^4R^5$;

cada R^{10} es, de modo independiente, H o alquilo; o R^9 y R^{10}, cuando están unidos al mismo átomo de nitrógeno, se toman opcionalmente juntos con el átomo de nitrógeno al que están unidos para formar un anillo heterocíclico de 3–6 miembros que tiene 0–2 heteroátomos adicionales seleccionados de N, O o S;

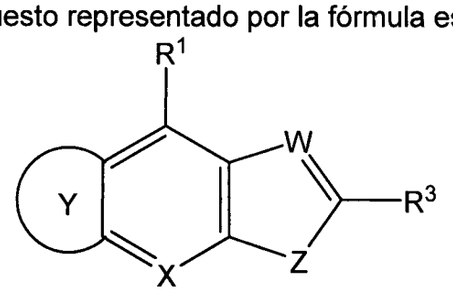
cada R^{11} es, de modo independiente, H o alquilo; o R^{10} y R^{11}, cuando están unidos al mismo átomo de nitrógeno, se toman opcionalmente juntos con el átomo de nitrógeno al que están unidos para formar un anillo heterocíclico de 3–6 miembros que tiene 0–2 heteroátomos adicionales seleccionados de N, O o S;

cada R^{12} está seleccionado, de modo independiente, del grupo que consiste en H, halo, alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo, heteroaralquilo, $-(CR^{10}R^{11})_{0-6}$ $-OR^7$, $-C(O)R^4$, $-C(S)R^4$, $-C(O)OR^7$, $-C(S)OR^7$, $-OC(O)R^7$, $-OC(S)R^7$, $-C(O)NR^4R^5$, $-C(S)NR^4R^5$, $-C(O)NR^4OR^7$, $-C(S)NR^4OR^7$, $-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, $-CN$, $-OCF_3$, $-SCF_3$, $-C(=NR^7)NR^4$, $-C(O)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}OR^7$, $-C(S)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(S)NR^7(CH_2)_{1-10}OR^7$, haloalquilo y alquilsililo, en donde cada uno de dichos alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo,

heterociclilalquilo, arilo, aralquilo, heteroarilo o heteroaralquilo está opcionalmente sustituido, de modo independiente, con 1–5 restos R^9; y

R^{40} está seleccionado del grupo que consiste en cicloalquilo, heterociclilo, arilo y heteroarilo, en donde cada uno de dichos cicloalquilo, heterociclilo, arilo y heteroarilo está opcionalmente sustituidos, de modo independiente, con 1–3 restos seleccionados, de modo independiente, del grupo que consiste en –CN, –OH, halo, alquilo, haloalquilo, alcoxi y $–NR^{10}R^{11}$;

b. Un compuesto representado por la fórmula estructural B:



fórmula B

o una de sus sales, solvatos o ésteres farmacéuticamente aceptables, en donde:

el anillo Y es un anillo de 5 a 7 miembros seleccionado del grupo que consiste en cicloalquilo, cicloalquenilo, heterociclilo o heterociclenilo fusionado tal como se indica en la fórmula B, en donde en cada uno de dichos anillos de 5 a 7 miembros, cada carbono del anillo sustituible está sustituido, de modo independiente, con 1–2 restos R^2 y cada heteroátomo del anillo sustituible está sustituido, de modo independiente, con R^6;

W es N o $C(R^{12})$;

X es N o N–óxido;

Z es S, S(=O) o $S(=O)_2$;

R^1 es H, alquilo, alcoxi, hidroxi, halo, –CN, $–S(O)_m–$alquilo, $–C(O)NR^9R^{10}$, $–(CR^9R^{10})_{1–6}OH$ o $–NR^4(CR^9R^{10})_{1–2}OR^9$; en donde m es 0 a 2;

cada R^2 está seleccionado, de modo independiente, del grupo que consiste en H, halo, alquilo, cicloalquilo, alquilsililo, cicloalquenilo, heterociclilo, heterociclenilo, arilo, heteroarilo, $-(CR^{10}R^{11})_{0-6}-OR^7$, $-C(O)R^4$, $-C(S)R^4$, $-C(O)OR^7$, $-C(S)OR^7$, $-OC(O)R^7$, $-OC(S)R^7$, $-C(O)NR^4R^5$, $-C(S)NR^4R^5$, $-C(O)NR^4OR^7$, $-C(S)NR^4OR^7$, $-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, $-CN$, $-OCF_3$, $-SCF_3$, $-C(=NR^7)NR^4$, $-C(O)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}OR^7$, $-C(S)NR^7(CH_2)_{1-10}NR^4R^5$ y $-C(S)NR^7(CH_2)_{1-10}OR^7$, en donde cada uno de dichos alquilo, cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, arilo y heteroarilo está opcionalmente sustituido, de modo independiente, con 1–5 restos R^9;

o dos grupos R^2 en el mismo átomo de carbono se toman opcionalmente juntos con el átomo de carbono al que están unidos para formar un grupo C=O, un grupo C=S o un grupo etilendioxi;

R^3 está seleccionado, de modo independiente, del grupo que consiste en H, halo, alquilo, cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, arilo, heteroarilo, $-(CR^{10}R^{11})_{0-6}-OR^7$, $-C(O)R^4$, $-C(S)R^4$, $-C(O)OR^7$, $-C(S)OR^7$, $-OC(O)R^7$, $-OC(S)R^7$, $-C(O)NR^4R^5$, $-C(S)NR^4R^5$, $-C(O)NR^4OR^7$, $-C(S)NR^4OR^7$, $-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, $-CN$, $-C(=NR^7)NR^4R^5$, $-C(O)N(R^7)-(CR^{40}R^{41})_{1-5}-C(=NR^7)NR^4R^5$, $-C(O)N(R^7)(CR^{40}R^{41})_{1-5}-NR^4R^5$, $-C(O)N(R^7)(CR^{40}R^{41})_{1-5}-C(O)-NR^4R^5$, $-C(O)N(R^7)(CR^{40}R^{41})_{1-5}-OR^7$, $-C(S)NR^7(CH_2)_{1-5}NR^4R^5$ y

$-C(S)NR^7(CH_2)_{1-5}OR^7$, en donde cada uno de dichos alquilo, cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, arilo y heteroarilo está opcionalmente sustituido, de modo independiente, con 1–5 restos R^9;

cada uno de R^4 y R^5 está seleccionado, de modo independiente, del grupo que consiste en H, alquilo, cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, arilo, heteroarilo,

$-OR^7$, $-C(O)R^7$ y $-C(O)OR^7$, en donde cada uno de dichos alquilo, cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, arilo y heteroarilo, está opcionalmente sustituido con 1–4 restos R^8;

o R^4 y R^5, cuando están unidos al mismo átomo de nitrógeno, se toman opcionalmente juntos con el átomo de nitrógeno al que están unidos para formar un anillo heterocíclico de 3–6 miembros que tiene 0–2 heteroátomos adicionales seleccionados de N, O o S;

cada R^6 está seleccionado, de modo independiente, del grupo que consiste en H, alquilo, arilo, aralquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, heteroarilo, heteroaralquilo, $-(CH_2)_{1-6}CF_3$, $-C(O)R^7$, $-C(O)OR^7$ y $-SO_2R^7$;

cada R^7 está seleccionado, de modo independiente, del grupo que consiste en H, alquilo, arilo, aralquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, heteroarilo y heteroaralquilo, en donde cada miembro de R^7 excepto H está opcionalmente sustituido con 1–4 restos R^8;

cada R^8 está seleccionado, de modo independiente, del grupo que consiste en halo, alquilo, cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, arilo, heteroarilo, $-NO_2$, $-OR^{10}$, $-$(alquil C_1–C_6)$-OR^{10}$, $-CN$, $-NR^{10}R^{11}$, $-C(O)R^{10}$, $-C(O)OR^{10}$, $-C(O)NR^{10}R^{11}$, $-CF_3$, $-OCF_3$, $-CF_2CF_3$, $-C(=NOH)R^{10}$, $-N(R^{10})C(O)R^{11}$, $-C(=NR^{10})NR^{10}R^{11}$ y $-NR^{10}C(O)OR^{11}$; en donde cada uno de dichos alquilo, cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, arilo y

heteroarilo está opcionalmente sustituido, de modo independiente, con 1–4 restos R^{42}; en donde cuando cada uno de dichos cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, arilo y heteroarilo contienen dos radicales en átomos de carbono adyacentes en cualquier parte dentro de dichos cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, arilo y heteroarilo, dichos radicales se pueden formar, opcional e independientemente en cualquier aparición, junto con los átomos de carbono a los que están unidos para formar un anillo carbocíclico o heterocíclico de cinco o seis miembros;

o dos grupos R^8, cuando están unidos al mismo carbono, se toman opcionalmente juntos con el átomo de carbono al que están unidos para formar un grupo C=O o un grupo C=S;

cada R^9 está seleccionado, de modo independiente, del grupo que consiste en H, alquilo, alcoxi, OH, CN, halo, $-(CR^{10}R^{11})_{0-4}NR^4R^5$, haloalquilo, hidroxialquilo, alcoxialquilo, $-C(O)NR^4R^5$, $-C(O)OR^7$, $-OC(O)NR^4R^5$, $-NR^4C(O)R^5$ y $-NR^4C(O)NR^4R^5$;

cada R^{10} es, de modo independiente, H o alquilo; o R^9 y R^{10}, cuando están unidos al mismo átomo de nitrógeno, se toman opcionalmente juntos con el átomo de nitrógeno al que están unidos para formar un anillo heterocíclico de 3–6 miembros que tiene 0–2 heteroátomos adicionales seleccionados de N, O o S;

cada R^{11} es, de modo independiente, H, alquilo, cicloalquilo, cicloalquenilo, arilo, heterociclilo, heterociclenilo o heteroarilo; o R^{10} y R^{11}, cuando están unidos al mismo átomo de nitrógeno, se toman opcionalmente juntos con el átomo de nitrógeno al que están unidos para formar un anillo heterocíclico de 3–6 miembros que tiene 0–2 heteroátomos adicionales seleccionados de N, O o S; en donde cada uno de dicho R^{11} alquilo, cicloalquilo, cicloalquenilo, arilo, heterociclilo, heterociclenilo y heteroarilo está opcionalmente sustituido, de modo independiente, con 1–3 restos seleccionados del grupo que consiste en –CN,

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–OH, $–NH_2$, –N(H)alquilo, $–N(alquilo)_2$, halo, haloalquilo, CF_3, alquilo, hidroxialquilo, alcoxi, arilo, ariloxi y heteroarilo;

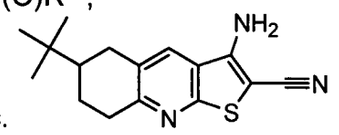
cada R^{12} está seleccionado, de modo independiente, del grupo que consiste en H, halo, alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo, heteroaralquilo, $–(CR^{10}R^{11})_{0–6}–OR^7$, $–C(O)R^4$, $–C(S)R^4$, $–C(O)OR^7$, $–C(S)OR^7$, $–OC(O)R^7$, $–OC(S)R^7$, $–C(O)NR^4R^5$, $–C(S)NR^4R^5$, $–C(O)NR^4OR^7$, $–C(S)NR^4OR^7$, $–C(O)NR^7NR^4R^5$, $–C(S)NR^7NR^4R^5$, $–C(S)NR^4OR^7$, $–C(O)SR^7$, $–NR^4R^5$, $–NR^4C(O)R^5$, $–NR^4C(S)R^5$, $–NR^4C(O)OR^7$, $–NR^4C(S)OR^7$, $–OC(O)NR^4R^5$, $–OC(S)NR^4R^5$, $–NR^4C(O)NR^4R^5$, $–NR^4C(S)NR^4R^5$, $–NR^4C(O)NR^4OR^7$, $–NR^4C(S)NR^4OR^7$, $–(CR^{10}R^{11})_{0–6}SR^7$, SO_2R^7, $–S(O)_{1–2}NR^4R^5$, $–N(R^7)SO_2R^7$, $–S(O)_{1–2}NR^5OR^7$, –CN, $–OCF_3$, $–SCF_3$, $–C(=NR^7)NR^4$, $–C(O)NR^7(CH_2)_{1–10}NR^4R^5$, $–C(O)NR^7(CH_2)_{1–10}OR^7$, $–C(S)NR^7(CH_2)_{1–10}NR^4R^5$, $–C(S)NR^7(CH_2)_{1–10}OR^7$, haloalquilo y alquilsililo, en donde cada uno de dichos alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo o heteroaralquilo está opcionalmente sustituido, de modo independiente, con 1–5 restos R^9;

R^{40} y R^{41} pueden ser iguales o diferentes, en donde cada uno está seleccionado, de modo independiente, del grupo que consiste en H, alquilo, arilo, heteroarilo, heterociclilo, heterociclenilo, cicloalquilo y cicloalquenilo;

cada R^{42} está seleccionado, de modo independiente, del grupo que consiste en halo, alquilo, cicloalquilo, heterociclilo, arilo, heteroarilo, $–NO_2$, $–OR^{10}$, –(alquilo $C_1–C_6$)–OR^{10}, –CN, $–NR^{10}R^{11}$, $–C(O)R^{10}$, $–C(O)OR^{10}$, $–C(O)NR^{10}R^{11}$, $–CF_3$, $–OCF_3$, $–N(R^{10})C(O)R^{11}$ y $–NR^{10}C(O)OR^{11}$;

con la condición de que, cuando W es $C(R^{12})$, R^{12} y R^3 se tomen opcionalmente juntos con los dos átomos de carbono del anillo a los que están unidos para formar un anillo de 6 miembros seleccionado del grupo que consiste

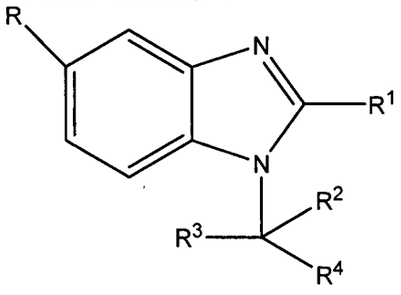
en cicloalquenilo, arilo, heteroarilo, heterociclilo y heterociclenilo, en donde dicho anillo de 6 miembros está opcionalmente sustituido con 1–3 restos seleccionados, de modo independiente, de oxo, tioxo, $-OR^{11}$, $-NR^{10}R^{11}$, $-C(O)R^{11}$, $-C(O)OR^{11}$, $-C(O)N(R^{10})(R^{11})$ o $-N(R^{10})C(O)R^{11}$;

c. 

fórmula C

o una de sus sales, solvatos o ésteres farmacéuticamente aceptables; y

d. Un compuesto de la fórmula D



fórmula D

o una de sus sales, solvatos o ésteres farmacéuticamente aceptables, en donde:

R está seleccionado del grupo que consiste en H, alquilo, ciano, haloalquilo, halo, —SH, –S–alquilo, –S–haloalquilo, $-S(=O)_2$alquilo, $-S(=O)_2OH$, $-S(=O)_2NH_2$, $-S(=O)_2$NH(alquilo), $S(=O)_2$NH(cicloalquilo), $-S(=O)_2N$(alquilo)$_2$, $-S(=O)_2$heterociclilo, $-S(=O)_2$heteroarilo, cicloalquilo, arilo, heterociclilo, heteroarilo, –NHC(=O)alquilo, $-C(=O)NH_2$, –C(=O)NH(alquilo), –C(=O)NH(cicloalquilo), –C(=O)N(alquilo)$_2$, –C(=O)OH, –C(=O)Oalquilo, –C(=O)heterociclilo, –C(=O)NH(arilo), en donde cuando cada uno de dichos cicloalquilo, arilo, heterociclilo, heteroarilo y las porciones de "heterociclilo" y "arilo" de dichos grupos R tiene dos sustituyentes en átomos de carbono adyacentes, dichos sustituyentes se pueden tomar opcionalmente juntos con los átomos de carbono a los que

están unidos para formar un anillo cicloalquilo, arilo, heterociclilo, heterociclenilo o heteroarilo de cinco o seis miembros; en donde cada uno de los R antes mencionados alquilo, arilo, cicloalquilo, heterociclilo y heteroarilo y las porciones de "alquilo", "cicloalquilo", "heterociclilo" y "arilo" de dichos grupos R, opcionalmente con dichos anillo arilo, heterociclilo, heterociclenilo o heteroarilo de cinco o seis miembros, está opcionalmente sustituido con 1–3 sustituyentes seleccionados, de modo independiente, del grupo que consiste en alquilo, alquenilo, alquinilo, hidroxilo, ciano, halo, haloalquilo, haloalcoxi, –C(O)OH, –C(=O)Oalquilo y $–C(O)NH_2$;

R^1 está seleccionado del grupo que consiste en alquilo, heterociclilo, –C(=O)arilo, $–NH_2$, –NH(alquilo), –NH(cicloalquilo), –N(alquil)(cicloalquilo), –NH(heterociclilo), –N(alquil)(heterociclilo), $N(alquilo)_2$, –NH(arilo), –N(alquil)(arilo), $–N(arilo)_2$, –NH(heteroarilo), –N(alquil)(heteroarilo), –NHC(=O)–alquilo, –N(alquil)C(=O)–alquilo, –NHC(=O)Oalquilo, –N(alquil)C(=O)O–alquilo, en donde cada uno de los alquilo, heterociclilo antes mencionados y las porciones de "alquilo", "cicloalquilo", "arilo" y "heteroarilo" de dichos grupos R^1 está opcionalmente sustituido con 1–3 sustituyentes seleccionados, de modo independiente, del grupo que consiste en halo, heterociclilo, arilo, heteroarilo, haloalquilo, haloalcoxi, ariloxi, ciano, –SH, –S–alquilo, –S–haloalquilo, $–S(=O)_2$alquilo, $–S(=O)_2OH$, $–S(=O)_2NH_2$, $–S(=O)_2$NH(alquilo), $S(=O)_2$NH(cicloalquilo), $–S(=O)_2N(alquilo)_2$, $–S(=O)_2$heterociclilo, $–S(=O)_2$heteroarilo, hidroxi, alquilo, alquenilo, alquinilo, $–NH_2$, –NH(alquilo), $–N(alquilo)_2$, alcoxi, –NHC(=O)alquilo, –C(=O)H, –C(=O)alquilo, –C(=O)arilo, –C(=O)heteroarilo, –C(=O)Oalquilo, $–C(=O)NH_2$, –C(O)NHalquilo, $–C(=O)N(alquilo)_2$; en donde cuando cada uno de dichos heterociclilo, arilo y heteroarilo tiene dos sustituyentes en átomos de carbono adyacentes, dichos sustituyentes se

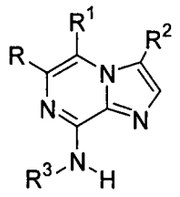
pueden tomar opcionalmente juntos con los átomos de carbono a los que están unidos para formar un anillo arilo, heterociclilo, heterociclenilo o heteroarilo de cinco a seis miembros;

R^2 y R^3 son, de modo independiente, H o alquilo o $-C(R^2)(R^3)-$ está ausente;

R^4 está seleccionado del grupo que consiste en alquilo, cicloalquilo, heterociclilo, arilo y heteroarilo, en donde cuando cada uno de dichos cicloalquilo, heterociclilo, arilo y heteroarilo tiene dos sustituyentes en átomos de carbono adyacentes, dichos sustituyentes se pueden tomar opcionalmente juntos con los átomos de carbono a los que están unidos para formar un anillo arilo, heterociclilo, heterociclenilo o heteroarilo de cinco a seis miembros; en donde cada uno de los R^4 antes mencionados alquilo, cicloalquilo, heterociclilo, arilo y heteroarilo, opcionalmente con dichos anillos arilo, heterociclilo, heterociclenilo o heteroarilo de cinco a seis miembros está opcionalmente sustituido con 1–3 sustituyentes seleccionados, de modo independiente, del grupo que consiste en ciano, halo, haloalquilo, alquilo, alcoxi, hidroxilo, haloalcoxi, cicloalquilo, heterociclilo, arilo, heteroarilo, $-S(=O)_2$alquilo, $-S(=O)_2NH_2$, $-S(=O)_2NH$(alquilo), $-S(=O)_2N$(alquilo)$_2$, –S–alquilo, –S–haloalquilo, $-C(=O)OH$, $-NH_2$, –NH(alquilo), $-N$(alquilo)$_2$ y $-C(=O)O$alquilo;

seguido de la administración de uno o varios de un segundo compuesto, en donde dicho segundo compuesto es un inhibidor de aurora quinasa seleccionado del grupo que consiste en compuestos representados por las fórmulas E–K mostrados más abajo en los puntos e–k:

e. Un compuesto representado por la fórmula estructural E:



fórmula E

o una de sus sales, solvatos, ésteres o profármacos farmacéuticamente aceptables, en donde:

R es H, CN, $-NR^5R^6$, cicloalquilo, cicloalquenilo, heterociclenilo, heteroarilo, $-C(O)NR^5R^6$, $-N(R^5)C(O)R^6$, heterociclilo, heteroarilo sustituido con $(CH_2)_{1-3}$ NR^5R^6, alquilo no sustituido o alquilo sustituido con uno o varios restos que pueden ser iguales o diferentes donde cada resto está seleccionado, de modo independiente, del grupo que consiste en $-OR^5$, heterociclilo, $-N(R^5)C(O)N(R^5R^6)$, $-N(R^5)-C(O)OR^6$, $-(CH_2)_{1-3}-N(R^5R^6)$ y $-NR^5R^6$;

R^1 es H, halo, arilo o heteroarilo, en donde cada uno de dichos arilo y heteroarilo puede no estar sustituido o puede estar sustituido con uno o varios restos que pueden ser iguales o diferentes donde cada resto está seleccionado, de modo independiente, del grupo que consiste en halo, alquilo, alquenilo, alquinilo, cicloalquilo, arilo, heteroarilo, heterociclilo, $-CH_2OR^5$, $-C(O)NR^5R^6$, $-C(O)OH$, $-C(O)NH_2$, $-NR^5R^6$ (en donde R^5 y R^6, junto con el N de dicho $-NR^5R^6$, forman un anillo heterociclilo), $-S(O)R^5$, $-S(O_2)R^5$, $-CN$, $-CHO$, $-SR^5$, $-C(O)OR^5$, $-C(O)R^5$ y $-OR^5$;

R^2 es H, halo, arilo, arilalquilo o heteroarilo, en donde cada uno de dichos arilo, arilalquilo y heteroarilo puede no estar sustituido o puede estar opcionalmente sustituido, de modo independiente, con uno o varios restos que pueden ser iguales o diferentes donde cada resto está seleccionado, de modo independiente, del grupo que consiste en halo, amida, alquilo, alquenilo, alquinilo, cicloalquilo, arilo,

–C(O)OH, –C(O)NH_2, –NR^5R^6 (en donde R^5 y R^6, junto con el N de dicho –NR^5R^6, forman un anillo heterociclilo), –CN, arilalquilo, –CH_2OR^5, –S(O)R^5, –S(O_2)R^5, –CN, –CHO, –SR^5, –C(O)OR^5, –C(O)R^5, heteroarilo y heterociclilo;

R^3 es H, alquilo, cicloalquilo, heterociclilo, arilo o heteroarilo, en donde:

– dicho alquilo mostrado con anterioridad para R^3 puede no estar sustituido o puede estar sustituido con uno o varios restos que pueden ser iguales o diferentes donde cada resto está seleccionado, de modo independiente, del grupo que consiste en –OR^5, alcoxi, heteroarilo y –NR^5R^6;

– dicho arilo mostrado con anterioridad para R^3 puede no estar sustituido o puede estar opcionalmente sustituido u opcionalmente fusionado, con halo, heteroarilo, heterociclilo, cicloalquilo o heteroarilalquilo, en donde cada uno de dichos heteroarilo, heterociclilo, cicloalquilo y heteroarilalquilo puede no estar sustituido o puede estar opcionalmente sustituido, de modo independiente, con uno o varios restos que pueden ser iguales o diferentes donde cada resto está seleccionado, de modo independiente, de alquilo, –OR^5, –N(R^5R^6) y –S(O_2)R^5; y

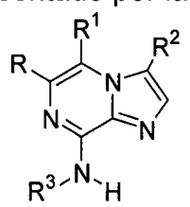
– dicho heteroarilo mostrado con anterioridad para R^3 puede no estar sustituido o puede estar opcionalmente sustituido u opcionalmente fusionado con uno o varios restos que pueden ser iguales o diferentes con donde cada resto está seleccionado, de modo independiente, del grupo que consiste en halo, amino, alcoxicarbonilo, –OR^5, alquilo, –CHO, – NR^5R^6, –S(O_2)N(R^5R^6), –C(O)N(R^5R^6), –SR^5, alquenilo, alquinilo, cicloalquilo, arilo, heteroarilo, heterociclenilo y heterociclilo;

R^5 es H, alquilo, aminoalquilo, arilo, heteroarilo, heterociclilo o cicloalquilo; y

R^6 es H, alquilo, arilo, arilalquilo, heteroarilo, heterociclilo o cicloalquilo;

también en donde en cualquier $-NR^5R^6$ en la fórmula I, dichos R^5 y R^6 pueden estar opcionalmente unidos junto con el N de dicho $-NR^5R^6$ para formar un anillo cíclico;

f. Un compuesto representado por la fórmula estructural:

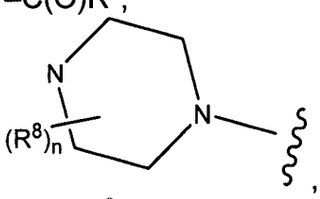
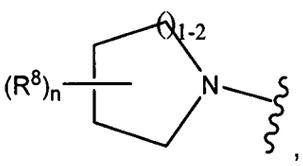
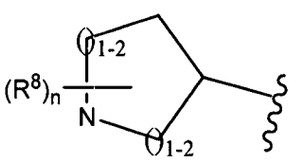
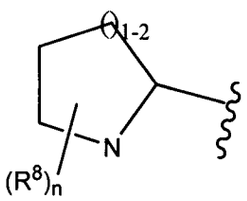


fórmula F

o una de sus sales, solvatos, ésteres o profármacos farmacéuticamente aceptables, en donde:

R está seleccionado del grupo que consiste en H, halógeno, arilo, heteroarilo, cicloalquilo, arilalquilo, heterociclilo, heterociclilalquilo, alquenilo, alquinilo,

$-C(O)R^7$,

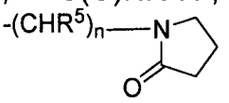
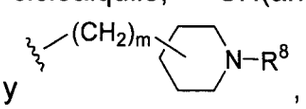

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y


en donde cada uno de dichos arilo, heteroarilo, cicloalquilo, arilalquilo, alquenilo, heterociclilo y los restos de heterociclilo cuyas estructuras se muestran inmediatamente antes para R pueden no estar sustituidas o pueden estar opcionalmente sustituidas, de modo independiente, con uno o varios restos que pueden ser iguales o diferentes, donde cada resto está seleccionado, de modo

independiente, del grupo que consiste en halógeno, alquilo, cicloalquilo, CF_3, CN, $-OCF_3$, $-OR^6$, $-C(O)R^7$, $-NR^5R^6$, $-C(O_2)R^6$, $-C(O)NR^5R^6$, $-(CHR^5)_nOR^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^6$;

R^1 es H, halógeno o alquilo;

R^2 es alquilo;

R^3 está seleccionado del grupo que consiste en H, arilo, heteroarilo, heterociclilo, $-(CHR^5)_n$–arilo, $-(CHR^5)_n$–heteroarilo, $-(CHR^5)_n-OR^6$, $-S(O_2)R^6$, $-C(O)R^6$, $-S(O_2)NR^5R^6$, $-C(O)OR^6$, $-C(O)NR^5R^6$, cicloalquilo, $-CH(arilo)_2$, $-(CH_2)_m-NR^8$, $-(CHR^5)_n-CH(arilo)_2$,  y  , en donde cada uno de dichos arilo, heteroarilo y heterociclilo puede estar sustituido u opcionalmente sustituido con uno o varios restos que pueden ser iguales o diferentes, donde cada resto está seleccionado, de modo independiente, del grupo que consiste en halógeno, alquilo, arilo, cicloalquilo, CF_3, CN, $-OCF_3$, $-OR^5$, $-NR^5R^6$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^6$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^6$;

R^5 es H o alquilo;

R^6 está seleccionado del grupo que consiste en H, alquilo, arilo, heteroarilo, arilalquilo y heteroarilalquilo, en donde cada uno de dichos alquilo, heteroarilalquilo, arilo, heteroarilo y arilalquilo puede no estar sustituido o puede estar opcionalmente sustituido con uno o varios restos que pueden ser iguales o diferentes, donde cada resto está seleccionado, de modo independiente, del grupo que consiste en halógeno, alquilo, arilo, cicloalquilo, CF_3, OCF_3, CN, $-OR^5$, $-NR^5R^6$, $-CH_2OR^5$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^6$;

R^7 está seleccionado del grupo que consiste en alquilo, arilo, heteroarilo, arilalquilo y heteroarilalquilo, en donde cada uno de dichos alquilo, heteroarilalquilo, arilo, heteroarilo y arilalquilo puede no estar sustituido o puede

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estar opcionalmente sustituido con uno o varios restos que pueden ser iguales o diferentes, donde cada resto está seleccionado, de modo independiente, del grupo que consiste en halógeno, alquilo, arilo, cicloalquilo, CF_3, OCF_3, CN, $-OR^5$, $-NR^5R^6$, $-CH_2OR^5$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^6$;

R^8 está seleccionado del grupo que consiste en R^6, $-C(O)NR^5R^6$, $-S(O_2)NR^5R^6$, $-C(O)R^7$, $-C(O_2)R^6$, $-S(O_2)R^7$ y $-(CH_2)$–arilo;

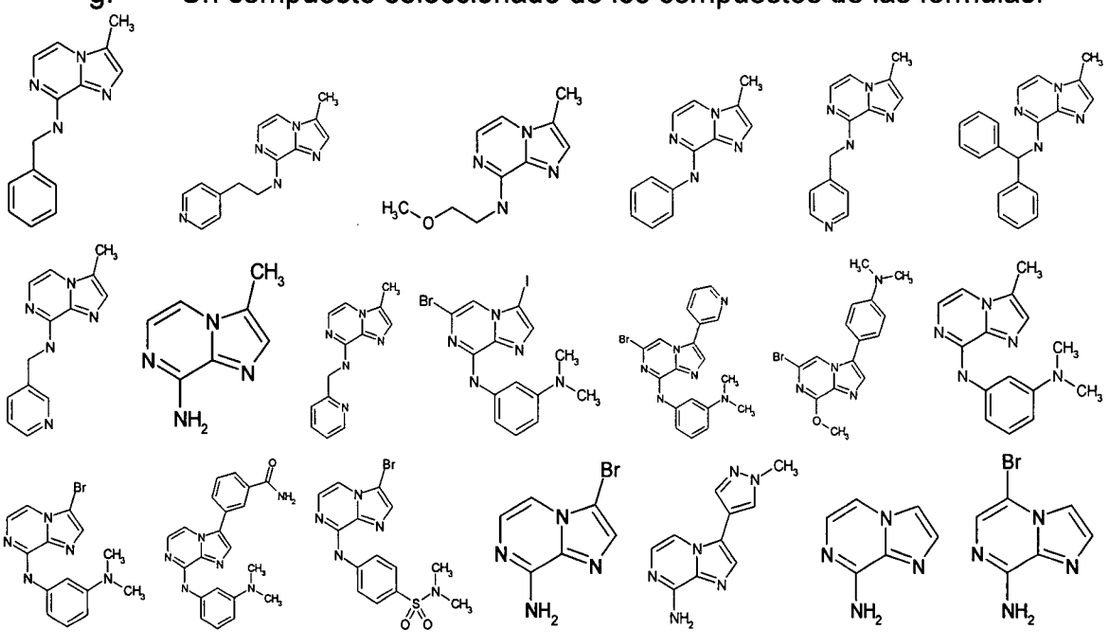
R^9 está seleccionado del grupo que consiste en halógeno, CN, NR^5R^6, $-C(O_2)R^6$, $-C(O)NR^5R^6$, $-OR^6$, $-C(O)R^7$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^6$;

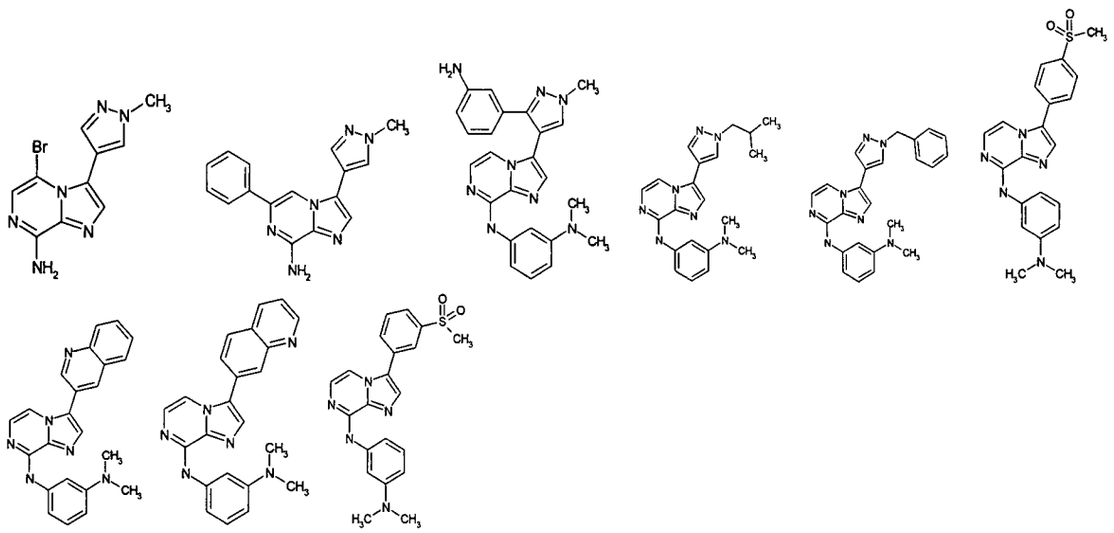
m es 0 a 4;

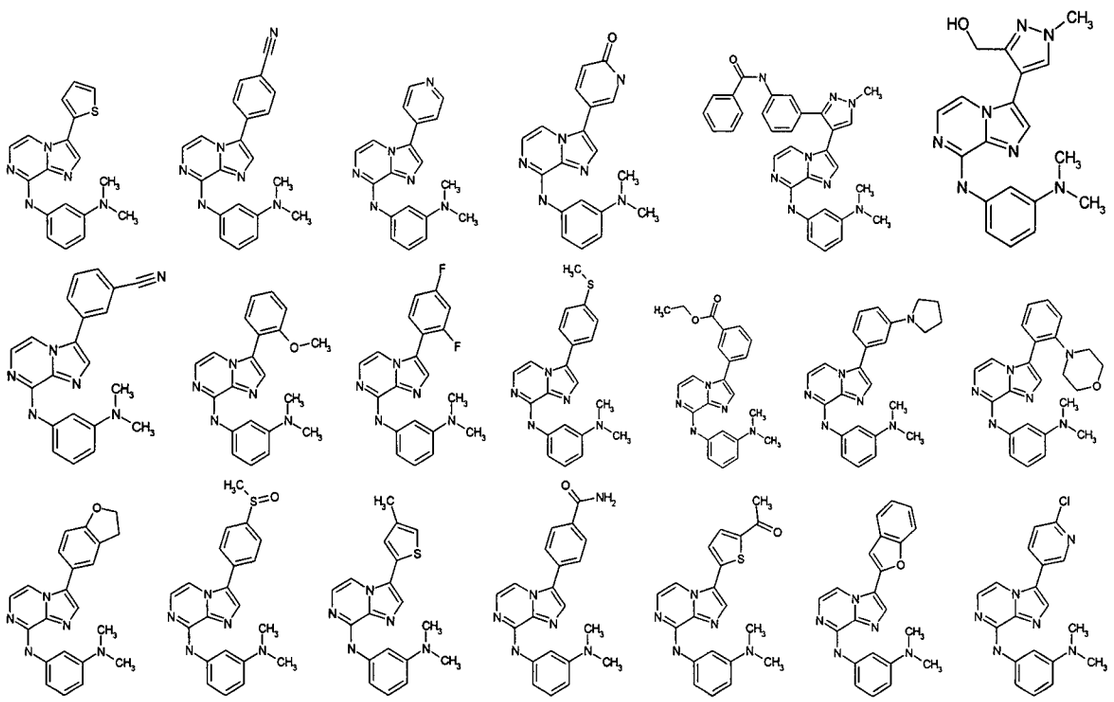
n es 1–4; y

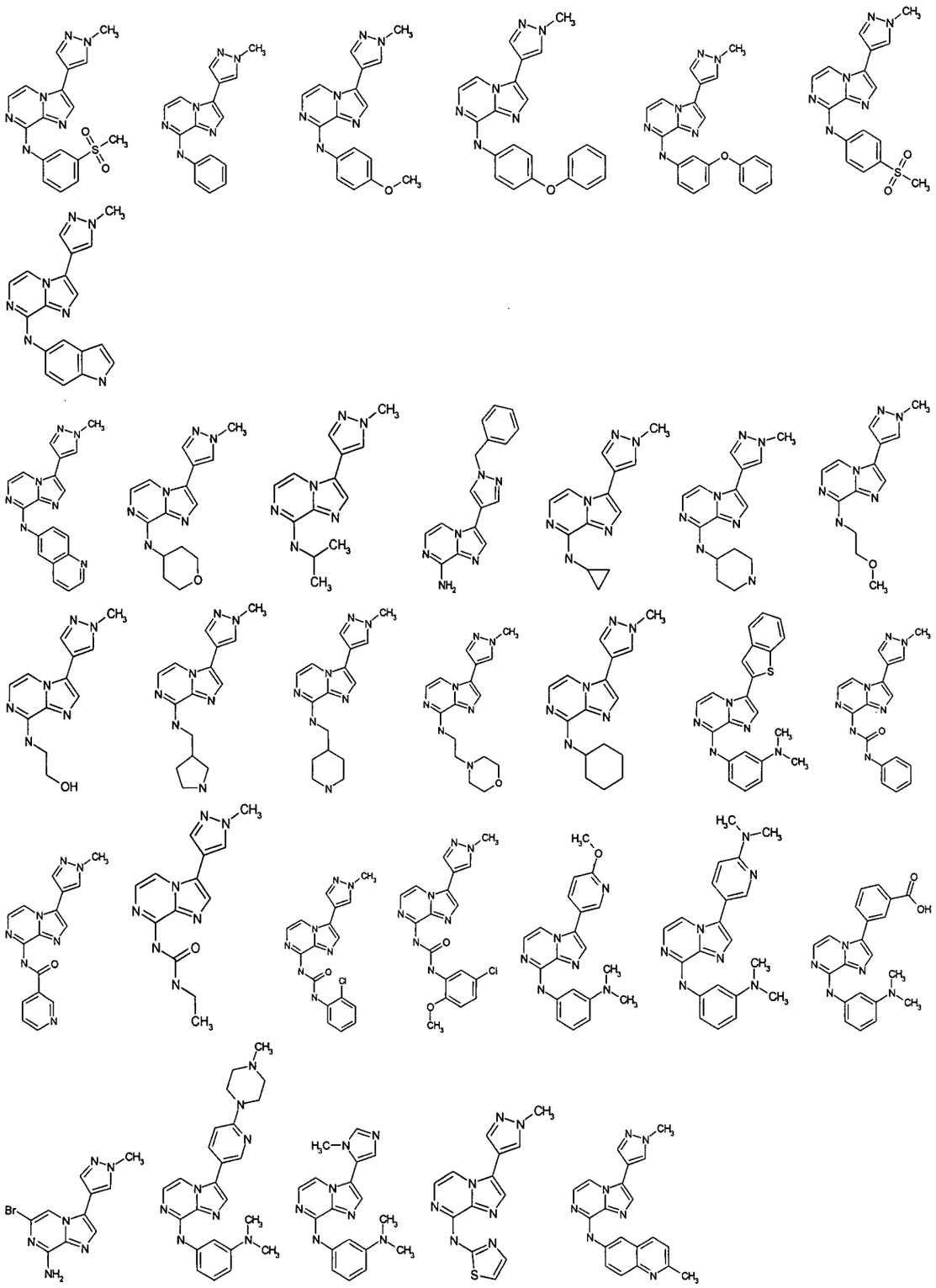
p es 0–3;

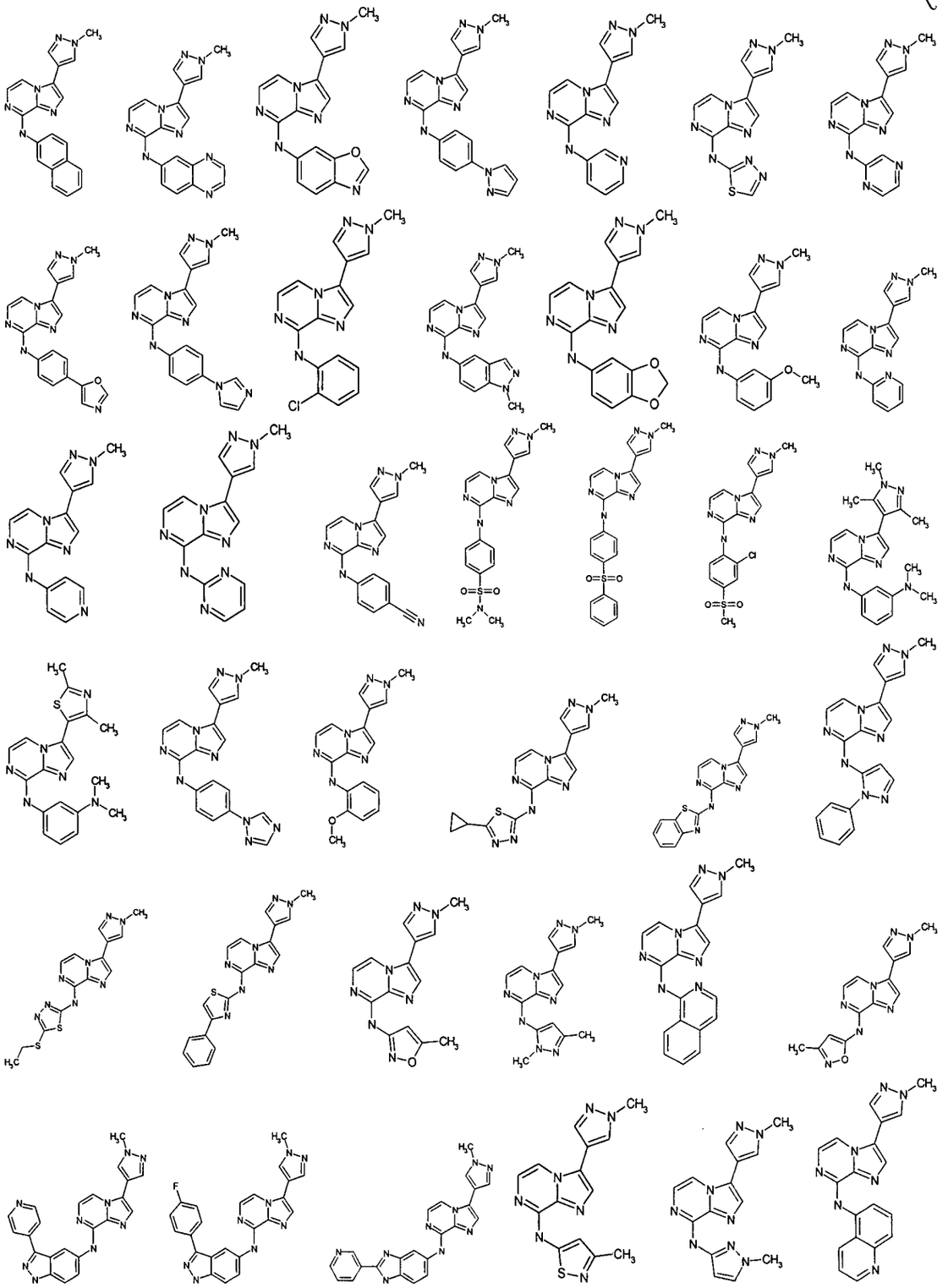
g. Un compuesto seleccionado de los compuestos de las fórmulas:

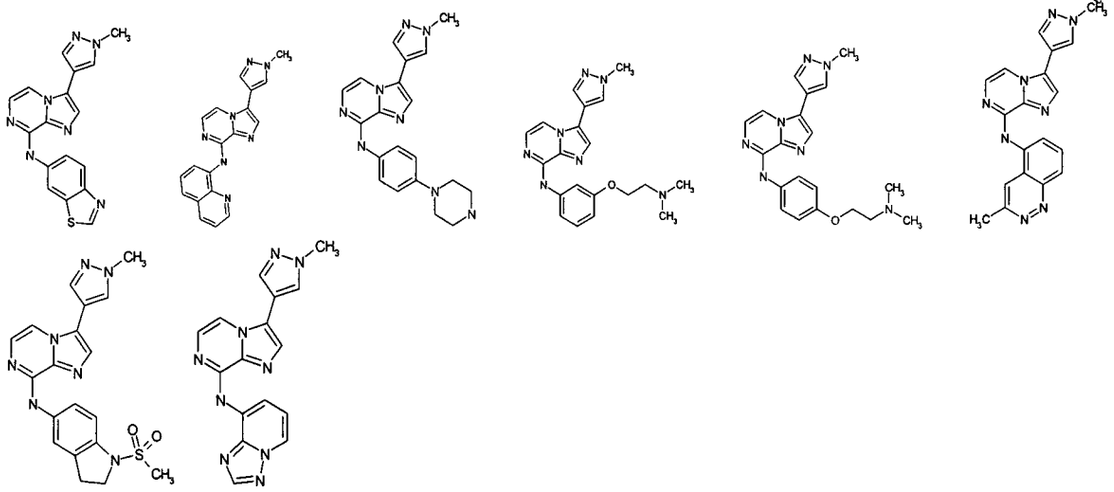


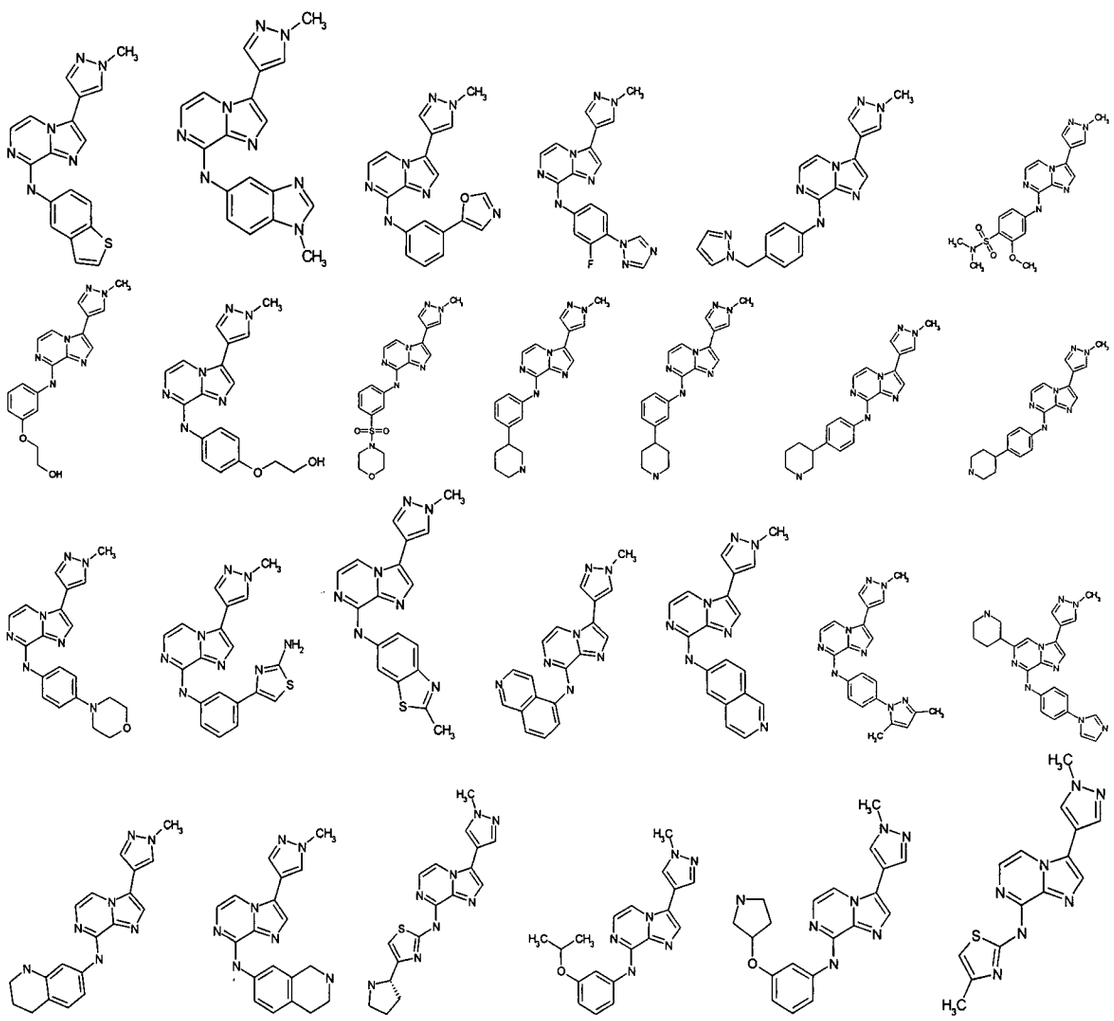


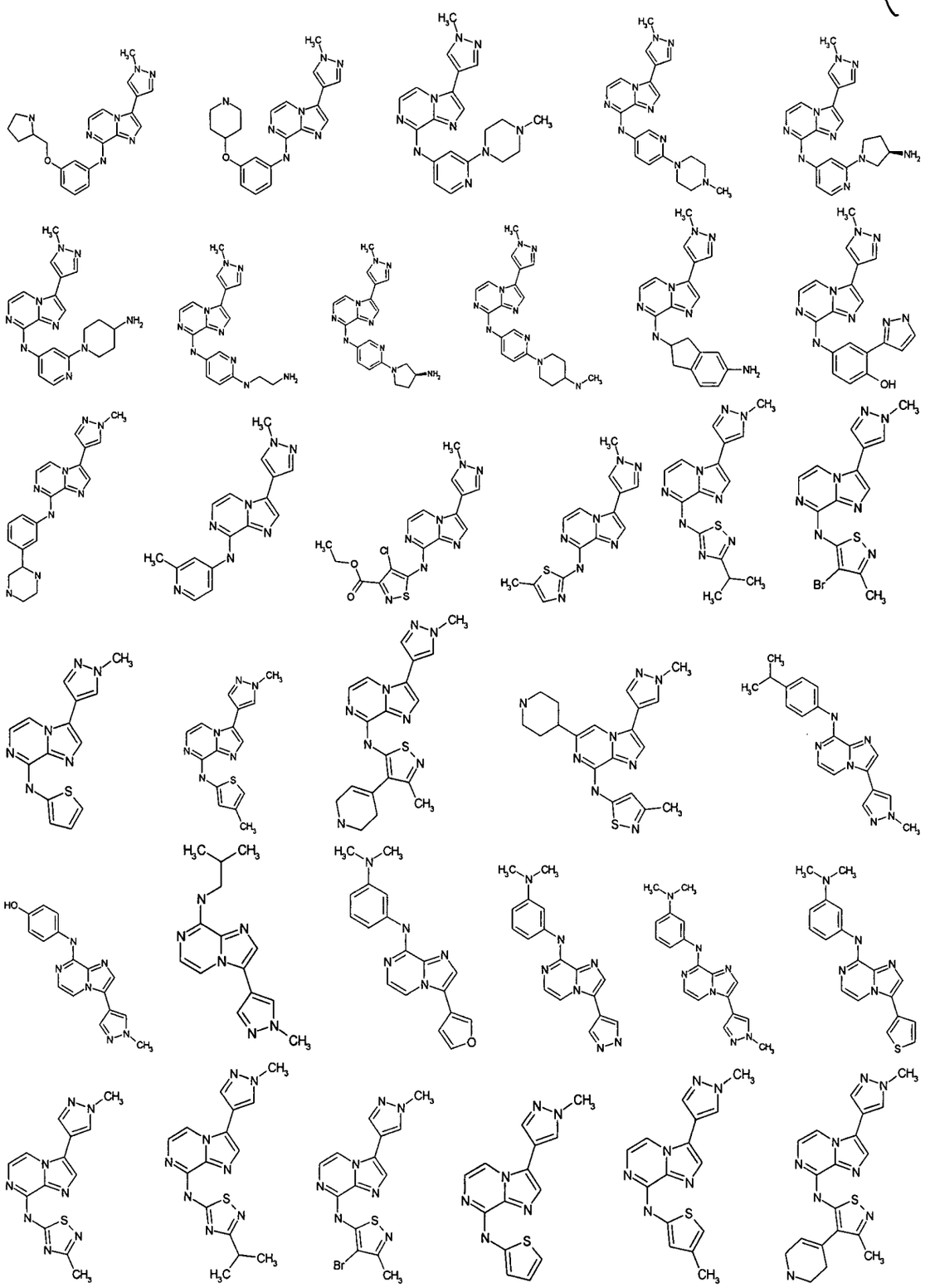


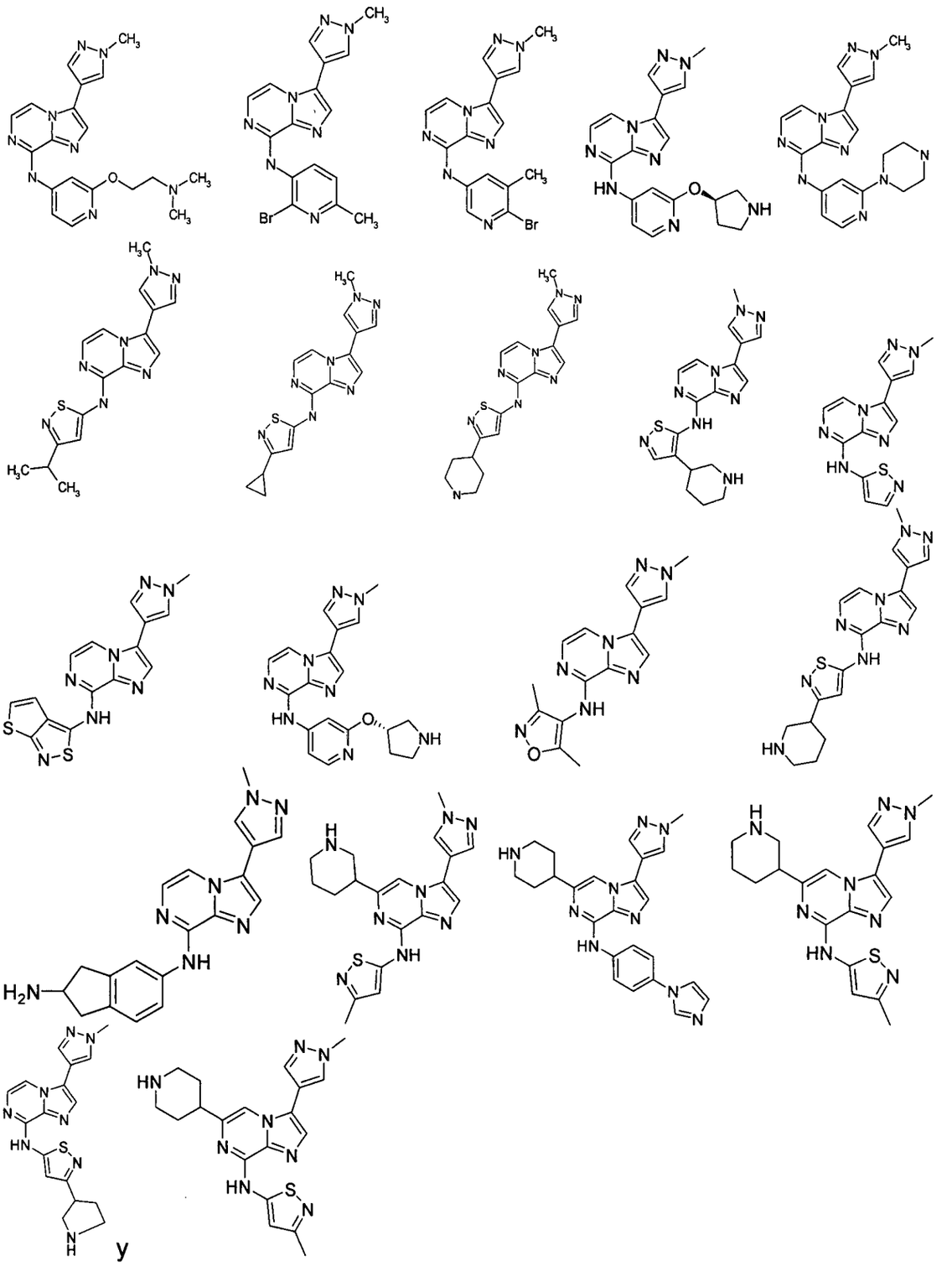








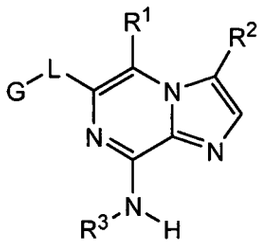




y

o una de sus sales, solvatos, ésteres o profármacos farmacéuticamente aceptables;

h. Un compuesto de la fórmula:



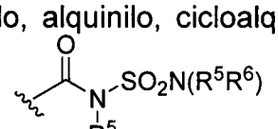
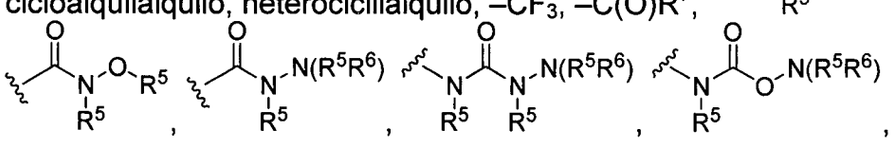
fórmula H

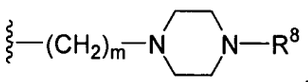
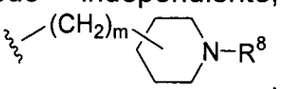
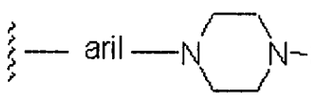
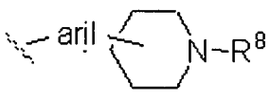
o una de sus sales, solvatos, ésteres o profármacos farmacéuticamente aceptables, en donde:

L está seleccionado del grupo que consiste en S, S(O) y $S(O_2)$;

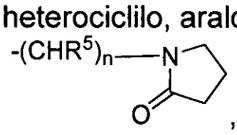
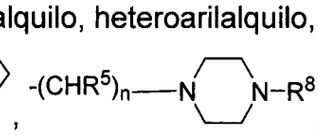
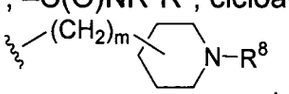
G es alquilo, alquenilo, cicloalquilo, cicloalquenilo, arilo, heteroarilo, heterociclenilo o heterociclilo, en donde cada uno de dichos alquilo, alquenilo, cicloalquilo, cicloalquenilo, arilo, heteroarilo, heterociclenilo o heterociclilo puede no estar sustituido o puede estar opcionalmente sustituido, de modo independiente, con uno o varios restos que están seleccionados, de modo independiente, del grupo que consiste en $-OR^5$, halo, $-CN$, $-C(O)NR^5R^6$, $-N(H)-C(O)R^5$,$-N(H)-C(O)-NR^5R^6$, $-S(O_2)NR^5R^6$, $-NR^5R^6$, $-C(O)R^5$, $-C(O_2)R^5$, $-SR^5$, $-S(O)R^5$, $-S(O_2)R^5$;

R^1 es H, halo, alquilo, arilo o heteroarilo, en donde cada uno de dichos alquilo, arilo y heteroarilo puede no estar sustituido o puede estar sustituido con uno o varios restos que pueden ser iguales o diferentes donde cada resto está seleccionado, de modo independiente, del grupo que consiste en halo, alquilo, alquenilo, alquinilo, cicloalquilo, arilo, heteroarilo, heterociclilo, $-C(O)NR^5R^6$ y $-OR^5$;

R^2 está seleccionado del grupo que consiste en H, R^9, alquilo, arilo, arilalquilo, heteroarilo, heteroarilalquilo, heterociclilo, alquenilo, alquinilo, cicloalquilo, cicloalquilalquilo, heterociclilalquilo, $-CF_3$, $-C(O)R^7$,  , 

alquilo sustituido con 1–6 R^9 que pueden ser iguales o diferentes, en donde cada R^9 está seleccionado, de modo independiente,  ,  ,  y  ,

en donde cada uno de dichos arilo, heteroarilo, cicloalquilo, arilalquilo y heterociclilo antes mencionados puede no estar sustituido o puede estar opcionalmente sustituido, de modo independiente, con uno o varios restos que pueden ser iguales o diferentes, donde cada resto está seleccionado, de modo independiente, del grupo que consiste en halo, alquilo, alquenilo, alquinilo, cicloalquilo, arilo, heteroarilo, heterociclilo, CF_3, CN, $-OCF_3$, $-OR^6$, $-C(O)R^7$, $-NR^5R^6$, $-C(O_2)R^6$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^6$;

R^3 está seleccionado del grupo que consiste en H, alquilo, arilo, heteroarilo, heterociclilo, aralquilo, heteroarilalquilo, cicloalquilalquilo, heterociclilalquilo,  ,  , $-(CHR^5)_n-OR^6$, $-S(O_2)R^6$, $-C(O)R^6$, $-S(O_2)NR^5R^6$, $-C(O)OR^6$, $-C(O)NR^5R^6$, cicloalquilo, $-CH(arilo)_2$, $-CH(heteroarilo)_2$, $-(CH_2)_m-NR^8$ y  , en donde cada uno de dichos alquilo, arilo, heteroarilo y heterociclilo puede estar sustituido u opcionalmente sustituido con uno o varios restos que pueden ser iguales o diferentes, donde cada resto está seleccionado, de modo independiente, del grupo que consiste en halo, alquilo, arilo, cicloalquilo, CF_3, CN, $-OCF_3$, $-OR^5$, $-NR^5R^6$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^6$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^6$;

R^5 es H, alquilo, arilo, heteroarilo, heterociclilo o cicloalquilo; y

R^6 está seleccionado del grupo que consiste en H, alquilo, arilo, heteroarilo, arilalquilo y heteroarilalquilo, en donde cada uno de dichos alquilo, heteroarilalquilo, arilo, heteroarilo y arilalquilo puede no estar sustituido o puede estar opcionalmente sustituido con uno o varios restos que pueden ser iguales o diferentes, donde cada resto está seleccionado, de modo independiente, del grupo que consiste en halógeno, alquilo, arilo, cicloalquilo, CF_3, OCF_3, CN, $-OR^5$, $-NR^5R^6$, $-CH_2OR^5$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^6$;

R^7 está seleccionado del grupo que consiste en alquilo, arilo, heteroarilo, arilalquilo y heteroarilalquilo, en donde cada uno de dichos alquilo, heteroarilalquilo, arilo, heteroarilo y arilalquilo puede no estar sustituido o puede estar opcionalmente sustituido con uno o varios restos que pueden ser iguales o diferentes, donde cada resto está seleccionado, de modo independiente, del grupo que consiste en halógeno, alquilo, arilo, cicloalquilo, CF_3, OCF_3, CN, $-OR^5$, $-NR^5R^6$, $-CH_2OR^5$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^6$;

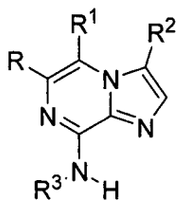
R^8 está seleccionado del grupo que consiste en R^6, $-C(O)NR^5R^6$, $-S(O_2)NR^5R^6$, $-C(O)R^7$, $-C(O_2)R^6$, $-S(O_2)R^7$ y $-(CH_2)$–arilo;

R^9 está seleccionado del grupo que consiste en halógeno, CN, NR^5R^6, $-C(O_2)R^6$, $-C(O)NR^5R^6$, $-OR^6$, $-C(O)R^7$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^6$;

m es 0 a 4; y

p es 0–3;

i. Un compuesto de la fórmula I:



fórmula I

o una de sus sales, solvatos, ésteres o profármacos farmacéuticamente aceptables, en donde:

R es H, CN, $-NR^5R^6$, cicloalquilo, cicloalquenilo, heterociclenilo, heteroarilo, $-C(O)NR^5R^6$, $-N(R^5)C(O)R^6$, heterociclilo, heteroarilo sustituido con $(CH_2)_{1-3}$ NR^5R^6, alquilo no sustituido o alquilo sustituido con uno o varios restos que pueden ser iguales o diferentes donde cada resto está seleccionado, de modo independiente, del grupo que consiste en $-OR^5$, heterociclilo, $-N(R^5)C(O)N(R^5R^6)$, $-N(R^5)-C(O)OR^6$, $-(CH_2)_{1-3}-N(R^5R^6)$ y $-NR^5R^6$;

R^1 es H, halo, arilo o heteroarilo, en donde cada uno de dichos arilo y heteroarilo pueden no estar sustituidos o pueden estar sustituidos con uno o varios restos que pueden ser iguales o diferentes donde cada resto está seleccionado, de modo independiente, del grupo que consiste en halo, alquilo, alquenilo, alquinilo, cicloalquilo, arilo, heteroarilo, heterociclilo, $-CH_2OR^5$, $-C(O)NR^5R^6$, $-C(O)OH$, $-C(O)NH_2$, $-NR^5R^6$ (en donde R^5 y R^6, junto con el N de dicho $-NR^5R^6$, forman un anillo heterociclilo), $-S(O)R^5$, $-S(O_2)R^5$, $-CN$, $-CHO$, $-SR^5$, $-C(O)OR^5$, $-C(O)R^5$ y $-OR^5$;

R^2 es H, halo, arilo, arilalquilo o heteroarilo, en donde cada uno de dichos arilo, arilalquilo y heteroarilo puede no estar sustituido o puede estar opcionalmente sustituido, de modo independiente, con uno o varios restos que pueden ser iguales o diferentes donde cada resto está seleccionado, de modo independiente, del grupo que consiste en halo, amida, alquilo, alquenilo, alquinilo, cicloalquilo, arilo, $-C(O)OH$, $-C(O)NH_2$, $-NR^5R^6$ (en donde R^5 y R^6, junto con el N de dicho $-NR^5R^6$, forman un anillo

heterociclilo), –CN, arilalquilo, $–CH_2OR^5$, $–S(O)R^5$, $–S(O_2)R^5$, –CN, –CHO, $–SR^5$, $–C(O)OR^5$, $–C(O)R^5$, heteroarilo y heterociclilo;

R^3 es heterociclil–$(CR^7R^8)_n$–X, heterociclenil–$(CR^7R^8)_n$–X, heteroaril–$(CR^7R^8)_n$–X o aril–$(CR^7R^8)_n$–X, en donde cada uno de los restos de heterociclilo, heterociclenilo, heteroarilo o arilo de dicho R^3 puede no estar sustituido o puede estar sustituido con uno o varios restos seleccionados, de modo independiente, del grupo que consiste en $–CONR^5R^6$, $–OR^5$ y alquilo,

n es 1–6,

X está seleccionado del grupo que consiste en $–NR^5R^6$, $–OR^5$, $–SO–R^5$ y $–SR^5$,

R^7 y R^8 son cada uno, de modo independiente, hidrógeno o alquilo;

R^5 está seleccionado del grupo que consiste en hidrógeno, alquilo, alquenilo, alcoxialquilo, –alquil–S–alquilo, aminoalquilo, arilo, heteroarilo, heterociclenilo, heterocicloalquilo, cicloalquilo, cicloalquenilo, heterociclilalcoxilo, –S–alquilheterociclilo, heterociclilo, heterociclenilo, alquil$N(alquilo)_2$, alquilNH(alquilo), alquil$N(alquenilo)_2$, –alquil$N(alcoxilo)_2$, –alquil–SH y hidroxialquilo, en donde cada uno de dichos arilo, heteroarilo, heterociclenilo, heterocicloalquilo, cicloalquilo, cicloalquenilo, heterociclilalcoxilo, –S–alquilheterociclilo, heterociclilo, heterociclenilo puede no estar sustituido o puede estar sustituido con uno o varios restos seleccionados, de modo independiente, del grupo que consiste en alquilo, alquilo, alquenilo, arilo, cicloalquenilo, cicloalquilo, arilalquilo, cicloalquenilalquilo, cicloalquilalquilo, heteroarilo, heterociclenilo, heterociclilo, heteroarilalquilo, heterociclenilalquilo, heterocicloalquilalquilo, alcoxialquilo, –alquil–S–alquilo, –alquilSH, alcoxilo, –S–alquilo, hidroxialquilo y aminoalquilo;

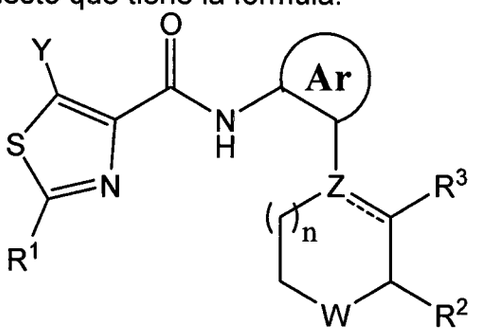
1130

R^6 está seleccionado del grupo que consiste en hidrógeno, alquilo, alquenilo, arilo, cicloalquenilo, cicloalquilo, arilalquilo, cicloalquenilalquilo, cicloalquilalquilo, heteroarilo, heterociclenilo, heterociclilo, heteroarilalquilo, heterociclenilalquilo, heterocicloalquilalquilo, alcoxialquilo, –alquil–S–alquilo, –alquilSH, alcoxilo, –S–alquilo, hidroxialquilo y aminoalquilo, en donde cada uno de dichos arilo, cicloalquenilo, cicloalquilo, arilalquilo, cicloalquenilalquilo, cicloalquilalquilo, heteroarilo, heterociclenilo, heterociclilo, heteroarilalquilo, heterociclenilalquilo, heterocicloalquilalquilo puede no estar sustituido o puede estar sustituido con uno o varios restos seleccionados, de modo independiente, del grupo que consiste en alquilo, alquilo, alquenilo, arilo, cicloalquenilo, cicloalquilo, arilalquilo, cicloalquenilalquilo, cicloalquilalquilo, heteroarilo, heterociclenilo, heterociclilo, heteroarilalquilo, heterociclenilalquilo, heterocicloalquilalquilo, alcoxialquilo, –alquil–S–alquilo, –alquilSH, alcoxilo, –S–alquilo, hidroxialquilo y aminoalquilo;

también en donde en cualquier $–NR^5R^6$ en la fórmula I, dichos R^5 y R^6 pueden estar opcionalmente unidos junto con el N de dicho $–NR^5R^6$ para formar un anillo cíclico o anillo cíclico en puente, en donde cada uno de dicho anillo cíclico o anillo cíclico en puente, pueden no estar sustituidos o pueden estar sustituidos con uno o varios restos, que pueden ser iguales o diferentes seleccionados, de modo independiente, del grupo que consiste en hidroxilo, –SH, alquilo, alquenilo, hidroxialquilo, –alquil–SH, alcoxilo, –S–alquilo, $–CO_2–$alquilo, $–CO_2–$alquenilo, arilalquilo, cicloalquenilalquilo, cicloalquilalquilo, heteroarilalquilo, heterociclenilalquilo,

heterocicloalquilalquilo, heteroarilo, arilo, cicloalquenilo, cicloalquilo, espiroheterociclilo, espiroheterociclenilo, espiroheteroarilo, espirociclilo, espirociclenilo, espiroarilo, alcoxialquilo, –alquil–S–alquilo, heterociclilo y heterociclenilo;

j. Un compuesto que tiene la fórmula:



(J)

o una de sus sales, solvatos, ésteres, prodrogas o estereoisómeros farmacéuticamente aceptables, en donde las líneas punteadas indican un enlace opcional y adicional y en donde:

R^1 es heteroarilo con contenido de nitrógeno, heterociclilo con contenido de nitrógeno, heteroarilo benzofusionado con contenido de nitrógeno o heterociclilo benzofusionado con contenido de nitrógeno, en donde R^1 está unido con el resto del compuesto de la fórmula (I) a través de un átomo de nitrógeno del anillo y en donde uno o varios átomos de carbono del anillo de un grupo heteroarilo con contenido de nitrógeno, heterociclilo con contenido de nitrógeno, heteroarilo benzofusionado con contenido de nitrógeno o heterociclilo benzofusionado con contenido de nitrógeno puede estar sustituido con hasta 5 sustituyentes, que pueden ser iguales o diferentes y están seleccionados, de modo independiente, de alquilo, arilo, halo, –OH, –O–alquilo, –O–arilo, $-N(R^8)_2$, $-CF_3$, $-NO_2$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)N(R^8)_2$, $-OC(O)R^8$ o $-NHC(O)R^8$;

R^2 es –H, –alquilo, $-NH_2$ o $-CH_2NH_2$;

R^3 es –H, –alquilo, $-NH_2$ o $-CH_2NH_2$;

cada aparición de R^4 es, de modo independiente, –H, –alquilo, $–NH_2$, –OH, –alquilen–OH, $–CH_2NH_2$, $–C(O)R^5$, $–C(O)NH_2$, –C(O)NH–alquilo, $–C(O)N(alquilo)_2$, $–NHC(O)R^6$ o $–NHS(O)_2R^6$;

R^5 es –H, –alquilo, –arilo, –heteroarilo, –NHOH;

R^6 es –H, –alquilo o $–CF_3$;

R^7 es –H, –OH, –alquilo C_1–C_6, –O–(alquilo C_1–C_6) o $–CF_3$;

R^8 es –H, alquilo, arilo, heterociclilo, heteroarilo o cicloalquilo;

Ar es –arileno– o –heteroarileno–, en donde el arileno o heteroarileno está unido a través de 2 de sus átomos de carbono del anillo adyacentes y en donde el –arileno– o –heteroarileno– pueden estar sustituidos con hasta 4 sustituyentes, que pueden ser iguales o diferentes y están seleccionados, de modo independiente, de –halo, alquilo, alcoxi, ariloxi, $–SR^8$, $–S(O)R^8$, $–S(O)_2R^8$, $–C(O)R^8$, $–C(O)OR^8$, $–C(O)N(R^8)_2$, $–NHC(O)R^8$, $–CF_3$, –CN o NO_2 y de modo tal que, cuando Ar es tetrahidronaftileno, R^1 y R^2 no puedan ser ambos hidrógeno

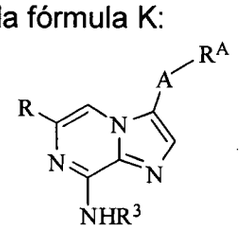
W es –NH– o $–C(R^4)_2–$, en donde ambos grupos R^4 y el átomo de carbono al que están unidos se pueden combinar para formar un grupo heterociclilo o heteroarilo de cinco a siete miembros;

Y es –H, –halo, –alquilo o –CN;

Z es $–CR^7–$ o –N–, cuando el enlace adicional opcional está ausente y –C– cuando el enlace adicional opcional está presente;

n es un número entero que va de 0 a 2; y

(k) Un compuesto de la fórmula K:



fórmula K

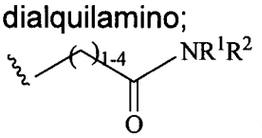
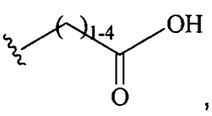
o una de sus sales, solvatos, ésteres, prodrogas o estereoisómeros

farmacéuticamente aceptables, en donde:

R es H, halo o alquilo;

R^3 es heteroaril–X, en donde X es heterociclilalquilo–, en donde dicho heterociclilo puede no estar sustituido o puede estar opcionalmente sustituido con 1–4 restos alquilo;

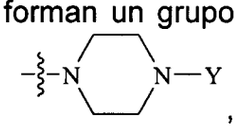
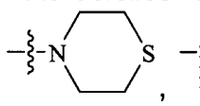
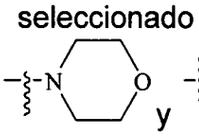
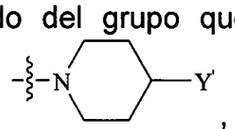
A es –arilo–, –heteroarilo–, $-N(R^1)$–arilo– o $-N(R^1)$–heteroarilo–, en donde cada uno de dichos arilo y heteroarilo puede no estar sustituido, de modo independiente, o puede estar opcionalmente sustituido con uno o varios sustituyentes que pueden ser iguales o diferentes, donde cada sustituyente está seleccionado, de modo independiente, del grupo que consiste en alquilo, $-NO_2$, halo, hidroxi, trihaloalquilo, alcoxi y dialquilamino;

R^A es $-(CH_2)_{1-4}$–heteroarilo,  o  , en donde dicho heteroarilo puede estar opcionalmente fusionado con un arilo, en donde cada uno de dichos arilo y heteroarilo puede estar opcionalmente sustituido, de modo independiente, con uno o varios restos donde cada resto está seleccionado, de modo independiente, del grupo que consiste en trihaloalquilo, $-NO_2$, halo, hidroxialquilo, alcoxialquilo y dialquilamino;

R^1 es H o alquilo;

R^2 es H, hidroxialquilo–, arilalquilo–, heteroarilo, arilo, heteroarilalquilo–, alquilo, dialquilaminoalquilo–, alquilaminoalquilo–, cicloalquilalquilo–, cicloalquilo, heterociclilalquilo– o heterociclilo, en donde dichos arilo y arilo de arilalquilo puede no estar sustituido o puede estar sustituido con uno o varios restos seleccionados, de modo independiente, del grupo que consiste en trihaloalquilo, $-NO_2$, halo, hidroxialquilo, alcoxialquilo, dialquilamino y heterociclilalquilo–, en donde dicho heterociclilalquilo puede no estar sustituido o puede estar sustituido con alquilo o $-SO_2NH_2$; dichos heteroarilo y heteroarilo de heteroarilalquilo pueden no estar sustituidos o

pueden estar sustituidos con uno o varios restos, donde cada resto está seleccionado, de modo independiente, del grupo que consiste en hidroxialquilo, alcoxi, alquilo, halo, hidroxilo y $-NO_2$; y dicho cicloalquilo no está sustituido o está sustituido con hidroxilo; o

R^1 y R^2 junto con N al que cada uno está unido, forman un grupo heterocíclico seleccionado del grupo que consiste en  ,  ,  y  , en donde

Y es alcoxialquilo, hidroxialquilo, dialquilaminoalquilo o alquilo, también en donde

Y' es hidroxilo.

4. El método de acuerdo con la reivindicación 3, en donde la endorreduplicación en células cancerosas da como resultado la muerte de las células cancerosas, en donde dicha célula cancerosa está seleccionada del grupo que consiste en tumor de vejiga, de mama (incluyendo cáncer de mama mutado con BRCA), colorrectal, de colon, de riñón, de hígado, de pulmón (incluyendo cáncer de pulmón de células pequeñas y cáncer de pulmón de células no pequeñas), de cabeza y cuello, se esófago, de vejiga, de vejiga biliar, de ovario, de páncreas, de estómago, de cérvix, de tiroides, de próstata y de piel, incluyendo carcinoma de células pavimentosas;

leucemia, leucemia linfocítica aguda, leucemia linfoblástica aguda, linfoma de células B, linfoma de células T, linfoma de Hodgkins, linfoma no Hodgkins, linfoma de células pilosas, linfoma de células del manto, mieloma y linfoma de Burkett;

leucemia linfocítica crónica ("CLL"),

leucemia mielógena aguda y crónica, síndrome mielodisplásico y leucemia promielocítica;

fibrosarcoma, rabdomiosarcoma;

linfoma de células del manto, mieloma;

astrocitoma, neuroblastoma, glioblastoma, tumores gliales malignos, carcinoma hepatocelular, tumores estromales gastrointestinales ("GIST") y schwannomas;

melanoma, mieloma múltiple, seminoma, teratocarcinoma, osteosarcoma, xenoderoma pigmentoso, queratoctantoma, cáncer folicular tiroideo y sarcoma de Kaposi.

5. El método de acuerdo con la reivindicación 4, en donde dicha célula cancerosa está seleccionada del grupo que consiste en célula de cáncer de colon, célula de cáncer de mama, célula de cáncer de pulmón, célula de cáncer de próstata y célula de cáncer de ovario.

6. El método de acuerdo con la reivindicación 3, en donde dicho pretratamiento de células cancerosas con al menos uno de dichos agentes antimitóticos es para al menos aproximadamente 12–24 horas.

7. El método de acuerdo con la reivindicación 6, en donde dicho pretratamiento de células cancerosas con al menos uno de dichos agentes antimitóticos es para al menos aproximadamente 16 horas.

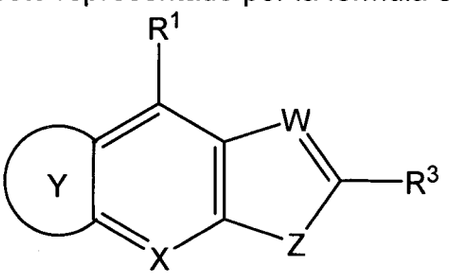
8. El método de acuerdo con la reivindicación 6, en donde después de dicho pretratamiento de células cancerosas con dicho agente antimitótico, las células cancerosas se exponen a al menos un inhibidor de aurora quinasa durante aproximadamente 2–12 horas.

9. El método de acuerdo con la reivindicación 7, en donde después de dicho pretratamiento de células cancerosas con dicho agente antimitótico, las

células cancerosas se exponen a al menos un inhibidor de aurora quinasa durante aproximadamente 4 horas.

10. Un método para retardar el crecimiento de un tumor in vivo que comprende las etapas de (a) administrar primero al tumor in vivo al menos un agente antimitótico seleccionado del grupo que consiste en un taxano, paclitaxel, docetaxel, un inhibidor de Cenp–E, abraxano, epotilona, monastrol, un inhibidor de KSP, ispinesib y compuestos representados por las fórmulas A–D mostradas en los puntos a–d que figuran más abajo:

a. Un compuesto representado por la fórmula estructural A:



fórmula A

o una de sus sales, solvatos o ésteres farmacéuticamente aceptables, en donde:

el anillo Y es un arilo de 5 ó 6 miembros o un heteroarilo de 5 ó 6 miembros fusionado tal como se indica en la fórmula A, en donde en dichos arilo y heteroarilo cada carbono del anillo sustituible está sustituido, de modo independiente, con R^2 y cada nitrógeno del anillo sustituible está sustituido, de modo independiente, con R^6;

W es N o $C(R^{12})$;

X es N o N–óxido;

Z es S, S(=O) o $S(=O)_2$;

R^1 es H, alquilo, alcoxi, hidroxi, halo, –CN, $–S(O)_m$–alquilo, $–C(O)NR^9R^{10}$, $–(CR^9R^{10})_{1–6}OH$ o $–NR^4(CR^9R^{10})_{1–2}OR^9$;

cada R^2 está seleccionado, de modo independiente, del grupo que consiste en H, halo, alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo, heteroaralquilo, $-(CR^{10}R^{11})_{0-6}$ $-OR^7$, $-C(O)R^4$, $-C(S)R^4$, $-C(O)OR^7$, $-C(S)OR^7$, $-OC(O)R^7$, $-OC(S)R^7$, $-C(O)NR^4R^5$, $-C(S)NR^4R^5$, $-C(O)NR^4OR^7$, $-C(S)NR^4OR^7$, $-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, $-CN$, $-OCF_3$, $-SCF_3$, $-C(=NR^7)NR^4$, $-C(O)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}OR^7$, $-C(S)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(S)NR^7(CH_2)_{1-10}OR^7$, haloalquilo y alquilsililo, en donde cada uno de dichos alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo o heteroaralquilo está opcionalmente sustituido, de modo independiente, con 1–5 restos R^9;

cada R^3 está seleccionado, de modo independiente, del grupo que consiste en H, halo, alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo, heteroaralquilo, $-(CR^{10}R^{11})_{0-6}$ $-OR^7$, $-C(O)R^4$, $-C(S)R^4$, $-C(O)OR^7$, $-C(S)OR^7$, $-OC(O)R^7$, $-OC(S)R^7$, $-C(O)NR^4R^5$, $-C(S)NR^4R^5$, $-C(O)NR^4OR^7$, $-C(S)NR^4OR^7$, $-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, $-CN$, $-OCF_3$, $-SCF_3$, $-C(=NR^7)NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}OR^7$, $-C(S)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(S)NR^7(CH_2)_{1-10}OR^7$, haloalquilo y alquilsililo, en donde cada uno de

dichos alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo o heteroaralquilo está opcionalmente sustituido, de modo independiente, con 1–5 restos R^9;

cada R^4 y R^5 está seleccionado, de modo independiente, del grupo que consiste en H, alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo, heteroaralquilo, $-OR^7$, $-C(O)R^7$ y $-C(O)OR^7$, en donde cada uno de dichos alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo o heteroaralquilo está opcionalmente sustituido con 1–4 restos R^8;

o R^4 y R^5, cuando están unidos al mismo átomo de nitrógeno, se toman opcionalmente juntos con el átomo de nitrógeno al que están unidos para formar un anillo heterocíclico de 3–6 miembros que tiene 0–2 heteroátomos adicionales seleccionados de N, O o S;

cada R^6 está seleccionado, de modo independiente, del grupo que consiste en H, alquilo, arilo, aralquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, heteroarilo, heteroaralquilo, $-(CH_2)_{1-6}CF_3$, $-C(O)R^7$, $-C(O)OR^7$ y $-SO_2R^7$;

cada R^7 está seleccionado, de modo independiente, del grupo que consiste en H, alquilo, arilo, aralquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, heteroarilo y heteroaralquilo, en donde cada miembro de R^7 excepto H está opcionalmente sustituido con 1–4 restos R^8;

cada R^8 está seleccionado, de modo independiente, del grupo que consiste en halo, alquilo, cicloalquilo, heterociclilo, arilo, heteroarilo, $-NO_2$, $-OR^{10}$, $-$(alquil C_1–C_6)$-OR^{10}$, $-CN$, $-NR^{10}R^{11}$, $-C(O)R^{10}$, $-C(O)OR^{10}$, $-C(O)NR^{10}R^{11}$, $-CF_3$, $-OCF_3$, $-CF_2CF_3$, $-C(=NOH)R^{10}$, $-N(R^{10})C(O)R^{11}$, $-C(=NR^{10})NR^{10}R^{11}$ y $-NR^{10}C(O)OR^{11}$, en donde cada uno de dichos alquilo, cicloalquilo, heterociclilo, arilo y heteroarilo está opcionalmente

sustituido, de modo independiente, con 1–3 restos seleccionados del grupo que consiste en halo, alquilo, cicloalquilo, heterociclilo, arilo, heteroarilo, $-NO_2$, $-OR^{10}$, –(alquil C_1–C_6)–OR^{10}, –CN, $-NR^{10}R^{11}$, $-C(O)OR^{10}$, $-C(O)NR^{10}R^{11}$, $-CF^3$, $-OCF_3$, $-NR^{10}C(O)OR^{11}$ y $-NR^{10}C(O)R^{40}$;

o dos grupos R^8, cuando están unidos al mismo átomo de carbono, se toman opcionalmente juntos con el átomo de carbono al que están unidos para formar un grupo C=O o un grupo C=S;

cada R^9 está seleccionado, de modo independiente, del grupo que consiste en H, alquilo, alcoxi, OH, CN, halo, $-(CR^{10}R^{11})_{0-4}NR^4R^5$, haloalquilo, hidroxialquilo, alcoxialquilo, $-C(O)NR^4R^5$, $-C(O)OR^7$, $-OC(O)NR^4R^5$, $-NR^4C(O)R^5$ y $-NR^4C(O)NR^4R^5$;

cada R^{10} es, de modo independiente, H o alquilo; o R^9 y R^{10}, cuando están unidos al mismo átomo de nitrógeno, se toman opcionalmente juntos con el átomo de nitrógeno al que están unidos para formar un anillo heterocíclico de 3–6 miembros que tiene 0–2 heteroátomos adicionales seleccionados de N, O o S;

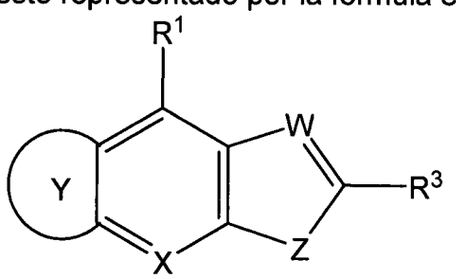
cada R^{11} es, de modo independiente, H o alquilo; o R^{10} y R^{11}, cuando están unidos al mismo átomo de nitrógeno, se toman opcionalmente juntos con el átomo de nitrógeno al que están unidos para formar un anillo heterocíclico de 3–6 miembros que tiene 0–2 heteroátomos adicionales seleccionados de N, O o S;

cada R^{12} está seleccionado, de modo independiente, del grupo que consiste en H, halo, alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo, heteroaralquilo, $-(CR^{10}R^{11})_{0-6}$ $-OR^7$, $-C(O)R^4$, $-C(S)R^4$, $-C(O)OR^7$, $-C(S)OR^7$, $-OC(O)R^7$, $-OC(S)R^7$, $-C(O)NR^4R^5$, $-C(S)NR^4R^5$, $-C(O)NR^4OR^7$, $-C(S)NR^4OR^7$, $-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$,

$-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, $-CN$, $-OCF_3$, $-SCF_3$, $-C(=NR^7)NR^4$, $-C(O)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}OR^7$, $-C(S)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(S)NR^7(CH_2)_{1-10}OR^7$, haloalquilo y alquilsililo, en donde cada uno de dichos alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo o heteroaralquilo está opcionalmente sustituido, de modo independiente, con 1–5 restos R^9; y

R^{40} está seleccionado del grupo que consiste en cicloalquilo, heterociclilo, arilo y heteroarilo, en donde cada uno de dichos cicloalquilo, heterociclilo, arilo y heteroarilo está opcionalmente sustituidos, de modo independiente, con 1–3 restos seleccionados, de modo independiente, del grupo que consiste en –CN, –OH, halo, alquilo, haloalquilo, alcoxi y $-NR^{10}R^{11}$;

b. Un compuesto representado por la fórmula estructural B:



fórmula B

o una de sus sales, solvatos o ésteres farmacéuticamente aceptables, en donde:

el anillo Y es un anillo de 5 a 7 miembros seleccionado del grupo que consiste en cicloalquilo, cicloalquenilo, heterociclilo o heterociclenilo fusionado tal como se indica en la fórmula B, en donde en cada uno de dichos anillos de 5 a 7 miembros, cada carbono del anillo sustituible está sustituido, de modo

independiente, con 1–2 restos R^2 y cada heteroátomo del anillo sustituible está sustituido, de modo independiente, con R^6;

W es N o $C(R^{12})$;

X es N o N–óxido;

Z es S, S(=O) o $S(=O)_2$;

R^1 es H, alquilo, alcoxi, hidroxi, halo, –CN, $–S(O)_m–$alquilo, $–C(O)NR^9R^{10}$, $–(CR^9R^{10})_{1–6}OH$ o $–NR^4(CR^9R^{10})_{1–2}OR^9$; en donde m es 0 a 2;

cada R^2 está seleccionado, de modo independiente, del grupo que consiste en H, halo, alquilo, cicloalquilo, alquilsililo, cicloalquenilo, heterociclilo, heterociclenilo, arilo, heteroarilo, $–(CR^{10}R^{11})_{0–6}–OR^7$, $–C(O)R^4$, $–C(S)R^4$, $–C(O)OR^7$, $–C(S)OR^7$, $–OC(O)R^7$, $–OC(S)R^7$, $–C(O)NR^4R^5$, $–C(S)NR^4R^5$, $–C(O)NR^4OR^7$, $–C(S)NR^4OR^7$, $–C(O)NR^7NR^4R^5$, $–C(S)NR^7NR^4R^5$, $–C(S)NR^4OR^7$, $–C(O)SR^7$, $–NR^4R^5$, $–NR^4C(O)R^5$, $–NR^4C(S)R^5$, $–NR^4C(O)OR^7$, $–NR^4C(S)OR^7$, $–OC(O)NR^4R^5$, $–OC(S)NR^4R^5$, $–NR^4C(O)NR^4R^5$, $–NR^4C(S)NR^4R^5$, $–NR^4C(O)NR^4OR^7$, $–NR^4C(S)NR^4OR^7$, $–(CR^{10}R^{11})_{0–6}SR^7$, SO_2R^7, $–S(O)_{1–2}NR^4R^5$, $–N(R^7)SO_2R^7$, $–S(O)_{1–2}NR^5OR^7$, –CN, $–OCF_3$, $–SCF_3$, $–C(=NR^7)NR^4$, $–C(O)NR^7(CH_2)_{1–10}NR^4R^5$, $–C(O)NR^7(CH_2)_{1–10}OR^7$, $–C(S)NR^7(CH_2)_{1–10}NR^4R^5$ y $–C(S)NR^7(CH_2)_{1–10}OR^7$, en donde cada uno de dichos alquilo, cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, arilo y heteroarilo está opcionalmente sustituido, de modo independiente, con 1–5 restos R^9;

o dos grupos R^2 en el mismo átomo de carbono se toman opcionalmente juntos con el átomo de carbono al que están unidos para formar un grupo C=O, un grupo C=S o un grupo etilendioxi;

R^3 está seleccionado, de modo independiente, del grupo que consiste en H, halo, alquilo, cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, arilo, heteroarilo, $–(CR^{10}R^{11})_{0–6}–OR^7$, $–C(O)R^4$, $–C(S)R^4$, $–C(O)OR^7$, $–C(S)OR^7$, $–OC(O)R^7$, $–OC(S)R^7$, $–C(O)NR^4R^5$, $–C(S)NR^4R^5$, $–C(O)NR^4OR^7$, $–C(S)NR^4OR^7$,

$-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, $-CN$, $-C(=NR^7)NR^4R^5$, $-C(O)N(R^7)-(CR^{40}R^{41})_{1-5}-C(=NR^7)NR^4R^5$, $-C(O)N(R^7)(CR^{40}R^{41})_{1-5}-NR^4R^5$, $-C(O)N(R^7)(CR^{40}R^{41})_{1-5}-C(O)-NR^4R^5$, $-C(O)N(R^7)(CR^{40}R^{41})_{1-5}-OR^7$, $-C(S)NR^7(CH_2)_{1-5}NR^4R^5$ y $-C(S)NR^7(CH_2)_{1-5}OR^7$, en donde cada uno de dichos alquilo, cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, arilo y heteroarilo está opcionalmente sustituido, de modo independiente, con 1–5 restos R^9;

cada uno de R^4 y R^5 está seleccionado, de modo independiente, del grupo que consiste en H, alquilo, cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, arilo, heteroarilo,

$-OR^7$, $-C(O)R^7$ y $-C(O)OR^7$, en donde cada uno de dichos alquilo, cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, arilo y heteroarilo, está opcionalmente sustituido con 1–4 restos R^8;

o R^4 y R^5, cuando están unidos al mismo átomo de nitrógeno, se toman opcionalmente juntos con el átomo de nitrógeno al que están unidos para formar un anillo heterocíclico de 3–6 miembros que tiene 0–2 heteroátomos adicionales seleccionados de N, O o S;

cada R^6 está seleccionado, de modo independiente, del grupo que consiste en H, alquilo, arilo, aralquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, heteroarilo, heteroaralquilo, $-(CH_2)_{1-6}CF_3$, $-C(O)R^7$, $-C(O)OR^7$ y $-SO_2R^7$;

cada R^7 está seleccionado, de modo independiente, del grupo que consiste en H, alquilo, arilo, aralquilo, cicloalquilo, cicloalquilalquilo, heterociclilo,

heterociclilalquilo, heteroarilo y heteroaralquilo, en donde cada miembro de R^7 excepto H está opcionalmente sustituido con 1–4 restos R^8;

cada R^8 está seleccionado, de modo independiente, del grupo que consiste en halo, alquilo, cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, arilo, heteroarilo, $-NO_2$, $-OR^{10}$, –(alquil C_1–C_6)–OR^{10}, –CN, $-NR^{10}R^{11}$, $-C(O)R^{10}$, $-C(O)OR^{10}$, $-C(O)NR^{10}R^{11}$, $-CF_3$, $-OCF_3$, $-CF_2CF_3$, $-C(=NOH)R^{10}$, $-N(R^{10})C(O)R^{11}$, $-C(=NR^{10})NR^{10}R^{11}$ y $-NR^{10}C(O)OR^{11}$; en donde cada uno de dichos alquilo, cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, arilo y heteroarilo está opcionalmente sustituido, de modo independiente, con 1–4 restos R^{42}; en donde cuando cada uno de dichos cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, arilo y heteroarilo contienen dos radicales en átomos de carbono adyacentes en cualquier parte dentro de dichos cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, arilo y heteroarilo, dichos radicales se pueden formar, opcional e independientemente en cualquier aparición, junto con los átomos de carbono a los que están unidos para formar un anillo carbocíclico o heterocíclico de cinco o seis miembros;

o dos grupos R^8, cuando están unidos al mismo carbono, se toman opcionalmente juntos con el átomo de carbono al que están unidos para formar un grupo C=O o un grupo C=S;

cada R^9 está seleccionado, de modo independiente, del grupo que consiste en H, alquilo, alcoxi, OH, CN, halo, $-(CR^{10}R^{11})_{0-4}NR^4R^5$, haloalquilo, hidroxialquilo, alcoxialquilo, $-C(O)NR^4R^5$, $-C(O)OR^7$, $-OC(O)NR^4R^5$, $-NR^4C(O)R^5$ y $-NR^4C(O)NR^4R^5$;

cada R^{10} es, de modo independiente, H o alquilo; o R^9 y R^{10}, cuando están unidos al mismo átomo de nitrógeno, se toman opcionalmente juntos con el átomo de nitrógeno al que están unidos para formar un anillo heterocíclico de 3–6 miembros que tiene 0–2 heteroátomos adicionales seleccionados de N, O o S;

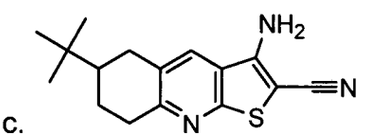
cada R^{11} es, de modo independiente, H, alquilo, cicloalquilo, cicloalquenilo, arilo, heterociclilo, heterociclenilo o heteroarilo; o R^{10} y R^{11}, cuando están unidos al mismo átomo de nitrógeno, se toman opcionalmente juntos con el átomo de nitrógeno al que están unidos para formar un anillo heterocíclico de 3–6 miembros que tiene 0–2 heteroátomos adicionales seleccionados de N, O o S; en donde cada uno de dicho R^{11} alquilo, cicloalquilo, cicloalquenilo, arilo, heterociclilo, heterociclenilo y heteroarilo está opcionalmente sustituido, de modo independiente, con 1–3 restos seleccionados del grupo que consiste en –CN, –OH, $–NH_2$, –N(H)alquilo, $–N(alquilo)_2$, halo, haloalquilo, CF_3, alquilo, hidroxialquilo, alcoxi, arilo, ariloxi y heteroarilo;

cada R^{12} está seleccionado, de modo independiente, del grupo que consiste en H, halo, alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo, heteroaralquilo, $–(CR^{10}R^{11})_{0–6}–OR^7$, $–C(O)R^4$, $–C(S)R^4$, $–C(O)OR^7$, $–C(S)OR^7$, $–OC(O)R^7$, $–OC(S)R^7$, $–C(O)NR^4R^5$, $–C(S)NR^4R^5$, $–C(O)NR^4OR^7$, $–C(S)NR^4OR^7$, $–C(O)NR^7NR^4R^5$, $–C(S)NR^7NR^4R^5$, $–C(S)NR^4OR^7$, $–C(O)SR^7$, $–NR^4R^5$, $–NR^4C(O)R^5$, $–NR^4C(S)R^5$, $–NR^4C(O)OR^7$, $–NR^4C(S)OR^7$, $–OC(O)NR^4R^5$, $–OC(S)NR^4R^5$, $–NR^4C(O)NR^4R^5$, $–NR^4C(S)NR^4R^5$, $–NR^4C(O)NR^4OR^7$, $–NR^4C(S)NR^4OR^7$, $–(CR^{10}R^{11})_{0–6}SR^7$, SO_2R^7, $–S(O)_{1–2}NR^4R^5$, $–N(R^7)SO_2R^7$, $–S(O)_{1–2}NR^5OR^7$, –CN, $–OCF_3$, $–SCF_3$, $–C(=NR^7)NR^4$, $–C(O)NR^7(CH_2)_{1–10}NR^4R^5$, $–C(O)NR^7(CH_2)_{1–10}OR^7$, $–C(S)NR^7(CH_2)_{1–10}NR^4R^5$, $–C(S)NR^7(CH_2)_{1–10}OR^7$, haloalquilo y alquilsililo, en donde cada uno de dichos alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo o heteroaralquilo está opcionalmente sustituido, de modo independiente, con 1–5 restos R^9;

R^{40} y R^{41} pueden ser iguales o diferentes, en donde cada uno está seleccionado, de modo independiente, del grupo que consiste en H, alquilo, arilo, heteroarilo, heterociclilo, heterociclenilo, cicloalquilo y cicloalquenilo;

cada R^{42} está seleccionado, de modo independiente, del grupo que consiste en halo, alquilo, cicloalquilo, heterociclilo, arilo, heteroarilo, $-NO_2$, $-OR^{10}$, $-$(alquil C_1–C_6)$-OR^{10}$, $-CN$, $-NR^{10}R^{11}$, $-C(O)R^{10}$, $-C(O)OR^{10}$, $-C(O)NR^{10}R^{11}$, $-CF_3$, $-OCF_3$, $-N(R^{10})C(O)R^{11}$ y $-NR^{10}C(O)OR^{11}$;

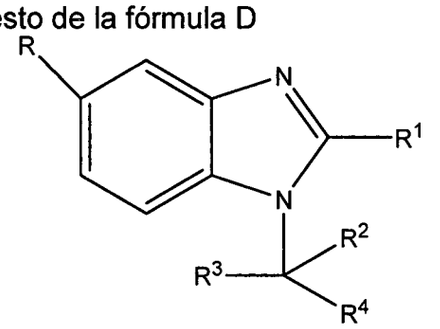
con la condición de que, cuando W es $C(R^{12})$, R^{12} y R^3 se tomen opcionalmente juntos con los dos átomos de carbono del anillo a los que están unidos para formar un anillo de 6 miembros seleccionado del grupo que consiste en cicloalquenilo, arilo, heteroarilo, heterociclilo y heterociclenilo, en donde dicho anillo de 6 miembros está opcionalmente sustituido con 1–3 restos seleccionados, de modo independiente, de oxo, tioxo, $-OR^{11}$, $-NR^{10}R^{11}$, $-C(O)R^{11}$, $-C(O)OR^{11}$, $-C(O)N(R^{10})(R^{11})$ o $-N(R^{10})C(O)R^{11}$;

c. 

fórmula C

o una de sus sales, solvatos o ésteres farmacéuticamente aceptables; y

d. Un compuesto de la fórmula D



fórmula D

o una de sus sales, solvatos o ésteres farmacéuticamente aceptables, en donde:

R está seleccionado del grupo que consiste en H, alquilo, ciano, haloalquilo, halo, —SH, –S–alquilo, –S–haloalquilo, $-S(=O)_2$alquilo, $-S(=O)_2OH$, $-S(=O)_2NH_2$, $-S(=O)_2NH$(alquilo), $S(=O)_2NH$(cicloalquilo),

$-S(=O)_2N(alquilo)_2$, $-S(=O)_2$heterociclilo, $-S(=O)_2$heteroarilo, cicloalquilo, arilo, heterociclilo, heteroarilo, –NHC(=O)alquilo, $-C(=O)NH_2$, –C(=O)NH(alquilo), –C(=O)NH(cicloalquilo), $-C(=O)N(alquilo)_2$, –C(=O)OH, –C(=O)Oalquilo, –C(=O)heterociclilo, –C(=O)NH(arilo), en donde cuando cada uno de dichos cicloalquilo, arilo, heterociclilo, heteroarilo y las porciones de "heterociclilo" y "arilo" de dichos grupos R tiene dos sustituyentes en átomos de carbono adyacentes, dichos sustituyentes se pueden tomar opcionalmente juntos con los átomos de carbono a los que están unidos para formar un anillo cicloalquilo, arilo, heterociclilo, heterociclenilo o heteroarilo de cinco o seis miembros; en donde cada uno de los R antes mencionados alquilo, arilo, cicloalquilo, heterociclilo y heteroarilo y las porciones de "alquilo", "cicloalquilo", "heterociclilo" y "arilo" de dichos grupos R, opcionalmente con dichos anillo arilo, heterociclilo, heterociclenilo o heteroarilo de cinco o seis miembros, está opcionalmente sustituido con 1–3 sustituyentes seleccionados, de modo independiente, del grupo que consiste en alquilo, alquenilo, alquinilo, hidroxilo, ciano, halo, haloalquilo, haloalcoxi, –C(O)OH, –C(=O)Oalquilo y $-C(O)NH_2$;

R^1 está seleccionado del grupo que consiste en alquilo, heterociclilo, –C(=O)arilo, $-NH_2$, –NH(alquilo), –NH(cicloalquilo), –N(alquil)(cicloalquilo), –NH(heterociclilo), –N(alquil)(heterociclilo), $N(alquilo)_2$, –NH(arilo), –N(alquil)(arilo), $-N(arilo)_2$, –NH(heteroarilo), –N(alquil)(heteroarilo), –NHC(=O)–alquilo, –N(alquil)C(=O)–alquilo, –NHC(=O)Oalquilo, –N(alquil)C(=O)O–alquilo, en donde cada uno de los alquilo, heterociclilo antes mencionados y las porciones de "alquilo", "cicloalquilo", "arilo" y "heteroarilo" de dichos grupos R^1 está opcionalmente sustituido con 1–3 sustituyentes seleccionados, de modo independiente, del grupo que consiste en halo, heterociclilo, arilo, heteroarilo, haloalquilo, haloalcoxi,

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ariloxi, ciano, –SH, –S–alquilo, –S–haloalquilo, $–S(=O)_2$alquilo, $–S(=O)_2OH$, $–S(=O)_2NH_2$, $–S(=O)_2$NH(alquilo), $S(=O)_2$NH(cicloalquilo), $–S(=O)_2$N(alquilo)$_2$, $–S(=O)_2$heterociclilo, $–S(=O)_2$heteroarilo, hidroxi, alquilo, alquenilo, alquinilo, $–NH_2$, –NH(alquilo), –N(alquilo)$_2$, alcoxi, –NHC(=O)alquilo, –C(=O)H, –C(=O)alquilo, –C(=O)arilo, –C(=O)heteroarilo, –C(=O)Oalquilo, $–C(=O)NH_2$, –C(O)NHalquilo, –C(=O)N(alquilo)$_2$; en donde cuando cada uno de dichos heterociclilo, arilo y heteroarilo tiene dos sustituyentes en átomos de carbono adyacentes, dichos sustituyentes se pueden tomar opcionalmente juntos con los átomos de carbono a los que están unidos para formar un anillo arilo, heterociclilo, heterociclenilo o heteroarilo de cinco a seis miembros;

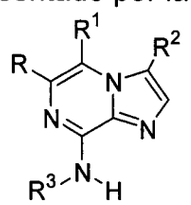
R^2 y R^3 son, de modo independiente, H o alquilo o $–C(R^2)(R^3)–$ está ausente;

R^4 está seleccionado del grupo que consiste en alquilo, cicloalquilo, heterociclilo, arilo y heteroarilo, en donde cuando cada uno de dichos cicloalquilo, heterociclilo, arilo y heteroarilo tiene dos sustituyentes en átomos de carbono adyacentes, dichos sustituyentes se pueden tomar opcionalmente juntos con los átomos de carbono a los que están unidos para formar un anillo arilo, heterociclilo, heterociclenilo o heteroarilo de cinco a seis miembros; en donde cada uno de los R^4 antes mencionados alquilo, cicloalquilo, heterociclilo, arilo y heteroarilo, opcionalmente con dichos anillos arilo, heterociclilo, heterociclenilo o heteroarilo de cinco a seis miembros está opcionalmente sustituido con 1–3 sustituyentes seleccionados, de modo independiente, del grupo que consiste en ciano, halo, haloalquilo, alquilo, alcoxi, hidroxilo, haloalcoxi, cicloalquilo, heterociclilo, arilo, heteroarilo, $–S(=O)_2$alquilo, $–S(=O)_2NH_2$,

$-S(=O)_2NH(alquilo)$, $-S(=O)_2N(alquilo)_2$, –S–alquilo, –S–haloalquilo, $-C(=O)OH$, $-NH_2$, –NH(alquilo), $-N(alquilo)_2$ y $-C(=O)Oalquilo$;

y (b) posteriormente administrar a dicho tumor al menos un inhibidor de aurora quinasa, en donde dicho inhibidor de aurora quinasa está seleccionado del grupo que consiste en un compuesto representado por las fórmulas E–K mostrados más abajo en los puntos e–k:

e. Un compuesto representado por la fórmula estructural E:



fórmula E

o una de sus sales, solvatos, ésteres o profármacos farmacéuticamente aceptables, en donde:

R es H, CN, $-NR^5R^6$, cicloalquilo, cicloalquenilo, heterociclenilo, heteroarilo, $-C(O)NR^5R^6$, $-N(R^5)C(O)R^6$, heterociclilo, heteroarilo sustituido con $(CH_2)_{1-3}$ NR^5R^6, alquilo no sustituido o alquilo sustituido con uno o varios restos que pueden ser iguales o diferentes donde cada resto está seleccionado, de modo independiente, del grupo que consiste en $-OR^5$, heterociclilo, $-N(R^5)C(O)N(R^5R^6)$, $-N(R^5)-C(O)OR^6$, $-(CH_2)_{1-3}-N(R^5R^6)$ y $-NR^5R^6$;

R^1 es H, halo, arilo o heteroarilo, en donde cada uno de dichos arilo y heteroarilo pueden no estar sustituidos o pueden estar sustituidos con uno o varios restos que pueden ser iguales o diferentes donde cada resto está seleccionado, de modo independiente, del grupo que consiste en halo, alquilo, alquenilo, alquinilo, cicloalquilo, arilo, heteroarilo, heterociclilo, $-CH_2OR^5$, $-C(O)NR^5R^6$, $-C(O)OH$, $-C(O)NH_2$, $-NR^5R^6$ (en donde R^5 y R^6, junto con el N de dicho $-NR^5R^6$, forman un anillo heterociclilo), $-S(O)R^5$, $-S(O_2)R^5$, $-CN$, $-CHO$, $-SR^5$, $-C(O)OR^5$, $-C(O)R^5$ y $-OR^5$;

R^2 es H, halo, arilo, arilalquilo o heteroarilo, en donde cada uno de dichos arilo, arilalquilo y heteroarilo puede no estar sustituido o puede estar opcionalmente sustituido, de modo independiente, con uno o varios restos que pueden ser iguales o diferentes donde cada resto está seleccionado, de modo independiente, del grupo que consiste en halo, amida, alquilo, alquenilo, alquinilo, cicloalquilo, arilo, $-C(O)OH$, $-C(O)NH_2$, $-NR^5R^6$ (en donde R^5 y R^6, junto con el N de dicho $-NR^5R^6$, forman un anillo heterociclilo), –CN, arilalquilo, $-CH_2OR^5$, $-S(O)R^5$, $-S(O_2)R^5$, –CN, –CHO, $-SR^5$, $-C(O)OR^5$, $-C(O)R^5$, heteroarilo y heterociclilo;

R^3 es H, alquilo, cicloalquilo, heterociclilo, arilo o heteroarilo, en donde:

– dicho alquilo mostrado con anterioridad para R^3 puede no estar sustituido o puede estar sustituido con uno o varios restos que pueden ser iguales o diferentes donde cada resto está seleccionado, de modo independiente, del grupo que consiste en $-OR^5$, alcoxi, heteroarilo y $-NR^5R^6$;

– dicho arilo mostrado con anterioridad para R^3 puede no estar sustituido o puede estar opcionalmente sustituido u opcionalmente fusionado, con halo, heteroarilo, heterociclilo, cicloalquilo o heteroarilalquilo, en donde cada uno de dichos heteroarilo, heterociclilo, cicloalquilo y heteroarilalquilo puede no estar sustituido o puede estar opcionalmente sustituido, de modo independiente, con uno o varios restos que pueden ser iguales o diferentes donde cada resto está seleccionado, de modo independiente, de alquilo, $-OR^5$, $-N(R^5R^6)$ y $-S(O_2)R^5$; y

– dicho heteroarilo mostrado con anterioridad para R^3 puede no estar sustituido o puede estar opcionalmente sustituido u opcionalmente fusionado con uno o varios restos que pueden ser iguales o

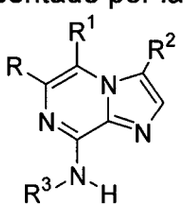
diferentes con donde cada resto está seleccionado, de modo independiente, del grupo que consiste en halo, amino, alcoxicarbonilo, $-OR^5$, alquilo, -CHO, $-NR^5R^6$, $-S(O_2)N(R^5R^6)$, $-C(O)N(R^5R^6)$, $-SR^5$, alquenilo, alquinilo, cicloalquilo, arilo, heteroarilo, heterociclenilo, y heterociclilo;

R^5 es H, alquilo, aminoalquilo, arilo, heteroarilo, heterociclilo o cicloalquilo; y

R^6 es H, alquilo, arilo, arilalquilo, heteroarilo, heterociclilo o cicloalquilo;

también en donde en cualquier $-NR^5R^6$ en la fórmula I, dichos R^5 y R^6 pueden estar opcionalmente unidos junto con el N de dicho $-NR^5R^6$ para formar un anillo cíclico;

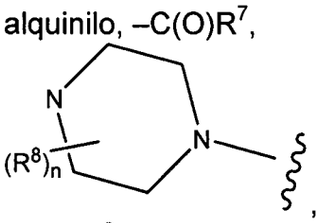
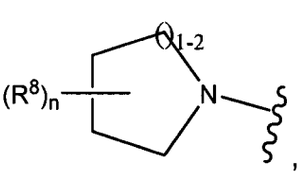
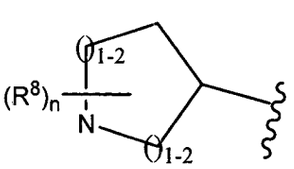
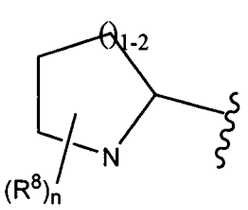
f. Un compuesto representado por la fórmula estructural:



fórmula F

o una de sus sales, solvatos, ésteres o profármacos farmacéuticamente aceptables, en donde:

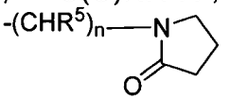
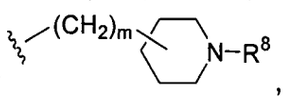
R está seleccionado del grupo que consiste en H, halógeno, arilo, heteroarilo, cicloalquilo, arilalquilo, heterociclilo, heterociclilalquilo, alquenilo, alquinilo, $-C(O)R^7$,


,

,

y


en donde cada uno de dichos arilo, heteroarilo, cicloalquilo, arilalquilo, alquenilo, heterociclilo y los restos de heterociclilo cuyas estructuras se muestran inmediatamente antes para R pueden no estar sustituidas o pueden estar opcionalmente sustituidas, de modo independiente, con uno o varios restos que pueden ser iguales o diferentes, donde cada resto está seleccionado, de modo independiente, del grupo que consiste en halógeno, alquilo, cicloalquilo, CF_3, CN, $-OCF_3$, $-OR^6$, $-C(O)R^7$, $-NR^5R^6$, $-C(O_2)R^6$, $-C(O)NR^5R^6$, $-(CHR^5)_nOR^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^6$;

R^1 es H, halógeno o alquilo;

R^2 es alquilo;

R^3 está seleccionado del grupo que consiste en H, arilo, heteroarilo, heterociclilo, $-(CHR^5)_n$–arilo, $-(CHR^5)_n$–heteroarilo, $-(CHR^5)_n-OR^6$, $-S(O_2)R^6$, $-C(O)R^6$, $-S(O_2)NR^5R^6$, $-C(O)OR^6$, $-C(O)NR^5R^6$, cicloalquilo, $-CH(arilo)_2$, $-(CH_2)_m-NR^8$, $-(CHR^5)_n-CH(arilo)_2$,  y  , en donde cada uno de dichos arilo, heteroarilo y heterociclilo puede estar sustituido u opcionalmente sustituido con uno o varios restos que pueden ser iguales o diferentes, donde cada resto está seleccionado, de modo independiente, del grupo que consiste en halógeno, alquilo, arilo, cicloalquilo, CF_3, CN, $-OCF_3$, $-OR^5$, $-NR^5R^6$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^6$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^6$;

R^5 es H o alquilo;

R^6 está seleccionado del grupo que consiste en H, alquilo, arilo, heteroarilo, arilalquilo y heteroarilalquilo, en donde cada uno de dichos alquilo, heteroarilalquilo, arilo, heteroarilo y arilalquilo puede no estar sustituido o puede estar opcionalmente sustituido con uno o varios restos que pueden ser iguales o diferentes, donde cada resto está seleccionado, de modo independiente, del grupo que consiste en halógeno, alquilo, arilo, cicloalquilo, CF_3, OCF_3, CN, $-OR^5$,

$-NR^5R^6$, $-CH_2OR^5$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^6$;

R^7 está seleccionado del grupo que consiste en alquilo, arilo, heteroarilo, arilalquilo y heteroarilalquilo, en donde cada uno de dichos alquilo, heteroarilalquilo, arilo, heteroarilo y arilalquilo puede no estar sustituido o puede estar opcionalmente sustituido con uno o varios restos que pueden ser iguales o diferentes, donde cada resto está seleccionado, de modo independiente, del grupo que consiste en halógeno, alquilo, arilo, cicloalquilo, CF_3, OCF_3, CN, $-OR^5$, $-NR^5R^6$, $-CH_2OR^5$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^6$;

R^8 está seleccionado del grupo que consiste en R^6, $-C(O)NR^5R^6$, $-S(O_2)NR^5R^6$, $-C(O)R^7$, $-C(O_2)R^6$, $-S(O_2)R^7$ y $-(CH_2)$–arilo;

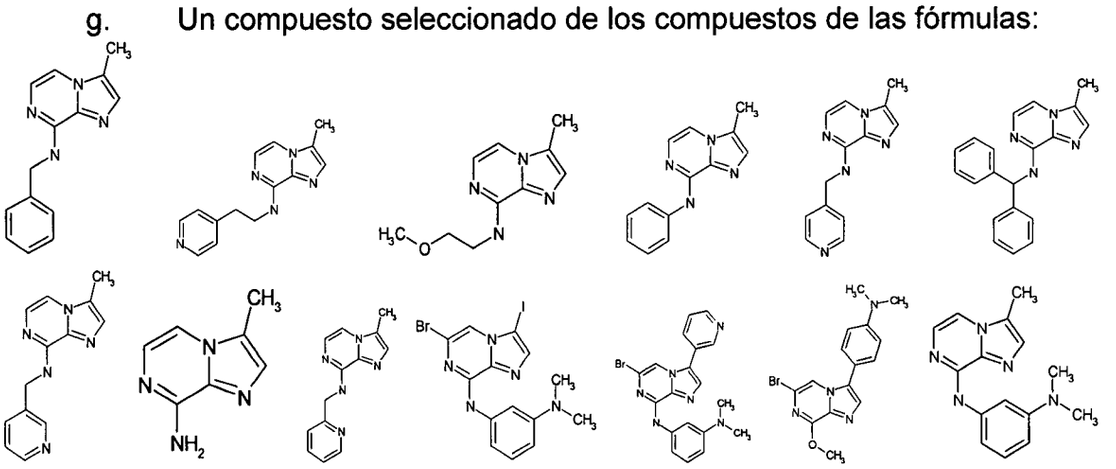
R^9 está seleccionado del grupo que consiste en halógeno, CN, NR^5R^6, $-C(O_2)R^6$, $-C(O)NR^5R^6$, $-OR^6$, $-C(O)R^7$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^6$;

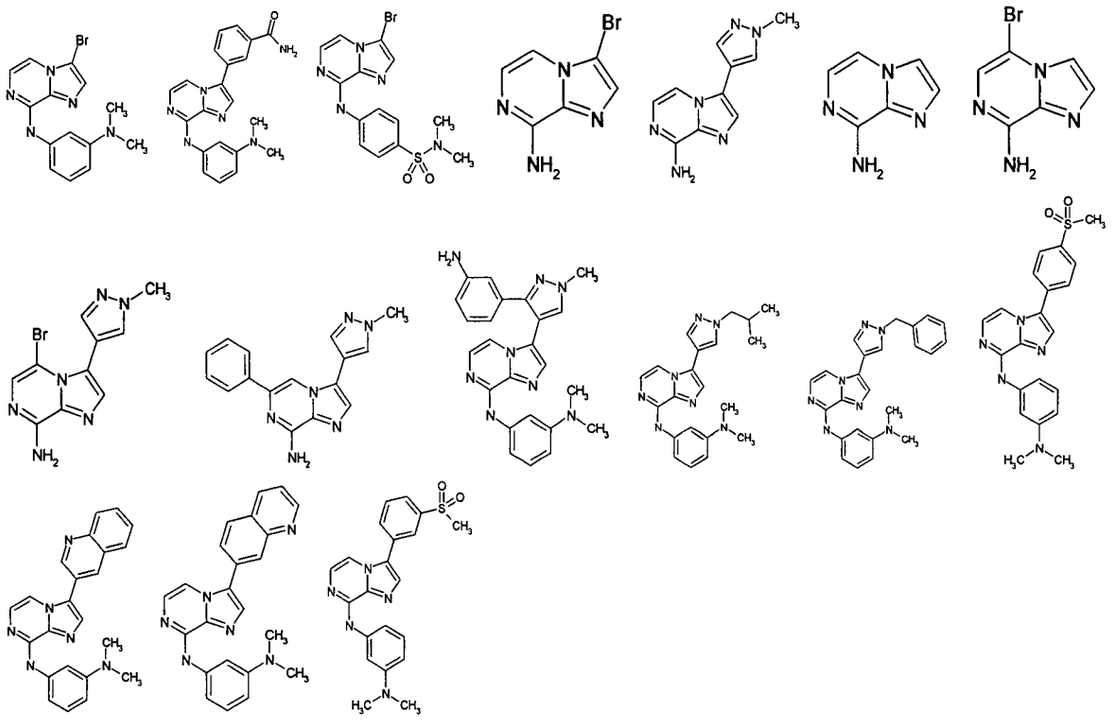
m es 0 a 4;

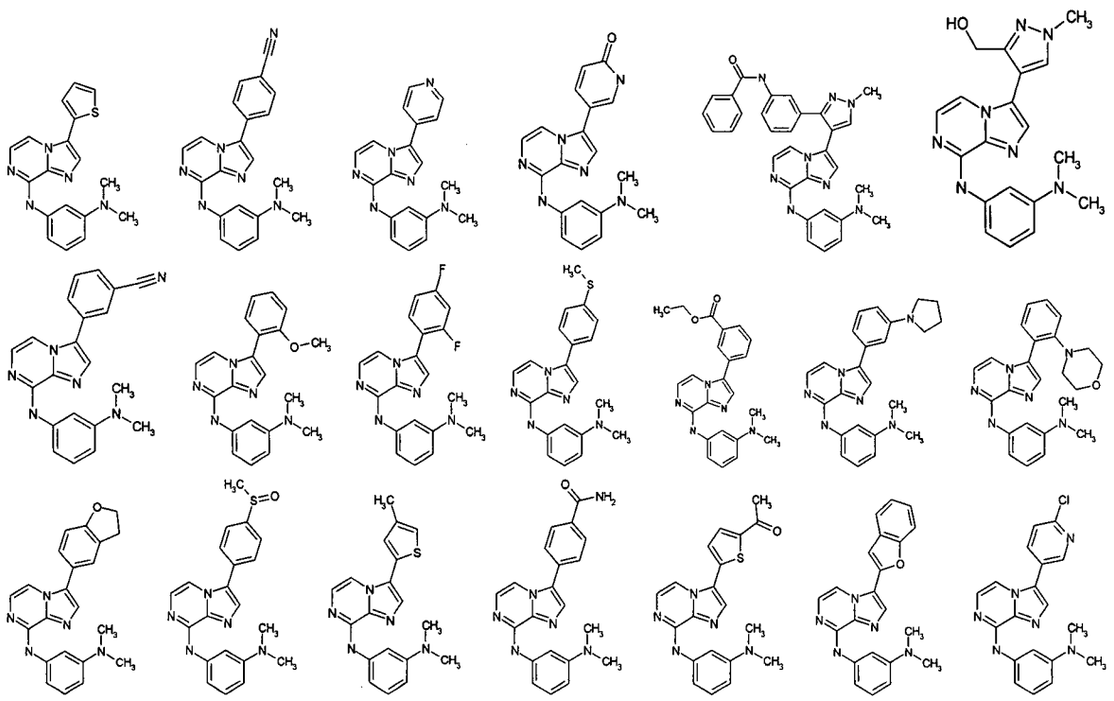
n es 1–4; y

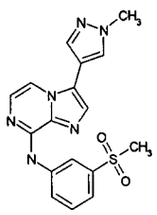
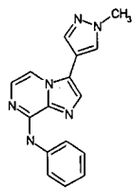
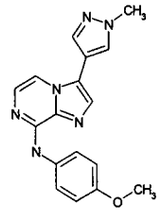
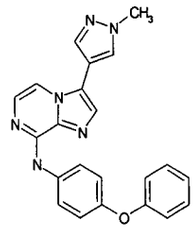
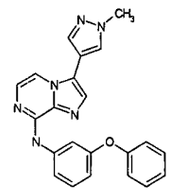
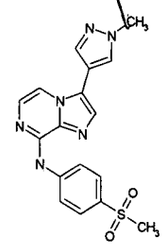
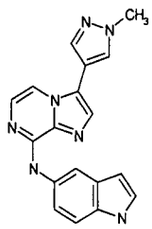
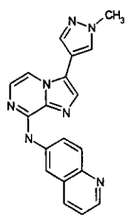
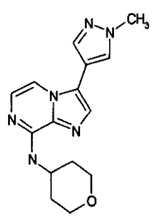
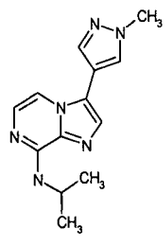
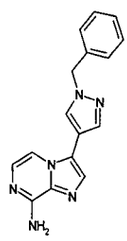
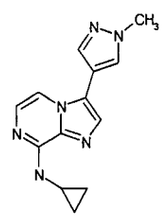
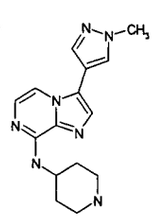
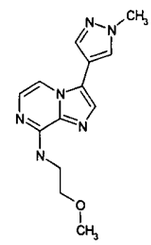
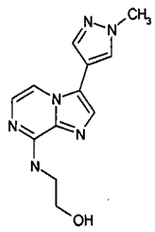
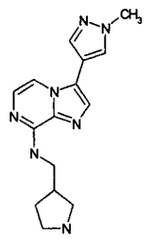
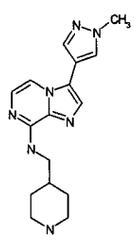
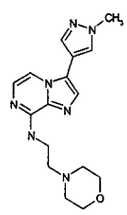
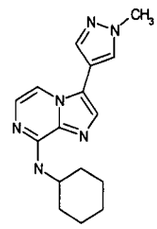
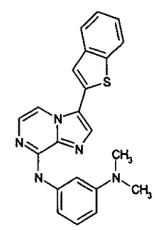
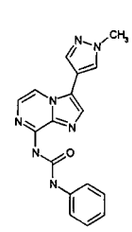
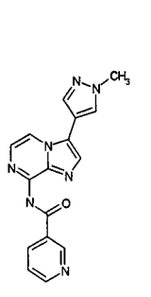
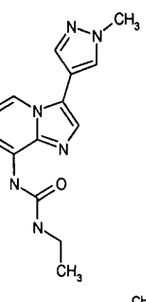
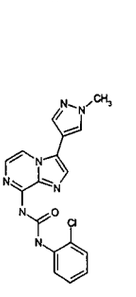
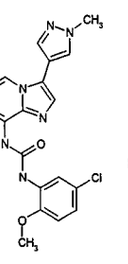
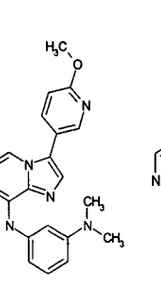
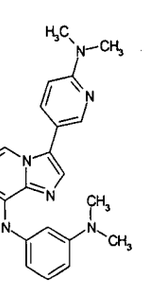
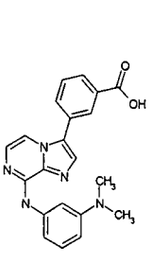
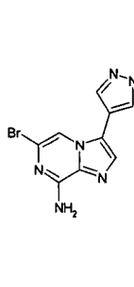
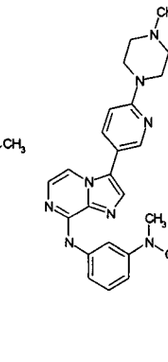
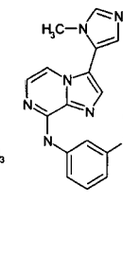
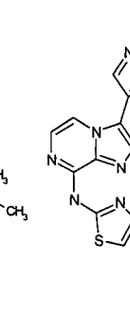
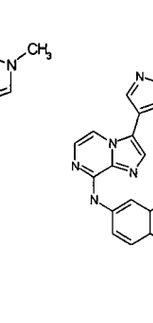
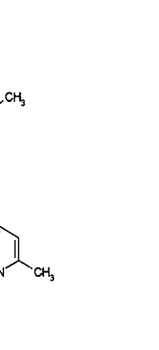
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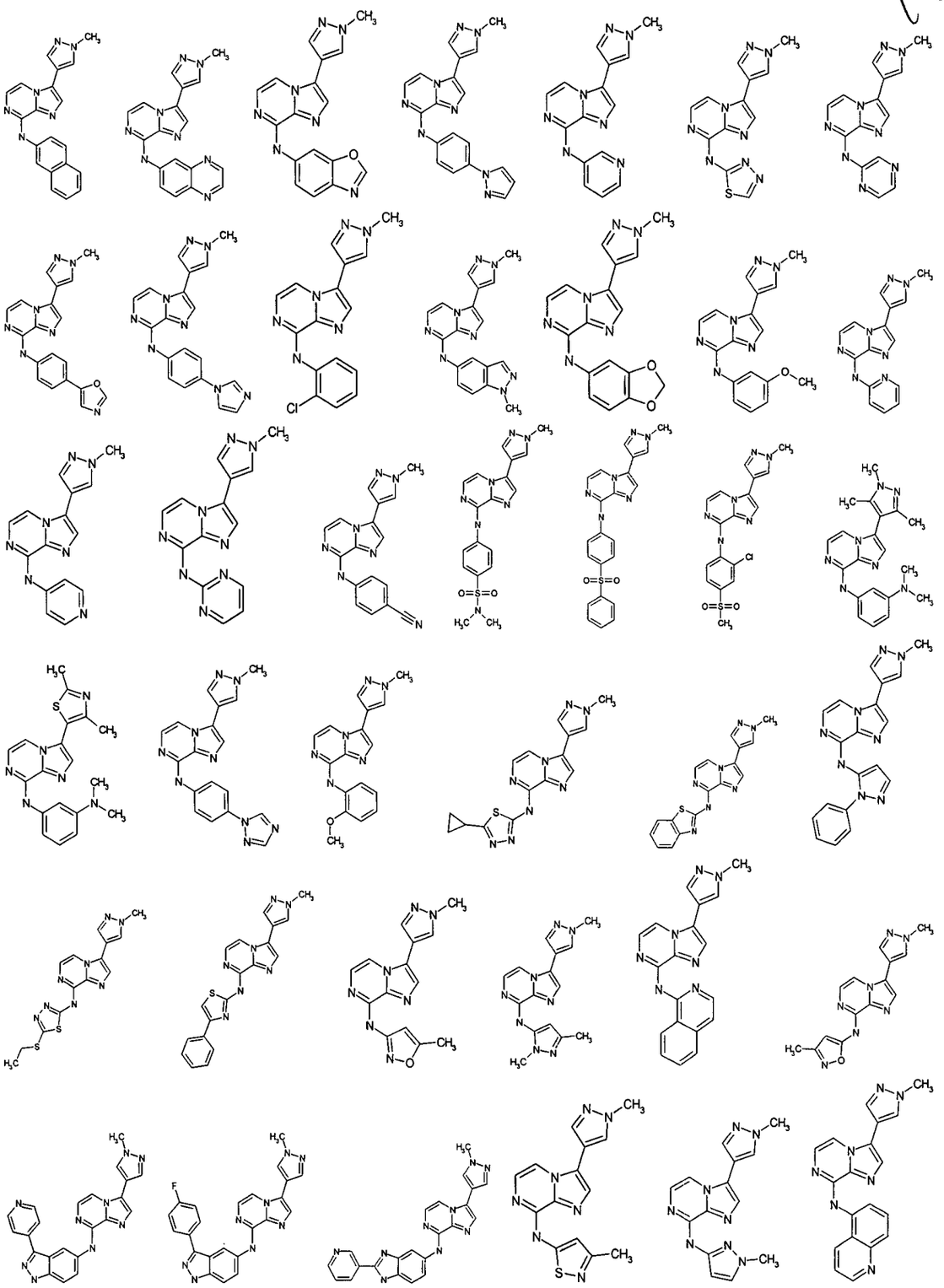
g. Un compuesto seleccionado de los compuestos de las fórmulas:

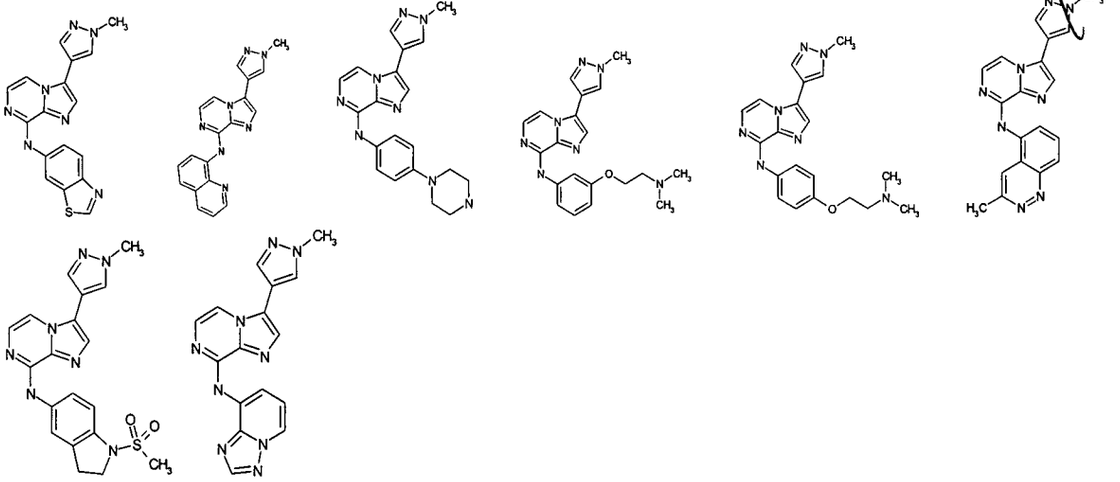


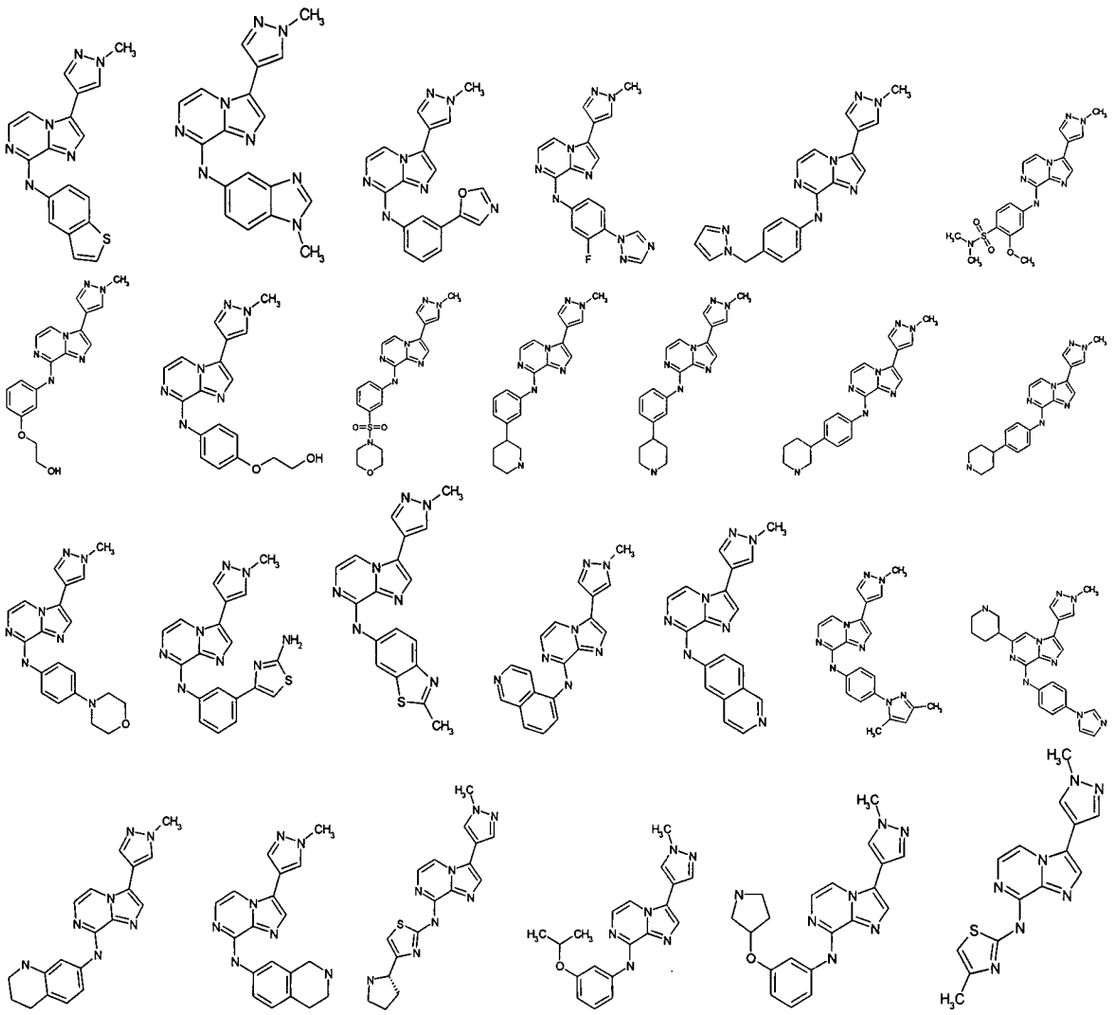


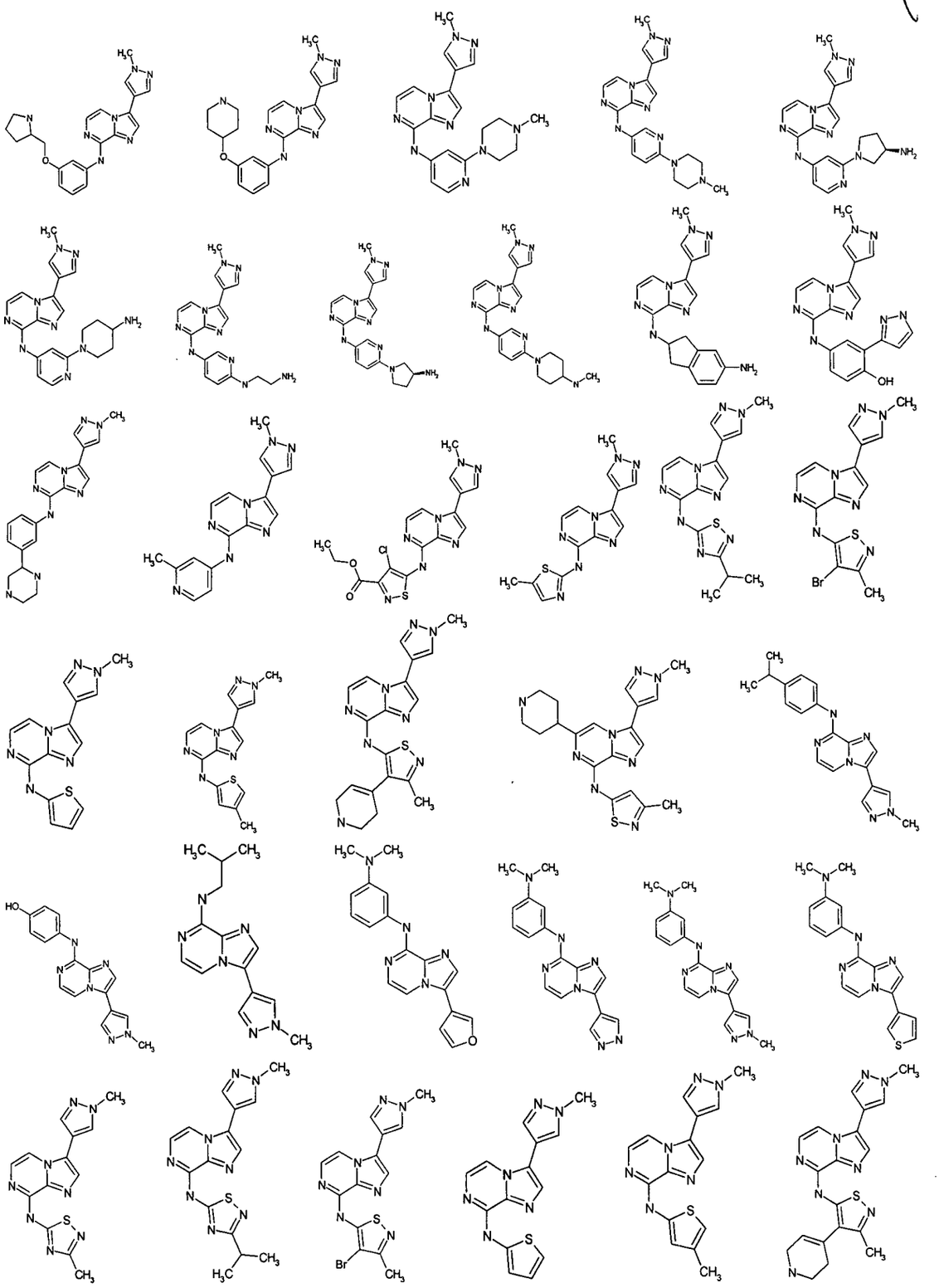


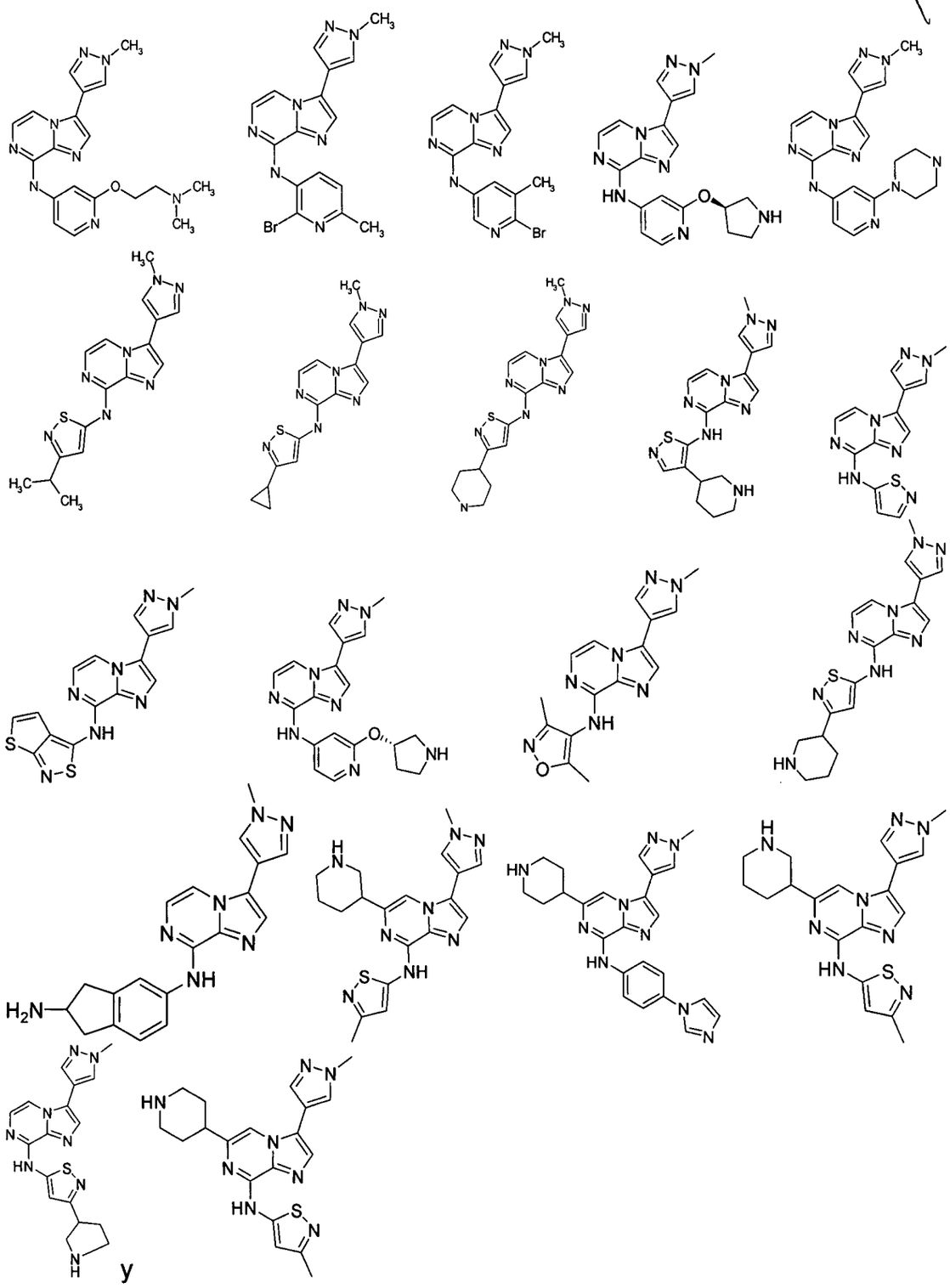









































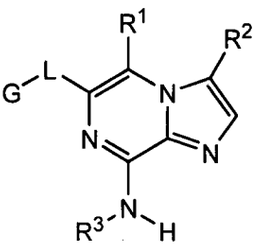




y

o una de sus sales, solvatos, ésteres o profármacos farmacéuticamente aceptables;

h. Un compuesto de la fórmula:



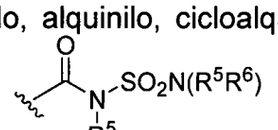
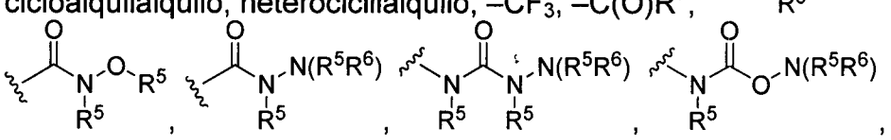
fórmula H

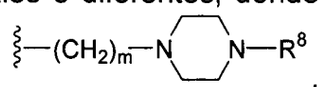
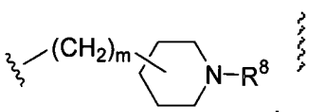
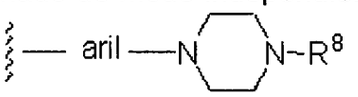
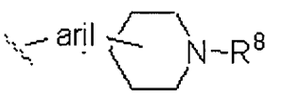
o una de sus sales, solvatos, ésteres o profármacos farmacéuticamente aceptables, en donde:

L está seleccionado del grupo que consiste en S, S(O) y $S(O_2)$;

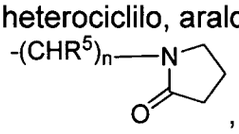
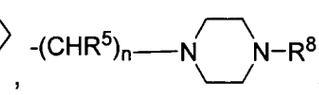
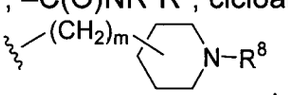
G es alquilo, alquenilo, cicloalquilo, cicloalquenilo, arilo, heteroarilo, heterociclenilo o heterociclilo, en donde cada uno de dichos alquilo, alquenilo, cicloalquilo, cicloalquenilo, arilo, heteroarilo, heterociclenilo o heterociclilo puede no estar sustituido o puede estar opcionalmente sustituido, de modo independiente, con uno o varios restos que están seleccionados, de modo independiente, del grupo que consiste en $-OR^5$, halo, $-CN$, $-C(O)NR^5R^6$, $-N(H)-C(O)R^5$,$-N(H)-C(O)-NR^5R^6$, $-S(O_2)NR^5R^6$, $-NR^5R^6$, $-C(O)R^5$, $-C(O_2)R^5$, $-SR^5$, $-S(O)R^5$, $-S(O_2)R^5$;

R^1 es H, halo, alquilo, arilo o heteroarilo, en donde cada uno de dichos alquilo, arilo y heteroarilo puede no estar sustituido o puede estar sustituido con uno o varios restos que pueden ser iguales o diferentes donde cada resto está seleccionado, de modo independiente, del grupo que consiste en halo, alquilo, alquenilo, alquinilo, cicloalquilo, arilo, heteroarilo, heterociclilo, $-C(O)NR^5R^6$ y $-OR^5$;

R^2 está seleccionado del grupo que consiste en H, R^9, alquilo, arilo, arilalquilo, heteroarilo, heteroarilalquilo, heterociclilo, alquenilo, alquinilo, cicloalquilo, cicloalquilalquilo, heterociclilalquilo, $-CF_3$, $-C(O)R^7$,  ,  ,

alquilo sustituido con 1–6 R^9 que pueden ser iguales o diferentes, donde cada R^9 está seleccionado de modo independiente,  ,  ,  , y  ,

en donde cada uno de dichos arilo, heteroarilo, cicloalquilo, arilalquilo y heterociclilo antes mencionados puede no estar sustituido o puede estar opcionalmente sustituido, de modo independiente, con uno o varios restos que pueden ser iguales o diferentes, donde cada resto está seleccionado, de modo independiente, del grupo que consiste en halo, alquilo, alquenilo, alquinilo, cicloalquilo, arilo, heteroarilo, heterociclilo, CF_3, CN, $-OCF_3$, $-OR^6$, $-C(O)R^7$, $-NR^5R^6$, $-C(O_2)R^6$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^6$;

R^3 está seleccionado del grupo que consiste en H, alquilo, arilo, heteroarilo, heterociclilo, aralquilo, heteroarilalquilo, cicloalquilalquilo, heterociclilalquilo,  ,  , $-(CHR^5)_n-OR^6$, $-S(O_2)R^6$, $-C(O)R^6$, $-S(O_2)NR^5R^6$, $-C(O)OR^6$, $-C(O)NR^5R^6$, cicloalquilo, $-CH(arilo)_2$, $-CH(heteroarilo)_2$, $-(CH_2)_m-NR^8$ y  , en donde cada uno de dichos alquilo, arilo, heteroarilo y heterociclilo puede estar sustituido u opcionalmente sustituido con uno o varios restos que pueden ser iguales o diferentes, donde cada resto está seleccionado, de modo independiente, del grupo que consiste en halo, alquilo, arilo, cicloalquilo, CF_3, CN, $-OCF_3$, $-OR^5$, $-NR^5R^6$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^6$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^6$;

R^5 es H, alquilo, arilo, heteroarilo, heterociclilo o cicloalquilo; y

R^6 está seleccionado del grupo que consiste en H, alquilo, arilo, heteroarilo, arilalquilo y heteroarilalquilo, en donde cada uno de dichos alquilo,

heteroarilalquilo, arilo, heteroarilo y arilalquilo puede no estar sustituido o puede estar opcionalmente sustituido con uno o varios restos que pueden ser iguales o diferentes, donde cada resto está seleccionado, de modo independiente, del grupo que consiste en halógeno, alquilo, arilo, cicloalquilo, CF_3, OCF_3, CN, $-OR^5$, $-NR^5R^6$, $-CH_2OR^5$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^6$;

R^7 está seleccionado del grupo que consiste en alquilo, arilo, heteroarilo, arilalquilo y heteroarilalquilo, en donde cada uno de dichos alquilo, heteroarilalquilo, arilo, heteroarilo y arilalquilo puede no estar sustituido o puede estar opcionalmente sustituido con uno o varios restos que pueden ser iguales o diferentes, donde cada resto está seleccionado, de modo independiente, del grupo que consiste en halógeno, alquilo, arilo, cicloalquilo, CF_3, OCF_3, CN, $-OR^5$, $-NR^5R^6$, $-CH_2OR^5$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^6$;

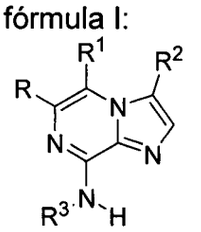
R^8 está seleccionado del grupo que consiste en R^6, $-C(O)NR^5R^6$, $-S(O_2)NR^5R^6$, $-C(O)R^7$, $-C(O_2)R^6$, $-S(O_2)R^7$ y $-(CH_2)$–arilo;

R^9 está seleccionado del grupo que consiste en halógeno, CN, NR^5R^6, $-C(O_2)R^6$, $-C(O)NR^5R^6$, $-OR^6$, $-C(O)R^7$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^6$;

m es 0 a 4; y

p es 0–3;

i. Un compuesto de la fórmula I:



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fórmula I

o una de sus sales, solvatos, ésteres o profármacos farmacéuticamente aceptables, en donde:

R es H, CN, $-NR^5R^6$, cicloalquilo, cicloalquenilo, heterociclenilo, heteroarilo, $-C(O)NR^5R^6$, $-N(R^5)C(O)R^6$, heterociclilo, heteroarilo sustituido con $(CH_2)_{1-3}$ NR^5R^6, alquilo no sustituido o alquilo sustituido con uno o varios restos que pueden ser iguales o diferentes donde cada resto está seleccionado, de modo independiente, del grupo que consiste en $-OR^5$, heterociclilo, $-N(R^5)C(O)N(R^5R^6)$, $-N(R^5)-C(O)OR^6$, $-(CH_2)_{1-3}-N(R^5R^6)$ y $-NR^5R^6$;

R^1 es H, halo, arilo o heteroarilo, en donde cada uno de dichos arilo y heteroarilo pueden no estar sustituidos o pueden estar sustituidos con uno o varios restos que pueden ser iguales o diferentes donde cada resto está seleccionado, de modo independiente, del grupo que consiste en halo, alquilo, alquenilo, alquinilo, cicloalquilo, arilo, heteroarilo, heterociclilo, $-CH_2OR^5$, $-C(O)NR^5R^6$, $-C(O)OH$, $-C(O)NH_2$, $-NR^5R^6$ (en donde R^5 y R^6, junto con el N de dicho $-NR^5R^6$, forman un anillo heterociclilo), $-S(O)R^5$, $-S(O_2)R^5$, $-CN$, $-CHO$, $-SR^5$, $-C(O)OR^5$, $-C(O)R^5$ y $-OR^5$;

R^2 es H, halo, arilo, arilalquilo o heteroarilo, en donde cada uno de dichos arilo, arilalquilo y heteroarilo puede no estar sustituido o puede estar opcionalmente sustituido, de modo independiente, con uno o varios restos que pueden ser iguales o diferentes donde cada resto está seleccionado, de modo independiente, del grupo que consiste en halo, amida, alquilo, alquenilo, alquinilo, cicloalquilo, arilo, $-C(O)OH$, $-C(O)NH_2$, $-NR^5R^6$ (en donde R^5 y R^6, junto con el N de dicho $-NR^5R^6$, forman un anillo heterociclilo), $-CN$, arilalquilo, $-CH_2OR^5$, $-S(O)R^5$, $-S(O_2)R^5$, $-CN$, $-CHO$, $-SR^5$, $-C(O)OR^5$, $-C(O)R^5$, heteroarilo y heterociclilo;

R^3 es heterociclil$-(CR^7R^8)_n-X$, heterociclenil$-(CR^7R^8)_n-X$, heteroaril$-(CR^7R^8)_n-X$ o

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aril–$(CR^7R^8)_n$–X, en donde cada uno de los restos de heterociclilo, heterociclenilo, heteroarilo o arilo de dicho R^3 puede no estar sustituido o puede estar sustituido con uno o varios restos seleccionados, de modo independiente, del grupo que consiste en $–CONR^5R^6$, $–OR^5$ y alquilo,

n es 1–6,

X está seleccionado del grupo que consiste en $–NR^5R^6$, $–OR^5$, $–SO–R^5$ y $–SR^5$,

R^7 y R^8 son cada uno, de modo independiente, hidrógeno o alquilo;

R^5 está seleccionado del grupo que consiste en hidrógeno, alquilo, alquenilo, alcoxialquilo, –alquil–S–alquilo, aminoalquilo, arilo, heteroarilo, heterociclenilo, heterocicloalquilo, cicloalquilo, cicloalquenilo, heterociclilalcoxilo, –S–alquilheterociclilo, heterociclilo, heterociclenilo, alquil$N(alquilo)_2$, alquilNH(alquilo), alquil$N(alquenilo)_2$, –alquil$N(alcoxilo)_2$, –alquil–SH y hidroxialquilo, en donde cada uno de dichos arilo, heteroarilo, heterociclenilo, heterocicloalquilo, cicloalquilo, cicloalquenilo, heterociclilalcoxilo, –S–alquilheterociclilo, heterociclilo, heterociclenilo puede no estar sustituido o puede estar sustituido con uno o varios restos seleccionados, de modo independiente, del grupo que consiste en alquilo, alquilo, alquenilo, arilo, cicloalquenilo, cicloalquilo, arilalquilo, cicloalquenilalquilo, cicloalquilalquilo, heteroarilo, heterociclenilo, heterociclilo, heteroarilalquilo, heterociclenilalquilo, heterocicloalquilalquilo, alcoxialquilo, –alquil–S–alquilo, –alquilSH, alcoxilo, –S–alquilo, hidroxialquilo y aminoalquilo;

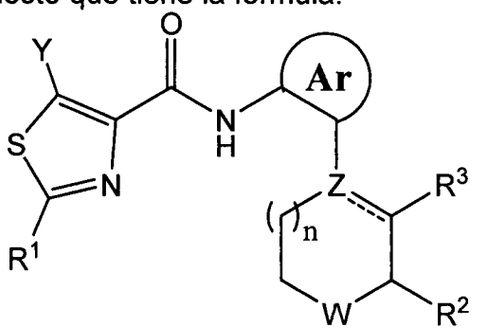
R^6 está seleccionado del grupo que consiste en hidrógeno, alquilo, alquenilo, arilo, cicloalquenilo, cicloalquilo, arilalquilo, cicloalquenilalquilo, cicloalquilalquilo, heteroarilo, heterociclenilo,

heterociclilo, heteroarilalquilo, heterociclenilalquilo, heterocicloalquilalquilo, alcoxialquilo, –alquil–S–alquilo, –alquilSH, alcoxilo, –S–alquilo, hidroxialquilo y aminoalquilo, en donde cada uno de dichos arilo, cicloalquenilo, cicloalquilo, arilalquilo, cicloalquenilalquilo, cicloalquilalquilo, heteroarilo, heterociclenilo, heterociclilo, heteroarilalquilo, heterociclenilalquilo, heterocicloalquilalquilo puede no estar sustituido o puede estar sustituido con uno o varios restos seleccionados, de modo independiente, del grupo que consiste en alquilo, alquilo, alquenilo, arilo, cicloalquenilo, cicloalquilo, arilalquilo, cicloalquenilalquilo, cicloalquilalquilo, heteroarilo, heterociclenilo, heterociclilo, heteroarilalquilo, heterociclenilalquilo, heterocicloalquilalquilo, alcoxialquilo, –alquil–S–alquilo, –alquilSH, alcoxilo, –S–alquilo, hidroxialquilo y aminoalquilo;

también en donde en cualquier $-NR^5R^6$ en la fórmula I, dichos R^5 y R^6 pueden estar opcionalmente unidos junto con el N de dicho $-NR^5R^6$ para formar un anillo cíclico o anillo cíclico en puente, en donde cada uno de dicho anillo cíclico o anillo cíclico en puente, pueden no estar sustituidos o pueden estar sustituidos con uno o varios restos, que pueden ser iguales o diferentes seleccionados, de modo independiente, del grupo que consiste en hidroxilo, –SH, alquilo, alquenilo, hidroxialquilo, –alquil–SH, alcoxilo, –S–alquilo, $-CO_2-$alquilo, $-CO_2-$alquenilo, arilalquilo, cicloalquenilalquilo, cicloalquilalquilo, heteroarilalquilo, heterociclenilalquilo, heterocicloalquilalquilo, heteroarilo, arilo, cicloalquenilo, cicloalquilo, espiroheterociclilo, espiroheterociclenilo, espiroheteroarilo, espirociclilo, espirociclenilo, espiroarilo, alcoxialquilo, –alquil–S–

alquilo, heterociclilo y heterociclenilo;

j. Un compuesto que tiene la fórmula:



(J)

o una de sus sales, solvatos, ésteres, prodrogas o estereoisómeros farmacéuticamente aceptables, en donde las líneas punteadas indican un enlace opcional y adicional y en donde:

R^1 es heteroarilo con contenido de nitrógeno, heterociclilo con contenido de nitrógeno, heteroarilo benzofusionado con contenido de nitrógeno o heterociclilo benzofusionado con contenido de nitrógeno, en donde R^1 está unido con el resto del compuesto de la fórmula (I) a través de un átomo de nitrógeno del anillo y en donde uno o varios átomos de carbono del anillo de un grupo heteroarilo con contenido de nitrógeno, heterociclilo con contenido de nitrógeno, heteroarilo benzofusionado con contenido de nitrógeno o heterociclilo benzofusionado con contenido de nitrógeno puede estar sustituido con hasta 5 sustituyentes, que pueden ser iguales o diferentes y están seleccionados, de modo independiente, de alquilo, arilo, halo, –OH, –O–alquilo, –O–arilo, $–N(R^8)_2$, $–CF_3$, $–NO_2$, $–C(O)R^8$, $–C(O)OR^8$, $–C(O)N(R^8)_2$, $–OC(O)R^8$ o $–NHC(O)R^8$;

R^2 es –H, –alquilo, $–NH_2$ o $–CH_2NH_2$;

R^3 es –H, –alquilo, $–NH_2$ o $–CH_2NH_2$;

cada aparición de R^4 es, de modo independiente, –H, –alquilo, $–NH_2$, –OH, –alquilen–OH, $–CH_2NH_2$, $–C(O)R^5$, $–C(O)NH_2$, –C(O)NH–alquilo, $–C(O)N(alquilo)_2$, $–NHC(O)R^6$ o $–NHS(O)_2R^6$;

R^5 es –H, –alquilo, –arilo, –heteroarilo, –NHOH;

R^6 es –H, –alquilo o $–CF_3$;

R^7 es –H, –OH, –alquilo C_1–C_6, –O–(alquilo C_1–C_6) o $–CF_3$;

R^8 es –H, alquilo, arilo, heterociclilo, heteroarilo o cicloalquilo;

Ar es –arileno– o –heteroarileno–, en donde el arileno o heteroarileno está unido a través de 2 de sus átomos de carbono del anillo adyacentes y en donde el –arileno– o –heteroarileno– pueden estar sustituidos con hasta 4 sustituyentes, que pueden ser iguales o diferentes y están seleccionados, de modo independiente, de –halo, alquilo, alcoxi, ariloxi, $–SR^8$, $–S(O)R^8$, $–S(O)_2R^8$, $–C(O)R^8$, $–C(O)OR^8$, $–C(O)N(R^8)_2$, $–NHC(O)R^8$, $–CF_3$, –CN o NO_2 y de modo tal que, cuando Ar es tetrahidronaftileno, R^1 y R^2 no puedan ser ambos hidrógeno

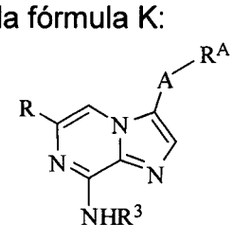
W es –NH– o $–C(R^4)_2–$, en donde ambos grupos R^4 y el átomo de carbono al que están unidos se pueden combinar para formar un grupo heterociclilo o heteroarilo de cinco a siete miembros;

Y es –H, –halo, –alquilo o –CN;

Z es $–CR^7–$ o –N–, cuando el enlace adicional opcional está ausente y –C– cuando el enlace adicional opcional está presente;

n es un número entero que va de 0 a 2; y

(k) Un compuesto de la fórmula K:



fórmula K

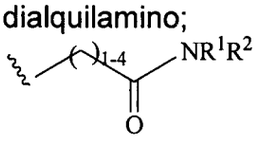
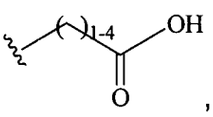
o una de sus sales, solvatos, ésteres, prodrogas o estereoisómeros farmacéuticamente aceptables, en donde:

R es H, halo o alquilo;

R^3 es heteroaril–X, en donde X es heterociclilalquilo–, en donde dicho

heterociclilo puede no estar sustituido o puede estar opcionalmente sustituido con 1–4 restos alquilo;

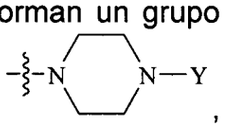
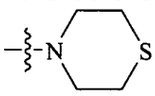
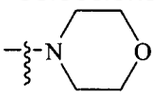
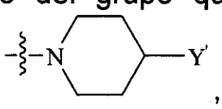
A es –arilo– , –heteroarilo–, –N(R^1)–arilo– o –N(R^1)–heteroarilo– , en donde cada uno de dichos arilo y heteroarilo puede no estar sustituido, de modo independiente, o puede estar opcionalmente sustituido con uno o varios sustituyentes que pueden ser iguales o diferentes, donde cada sustituyente está seleccionado, de modo independiente, del grupo que consiste en alquilo, –NO_2, halo, hidroxi, trihaloalquilo, alcoxi y dialquilamino;

R^A es –$(CH_2)_{1-4}$–heteroarilo,  o  , en donde dicho heteroarilo puede estar opcionalmente fusionado con un arilo, en donde cada uno de dichos arilo y heteroarilo puede estar opcionalmente sustituido, de modo independiente, con uno o varios restos donde cada resto está seleccionado, de modo independiente, del grupo que consiste en trihaloalquilo, –NO_2, halo, hidroxialquilo, alcoxialquilo y dialquilamino;

R^1 es H o alquilo;

R^2 es H, hidroxialquilo–, arilalquilo–, heteroarilo, arilo, heteroarilalquilo–, alquilo, dialquilaminoalquilo–, alquilaminoalquilo–, cicloalquilalquilo–, cicloalquilo, heterociclilalquilo– o heterociclilo, en donde dichos arilo y arilo de arilalquilo puede no estar sustituido o puede estar sustituido con uno o varios restos seleccionados, de modo independiente, del grupo que consiste en trihaloalquilo, –NO_2, halo, hidroxialquilo, alcoxialquilo, dialquilamino y heterociclilalquilo–, en donde dicho heterociclilalquilo puede no estar sustituido o puede estar sustituido con alquilo o –SO_2NH_2; dichos heteroarilo y heteroarilo de heteroarilalquilo pueden no estar sustituidos o pueden estar sustituidos con uno o varios restos, donde cada resto está seleccionado, de modo independiente, del grupo que consiste en hidroxialquilo, alcoxi, alquilo, halo, hidroxilo y –NO_2; y dicho cicloalquilo no

está sustituido o está sustituido con hidroxilo; o

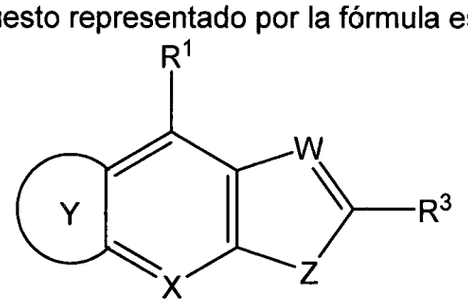
R^1 y R^2 junto con N al que cada uno está unido, forman un grupo heterocíclico seleccionado del grupo que consiste en  ,  ,  y  , en donde

Y es alcoxialquilo, hidroxialquilo, dialquilaminoalquilo o alquilo, también en donde

Y' es hidroxilo.

11. Un método de inducción de poliploides en células cancerosas que comprende las etapas de administrar primero a una célula cancerosa in vivo al menos un agente antimitótico seleccionado del grupo que consiste en un taxano, paclitaxel, docetaxel, un inhibidor de Cenp–E, abraxano, epotilona, monastrol, inhibidores de KSP que incluyen ispinesib SB–715992 (Cytokinetics) y compuestos representados por las fórmulas A–D mostradas en los puntos a–d que figuran más abajo:

a. Un compuesto representado por la fórmula estructural A:



fórmula A

o una de sus sales, solvatos o ésteres farmacéuticamente aceptables, en donde:

el anillo Y es un arilo de 5 ó 6 miembros o un heteroarilo de 5 ó 6 miembros fusionado tal como se indica en la fórmula A, en donde en dichos arilo y heteroarilo cada carbono del anillo sustituible está sustituido, de modo

independiente, con R^2 y cada nitrógeno del anillo sustituible está sustituido, de modo independiente, con R^6;

W es N o $C(R^{12})$;

X es N o N–óxido;

Z es S, S(=O) o $S(=O)_2$;

R^1 es H, alquilo, alcoxi, hidroxi, halo, –CN, $–S(O)_m–$alquilo, $–C(O)NR^9R^{10}$, $–(CR^9R^{10})_{1–6}OH$ o $–NR^4(CR^9R^{10})_{1–2}OR^9$;

cada R^2 está seleccionado, de modo independiente, del grupo que consiste en H, halo, alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo, heteroaralquilo, $–(CR^{10}R^{11})_{0–6}$ $–OR^7$, $–C(O)R^4$, $–C(S)R^4$, $–C(O)OR^7$, $–C(S)OR^7$, $–OC(O)R^7$, $–OC(S)R^7$, $–C(O)NR^4R^5$, $–C(S)NR^4R^5$, $–C(O)NR^4OR^7$, $–C(S)NR^4OR^7$, $–C(O)NR^7NR^4R^5$, $–C(S)NR^7NR^4R^5$, $–C(S)NR^4OR^7$, $–C(O)SR^7$, $–NR^4R^5$, $–NR^4C(O)R^5$, $–NR^4C(S)R^5$, $–NR^4C(O)OR^7$, $–NR^4C(S)OR^7$, $–OC(O)NR^4R^5$, $–OC(S)NR^4R^5$, $–NR^4C(O)NR^4R^5$, $–NR^4C(S)NR^4R^5$, $–NR^4C(O)NR^4OR^7$, $–NR^4C(S)NR^4OR^7$, $–(CR^{10}R^{11})_{0–6}SR^7$, SO_2R^7, $–S(O)_{1–2}NR^4R^5$, $–N(R^7)SO_2R^7$, $–S(O)_{1–2}NR^5OR^7$, –CN, $–OCF_3$, $–SCF_3$, $–C(=NR^7)NR^4$, $–C(O)NR^7(CH_2)_{1–10}NR^4R^5$, $–C(O)NR^7(CH_2)_{1–10}OR^7$, $–C(S)NR^7(CH_2)_{1–10}NR^4R^5$, $–C(S)NR^7(CH_2)_{1–10}OR^7$, haloalquilo y alquilsililo, en donde cada uno de dichos alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo o heteroaralquilo está opcionalmente sustituido, de modo independiente, con 1–5 restos R^9;

cada R^3 está seleccionado, de modo independiente, del grupo que consiste en H, halo, alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo, heteroaralquilo, $–(CR^{10}R^{11})_{0–6}$ $–OR^7$, $–C(O)R^4$, $–C(S)R^4$, $–C(O)OR^7$, $–C(S)OR^7$, $–OC(O)R^7$, $–OC(S)R^7$, $–C(O)NR^4R^5$, $–C(S)NR^4R^5$, $–C(O)NR^4OR^7$, $–C(S)NR^4OR^7$,

$-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, $-CN$, $-OCF_3$, $-SCF_3$, $-C(=NR^7)NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}OR^7$, $-C(S)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(S)NR^7(CH_2)_{1-10}OR^7$, haloalquilo y alquilsililo, en donde cada uno de dichos alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo o heteroaralquilo está opcionalmente sustituido, de modo independiente, con 1–5 restos R^9;

cada R^4 y R^5 está seleccionado, de modo independiente, del grupo que consiste en H, alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo, heteroaralquilo, $-OR^7$, $-C(O)R^7$ y $-C(O)OR^7$, en donde cada uno de dichos alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo o heteroaralquilo está opcionalmente sustituido con 1–4 restos R^8;

o R^4 y R^5, cuando están unidos al mismo átomo de nitrógeno, se toman opcionalmente juntos con el átomo de nitrógeno al que están unidos para formar un anillo heterocíclico de 3–6 miembros que tiene 0–2 heteroátomos adicionales seleccionados de N, O o S;

cada R^6 está seleccionado, de modo independiente, del grupo que consiste en H, alquilo, arilo, aralquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, heteroarilo, heteroaralquilo, $-(CH_2)_{1-6}CF_3$, $-C(O)R^7$, $-C(O)OR^7$ y $-SO_2R^7$;

cada R^7 está seleccionado, de modo independiente, del grupo que consiste en H, alquilo, arilo, aralquilo, cicloalquilo, cicloalquilalquilo,

heterociclilo, heterociclilalquilo, heteroarilo y heteroaralquilo, en donde cada miembro de R^7 excepto H está opcionalmente sustituido con 1–4 restos R^8;

cada R^8 está seleccionado, de modo independiente, del grupo que consiste en halo, alquilo, cicloalquilo, heterociclilo, arilo, heteroarilo, $-NO_2$, $-OR^{10}$, –(alquil C_1–C_6)–OR^{10}, –CN, $-NR^{10}R^{11}$, $-C(O)R^{10}$, $-C(O)OR^{10}$, $-C(O)NR^{10}R^{11}$, $-CF_3$, $-OCF_3$, $-CF_2CF_3$, $-C(=NOH)R^{10}$, $-N(R^{10})C(O)R^{11}$, $-C(=NR^{10})NR^{10}R^{11}$ y $-NR^{10}C(O)OR^{11}$, en donde cada uno de dichos alquilo, cicloalquilo, heterociclilo, arilo y heteroarilo está opcionalmente sustituido, de modo independiente, con 1–3 restos seleccionados del grupo que consiste en halo, alquilo, cicloalquilo, heterociclilo, arilo, heteroarilo, $-NO_2$, $-OR^{10}$, –(alquil C_1–C_6)–OR^{10}, –CN, $-NR^{10}R^{11}$, $-C(O)OR^{10}$, $-C(O)NR^{10}R^{11}$, $-CF^3$, $-OCF_3$, $-NR^{10}C(O)OR^{11}$ y $-NR^{10}C(O)R^{40}$;

o dos grupos R^8, cuando están unidos al mismo átomo de carbono, se toman opcionalmente juntos con el átomo de carbono al que están unidos para formar un grupo C=O o un grupo C=S;

cada R^9 está seleccionado, de modo independiente, del grupo que consiste en H, alquilo, alcoxi, OH, CN, halo, $-(CR^{10}R^{11})_{0-4}NR^4R^5$, haloalquilo, hidroxialquilo, alcoxialquilo, $-C(O)NR^4R^5$, $-C(O)OR^7$, $-OC(O)NR^4R^5$, $-NR^4C(O)R^5$ y $-NR^4C(O)NR^4R^5$;

cada R^{10} es, de modo independiente, H o alquilo; o R^9 y R^{10}, cuando están unidos al mismo átomo de nitrógeno, se toman opcionalmente juntos con el átomo de nitrógeno al que están unidos para formar un anillo heterocíclico de 3–6 miembros que tiene 0–2 heteroátomos adicionales seleccionados de N, O o S;

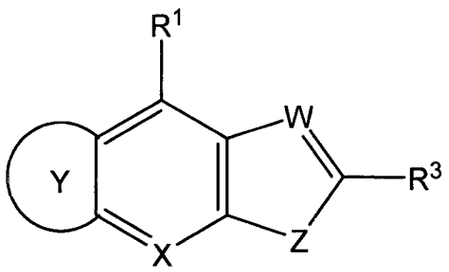
cada R^{11} es, de modo independiente, H o alquilo; o R^{10} y R^{11}, cuando están unidos al mismo átomo de nitrógeno, se toman opcionalmente juntos con el átomo de nitrógeno al que están unidos para

formar un anillo heterocíclico de 3–6 miembros que tiene 0–2 heteroátomos adicionales seleccionados de N, O o S;

cada R^{12} está seleccionado, de modo independiente, del grupo que consiste en H, halo, alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo, heteroaralquilo, $-(CR^{10}R^{11})_{0-6}-OR^7$, $-C(O)R^4$, $-C(S)R^4$, $-C(O)OR^7$, $-C(S)OR^7$, $-OC(O)R^7$, $-OC(S)R^7$, $-C(O)NR^4R^5$, $-C(S)NR^4R^5$, $-C(O)NR^4OR^7$, $-C(S)NR^4OR^7$, $-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, $-CN$, $-OCF_3$, $-SCF_3$, $-C(=NR^7)NR^4$, $-C(O)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}OR^7$, $-C(S)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(S)NR^7(CH_2)_{1-10}OR^7$, haloalquilo y alquilsililo, en donde cada uno de dichos alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo o heteroaralquilo está opcionalmente sustituido, de modo independiente, con 1–5 restos R^9; y

R^{40} está seleccionado del grupo que consiste en cicloalquilo, heterociclilo, arilo y heteroarilo, en donde cada uno de dichos cicloalquilo, heterociclilo, arilo y heteroarilo está opcionalmente sustituidos, de modo independiente, con 1–3 restos seleccionados, de modo independiente, del grupo que consiste en –CN, –OH, halo, alquilo, haloalquilo, alcoxi y $-NR^{10}R^{11}$;

b. Un compuesto representado por la fórmula estructural B:



fórmula B

o una de sus sales, solvatos o ésteres farmacéuticamente aceptables, en donde:

el anillo Y es un anillo de 5 a 7 miembros seleccionado del grupo que consiste en cicloalquilo, cicloalquenilo, heterociclilo o heterociclenilo fusionado tal como se indica en la fórmula B, en donde en cada uno de dichos anillos de 5 a 7 miembros, cada carbono del anillo sustituible está sustituido, de modo independiente, con 1–2 restos R^2 y cada heteroátomo del anillo sustituible está sustituido, de modo independiente, con R^6;

W es N o $C(R^{12})$;

X es N o N–óxido;

Z es S, S(=O) o $S(=O)_2$;

R^1 es H, alquilo, alcoxi, hidroxi, halo, –CN, $–S(O)_m–$alquilo, $–C(O)NR^9R^{10}$, $–(CR^9R^{10})_{1–6}OH$ o $–NR^4(CR^9R^{10})_{1–2}OR^9$; en donde m es 0 a 2;

cada R^2 está seleccionado, de modo independiente, del grupo que consiste en H, halo, alquilo, cicloalquilo, alquilsililo, cicloalquenilo, heterociclilo, heterociclenilo, arilo, heteroarilo, $–(CR^{10}R^{11})_{0–6}–OR^7$, $–C(O)R^4$, $–C(S)R^4$, $–C(O)OR^7$, $–C(S)OR^7$, $–OC(O)R^7$, $–OC(S)R^7$, $–C(O)NR^4R^5$, $–C(S)NR^4R^5$, $–C(O)NR^4OR^7$, $–C(S)NR^4OR^7$, $–C(O)NR^7NR^4R^5$, $–C(S)NR^7NR^4R^5$, $–C(S)NR^4OR^7$, $–C(O)SR^7$, $–NR^4R^5$, $–NR^4C(O)R^5$, $–NR^4C(S)R^5$, $–NR^4C(O)OR^7$, $–NR^4C(S)OR^7$, $–OC(O)NR^4R^5$, $–OC(S)NR^4R^5$, $–NR^4C(O)NR^4R^5$, $–NR^4C(S)NR^4R^5$, $–NR^4C(O)NR^4OR^7$, $–NR^4C(S)NR^4OR^7$, $–(CR^{10}R^{11})_{0–6}SR^7$, SO_2R^7, $–S(O)_{1–2}NR^4R^5$, $–N(R^7)SO_2R^7$, $–S(O)_{1–2}NR^5OR^7$, –CN, $–OCF_3$, $–SCF_3$, $–C(=NR^7)NR^4$, $–C(O)NR^7(CH_2)_{1–10}NR^4R^5$, $–C(O)NR^7(CH_2)_{1–10}OR^7$, $–C(S)NR^7(CH_2)_{1–10}NR^4R^5$ y

$-C(S)NR^7(CH_2)_{1-10}OR^7$, en donde cada uno de dichos alquilo, cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, arilo y heteroarilo está opcionalmente sustituido, de modo independiente, con 1–5 restos R^9;

o dos grupos R^2 en el mismo átomo de carbono se toman opcionalmente juntos con el átomo de carbono al que están unidos para formar un grupo C=O, un grupo C=S o un grupo etilendioxi;

R^3 está seleccionado, de modo independiente, del grupo que consiste en H, halo, alquilo, cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, arilo, heteroarilo, $-(CR^{10}R^{11})_{0-6}-OR^7$, $-C(O)R^4$, $-C(S)R^4$, $-C(O)OR^7$, $-C(S)OR^7$, $-OC(O)R^7$, $-OC(S)R^7$, $-C(O)NR^4R^5$, $-C(S)NR^4R^5$, $-C(O)NR^4OR^7$, $-C(S)NR^4OR^7$, $-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, $-CN$, $-C(=NR^7)NR^4R^5$, $-C(O)N(R^7)-(CR^{40}R^{41})_{1-5}-C(=NR^7)NR^4R^5$, $-C(O)N(R^7)(CR^{40}R^{41})_{1-5}-NR^4R^5$, $-C(O)N(R^7)(CR^{40}R^{41})_{1-5}-C(O)-NR^4R^5$, $-C(O)N(R^7)(CR^{40}R^{41})_{1-5}-OR^7$, $-C(S)NR^7(CH_2)_{1-5}NR^4R^5$ y $-C(S)NR^7(CH_2)_{1-5}OR^7$, en donde cada uno de dichos alquilo, cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, arilo y heteroarilo está opcionalmente sustituido, de modo independiente, con 1–5 restos R^9;

cada uno de R^4 y R^5 está seleccionado, de modo independiente, del grupo que consiste en H, alquilo, cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, arilo, heteroarilo, $-OR^7$, $-C(O)R^7$ y $-C(O)OR^7$, en donde cada uno de dichos alquilo, cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, arilo y heteroarilo, está opcionalmente sustituido con 1–4 restos R^8;

o R^4 y R^5, cuando están unidos al mismo átomo de nitrógeno, se toman opcionalmente juntos con el átomo de nitrógeno al que están unidos para formar

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un anillo heterocíclico de 3–6 miembros que tiene 0–2 heteroátomos adicionales seleccionados de N, O o S;

cada R^6 está seleccionado, de modo independiente, del grupo que consiste en H, alquilo, arilo, aralquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, heteroarilo, heteroaralquilo, $-(CH_2)_{1-6}CF_3$, $-C(O)R^7$, $-C(O)OR^7$ y $-SO_2R^7$;

cada R^7 está seleccionado, de modo independiente, del grupo que consiste en H, alquilo, arilo, aralquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, heteroarilo y heteroaralquilo, en donde cada miembro de R^7 excepto H está opcionalmente sustituido con 1–4 restos R^8;

cada R^8 está seleccionado, de modo independiente, del grupo que consiste en halo, alquilo, cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, arilo, heteroarilo, $-NO_2$, $-OR^{10}$, $-$(alquil C_1–C_6)$-OR^{10}$, $-CN$, $-NR^{10}R^{11}$, $-C(O)R^{10}$, $-C(O)OR^{10}$, $-C(O)NR^{10}R^{11}$, $-CF_3$, $-OCF_3$, $-CF_2CF_3$, $-C(=NOH)R^{10}$, $-N(R^{10})C(O)R^{11}$, $-C(=NR^{10})NR^{10}R^{11}$ y $-NR^{10}C(O)OR^{11}$; en donde cada uno de dichos alquilo, cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, arilo y heteroarilo está opcionalmente sustituido, de modo independiente, con 1–4 restos R^{42}; en donde cuando cada uno de dichos cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, arilo y heteroarilo contienen dos radicales en átomos de carbono adyacentes en cualquier parte dentro de dichos cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, arilo y heteroarilo, dichos radicales se pueden formar, opcional e independientemente en cualquier aparición, junto con los átomos de carbono a los que están unidos para formar un anillo carbocíclico o heterocíclico de cinco o seis miembros;

o dos grupos R^8, cuando están unidos al mismo carbono, se toman opcionalmente juntos con el átomo de carbono al que están unidos para formar un grupo C=O o un grupo C=S;

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cada R^9 está seleccionado, de modo independiente, del grupo que consiste en H, alquilo, alcoxi, OH, CN, halo, $-(CR^{10}R^{11})_{0-4}NR^4R^5$, haloalquilo, hidroxialquilo, alcoxialquilo, $-C(O)NR^4R^5$, $-C(O)OR^7$, $-OC(O)NR^4R^5$, $-NR^4C(O)R^5$ y $-NR^4C(O)NR^4R^5$;

cada R^{10} es, de modo independiente, H o alquilo; o R^9 y R^{10}, cuando están unidos al mismo átomo de nitrógeno, se toman opcionalmente juntos con el átomo de nitrógeno al que están unidos para formar un anillo heterocíclico de 3–6 miembros que tiene 0–2 heteroátomos adicionales seleccionados de N, O o S;

cada R^{11} es, de modo independiente, H, alquilo, cicloalquilo, cicloalquenilo, arilo, heterociclilo, heterociclenilo o heteroarilo; o R^{10} y R^{11}, cuando están unidos al mismo átomo de nitrógeno, se toman opcionalmente juntos con el átomo de nitrógeno al que están unidos para formar un anillo heterocíclico de 3–6 miembros que tiene 0–2 heteroátomos adicionales seleccionados de N, O o S; en donde cada uno de dicho R^{11} alquilo, cicloalquilo, cicloalquenilo, arilo, heterociclilo, heterociclenilo y heteroarilo está opcionalmente sustituido, de modo independiente, con 1–3 restos seleccionados del grupo que consiste en –CN, –OH, $-NH_2$, –N(H)alquilo, $-N(alquilo)_2$, halo, haloalquilo, CF_3, alquilo, hidroxialquilo, alcoxi, arilo, ariloxi y heteroarilo;

cada R^{12} está seleccionado, de modo independiente, del grupo que consiste en H, halo, alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo, heteroaralquilo, $-(CR^{10}R^{11})_{0-6}-OR^7$, $-C(O)R^4$, $-C(S)R^4$, $-C(O)OR^7$, $-C(S)OR^7$, $-OC(O)R^7$, $-OC(S)R^7$, $-C(O)NR^4R^5$, $-C(S)NR^4R^5$, $-C(O)NR^4OR^7$, $-C(S)NR^4OR^7$, $-C(O)NR^7NR^4R^5$, $-C(S)NR^7NR^4R^5$, $-C(S)NR^4OR^7$, $-C(O)SR^7$, $-NR^4R^5$, $-NR^4C(O)R^5$, $-NR^4C(S)R^5$, $-NR^4C(O)OR^7$, $-NR^4C(S)OR^7$, $-OC(O)NR^4R^5$, $-OC(S)NR^4R^5$, $-NR^4C(O)NR^4R^5$, $-NR^4C(S)NR^4R^5$, $-NR^4C(O)NR^4OR^7$, $-NR^4C(S)NR^4OR^7$, $-(CR^{10}R^{11})_{0-6}SR^7$, SO_2R^7, $-S(O)_{1-2}NR^4R^5$, $-N(R^7)SO_2R^7$, $-S(O)_{1-2}NR^5OR^7$, –CN, $-OCF_3$, $-SCF_3$, $-C(=NR^7)NR^4$,

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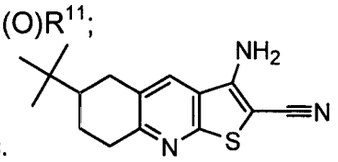
$-C(O)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(O)NR^7(CH_2)_{1-10}OR^7$, $-C(S)NR^7(CH_2)_{1-10}NR^4R^5$, $-C(S)NR^7(CH_2)_{1-10}OR^7$, haloalquilo y alquilsililo, en donde cada uno de dichos alquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, arilo, aralquilo, heteroarilo o heteroaralquilo está opcionalmente sustituido, de modo independiente, con 1–5 restos R^9;

R^{40} y R^{41} pueden ser iguales o diferentes, en donde cada uno está seleccionado, de modo independiente, del grupo que consiste en H, alquilo, arilo, heteroarilo, heterociclilo, heterociclenilo, cicloalquilo y cicloalquenilo;

cada R^{42} está seleccionado, de modo independiente, del grupo que consiste en halo, alquilo, cicloalquilo, heterociclilo, arilo, heteroarilo, $-NO_2$, $-OR^{10}$, –(alquil C_1–C_6)–OR^{10}, –CN, $-NR^{10}R^{11}$, $-C(O)R^{10}$, $-C(O)OR^{10}$, $-C(O)NR^{10}R^{11}$, $-CF_3$, $-OCF_3$, $-N(R^{10})C(O)R^{11}$ y $-NR^{10}C(O)OR^{11}$;

con la condición de que, cuando W es $C(R^{12})$, R^{12} y R^3 se tomen opcionalmente juntos con los dos átomos de carbono del anillo a los que están unidos para formar un anillo de 6 miembros seleccionado del grupo que consiste en cicloalquenilo, arilo, heteroarilo, heterociclilo y heterociclenilo, en donde dicho anillo de 6 miembros está opcionalmente sustituido con 1–3 restos seleccionados, de modo independiente, de oxo, tioxo, $-OR^{11}$, $-NR^{10}R^{11}$, $-C(O)R^{11}$, $-C(O)OR^{11}$, $-C(O)N(R^{10})(R^{11})$ o $-N(R^{10})C(O)R^{11}$;

c.

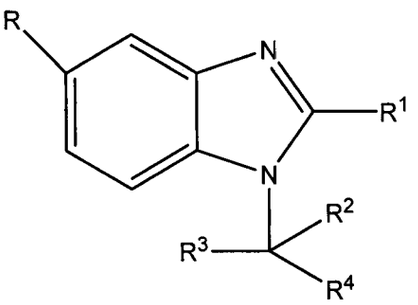


fórmula C

o una de sus sales, solvatos o ésteres farmacéuticamente aceptables; y

d. Un compuesto de la fórmula D

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fórmula D

o una de sus sales, solvatos o ésteres farmacéuticamente aceptables, en donde:

R está seleccionado del grupo que consiste en H, alquilo, ciano, haloalquilo, halo, —SH, –S–alquilo, –S–haloalquilo, $-S(=O)_2$alquilo, $-S(=O)_2OH$, $-S(=O)_2NH_2$, $-S(=O)_2NH$(alquilo), $S(=O)_2NH$(cicloalquilo), $-S(=O)_2N$(alquilo)$_2$, $-S(=O)_2$heterociclilo, $-S(=O)_2$heteroarilo, cicloalquilo, arilo, heterociclilo, heteroarilo, –NHC(=O)alquilo, $-C(=O)NH_2$, –C(=O)NH(alquilo), –C(=O)NH(cicloalquilo), $-C(=O)N$(alquilo)$_2$, –C(=O)OH, –C(=O)Oalquilo, –C(=O)heterociclilo, –C(=O)NH(arilo), en donde cuando cada uno de dichos cicloalquilo, arilo, heterociclilo, heteroarilo y las porciones de "heterociclilo" y "arilo" de dichos grupos R tiene dos sustituyentes en átomos de carbono adyacentes, dichos sustituyentes se pueden tomar opcionalmente juntos con los átomos de carbono a los que están unidos para formar un anillo cicloalquilo, arilo, heterociclilo, heterociclenilo o heteroarilo de cinco o seis miembros; en donde cada uno de los R antes mencionados alquilo, arilo, cicloalquilo, heterociclilo y heteroarilo y las porciones de "alquilo", "cicloalquilo", "heterociclilo" y "arilo" de dichos grupos R, opcionalmente con dichos anillo arilo, heterociclilo, heterociclenilo o heteroarilo de cinco o seis miembros, está opcionalmente sustituido con 1–3 sustituyentes seleccionados, de modo independiente, del grupo que consiste en alquilo, alquenilo, alquinilo,

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hidroxilo, ciano, halo, haloalquilo, haloalcoxi, –C(O)OH, –C(=O)Oalquilo y $–C(O)NH_2$;

R^1 está seleccionado del grupo que consiste en alquilo, heterociclilo, –C(=O)arilo, $–NH_2$, –NH(alquilo), –NH(cicloalquilo), –N(alquil)(cicloalquilo), –NH(heterociclilo), –N(alquil)(heterociclilo), $N(alquilo)_2$, –NH(arilo), –N(alquil)(arilo), $–N(arilo)_2$, –NH(heteroarilo), –N(alquil)(heteroarilo), –NHC(=O)–alquilo, –N(alquil)C(=O)–alquilo, –NHC(=O)Oalquilo, –N(alquil)C(=O)O–alquilo, en donde cada uno de los alquilo, heterociclilo antes mencionados y las porciones de "alquilo", "cicloalquilo", "arilo" y "heteroarilo" de dichos grupos R^1 está opcionalmente sustituido con 1–3 sustituyentes seleccionados, de modo independiente, del grupo que consiste en halo, heterociclilo, arilo, heteroarilo, haloalquilo, haloalcoxi, ariloxi, ciano, –SH, –S–alquilo, –S–haloalquilo, $–S(=O)_2$alquilo, $–S(=O)_2OH$, $–S(=O)_2NH_2$, $–S(=O)_2$NH(alquilo), $S(=O)_2$NH(cicloalquilo), $–S(=O)_2N(alquilo)_2$, $–S(=O)_2$heterociclilo, $–S(=O)_2$heteroarilo, hidroxi, alquilo, alquenilo, alquinilo, $–NH_2$, –NH(alquilo), $–N(alquilo)_2$, alcoxi, –NHC(=O)alquilo, –C(=O)H, –C(=O)alquilo, –C(=O)arilo, –C(=O)heteroarilo, –C(=O)Oalquilo, $–C(=O)NH_2$, –C(O)NHalquilo, $–C(=O)N(alquilo)_2$; en donde cuando cada uno de dichos heterociclilo, arilo y heteroarilo tiene dos sustituyentes en átomos de carbono adyacentes, dichos sustituyentes se pueden tomar opcionalmente juntos con los átomos de carbono a los que están unidos para formar un anillo arilo, heterociclilo, heterociclenilo o heteroarilo de cinco a seis miembros;

R^2 y R^3 son, de modo independiente, H o alquilo o $–C(R^2)(R^3)–$ está ausente;

R^4 está seleccionado del grupo que consiste en alquilo, cicloalquilo, heterociclilo, arilo y heteroarilo, en donde cuando cada uno de dichos

cicloalquilo, heterociclilo, arilo y heteroarilo tiene dos sustituyentes en átomos de carbono adyacentes, dichos sustituyentes se pueden tomar opcionalmente juntos con los átomos de carbono a los que están unidos para formar un anillo arilo, heterociclilo, heterociclenilo o heteroarilo de cinco a seis miembros; en donde cada uno de los R^4 antes mencionados alquilo, cicloalquilo, heterociclilo, arilo y heteroarilo, opcionalmente con dichos anillos arilo, heterociclilo, heterociclenilo o heteroarilo de cinco a seis miembros está opcionalmente sustituido con 1–3 sustituyentes seleccionados, de modo independiente, del grupo que consiste en ciano, halo, haloalquilo, alquilo, alcoxi, hidroxilo, haloalcoxi, cicloalquilo, heterociclilo, arilo, heteroarilo, $-S(=O)_2$alquilo, $-S(=O)_2NH_2$, $-S(=O)_2NH$(alquilo), $-S(=O)_2N$(alquilo)$_2$, –S–alquilo, –S–haloalquilo, –C(=O)OH, $-NH_2$, –NH(alquilo), $-N$(alquilo)$_2$ y –C(=O)Oalquilo;

posteriormente administrar a dicha célula cancerosa al menos un inhibidor de aurora quinasa, en donde dicho inhibidor de aurora quinasa está seleccionado del grupo que consiste en un compuesto representado por las fórmulas E–K mostrados más abajo en los puntos e–k:

e. Un compuesto representado por la fórmula estructural E:



fórmula E

o una de sus sales, solvatos, ésteres o profármacos farmacéuticamente aceptables, en donde:

R es H, CN, $-NR^5R^6$, cicloalquilo, cicloalquenilo, heterociclenilo, heteroarilo, $-C(O)NR^5R^6$, $-N(R^5)C(O)R^6$, heterociclilo, heteroarilo sustituido con $(CH_2)_{1-3}$ NR^5R^6, alquilo no sustituido o alquilo sustituido con uno o varios restos que

pueden ser iguales o diferentes donde cada resto está seleccionado, de modo independiente, del grupo que consiste en $-OR^5$, heterociclilo, $-N(R^5)C(O)N(R^5R^6)$, $-N(R^5)-C(O)OR^6$, $-(CH_2)_{1-3}-N(R^5R^6)$ y $-NR^5R^6$;

R^1 es H, halo, arilo o heteroarilo, en donde cada uno de dichos arilo y heteroarilo pueden no estar sustituidos o pueden estar sustituidos con uno o varios restos que pueden ser iguales o diferentes donde cada resto está seleccionado, de modo independiente, del grupo que consiste en halo, alquilo, alquenilo, alquinilo, cicloalquilo, arilo, heteroarilo, heterociclilo, $-CH_2OR^5$, $-C(O)NR^5R^6$, $-C(O)OH$, $-C(O)NH_2$, $-NR^5R^6$ (en donde R^5 y R^6, junto con el N de dicho $-NR^5R^6$, forman un anillo heterociclilo), $-S(O)R^5$, $-S(O_2)R^5$, $-CN$, $-CHO$, $-SR^5$, $-C(O)OR^5$, $-C(O)R^5$ y $-OR^5$;

R^2 es H, halo, arilo, arilalquilo o heteroarilo, en donde cada uno de dichos arilo, arilalquilo y heteroarilo puede no estar sustituido o puede estar opcionalmente sustituido, de modo independiente, con uno o varios restos que pueden ser iguales o diferentes donde cada resto está seleccionado, de modo independiente, del grupo que consiste en halo, amida, alquilo, alquenilo, alquinilo, cicloalquilo, arilo, $-C(O)OH$, $-C(O)NH_2$, $-NR^5R^6$ (en donde R^5 y R^6, junto con el N de dicho $-NR^5R^6$, forman un anillo heterociclilo), $-CN$, arilalquilo, $-CH_2OR^5$, $-S(O)R^5$, $-S(O_2)R^5$, $-CN$, $-CHO$, $-SR^5$, $-C(O)OR^5$, $-C(O)R^5$, heteroarilo y heterociclilo;

R^3 es H, alquilo, cicloalquilo, heterociclilo, arilo o heteroarilo, en donde:

– dicho alquilo mostrado con anterioridad para R^3 puede no estar sustituido o puede estar sustituido con uno o varios restos que pueden ser iguales o diferentes donde cada resto está seleccionado, de modo independiente, del grupo que consiste en $-OR^5$, alcoxi, heteroarilo y $-NR^5R^6$;

– dicho arilo mostrado con anterioridad para R^3 puede no estar sustituido o

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puede estar opcionalmente sustituido u opcionalmente fusionado, con halo, heteroarilo, heterociclilo, cicloalquilo o heteroarilalquilo, en donde cada uno de dichos heteroarilo, heterociclilo, cicloalquilo y heteroarilalquilo puede no estar sustituido o puede estar opcionalmente sustituido, de modo independiente, con uno o varios restos que pueden ser iguales o diferentes donde cada resto está seleccionado, de modo independiente, de alquilo, $-OR^5$, $-N(R^5R^6)$ y $-S(O_2)R^5$; y

– dicho heteroarilo mostrado con anterioridad para R^3 puede no estar sustituido o puede estar opcionalmente sustituido u opcionalmente fusionado con uno o varios restos que pueden ser iguales o diferentes con donde cada resto está seleccionado, de modo independiente, del grupo que consiste en halo, amino, alcoxicarbonilo, $-OR^5$, alquilo, –CHO, – NR^5R^6, $-S(O_2)N(R^5R^6)$, $-C(O)N(R^5R^6)$, $-SR^5$, alquenilo, alquinilo, cicloalquilo, arilo, heteroarilo, heterociclenilo, y heterociclilo;

R^5 es H, alquilo, aminoalquilo, arilo, heteroarilo, heterociclilo o cicloalquilo; y

R^6 es H, alquilo, arilo, arilalquilo, heteroarilo, heterociclilo o cicloalquilo;

también en donde en cualquier $-NR^5R^6$ en la fórmula I, dichos R^5 y R^6 pueden estar opcionalmente unidos junto con el N de dicho $-NR^5R^6$ para formar un anillo cíclico;

f. Un compuesto representado por la fórmula estructural:



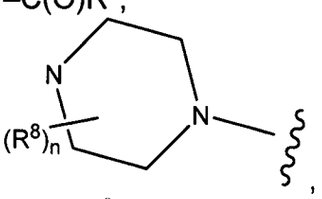
fórmula F

o una de sus sales, solvatos, ésteres o profármacos farmacéuticamente

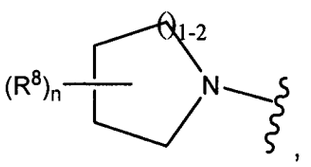
aceptables, en donde:

R está seleccionado del grupo que consiste en H, halógeno, arilo, heteroarilo, cicloalquilo, arilalquilo, heterociclilo, heterociclilalquilo, alquenilo, alquinilo,

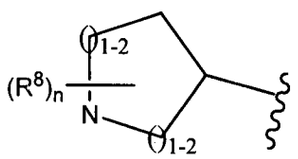
$-C(O)R^7$,



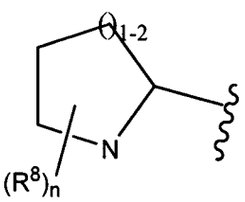
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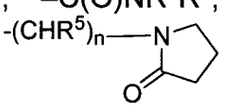
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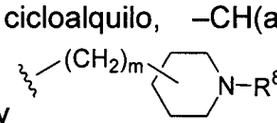


en donde cada uno de dichos arilo, heteroarilo, cicloalquilo, arilalquilo, alquenilo, heterociclilo y los restos de heterociclilo cuyas estructuras se muestran inmediatamente antes para R pueden no estar sustituidas o pueden estar opcionalmente sustituidas, de modo independiente, con uno o varios restos que pueden ser iguales o diferentes, donde cada resto está seleccionado, de modo independiente, del grupo que consiste en halógeno, alquilo, cicloalquilo, CF_3, CN, $-OCF_3$, $-OR^6$, $-C(O)R^7$, $-NR^5R^6$, $-C(O_2)R^6$, $-C(O)NR^5R^6$, $-(CHR^5)_nOR^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^6$;

R^1 es H, halógeno o alquilo;

R^2 es alquilo;

R^3 está seleccionado del grupo que consiste en H, arilo, heteroarilo, heterociclilo, $-(CHR^5)_n$–arilo, – $(CHR^5)_n$–heteroarilo, $-(CHR^5)_n-OR^6$, $-S(O_2)R^6$, $-C(O)R^6$, $-S(O_2)NR^5R^6$, $-C(O)OR^6$, $-C(O)NR^5R^6$, cicloalquilo, $-CH(arilo)_2$, $-(CH_2)_m-NR^8$, $-(CHR^5)_n-CH(arilo)_2$, 

y 

, en donde cada uno de dichos arilo, heteroarilo y heterociclilo puede estar sustituido u opcionalmente sustituido con uno o varios restos que pueden ser iguales o

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diferentes, donde cada resto está seleccionado, de modo independiente, del grupo que consiste en halógeno, alquilo, arilo, cicloalquilo, CF_3, CN, $-OCF_3$, $-OR^5$, $-NR^5R^6$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^6$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^6$;

R^5 es H o alquilo;

R^6 está seleccionado del grupo que consiste en H, alquilo, arilo, heteroarilo, arilalquilo y heteroarilalquilo, en donde cada uno de dichos alquilo, heteroarilalquilo, arilo, heteroarilo y arilalquilo puede no estar sustituido o puede estar opcionalmente sustituido con uno o varios restos que pueden ser iguales o diferentes, donde cada resto está seleccionado, de modo independiente, del grupo que consiste en halógeno, alquilo, arilo, cicloalquilo, CF_3, OCF_3, CN, $-OR^5$, $-NR^5R^6$, $-CH_2OR^5$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^6$;

R^7 está seleccionado del grupo que consiste en alquilo, arilo, heteroarilo, arilalquilo y heteroarilalquilo, en donde cada uno de dichos alquilo, heteroarilalquilo, arilo, heteroarilo y arilalquilo puede no estar sustituido o puede estar opcionalmente sustituido con uno o varios restos que pueden ser iguales o diferentes, donde cada resto está seleccionado, de modo independiente, del grupo que consiste en halógeno, alquilo, arilo, cicloalquilo, CF_3, OCF_3, CN, $-OR^5$, $-NR^5R^6$, $-CH_2OR^5$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^6$;

R^8 está seleccionado del grupo que consiste en R^6, $-C(O)NR^5R^6$, $-S(O_2)NR^5R^6$, $-C(O)R^7$, $-C(O_2)R^6$, $-S(O_2)R^7$ y $-(CH_2)$–arilo;

R^9 está seleccionado del grupo que consiste en halógeno, CN, NR^5R^6, $-C(O_2)R^6$, $-C(O)NR^5R^6$, $-OR^6$, $-C(O)R^7$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^6$;

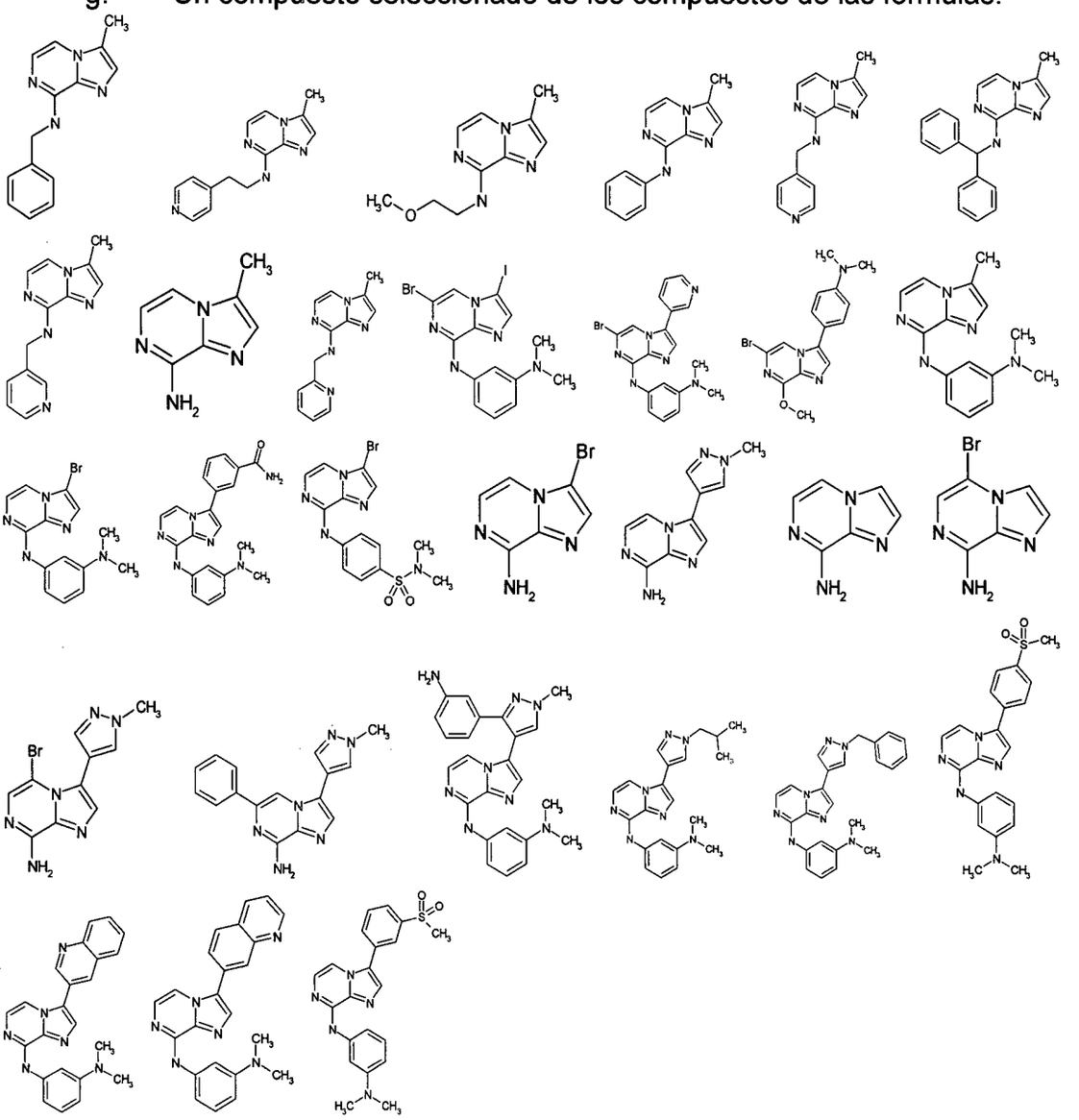
m es 0 a 4;

1121

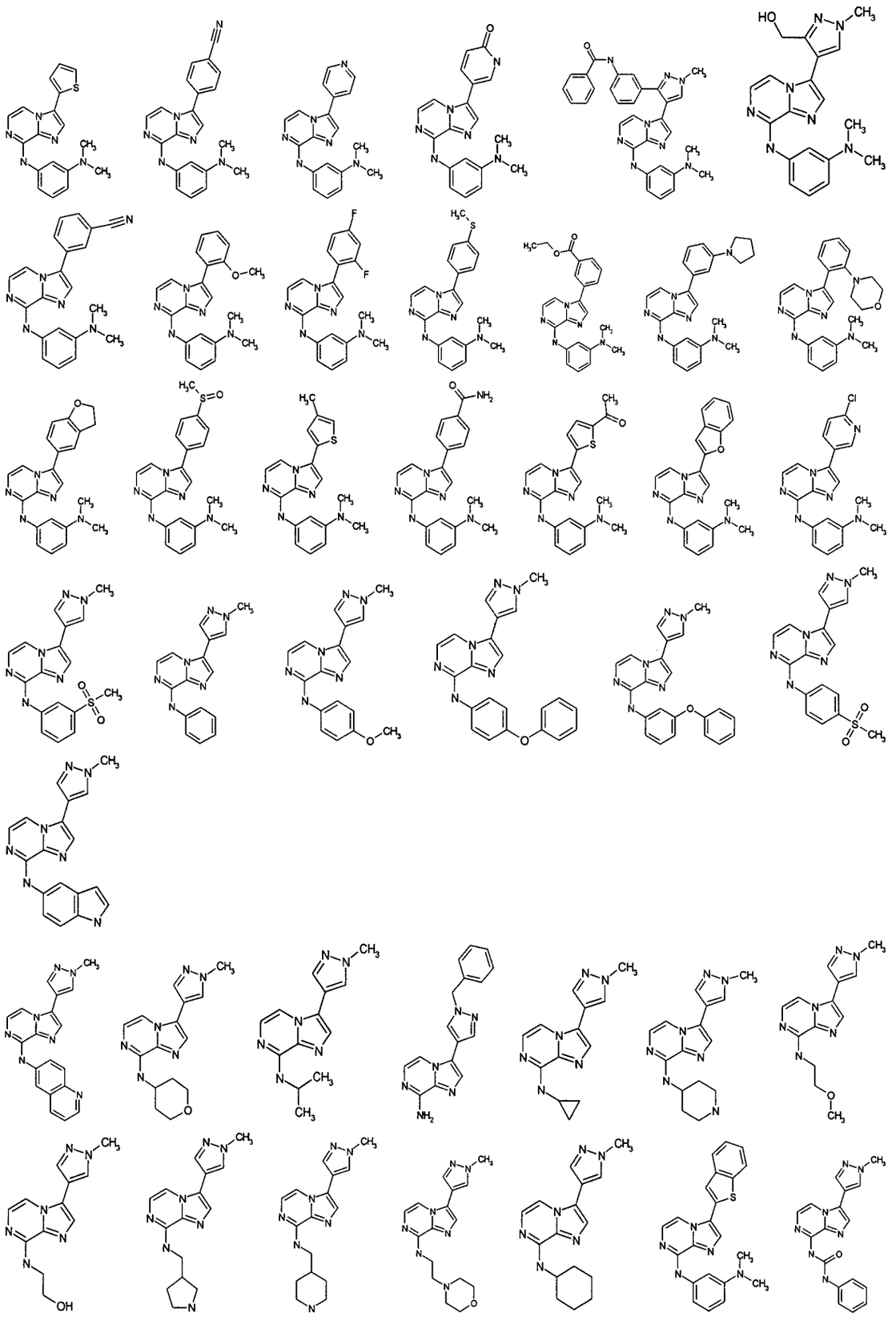
n es 1–4; y

p es 0–3;

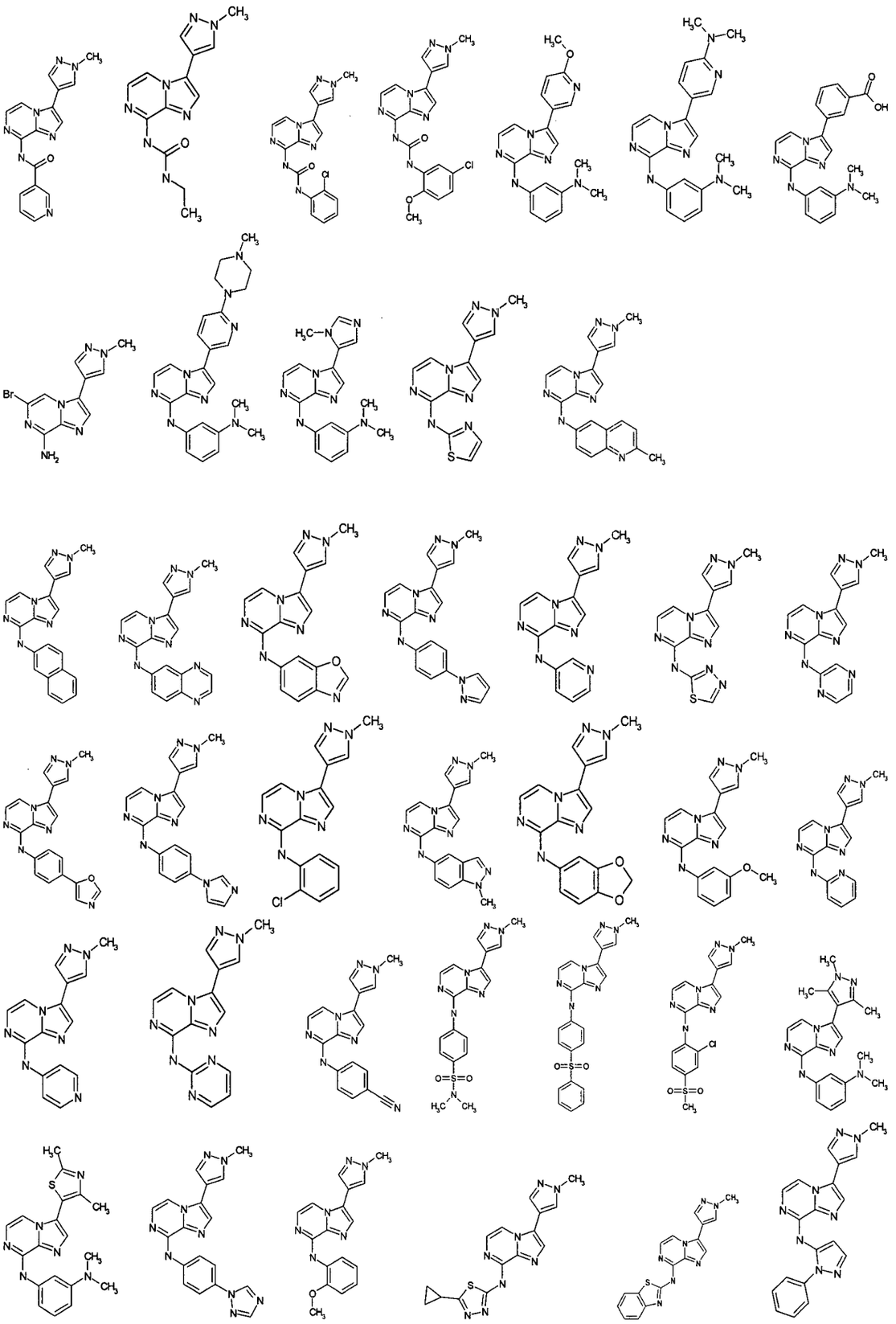
g. Un compuesto seleccionado de los compuestos de las fórmulas:



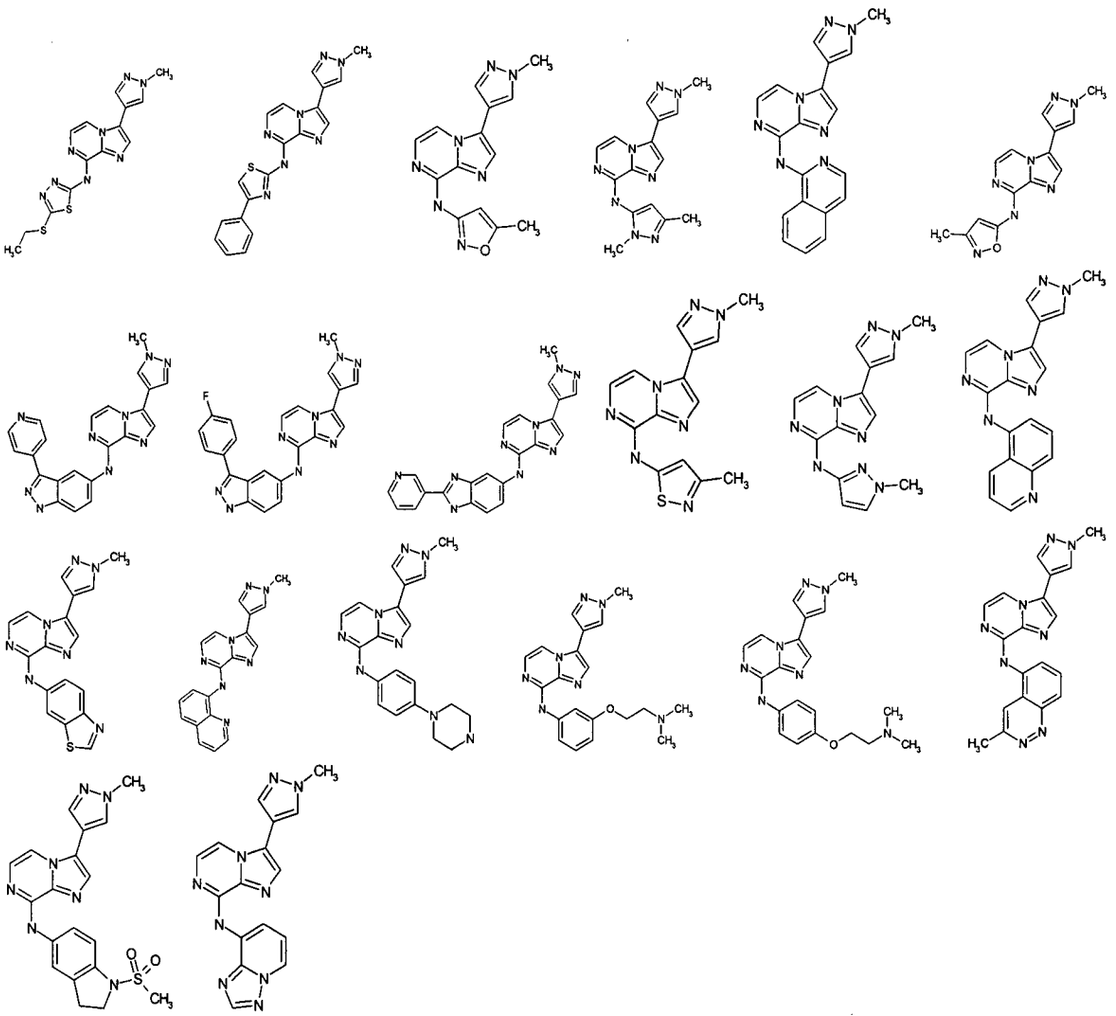
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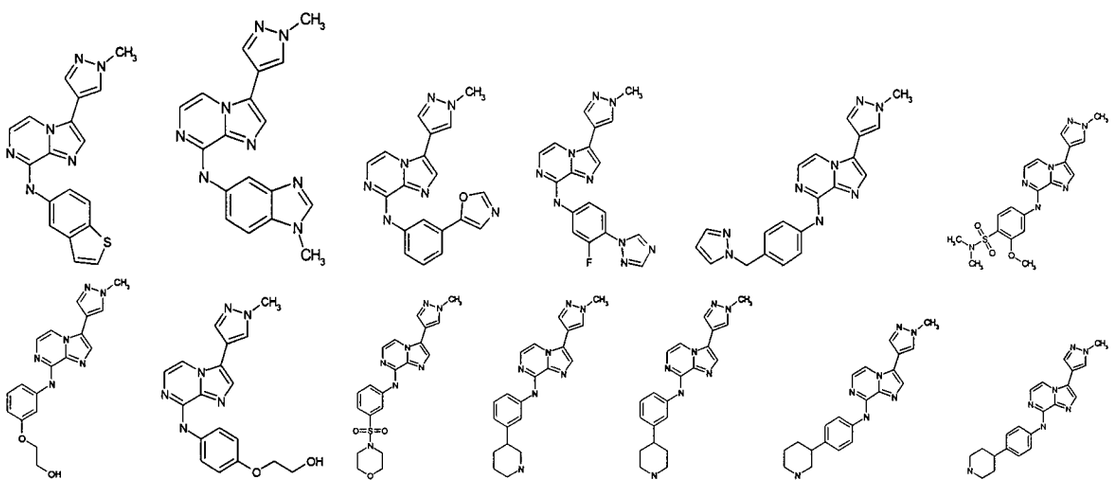


1193

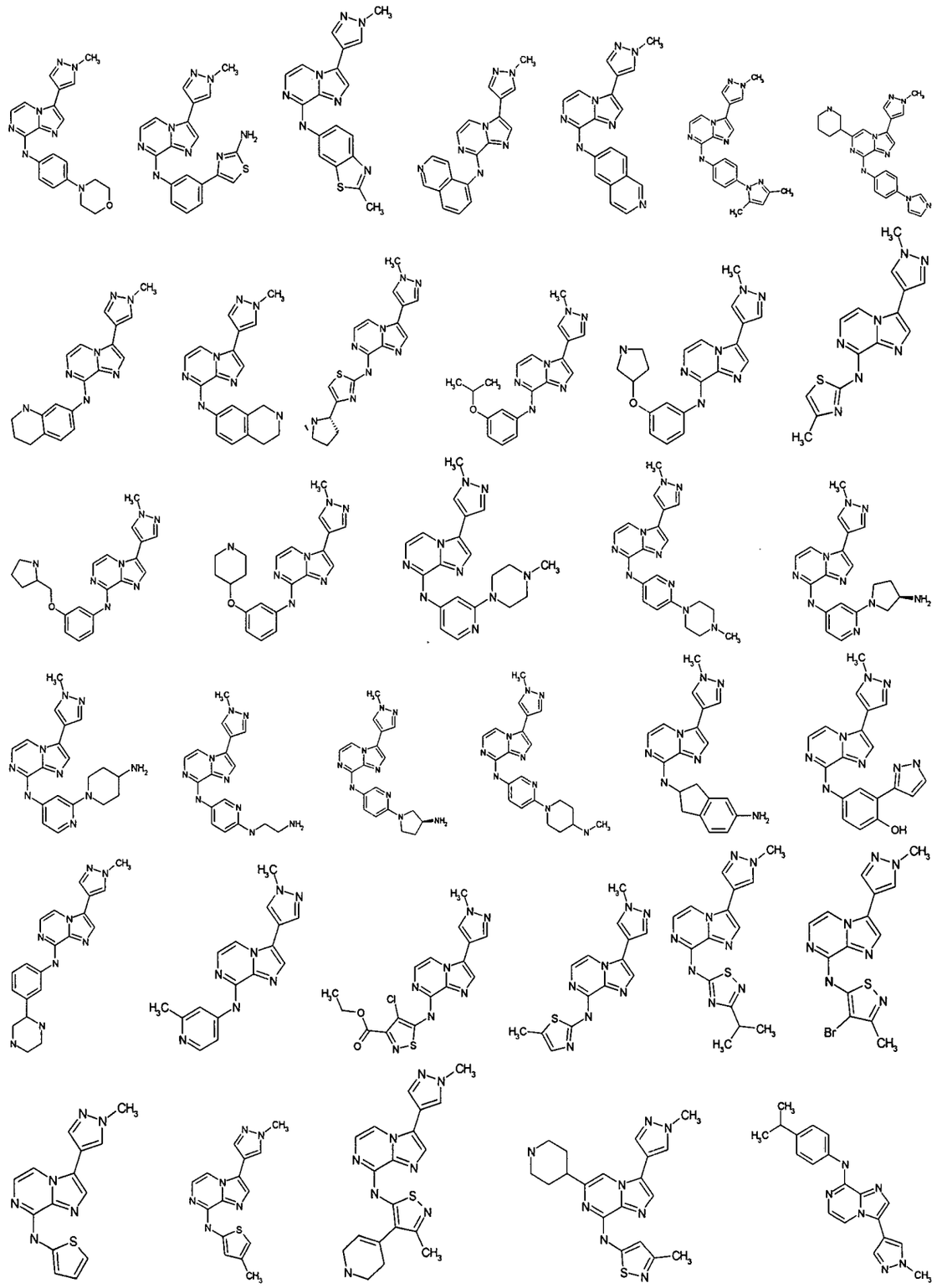


1194

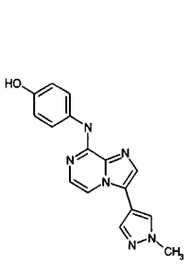
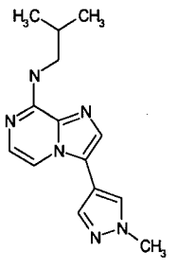
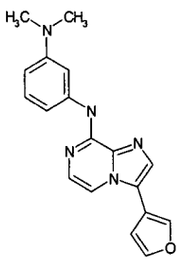
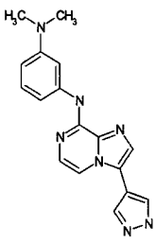
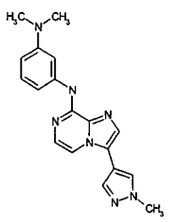
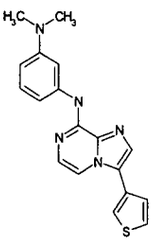
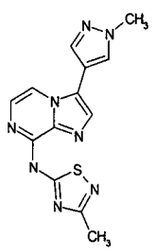
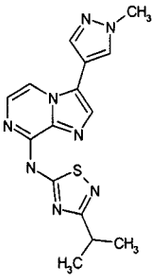
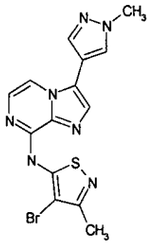
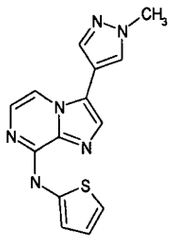
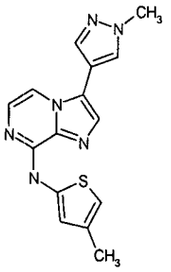
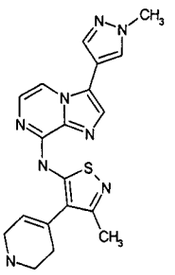
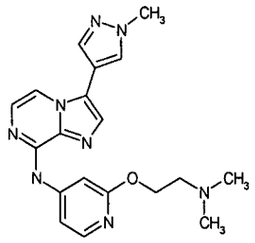
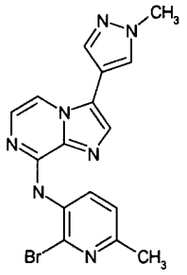
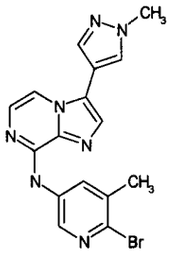
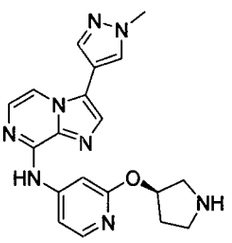
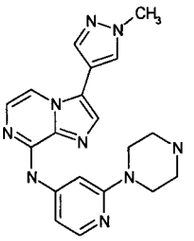
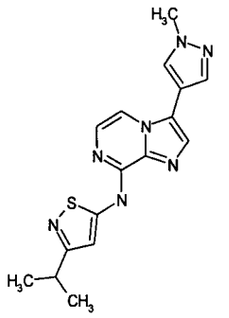
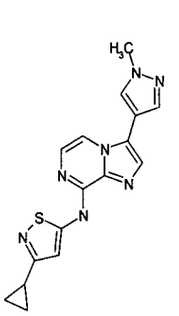
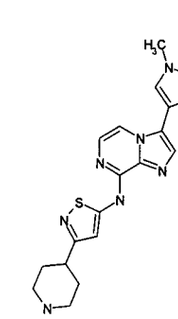
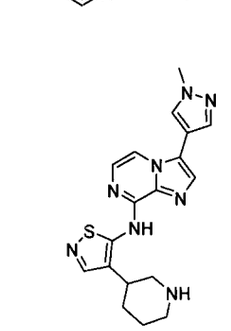
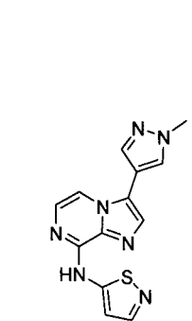
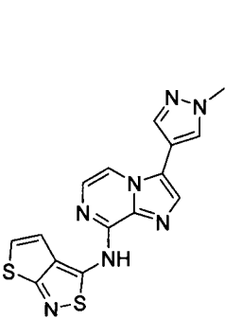
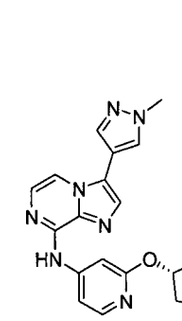
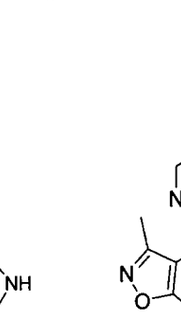
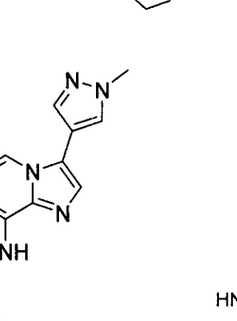
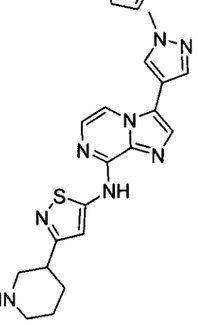


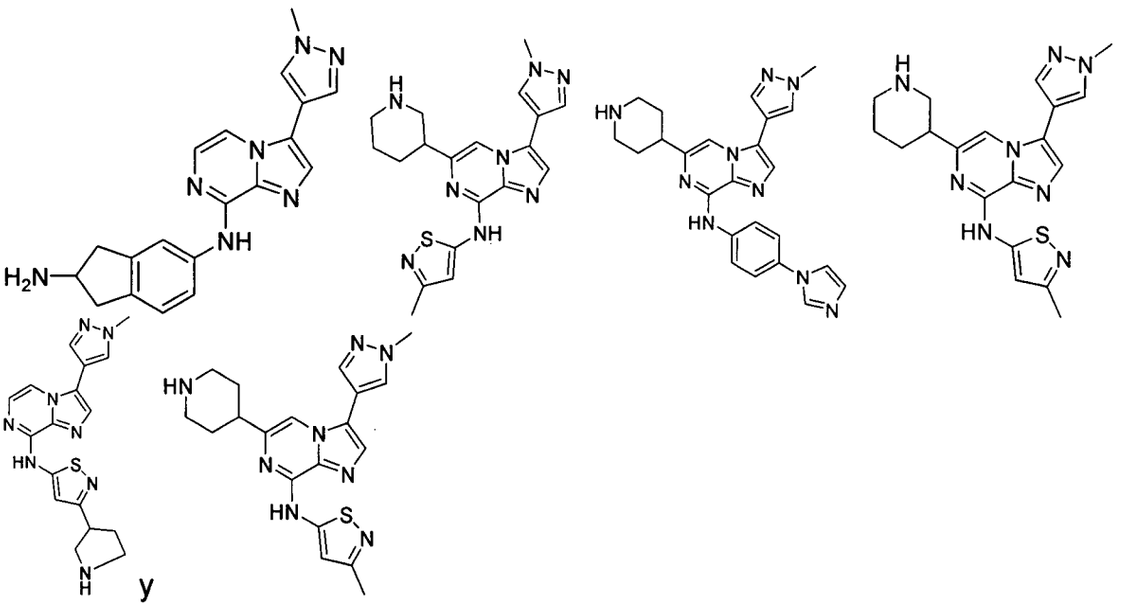


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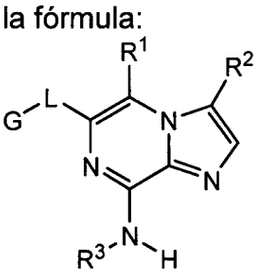






























y

o una de sus sales, solvatos, ésteres o profármacos farmacéuticamente aceptables;

h. Un compuesto de la fórmula:



fórmula H

o una de sus sales, solvatos, ésteres o profármacos farmacéuticamente aceptables, en donde:

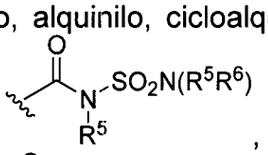
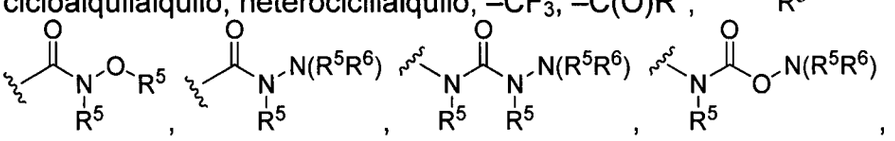
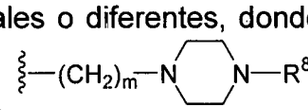
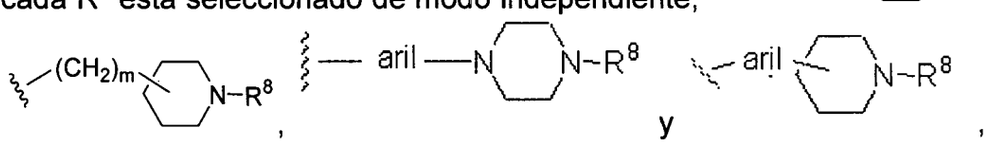
L está seleccionado del grupo que consiste en S, S(O) y $S(O_2)$;

G es alquilo, alquenilo, cicloalquilo, cicloalquenilo, arilo, heteroarilo, heterociclenilo o heterociclilo, en donde cada uno de dichos alquilo, alquenilo, cicloalquilo, cicloalquenilo, arilo, heteroarilo, heterociclenilo o heterociclilo puede no estar sustituido o puede estar opcionalmente sustituido, de modo independiente, con uno o varios restos que están seleccionados, de modo independiente, del grupo que consiste en $-OR^5$, halo, $-CN$, $-C(O)NR^5R^6$, $-N(H)-C(O)R^5$,$-N(H)-C(O)-NR^5R^6$, $-S(O_2)NR^5R^6$, $-NR^5R^6$, $-C(O)R^5$,

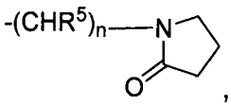
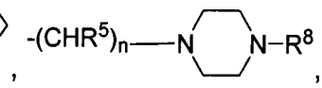
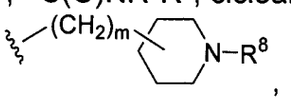
1108

$-C(O_2)R^5$, $-SR^5$, $-S(O)R^5$, $-S(O_2)R^5$;

R^1 es H, halo, alquilo, arilo o heteroarilo, en donde cada uno de dichos alquilo, arilo y heteroarilo puede no estar sustituido o puede estar sustituido con uno o varios restos que pueden ser iguales o diferentes donde cada resto está seleccionado, de modo independiente, del grupo que consiste en halo, alquilo, alquenilo, alquinilo, cicloalquilo, arilo, heteroarilo, heterociclilo, $-C(O)NR^5R^6$ y $-OR^5$;

R^2 está seleccionado del grupo que consiste en H, R^9, alquilo, arilo, arilalquilo, heteroarilo, heteroarilalquilo, heterociclilo, alquenilo, alquinilo, cicloalquilo, cicloalquilalquilo, heterociclilalquilo, $-CF_3$, $-C(O)R^7$,  ,  , alquilo sustituido con 1–6 R^9 que pueden ser iguales o diferentes, donde cada R^9 está seleccionado de modo independiente,  ,  , en donde cada uno de dichos arilo, heteroarilo, cicloalquilo, arilalquilo y heterociclilo antes mencionados puede no estar sustituido o puede estar opcionalmente sustituido, de modo independiente, con uno o varios restos que pueden ser iguales o diferentes, donde cada resto está seleccionado, de modo independiente, del grupo que consiste en halo, alquilo, alquenilo, alquinilo, cicloalquilo, arilo, heteroarilo, heterociclilo, CF_3, CN, $-OCF_3$, $-OR^6$, $-C(O)R^7$, $-NR^5R^6$, $-C(O_2)R^6$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^6$;

R^3 está seleccionado del grupo que consiste en H, alquilo, arilo, heteroarilo, heterociclilo, aralquilo, heteroarilalquilo, cicloalquilalquilo, heterociclilalquilo,



, $-(CHR^5)_n-OR^6$, $-S(O_2)R^6$, $-C(O)R^6$, $-S(O_2)NR^5R^6$, $-C(O)OR^6$, $-C(O)NR^5R^6$, cicloalquilo, $-CH(arilo)_2$, $-CH(heteroarilo)_2$, $-(CH_2)_m-NR^8$ y  , en donde cada uno de dichos alquilo, arilo, heteroarilo y heterociclilo puede estar sustituido u opcionalmente sustituido con uno o varios restos que pueden ser iguales o diferentes, donde cada resto está seleccionado, de modo independiente, del grupo que consiste en halo, alquilo, arilo, cicloalquilo, CF_3, CN, $-OCF_3$, $-OR^5$, $-NR^5R^6$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^6$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^6$;

R^5 es H, alquilo, arilo, heteroarilo, heterociclilo o cicloalquilo; y

R^6 está seleccionado del grupo que consiste en H, alquilo, arilo, heteroarilo, arilalquilo y heteroarilalquilo, en donde cada uno de dichos alquilo, heteroarilalquilo, arilo, heteroarilo y arilalquilo puede no estar sustituido o puede estar opcionalmente sustituido con uno o varios restos que pueden ser iguales o diferentes, donde cada resto está seleccionado, de modo independiente, del grupo que consiste en halógeno, alquilo, arilo, cicloalquilo, CF_3, OCF_3, CN, $-OR^5$, $-NR^5R^6$, $-CH_2OR^5$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^6$;

R^7 está seleccionado del grupo que consiste en alquilo, arilo, heteroarilo, arilalquilo y heteroarilalquilo, en donde cada uno de dichos alquilo, heteroarilalquilo, arilo, heteroarilo y arilalquilo puede no estar sustituido o puede estar opcionalmente sustituido con uno o varios restos que pueden ser iguales o diferentes, donde cada resto está seleccionado, de modo independiente, del grupo que consiste en halógeno, alquilo, arilo, cicloalquilo, CF_3, OCF_3, CN, $-OR^5$, $-NR^5R^6$, $-CH_2OR^5$, $-C(O_2)R^5$,

1200

$-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^6$;

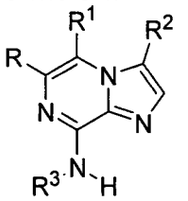
R^8 está seleccionado del grupo que consiste en R^6, $-C(O)NR^5R^6$, $-S(O_2)NR^5R^6$, $-C(O)R^7$, $-C(O_2)R^6$, $-S(O_2)R^7$ y $-(CH_2)$–arilo;

R^9 está seleccionado del grupo que consiste en halógeno, CN, NR^5R^6, $-C(O_2)R^6$, $-C(O)NR^5R^6$, $-OR^6$, $-C(O)R^7$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^6$;

m es 0 a 4; y

p es 0–3;

i. Un compuesto de la fórmula I:



fórmula I

o una de sus sales, solvatos, ésteres o profármacos farmacéuticamente aceptables, en donde:

R es H, CN, $-NR^5R^6$, cicloalquilo, cicloalquenilo, heterociclenilo, heteroarilo, $-C(O)NR^5R^6$, $-N(R^5)C(O)R^6$, heterociclilo, heteroarilo sustituido con $(CH_2)_{1-3}NR^5R^6$, alquilo no sustituido o alquilo sustituido con uno o varios restos que pueden ser iguales o diferentes donde cada resto está seleccionado, de modo independiente, del grupo que consiste en $-OR^5$, heterociclilo, $-N(R^5)C(O)N(R^5R^6)$, $-N(R^5)$–$C(O)OR^6$, $-(CH_2)_{1-3}$–$N(R^5R^6)$ y $-NR^5R^6$;

R^1 es H, halo, arilo o heteroarilo, en donde cada uno de dichos arilo y heteroarilo pueden no estar sustituidos o pueden estar sustituidos con uno o varios restos que pueden ser iguales o diferentes donde cada resto está seleccionado, de modo independiente, del grupo que consiste en halo, alquilo, alquenilo, alquinilo, cicloalquilo, arilo, heteroarilo, heterociclilo,

(201)

$-CH_2OR^5$, $-C(O)NR^5R^6$, $-C(O)OH$, $-C(O)NH_2$, $-NR^5R^6$ (en donde R^5 y R^6, junto con el N de dicho $-NR^5R^6$, forman un anillo heterociclilo), $-S(O)R^5$, $-S(O_2)R^5$, $-CN$, $-CHO$, $-SR^5$, $-C(O)OR^5$, $-C(O)R^5$ y $-OR^5$;

R^2 es H, halo, arilo, arilalquilo o heteroarilo, en donde cada uno de dichos arilo, arilalquilo y heteroarilo puede no estar sustituido o puede estar opcionalmente sustituido, de modo independiente, con uno o varios restos que pueden ser iguales o diferentes donde cada resto está seleccionado, de modo independiente, del grupo que consiste en halo, amida, alquilo, alquenilo, alquinilo, cicloalquilo, arilo, $-C(O)OH$, $-C(O)NH_2$, $-NR^5R^6$ (en donde R^5 y R^6, junto con el N de dicho $-NR^5R^6$, forman un anillo heterociclilo), $-CN$, arilalquilo, $-CH_2OR^5$, $-S(O)R^5$, $-S(O_2)R^5$, $-CN$, $-CHO$, $-SR^5$, $-C(O)OR^5$, $-C(O)R^5$, heteroarilo y heterociclilo;

R^3 es heterociclil–$(CR^7R^8)_n$–X, heterociclenil–$(CR^7R^8)_n$–X, heteroaril–$(CR^7R^8)_n$–X o aril–$(CR^7R^8)_n$–X, en donde cada uno de los restos de heterociclilo, heterociclenilo, heteroarilo o arilo de dicho R^3 puede no estar sustituido o puede estar sustituido con uno o varios restos seleccionados, de modo independiente, del grupo que consiste en $-CONR^5R^6$, $-OR^5$ y alquilo,

n es 1–6,

X está seleccionado del grupo que consiste en $-NR^5R^6$, $-OR^5$, $-SO-R^5$ y $-SR^5$,

R^7 y R^8 son cada uno, de modo independiente, hidrógeno o alquilo;

R^5 está seleccionado del grupo que consiste en hidrógeno, alquilo, alquenilo, alcoxialquilo, –alquil–S–alquilo, aminoalquilo, arilo, heteroarilo, heterociclenilo, heterocicloalquilo, cicloalquilo, cicloalquenilo, heterociclilalcoxilo, –S–alquilheterociclilo, heterociclilo, heterociclenilo, alquilN(alquilo)$_2$, alquilNH(alquilo), alquilN(alquenilo)$_2$, –alquilN(alcoxilo)$_2$, –alquil–SH y hidroxialquilo, en

1202

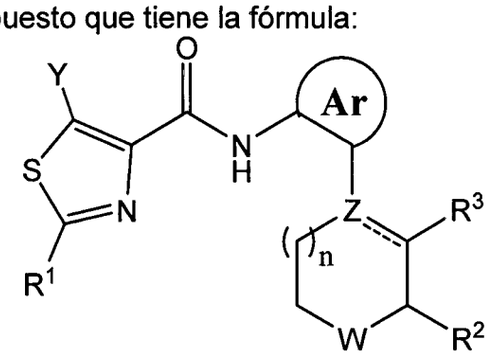
donde cada uno de dichos arilo, heteroarilo, heterociclenilo, heterocicloalquilo, cicloalquilo, cicloalquenilo, heterociclilalcoxilo, –S–alquilheterociclilo, heterociclilo, heterociclenilo puede no estar sustituido o puede estar sustituido con uno o varios restos seleccionados, de modo independiente, del grupo que consiste en alquilo, alquilo, alquenilo, arilo, cicloalquenilo, cicloalquilo, arilalquilo, cicloalquenilalquilo, cicloalquilalquilo, heteroarilo, heterociclenilo, heterociclilo, heteroarilalquilo, heterociclenilalquilo, heterocicloalquilalquilo, alcoxialquilo, –alquil–S–alquilo, –alquilSH, alcoxilo, –S–alquilo, hidroxialquilo y aminoalquilo;

R^6 está seleccionado del grupo que consiste en hidrógeno, alquilo, alquenilo, arilo, cicloalquenilo, cicloalquilo, arilalquilo, cicloalquenilalquilo, cicloalquilalquilo, heteroarilo, heterociclenilo, heterociclilo, heteroarilalquilo, heterociclenilalquilo, heterocicloalquilalquilo, alcoxialquilo, –alquil–S–alquilo, –alquilSH, alcoxilo, –S–alquilo, hidroxialquilo y aminoalquilo, en donde cada uno de dichos arilo, cicloalquenilo, cicloalquilo, arilalquilo, cicloalquenilalquilo, cicloalquilalquilo, heteroarilo, heterociclenilo, heterociclilo, heteroarilalquilo, heterociclenilalquilo, heterocicloalquilalquilo puede no estar sustituido o puede estar sustituido con uno o varios restos seleccionados, de modo independiente, del grupo que consiste en alquilo, alquilo, alquenilo, arilo, cicloalquenilo, cicloalquilo, arilalquilo, cicloalquenilalquilo, cicloalquilalquilo, heteroarilo, heterociclenilo, heterociclilo, heteroarilalquilo, heterociclenilalquilo, heterocicloalquilalquilo, alcoxialquilo, –alquil–S–alquilo, –alquilSH, alcoxilo, –S–alquilo, hidroxialquilo y aminoalquilo;

1203

también en donde en cualquier $-NR^5R^6$ en la fórmula I, dichos R^5 y R^6 pueden estar opcionalmente unidos junto con el N de dicho $-NR^5R^6$ para formar un anillo cíclico o anillo cíclico en puente, en donde cada uno de dicho anillo cíclico o anillo cíclico en puente, pueden no estar sustituidos o pueden estar sustituidos con uno o varios restos, que pueden ser iguales o diferentes seleccionados, de modo independiente, del grupo que consiste en hidroxilo, –SH, alquilo, alquenilo, hidroxialquilo, –alquil–SH, alcoxilo, –S–alquilo, $–CO_2–$alquilo, $–CO_2–$alquenilo, arilalquilo, cicloalquenilalquilo, cicloalquilalquilo, heteroarilalquilo, heterociclenilalquilo, heterocicloalquilalquilo, heteroarilo, arilo, cicloalquenilo, cicloalquilo, espiroheterociclilo, espiroheterociclenilo, espiroheteroarilo, espirociclilo, espirociclenilo, espiroarilo, alcoxialquilo, –alquil–S–alquilo, heterociclilo y heterociclenilo;

j. Un compuesto que tiene la fórmula:



(J)

o una de sus sales, solvatos, ésteres, prodrogas o estereoisómeros farmacéuticamente aceptables, en donde las líneas punteadas indican un enlace opcional y adicional y en donde:

R^1 es heteroarilo con contenido de nitrógeno, heterociclilo con contenido de nitrógeno, heteroarilo benzofusionado con contenido de nitrógeno o heterociclilo benzofusionado con contenido de nitrógeno, en donde R^1 está unido con el resto

1204

del compuesto de la fórmula (I) a través de un átomo de nitrógeno del anillo y en donde uno o varios átomos de carbono del anillo de un grupo heteroarilo con contenido de nitrógeno, heterociclilo con contenido de nitrógeno, heteroarilo benzofusionado con contenido de nitrógeno o heterociclilo benzofusionado con contenido de nitrógeno puede estar sustituido con hasta 5 sustituyentes, que pueden ser iguales o diferentes y están seleccionados, de modo independiente, de alquilo, arilo, halo, –OH, –O–alquilo, –O–arilo, $-N(R^8)_2$, $-CF_3$, $-NO_2$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)N(R^8)_2$, $-OC(O)R^8$ o $-NHC(O)R^8$;

R^2 es –H, –alquilo, $-NH_2$ o $-CH_2NH_2$;

R^3 es –H, –alquilo, $-NH_2$ o $-CH_2NH_2$;

cada aparición de R^4 es, de modo independiente, –H, –alquilo, $-NH_2$, –OH, –alquilen–OH, $-CH_2NH_2$, $-C(O)R^5$, $-C(O)NH_2$, –C(O)NH–alquilo, $-C(O)N(alquilo)_2$, $-NHC(O)R^6$ o $-NHS(O)_2R^6$;

R^5 es –H, –alquilo, –arilo, –heteroarilo, –NHOH;

R^6 es –H, –alquilo o $-CF_3$;

R^7 es –H, –OH, –alquilo C_1–C_6, –O–(alquilo C_1–C_6) o $-CF_3$;

R^8 es –H, alquilo, arilo, heterociclilo, heteroarilo o cicloalquilo;

Ar es –arileno– o –heteroarileno–, en donde el arileno o heteroarileno está unido a través de 2 de sus átomos de carbono del anillo adyacentes y en donde el –arileno– o –heteroarileno– pueden estar sustituidos con hasta 4 sustituyentes, que pueden ser iguales o diferentes y están seleccionados, de modo independiente, de –halo, alquilo, alcoxi, ariloxi, $-SR^8$, $-S(O)R^8$, $-S(O)_2R^8$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)N(R^8)_2$, $-NHC(O)R^8$, $-CF_3$, –CN o NO_2 y de modo tal que, cuando Ar es tetrahidronaftileno, R^1 y R^2 no puedan ser ambos hidrógeno

W es –NH– o $-C(R^4)_2-$, en donde ambos grupos R^4 y el átomo de carbono al que están unidos se pueden combinar para formar un grupo heterociclilo o heteroarilo de cinco a siete miembros;

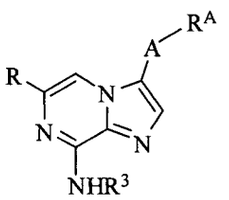
1205

Y es –H, –halo, –alquilo o –CN;

Z es $–CR^7–$ o –N–, cuando el enlace adicional opcional está ausente y –C– cuando el enlace adicional opcional está presente;

n es un número entero que va de 0 a 2; y

(k) Un compuesto de la fórmula K:



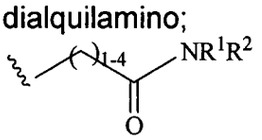
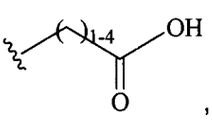
fórmula K

o una de sus sales, solvatos, ésteres, prodrogas o estereoisómeros farmacéuticamente aceptables, en donde:

R es H, halo o alquilo;

R^3 es heteroaril–X, en donde X es heterociclilalquilo–, en donde dicho heterociclilo puede no estar sustituido o puede estar opcionalmente sustituido con 1–4 restos alquilo;

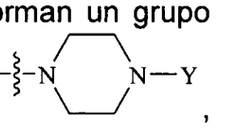
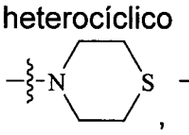
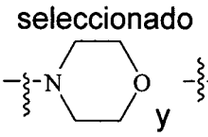
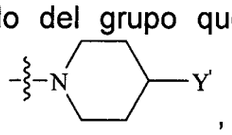
A es –arilo–, –heteroarilo–, $–N(R^1)–$aril– o $–N(R^1)–$heteroarilo–, en donde cada uno de dichos arilo y heteroarilo puede no estar sustituido, de modo independiente, o puede estar opcionalmente sustituido con uno o varios sustituyentes que pueden ser iguales o diferentes, donde cada sustituyente está seleccionado, de modo independiente, del grupo que consiste en alquilo, $–NO_2$, halo, hidroxi, trihaloalquilo, alcoxi y dialquilamino;

R^A es $–(CH_2)_{1–4}$–heteroarilo,  o  , en donde dicho heteroarilo puede estar opcionalmente fusionado con un arilo, en donde cada uno de dichos arilo y heteroarilo puede estar opcionalmente sustituido, de modo independiente, con uno o varios restos donde cada resto está seleccionado, de modo independiente, del grupo que consiste en trihaloalquilo, $–NO_2$, halo, hidroxialquilo, alcoxialquilo y dialquilamino;

1206

R^1 es H o alquilo;

R^2 es H, hidroxialquilo–, arilalquilo–, heteroarilo, arilo, heteroarilalquilo–, alquilo, dialquilaminoalquilo–, alquilaminoalquilo–, cicloalquilalquilo–, cicloalquilo, heterociclilalquilo– o heterociclilo, en donde dichos arilo y arilo de arilalquilo puede no estar sustituido o puede estar sustituido con uno o varios restos seleccionados, de modo independiente, del grupo que consiste en trihaloalquilo, $–NO_2$, halo, hidroxialquilo, alcoxialquilo, dialquilamino y heterociclilalquilo–, en donde dicho heterociclilalquilo puede no estar sustituido o puede estar sustituido con alquilo o $–SO_2NH_2$; dichos heteroarilo y heteroarilo de heteroarilalquilo pueden no estar sustituidos o pueden estar sustituidos con uno o varios restos, donde cada resto está seleccionado, de modo independiente, del grupo que consiste en hidroxialquilo, alcoxi, alquilo, halo, hidroxilo y $–NO_2$; y dicho cicloalquilo no está sustituido o está sustituido con hidroxilo; o

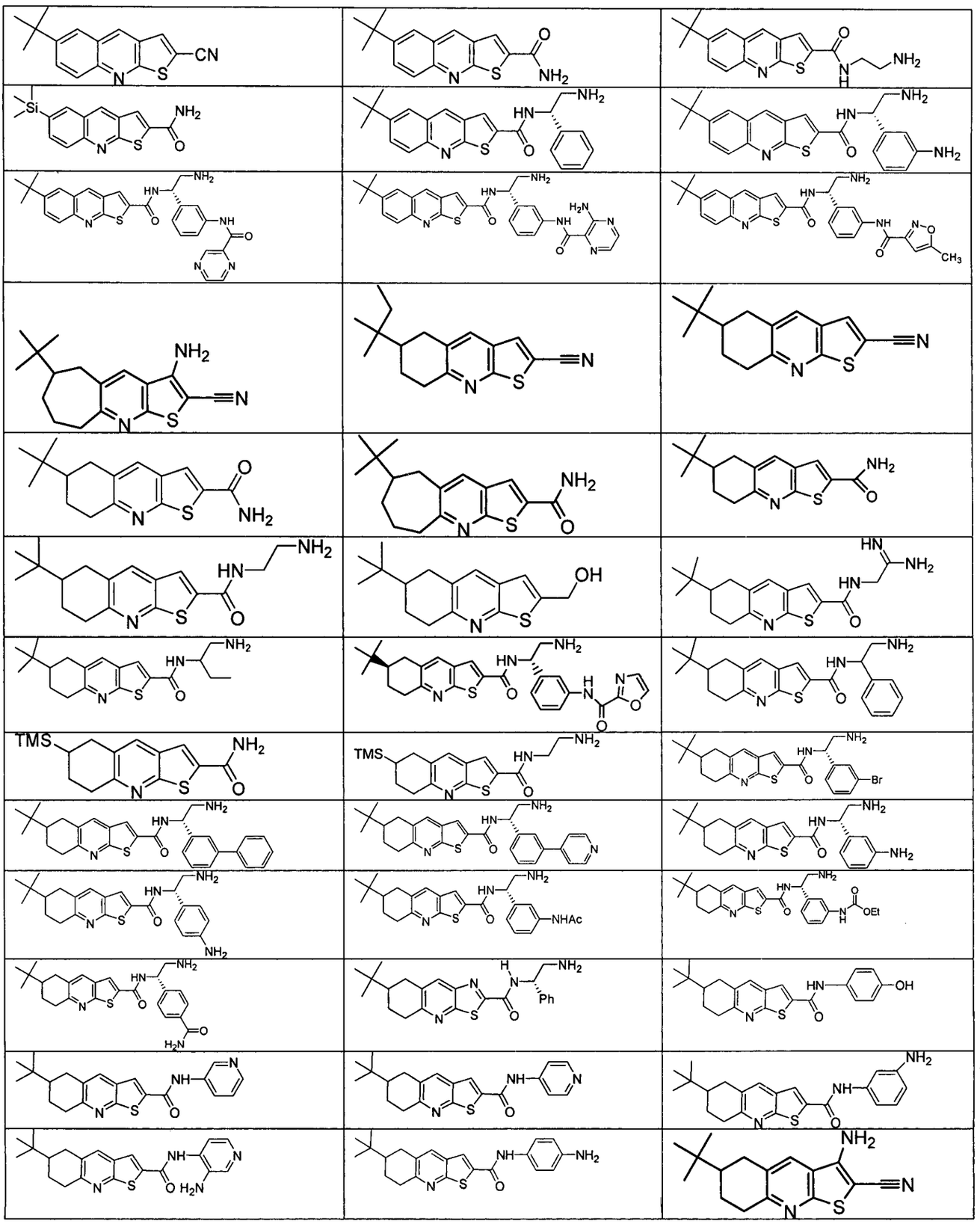
R^1 y R^2 junto con N al que cada uno está unido, forman un grupo heterocíclico seleccionado del grupo que consiste en  ,  ,  y  , en donde

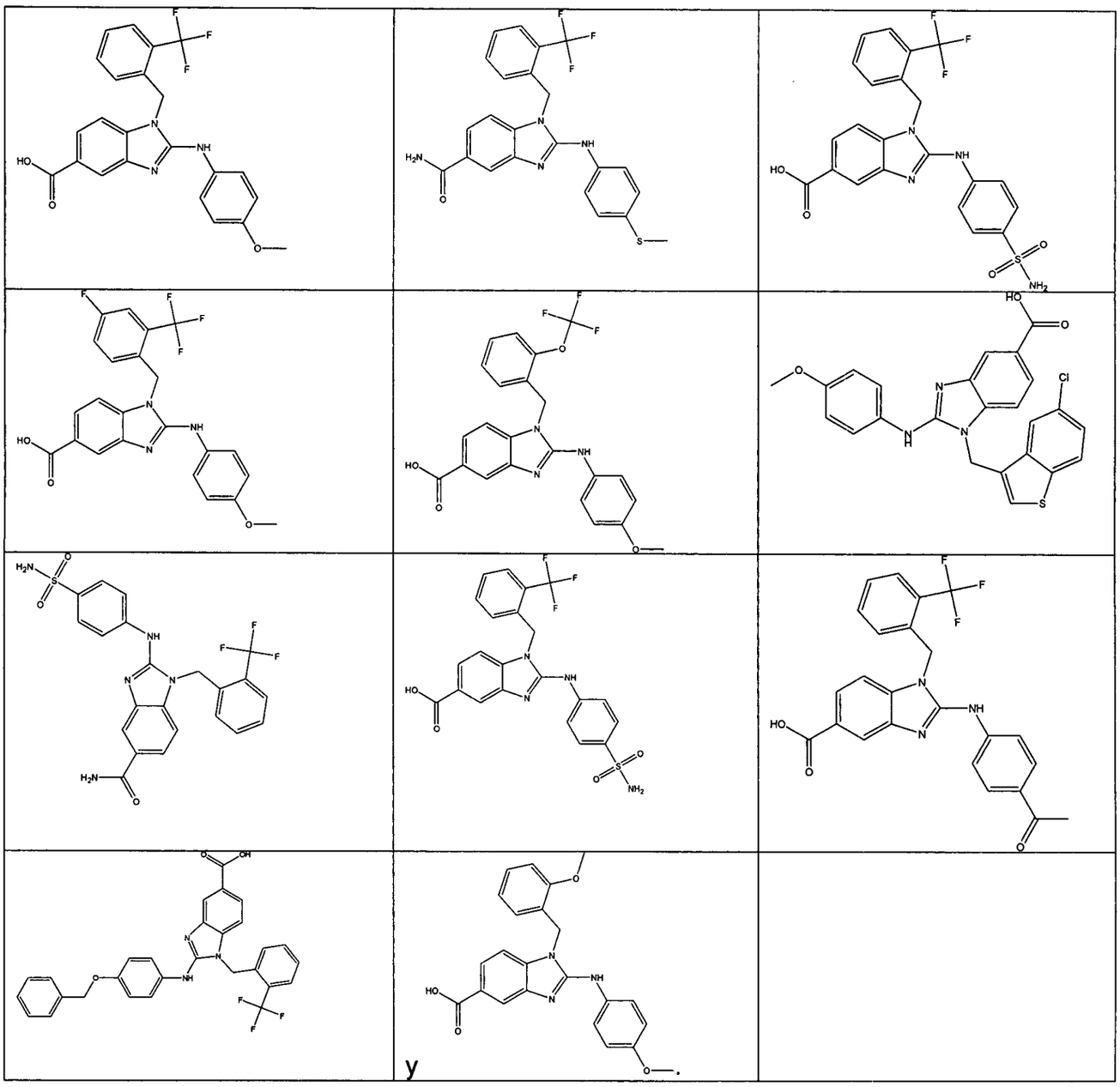
Y es alcoxialquilo, hidroxialquilo, dialquilaminoalquilo o alquilo, también en donde

Y' es hidroxilo.

12. La composición farmacéutica de acuerdo con la reivindicación 1, en donde dicho inhibidor de KSP representado por las fórmulas A–D está seleccionado del grupo que consiste en:

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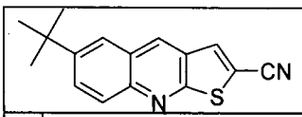
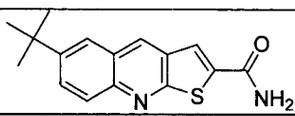
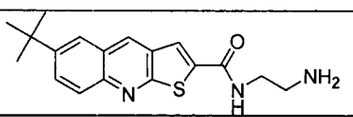
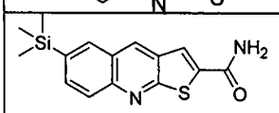
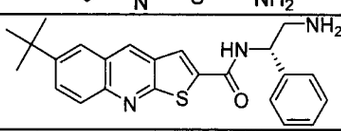
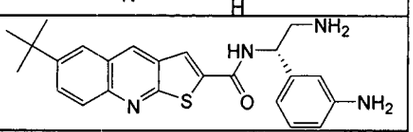
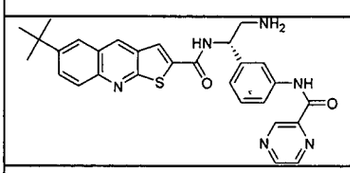
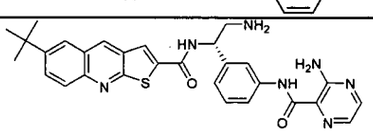
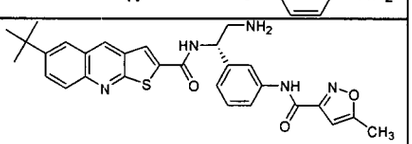
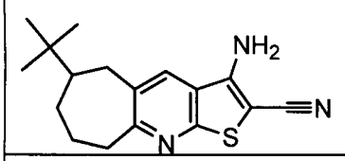
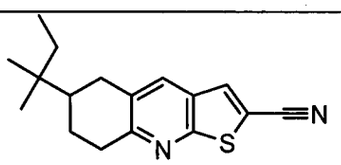
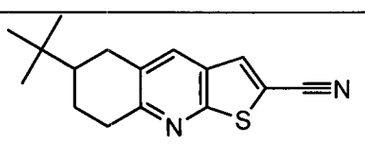
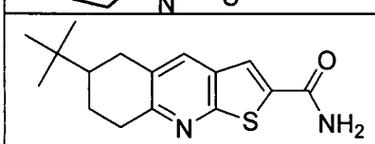
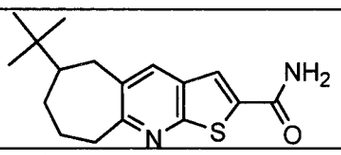
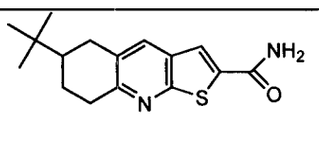
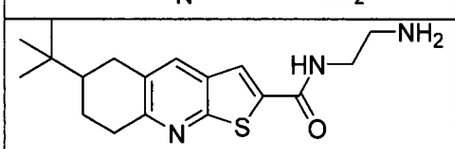
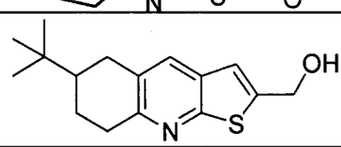
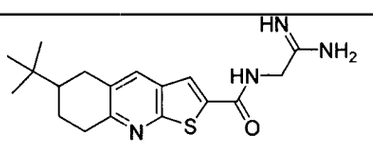
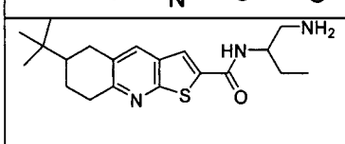
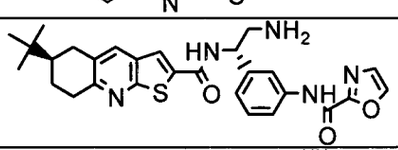
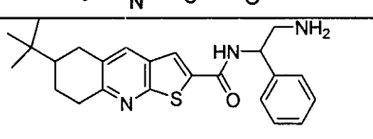
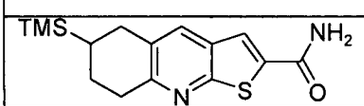
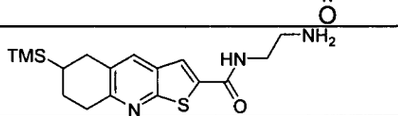
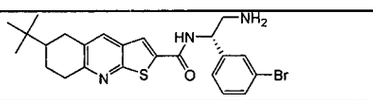
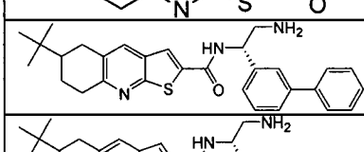
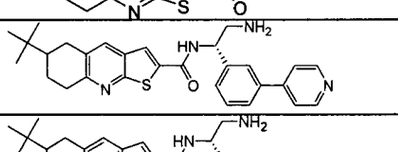
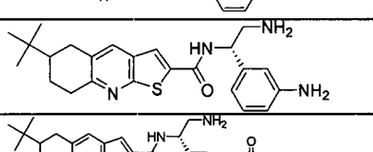
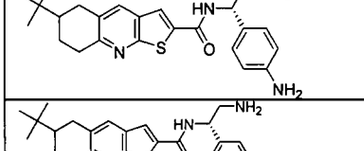
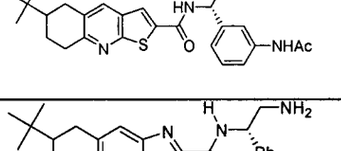
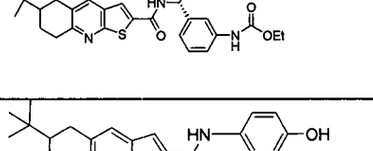
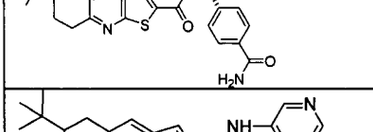
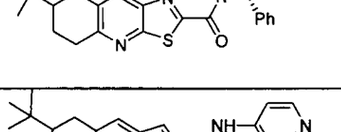
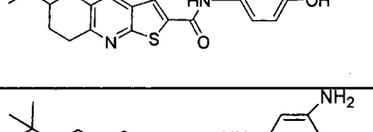
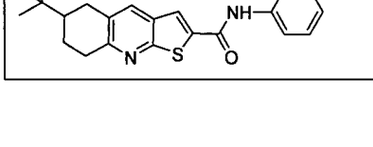
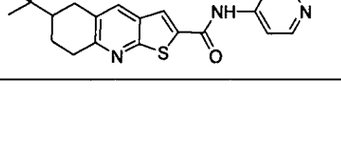
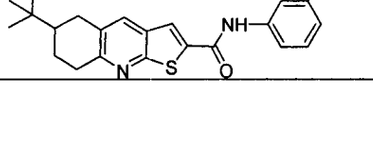




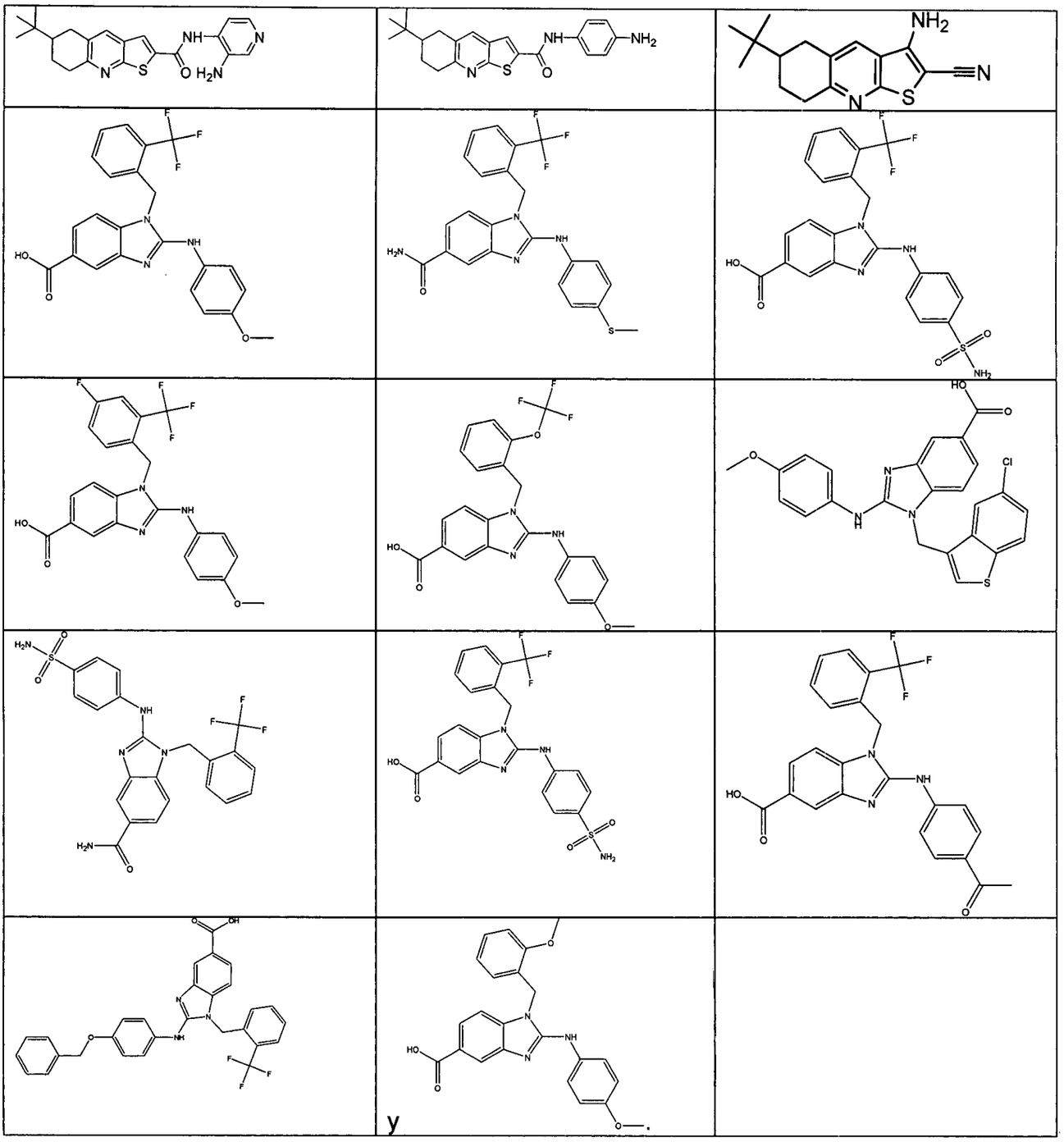
y

o una de sus sales, solvatos, ésteres o profármacos farmacéuticamente aceptables.

13. El método de acuerdo con la reivindicación 2, en donde dicho inhibidor de KSP representado por las fórmulas A–D está seleccionado del grupo que consiste en:

1210

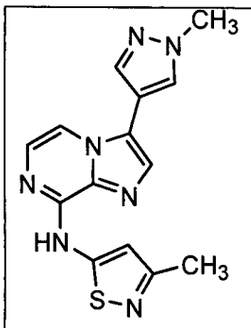
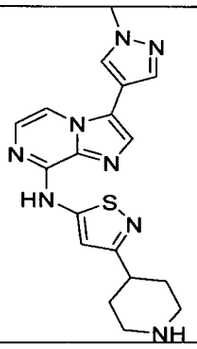
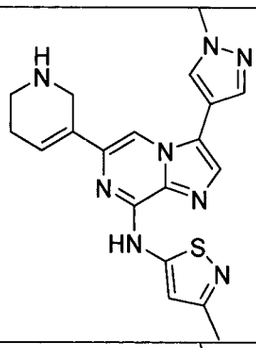
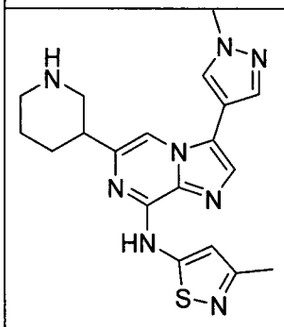
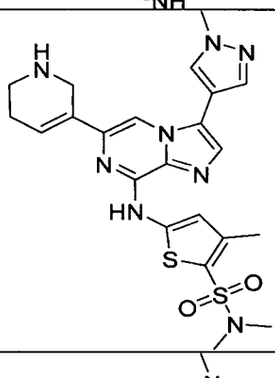
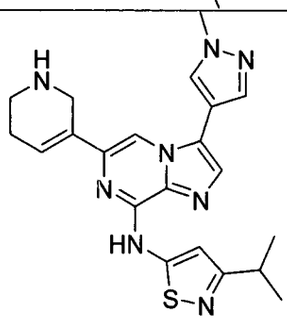
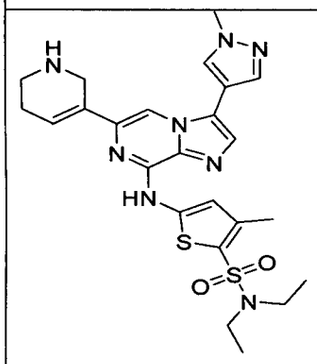
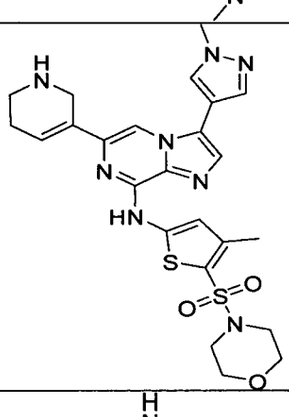
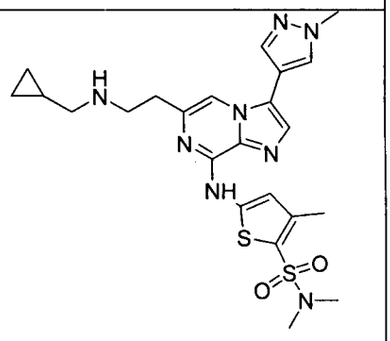
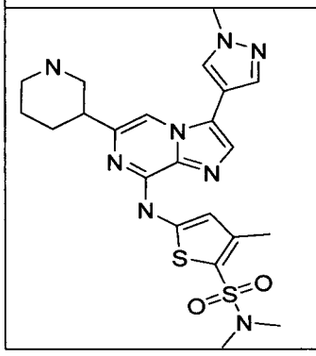


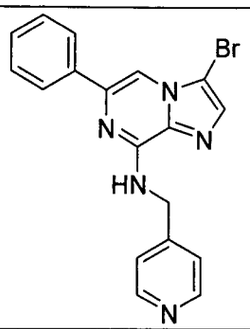
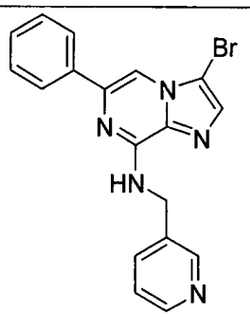
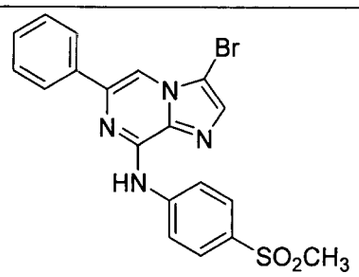
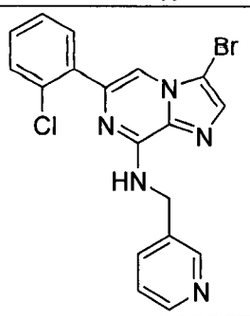
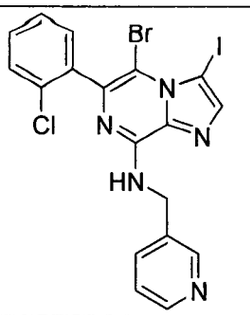
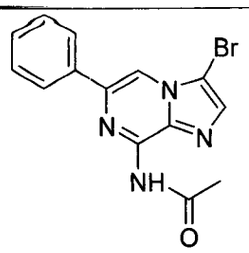
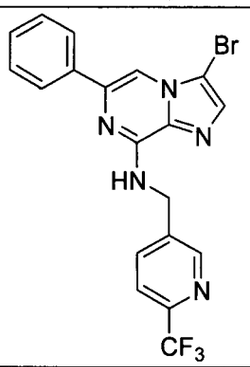
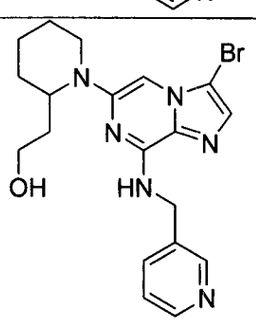
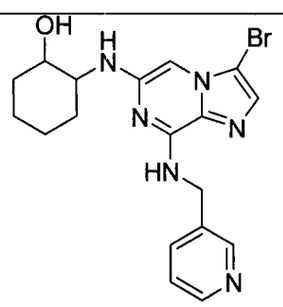
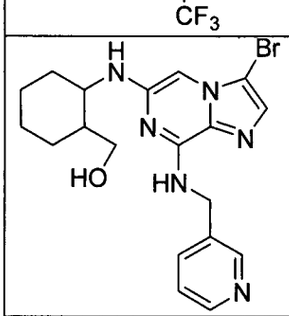
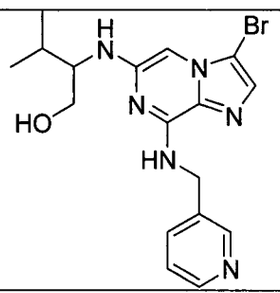
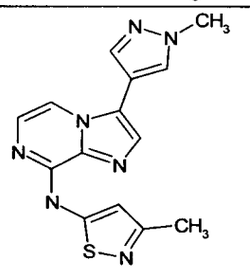
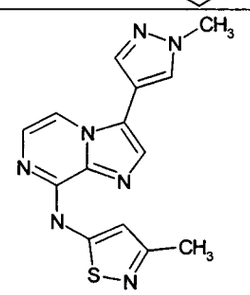
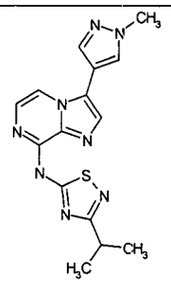
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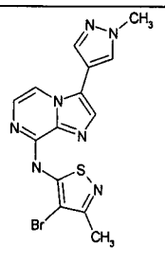
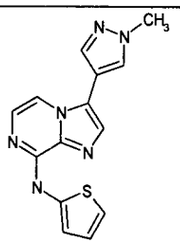
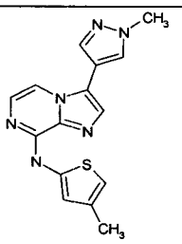
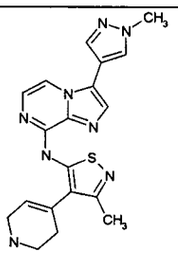
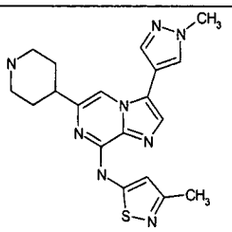
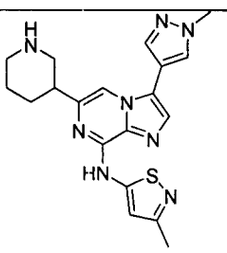
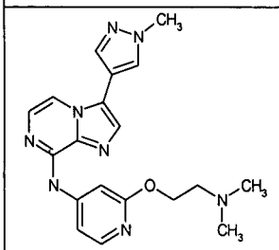
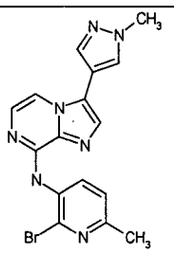
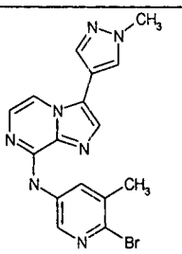
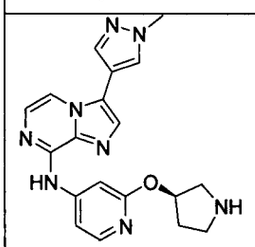
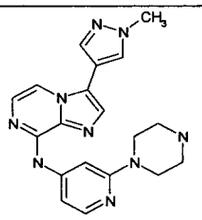
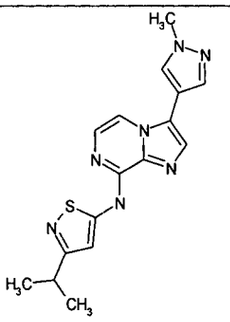
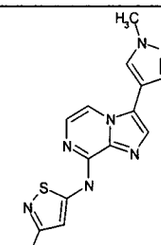
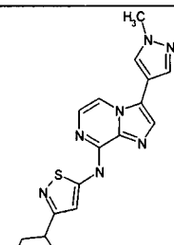
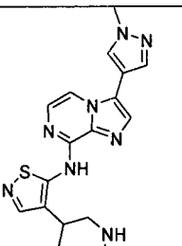
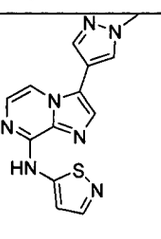
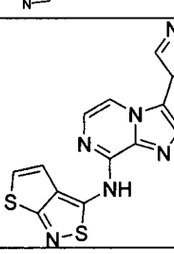
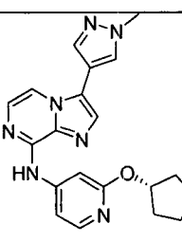
14. La composición farmacéutica de acuerdo con la reivindicación 1, en donde dicho inhibidor de aurora quinasa, representado por las fórmulas E–K, está seleccionado del grupo que consiste en:

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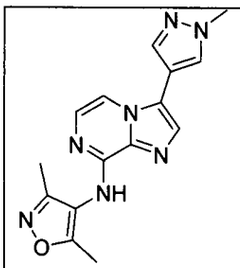
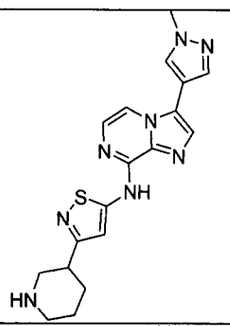
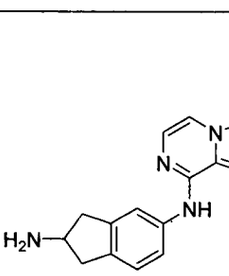
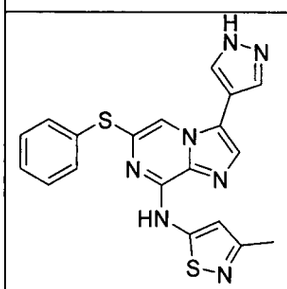
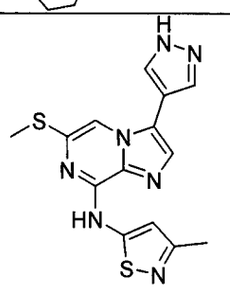
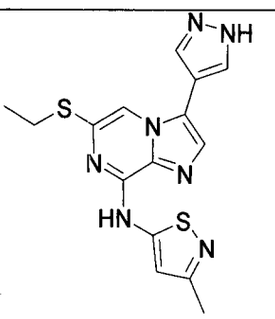
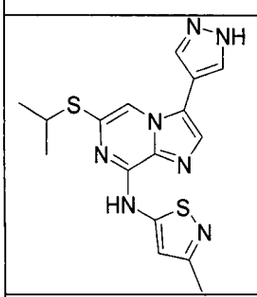
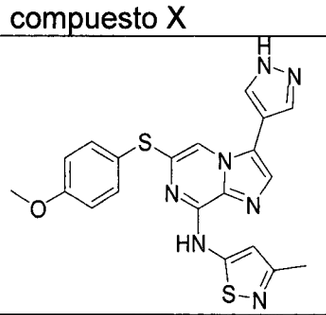
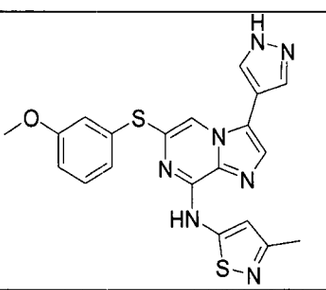
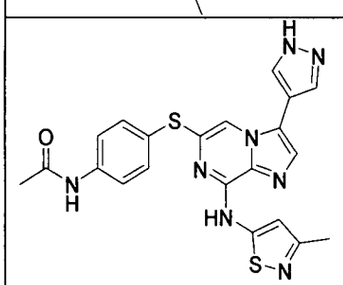
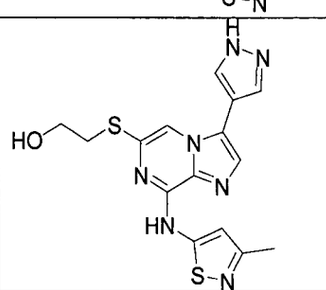
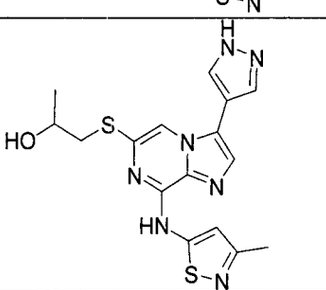
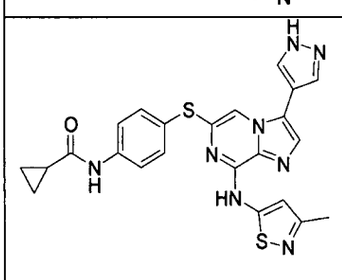
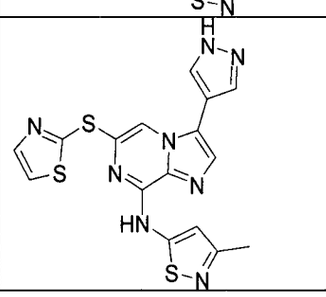
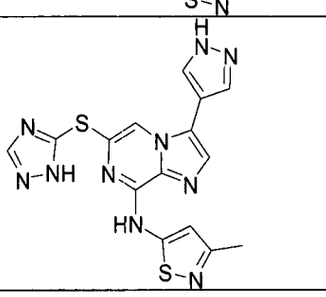
		
		
		
		

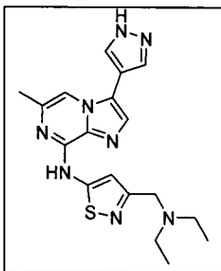
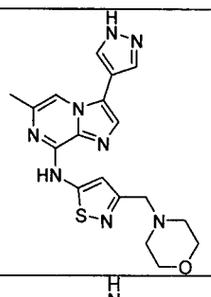
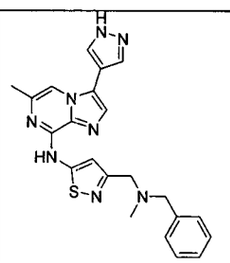
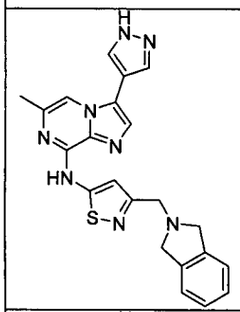
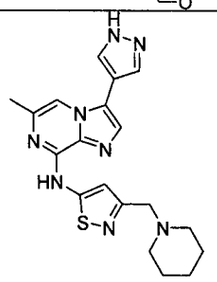
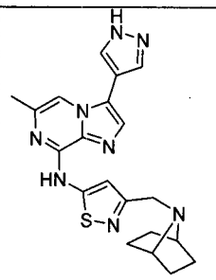
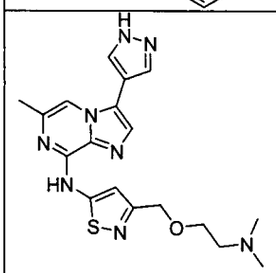
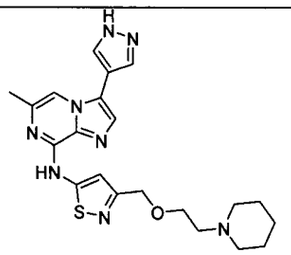
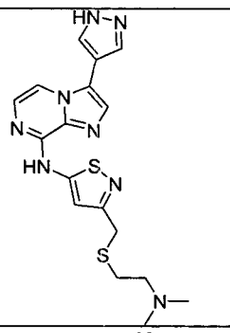
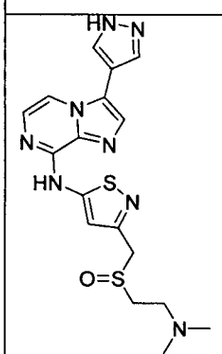
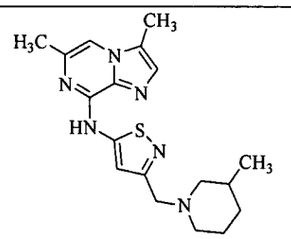
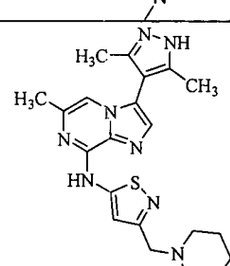
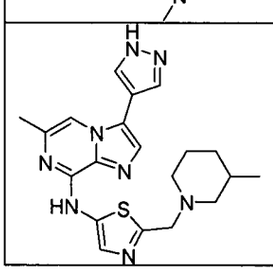
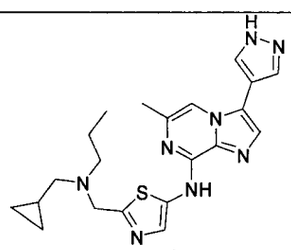
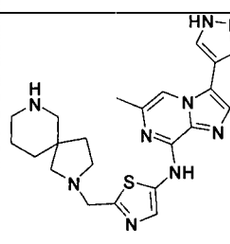
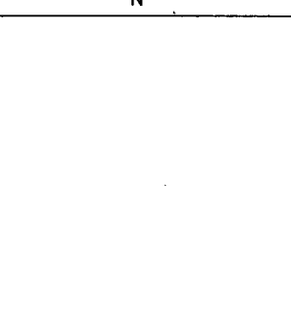
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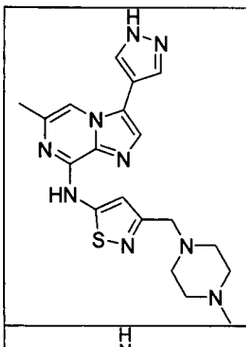
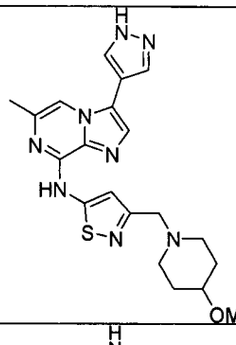
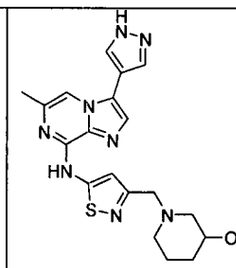
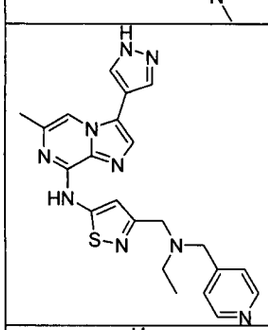
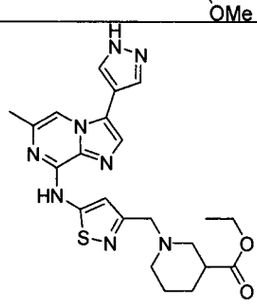
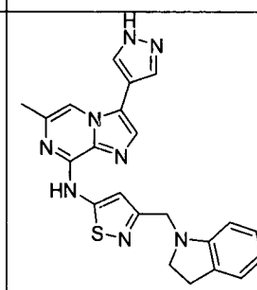
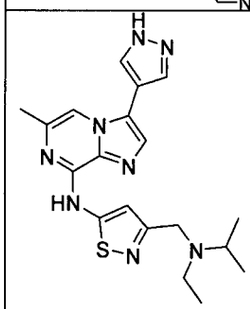
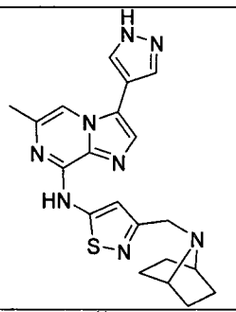
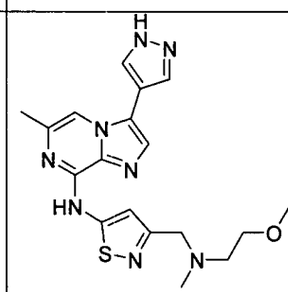
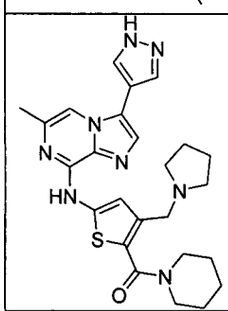
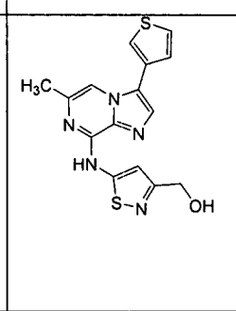
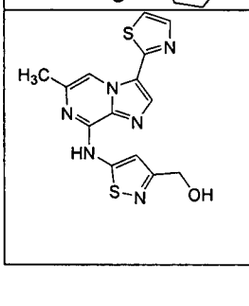
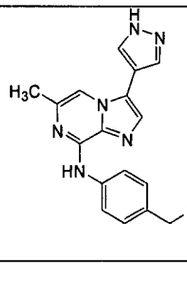
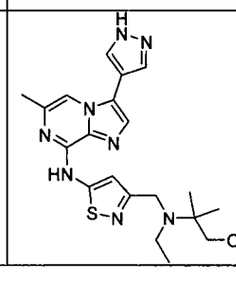
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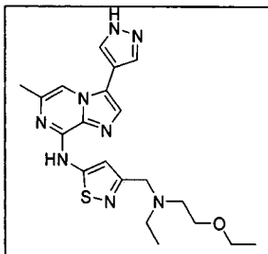
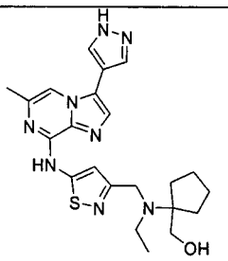
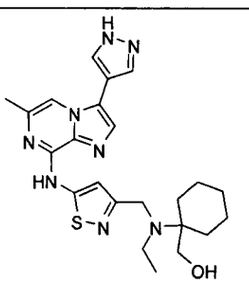
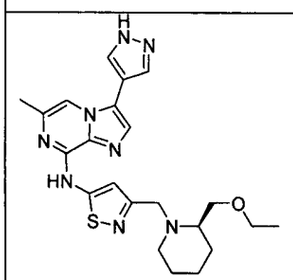
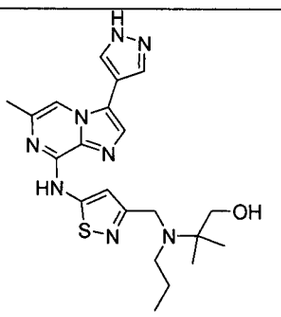
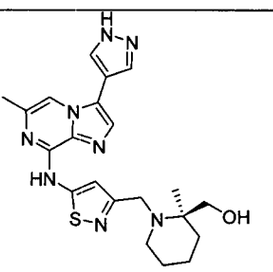
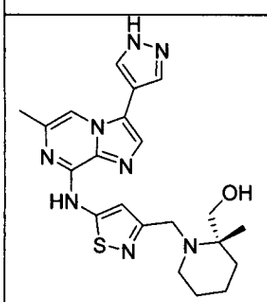
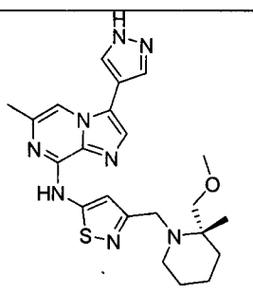
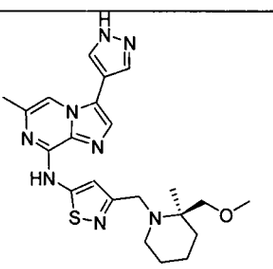
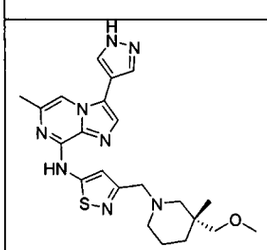
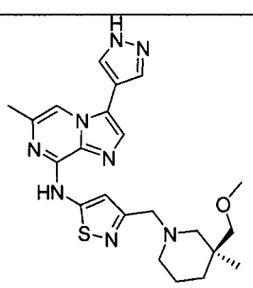
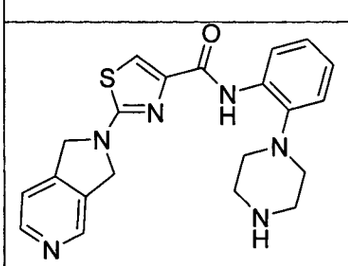
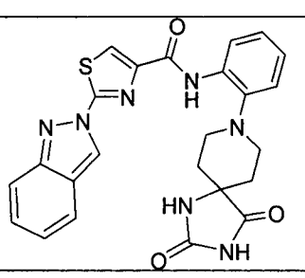
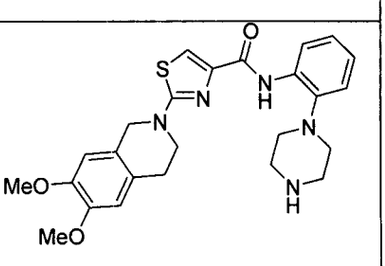
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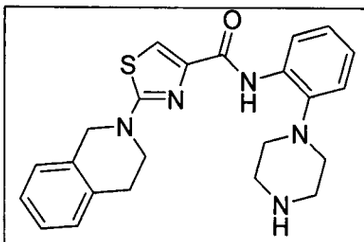
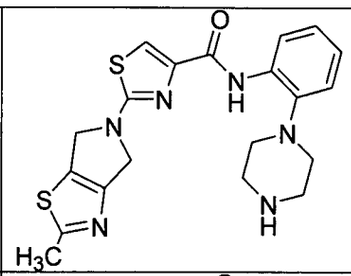
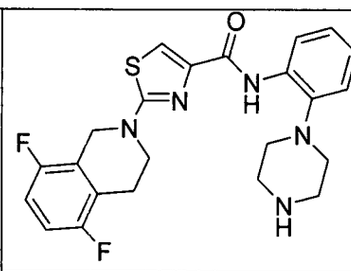
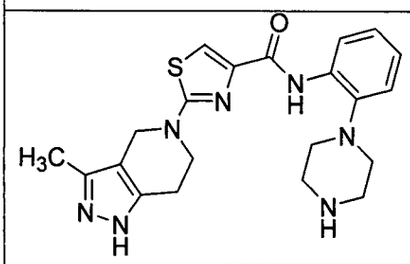
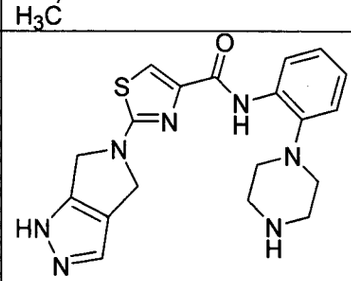
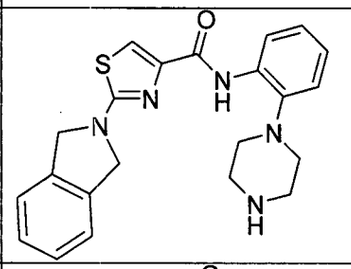
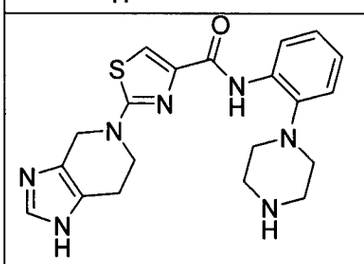
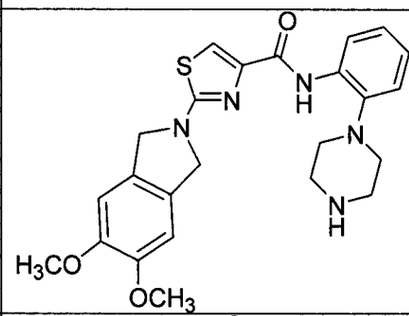
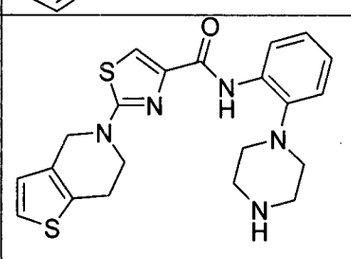
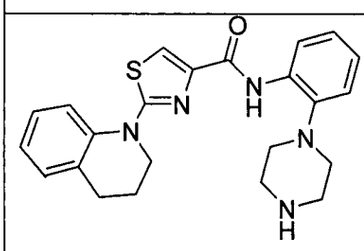
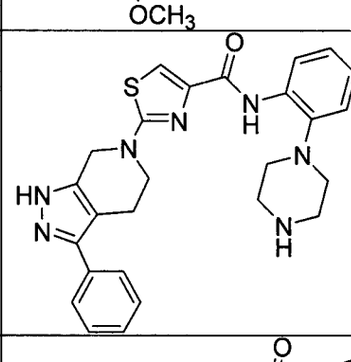
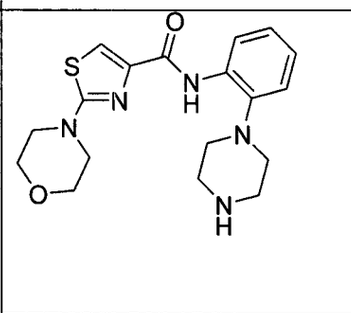
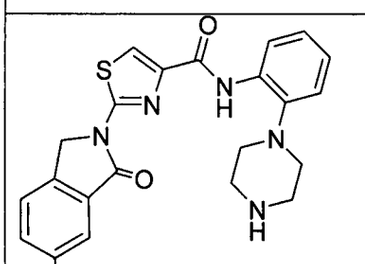
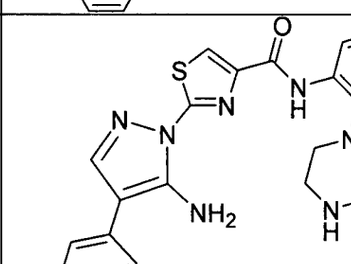
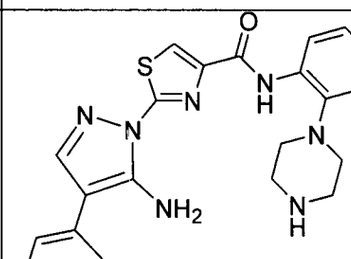
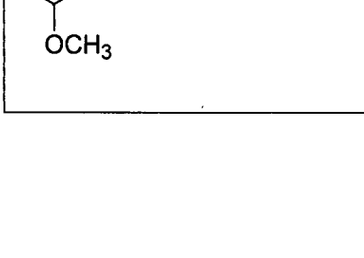
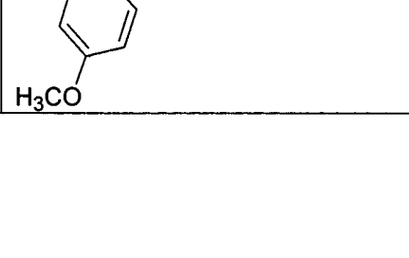
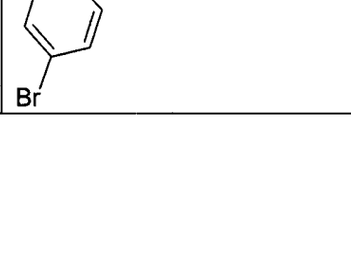
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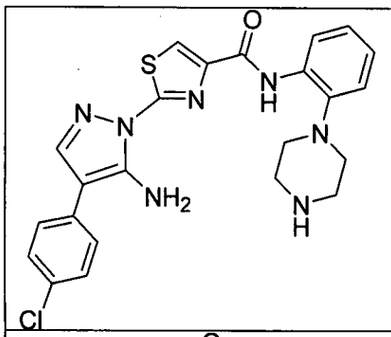
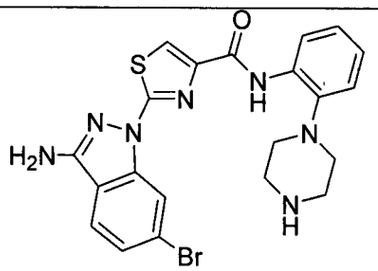
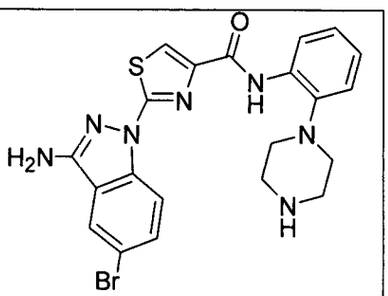
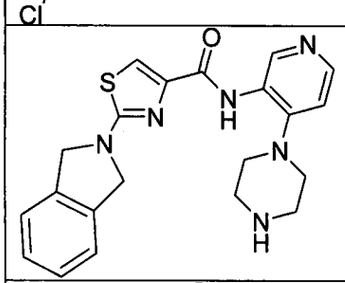
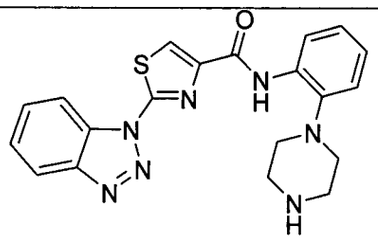
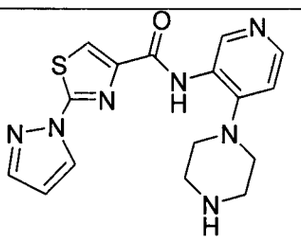
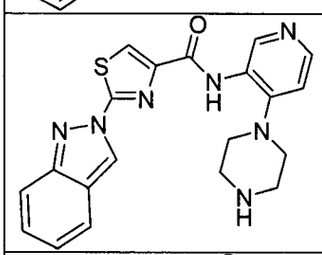
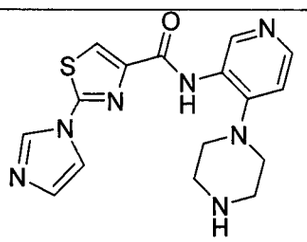
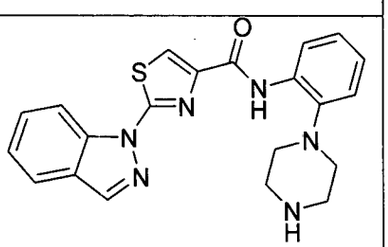
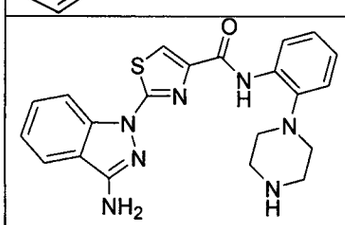
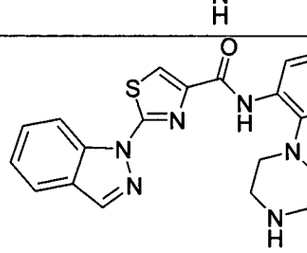
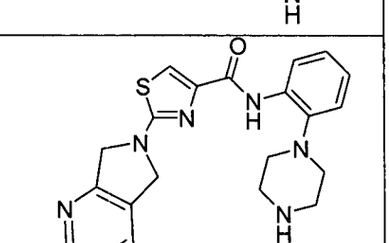
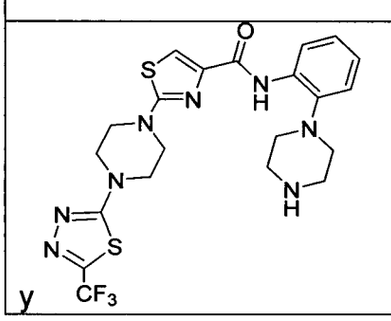
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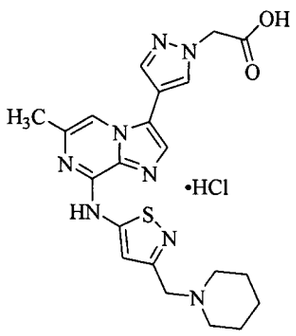
		
		
		
		
		

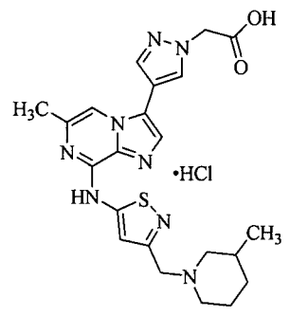
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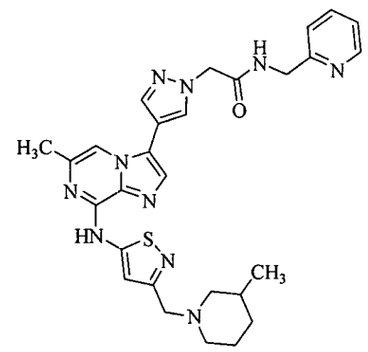
		
		
		
		
		
		

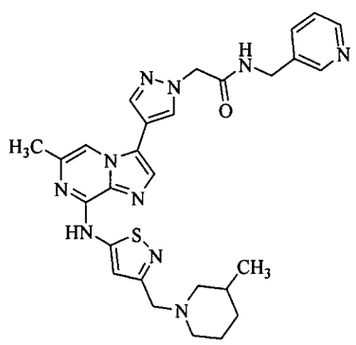
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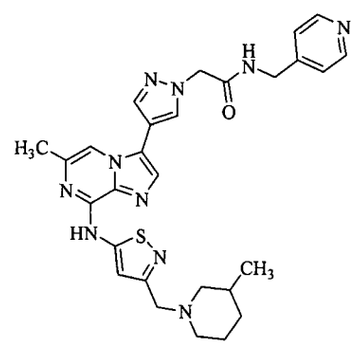
		
		
		
		
		

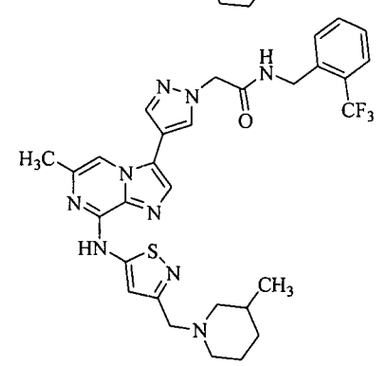


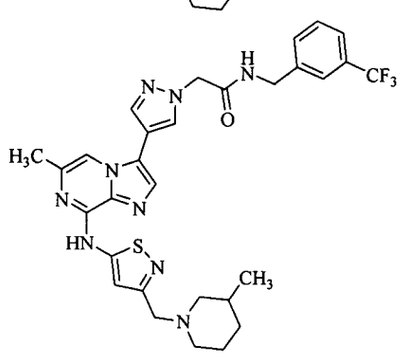


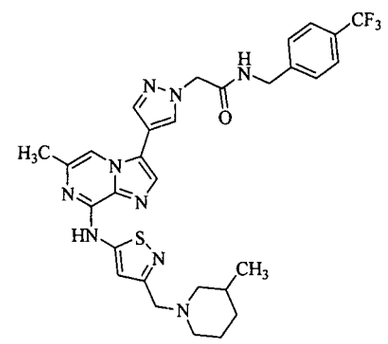


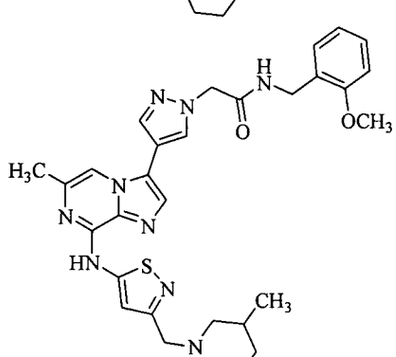


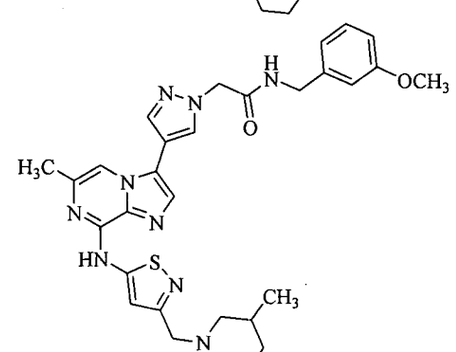


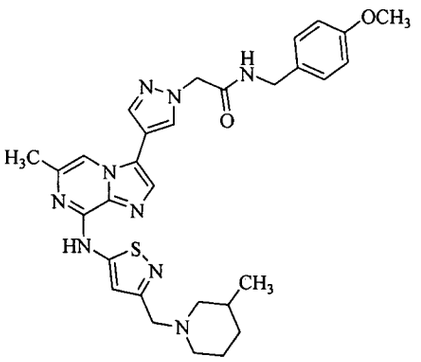


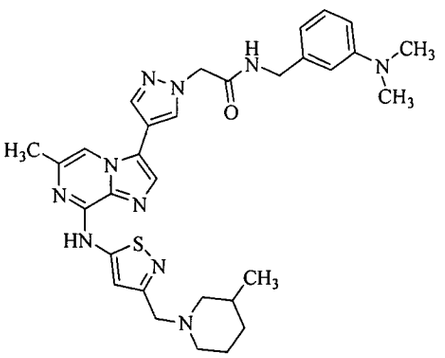


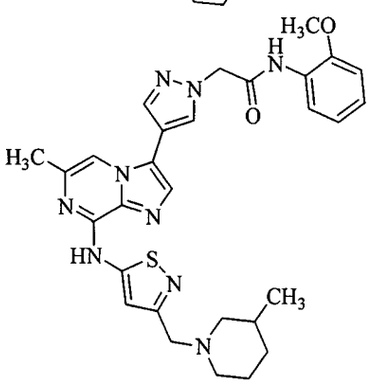


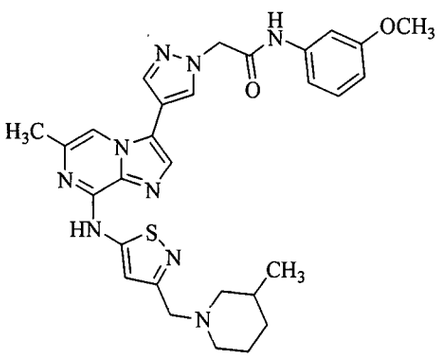


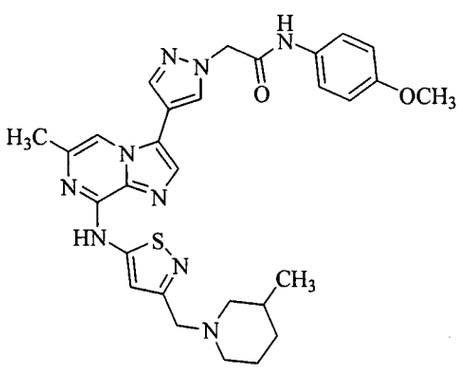


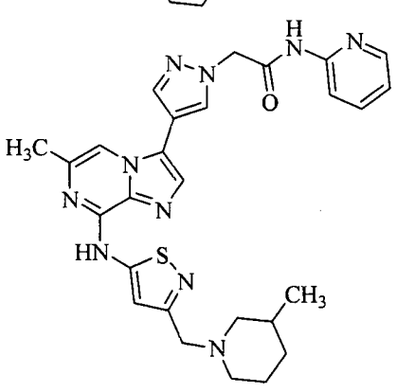


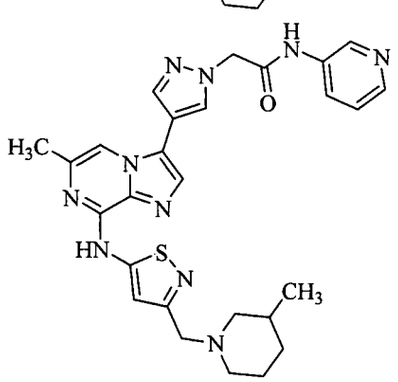


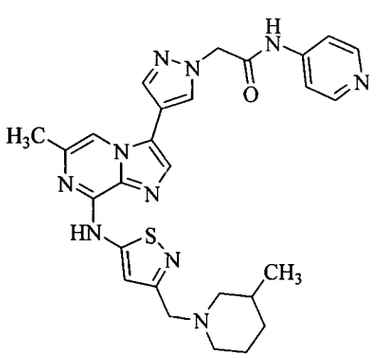


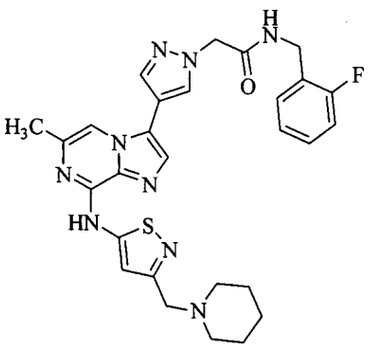


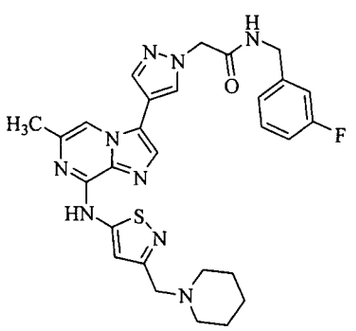


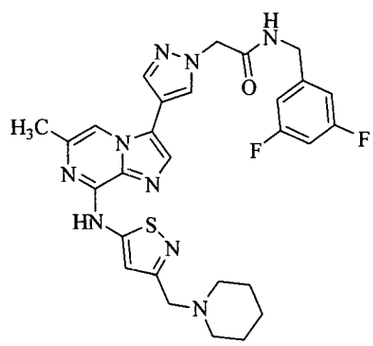


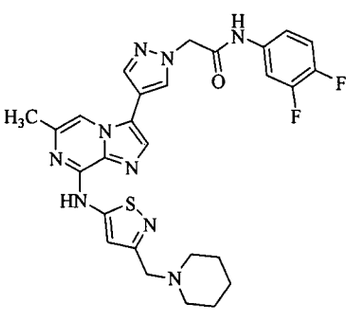


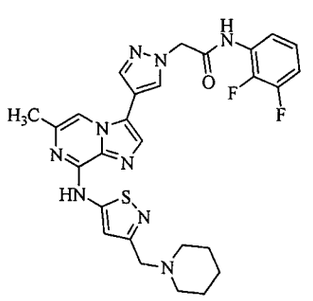


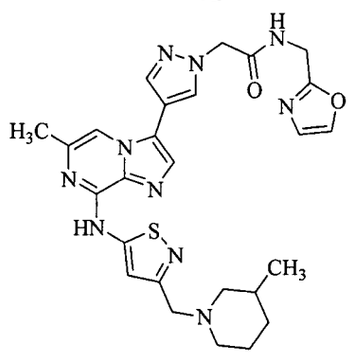


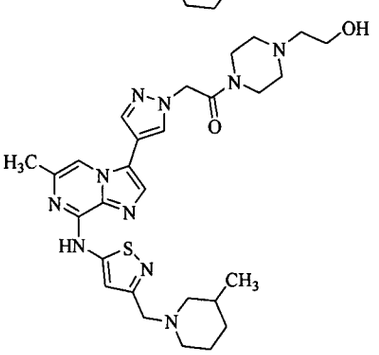


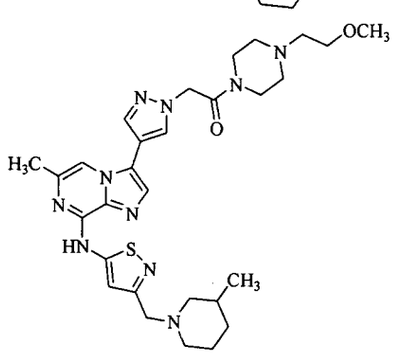


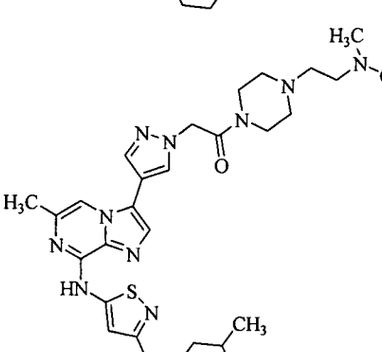


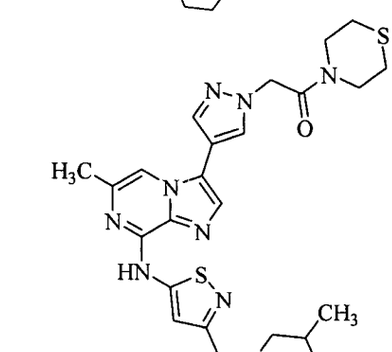


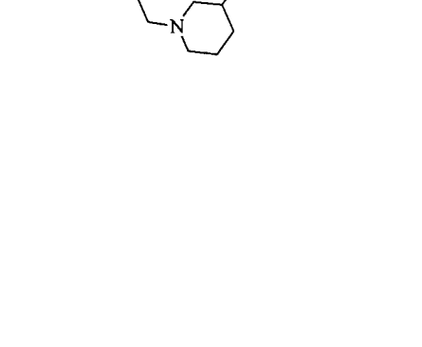


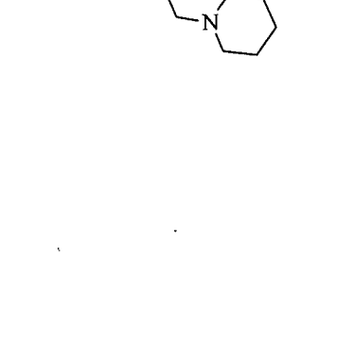




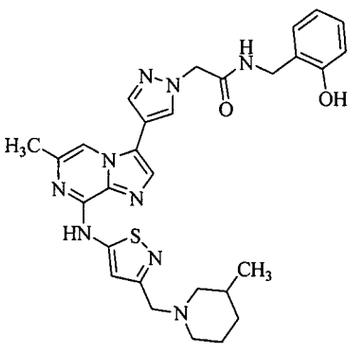


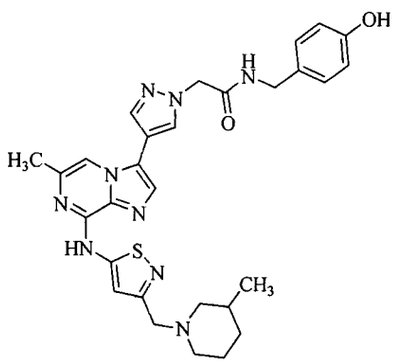


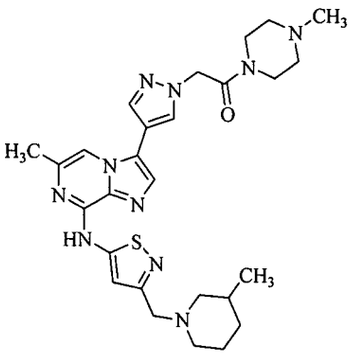


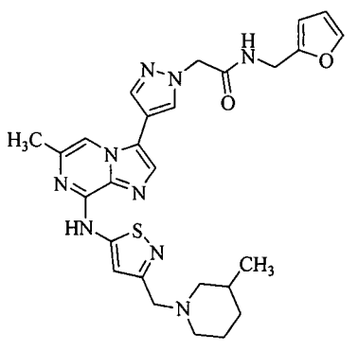


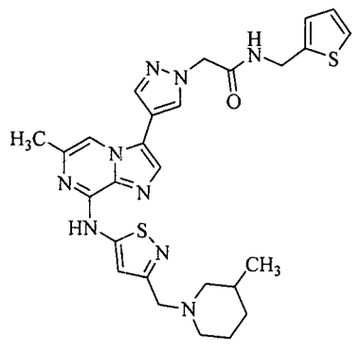
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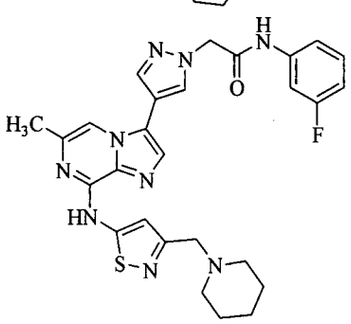


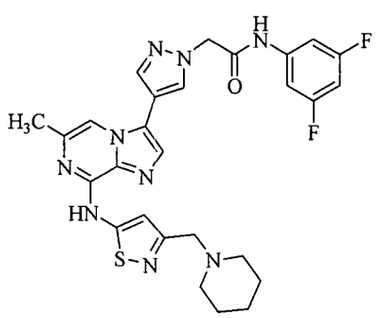


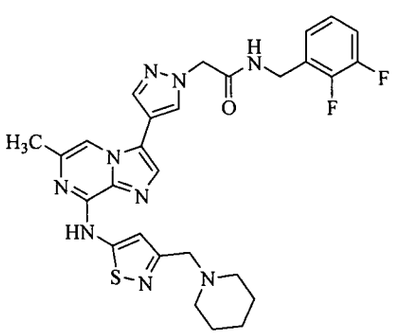


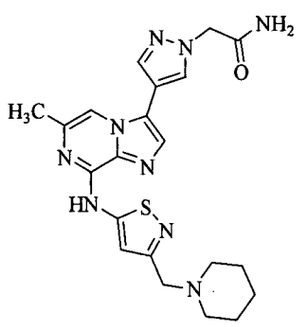


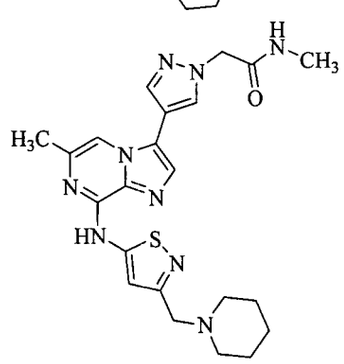


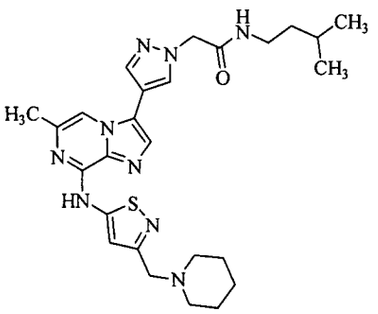


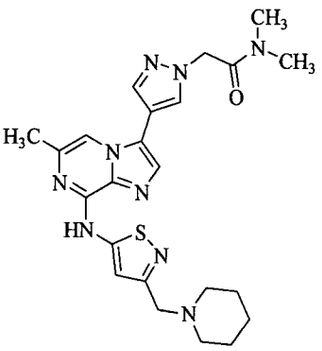


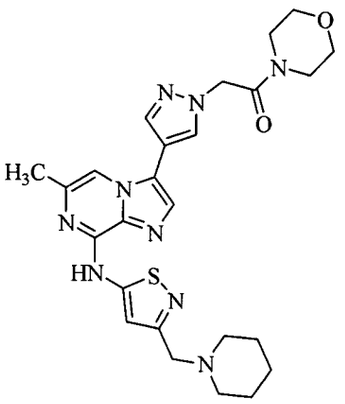


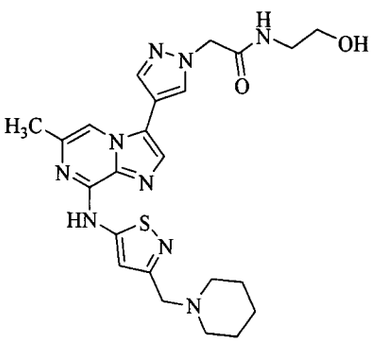


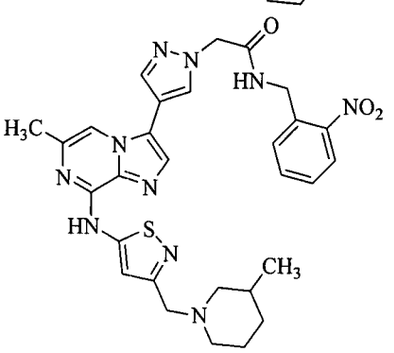


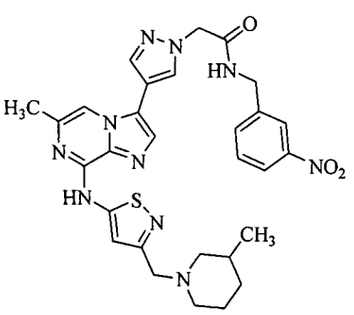


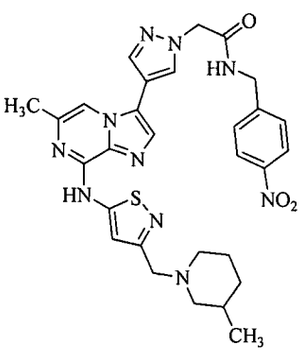


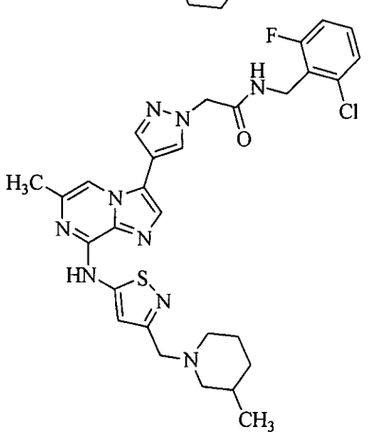


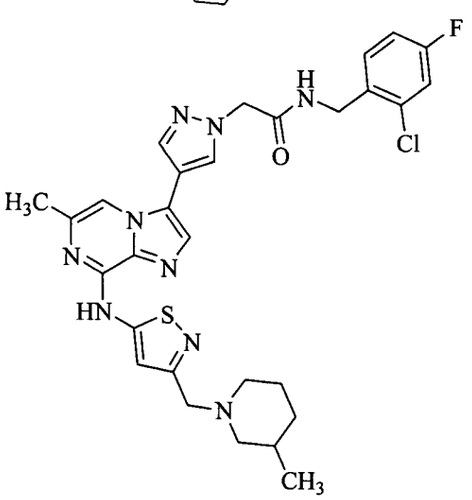




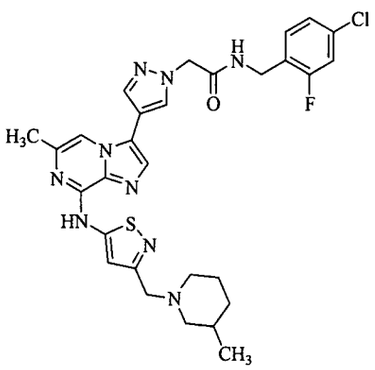


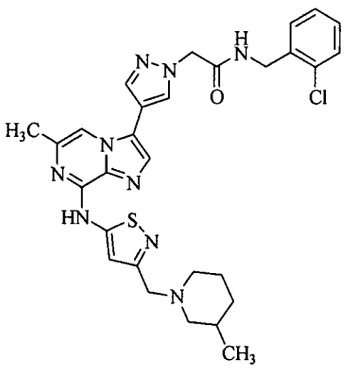


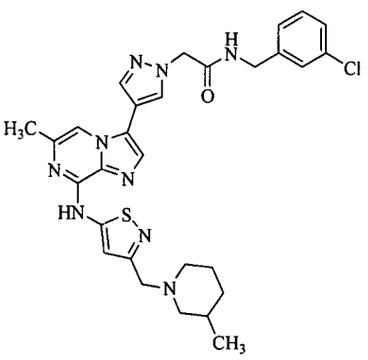


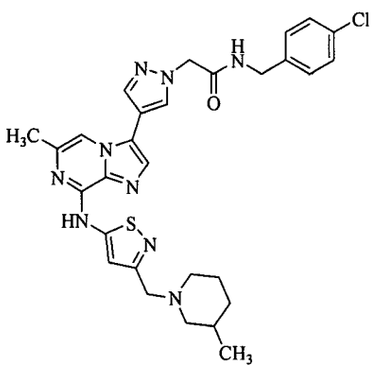


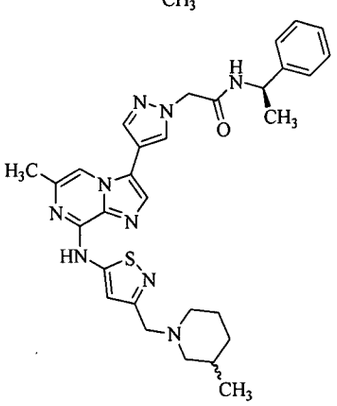
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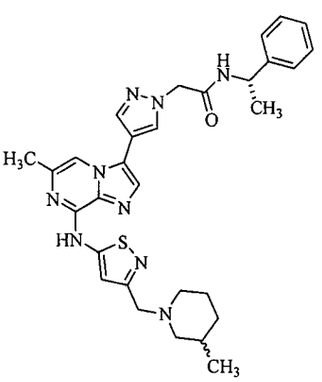


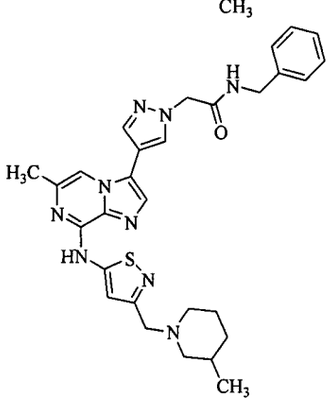


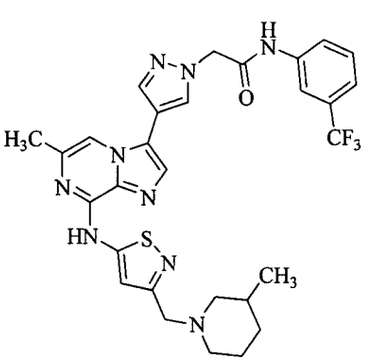


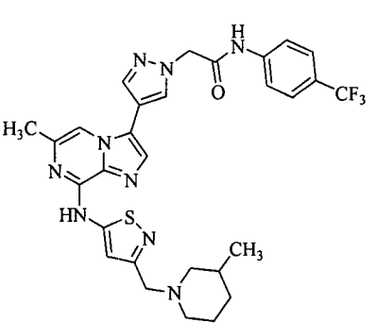


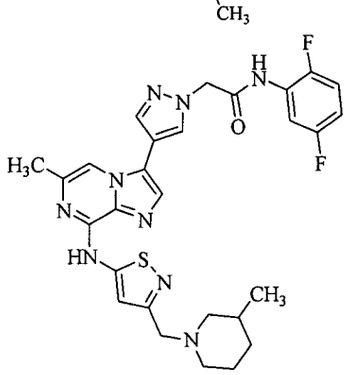


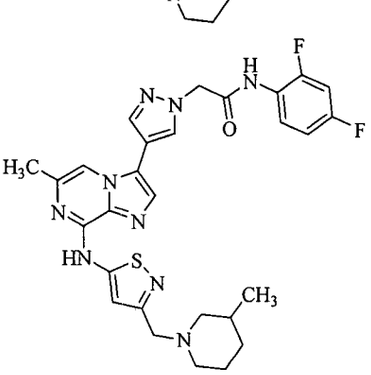




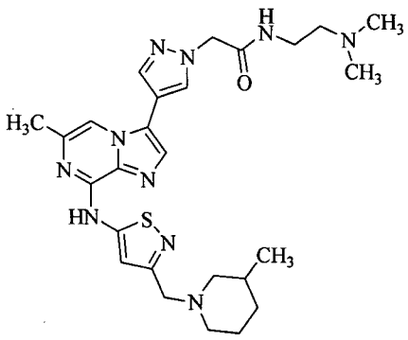


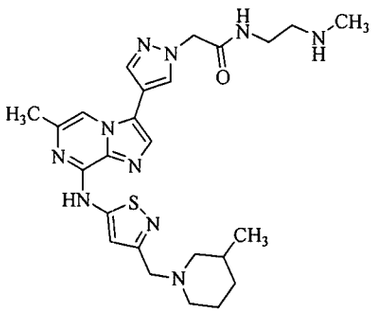


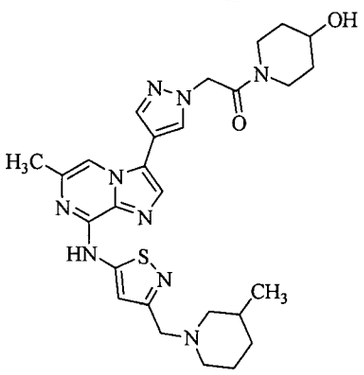


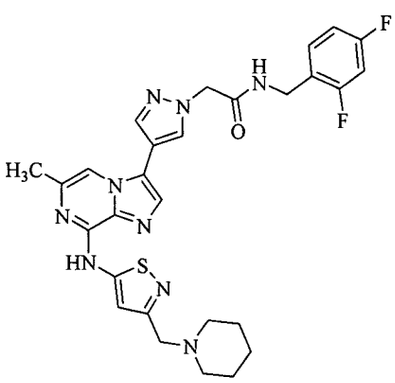


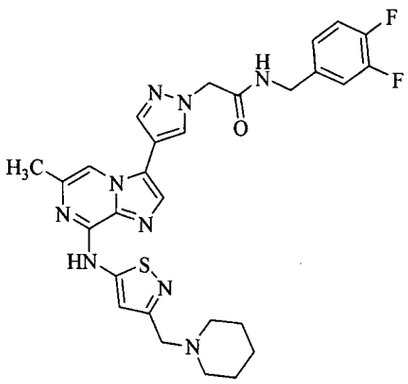
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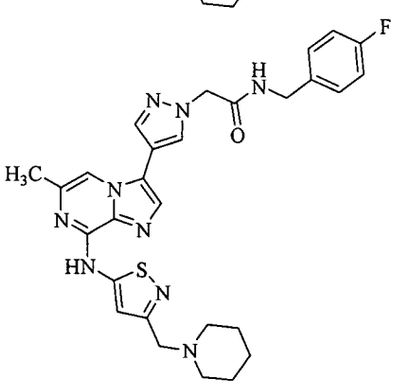


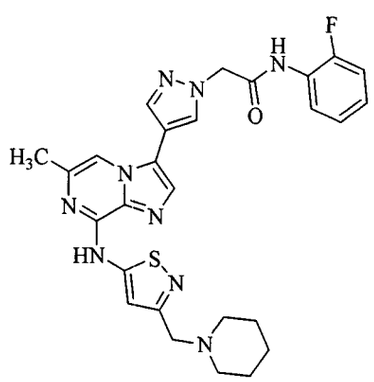


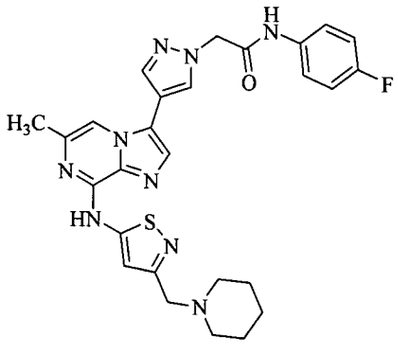


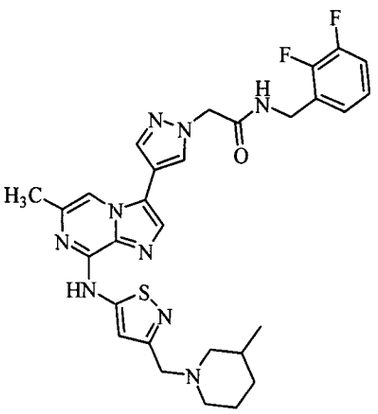


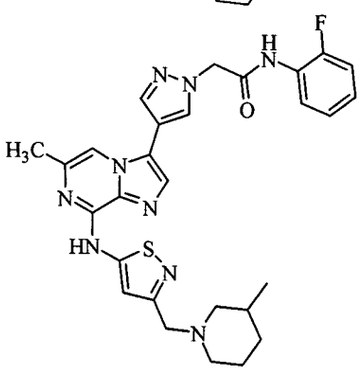


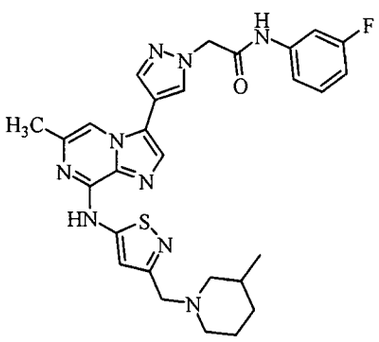


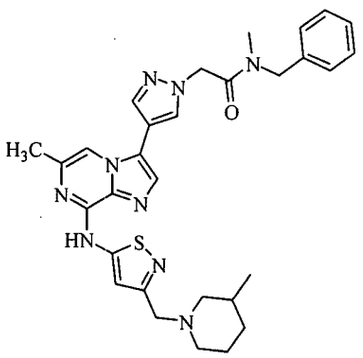


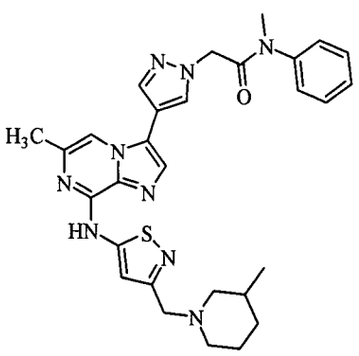


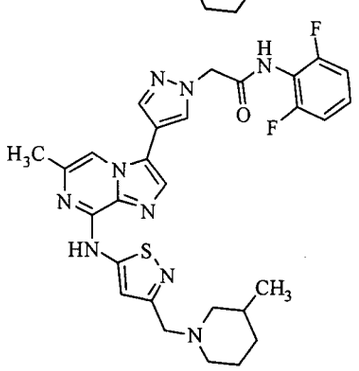


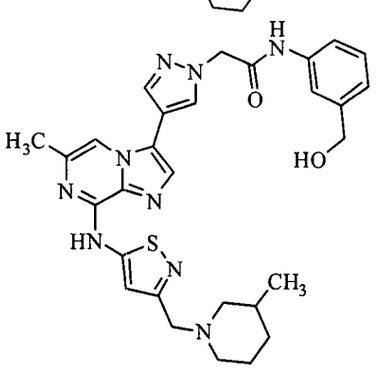


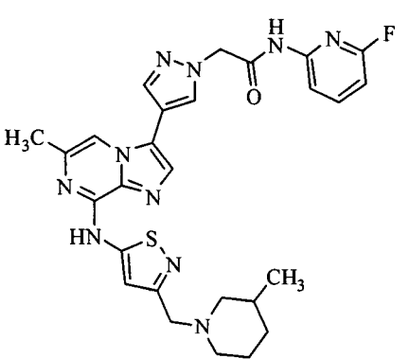


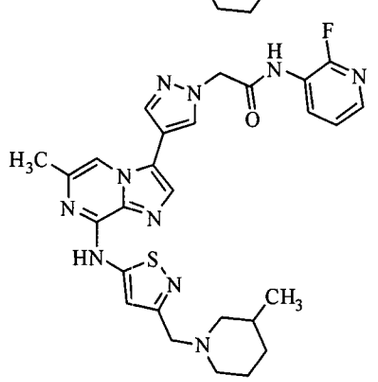




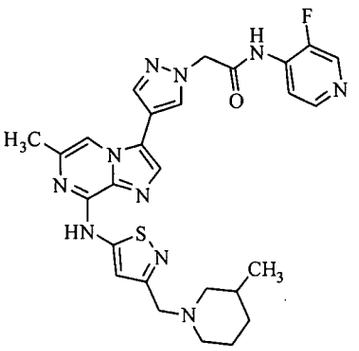


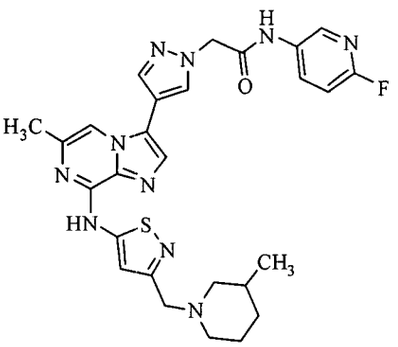


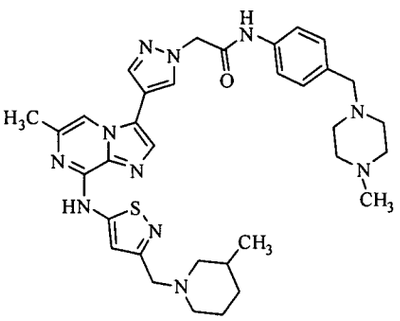


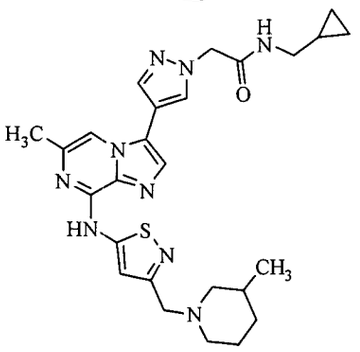


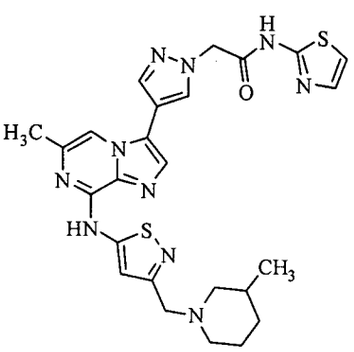
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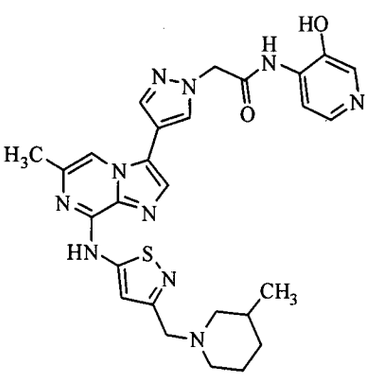


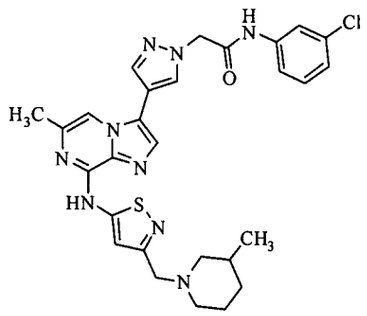


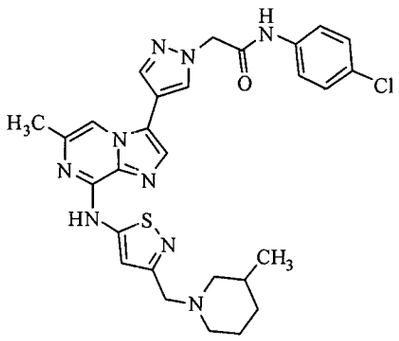


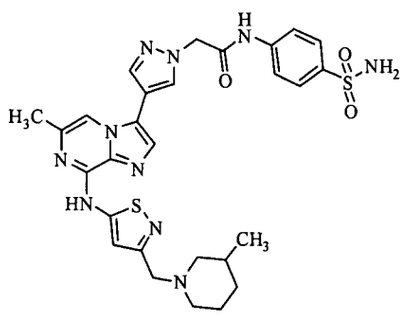


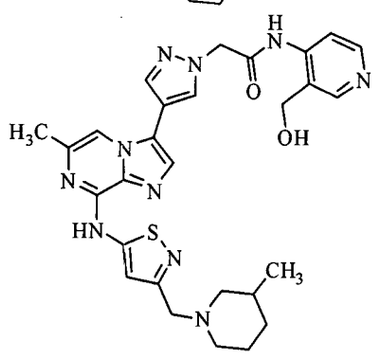


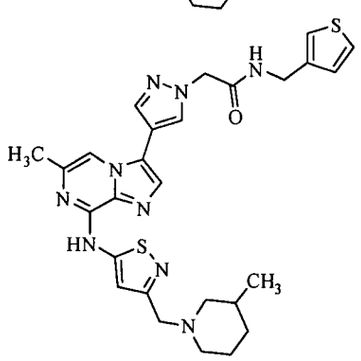


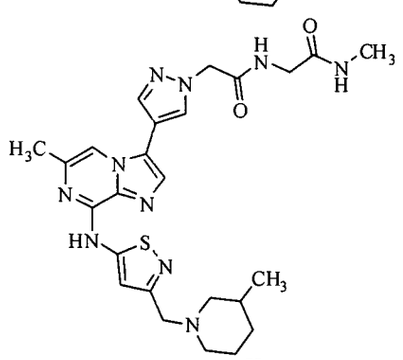


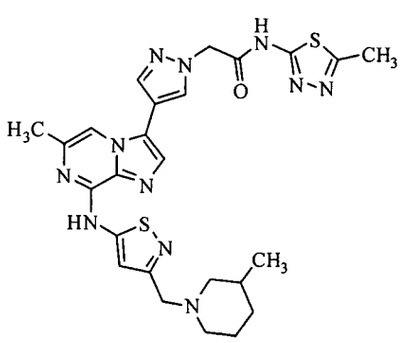


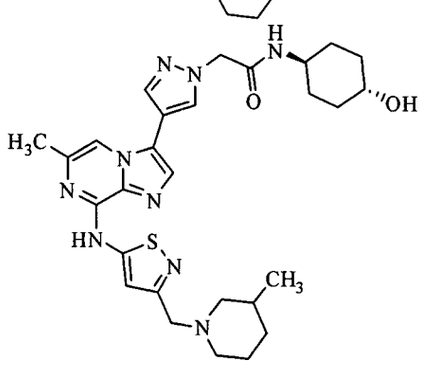




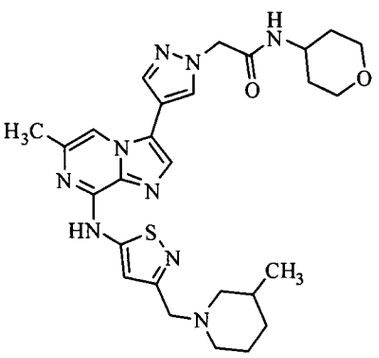


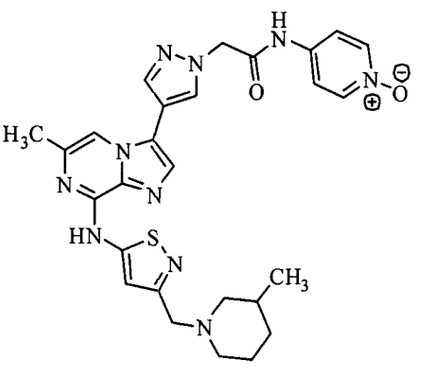


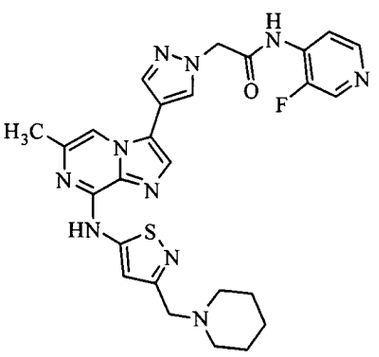


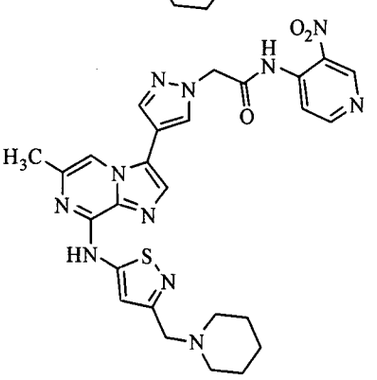


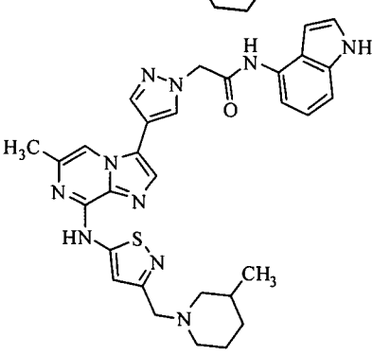
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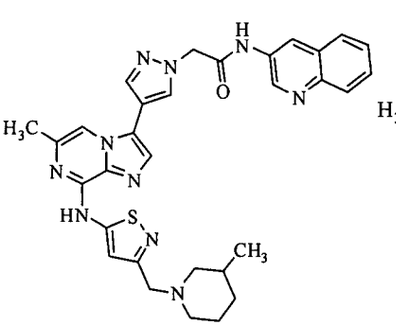


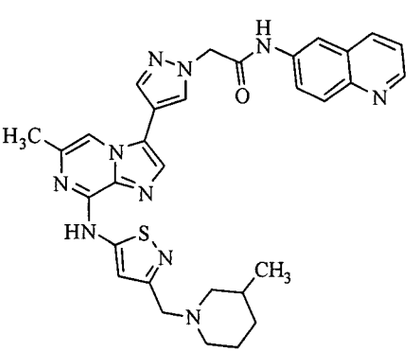




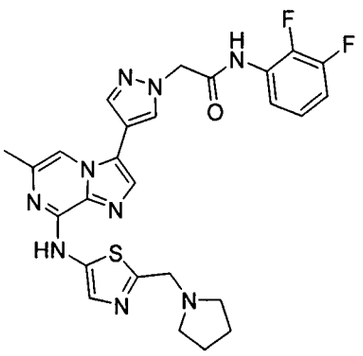


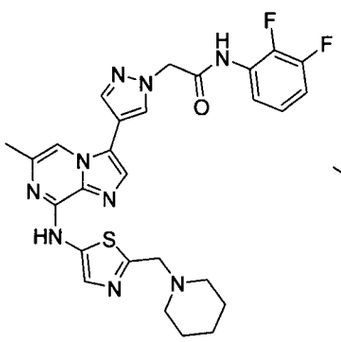


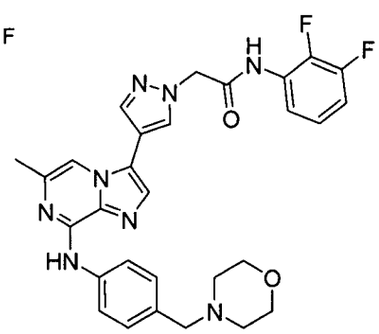


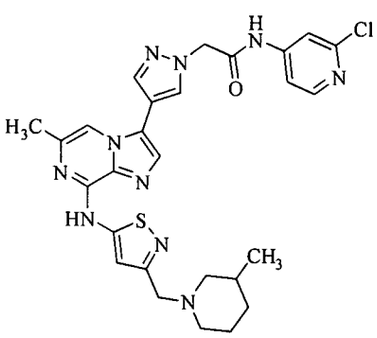


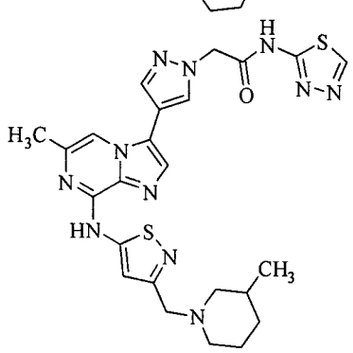
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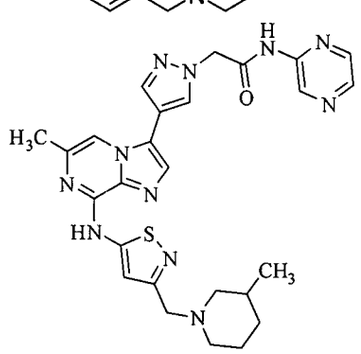


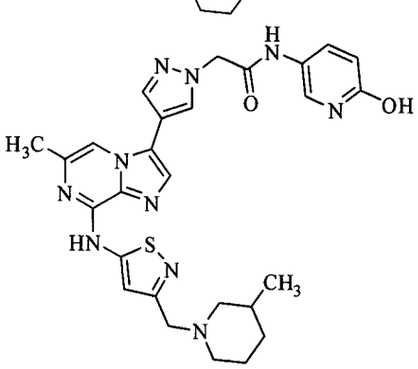


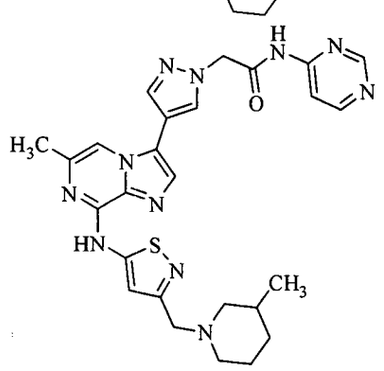


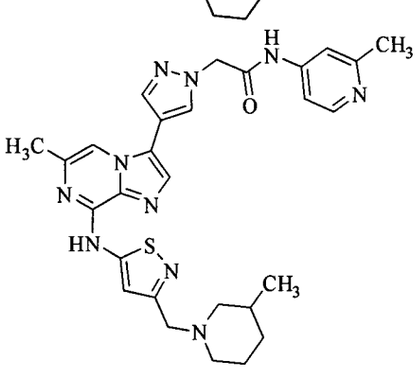


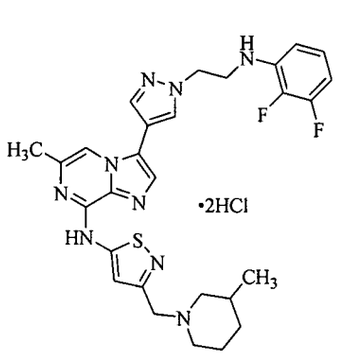


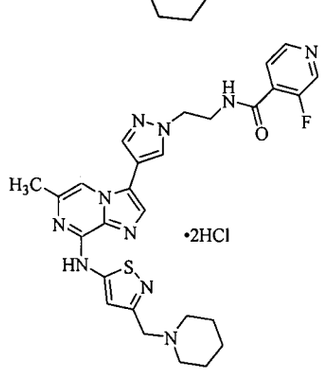








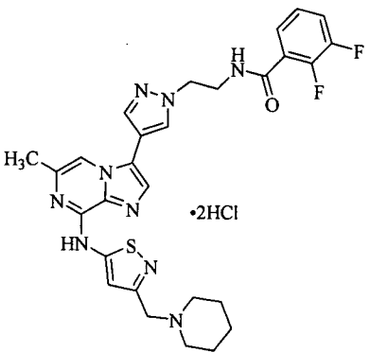


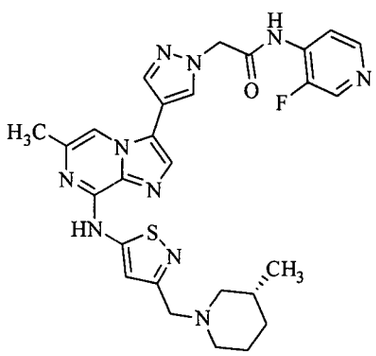


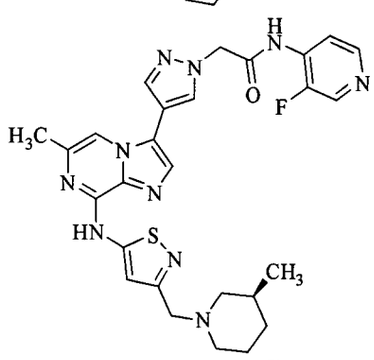
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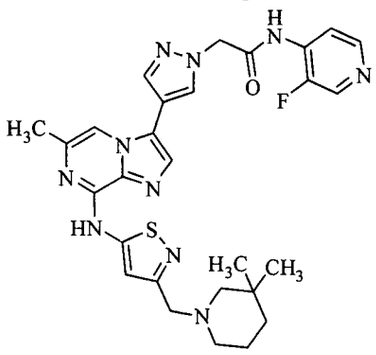
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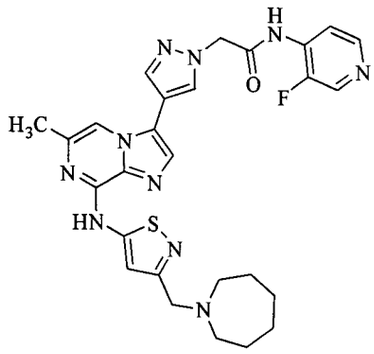
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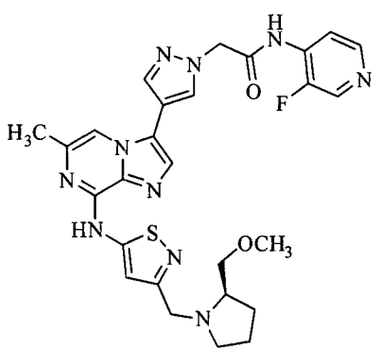


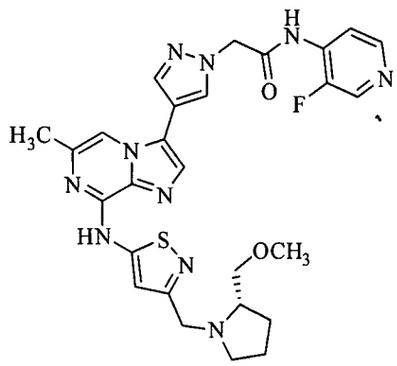


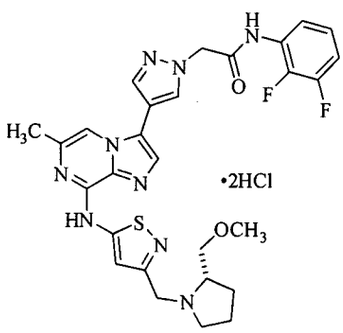


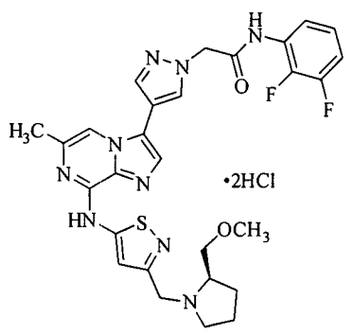




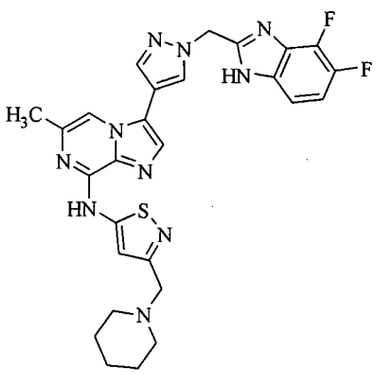


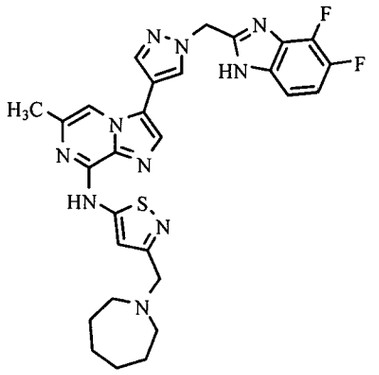


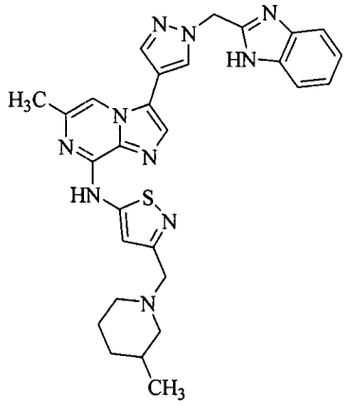


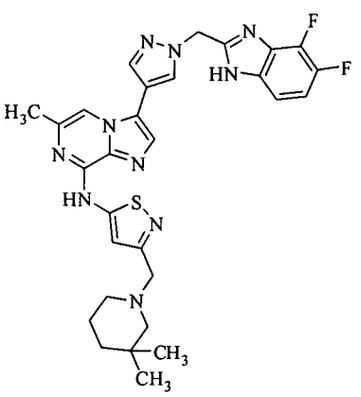


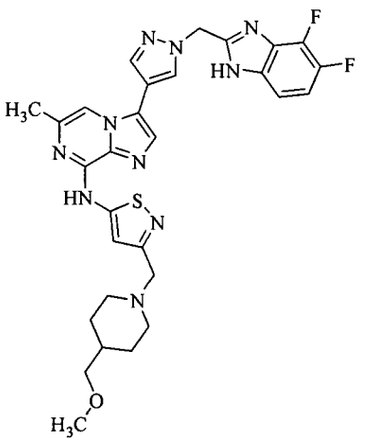
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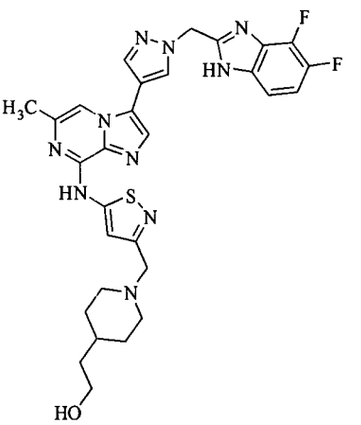


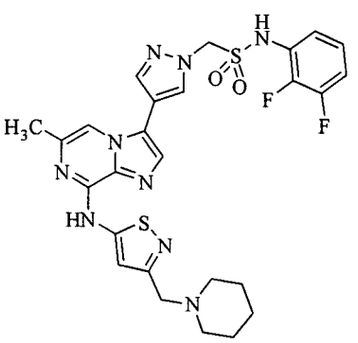


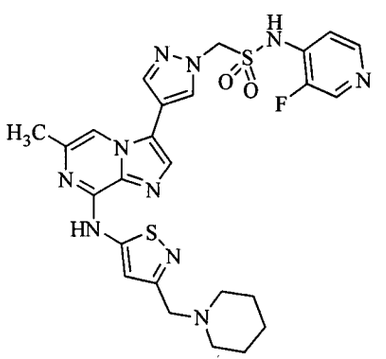


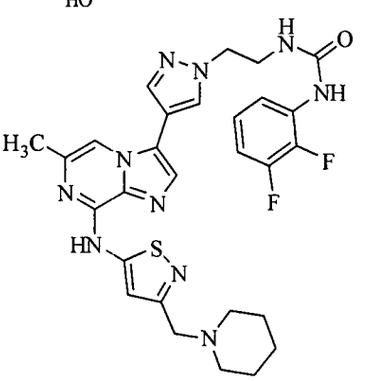


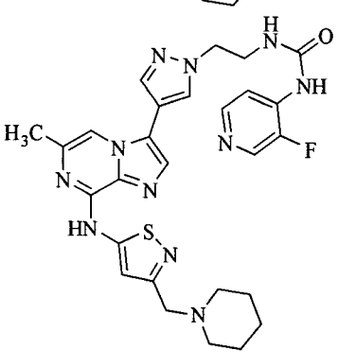


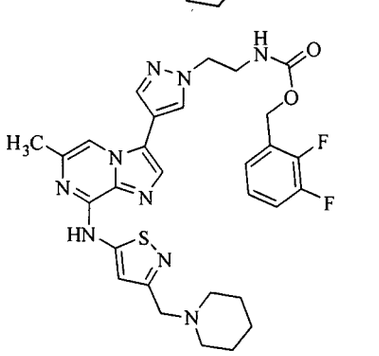


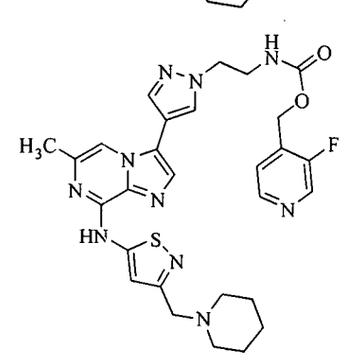




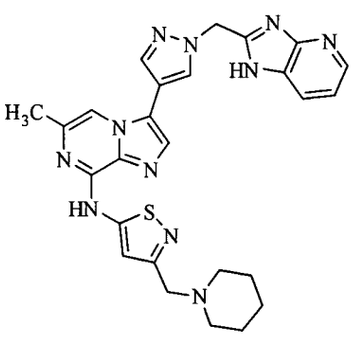


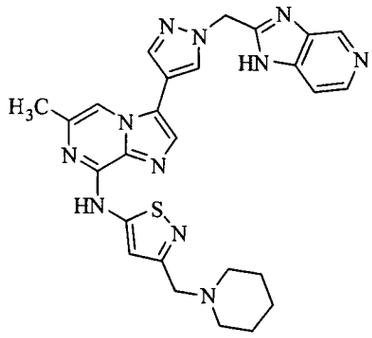


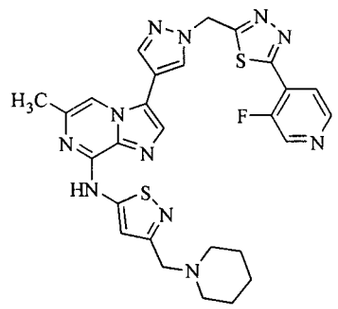


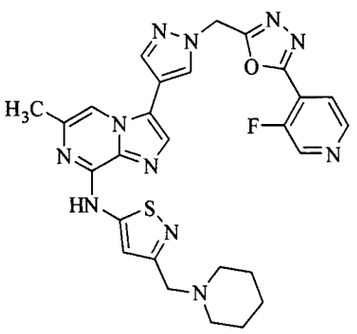


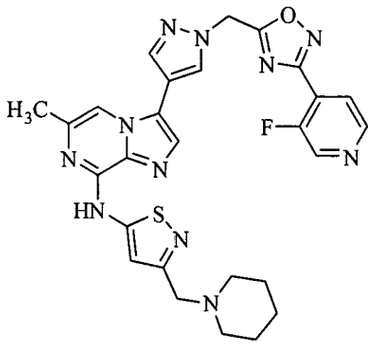
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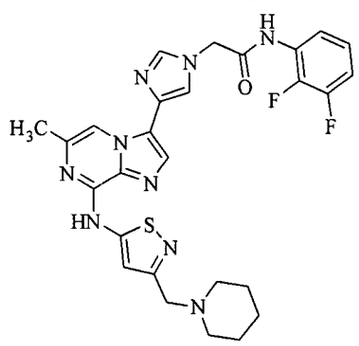


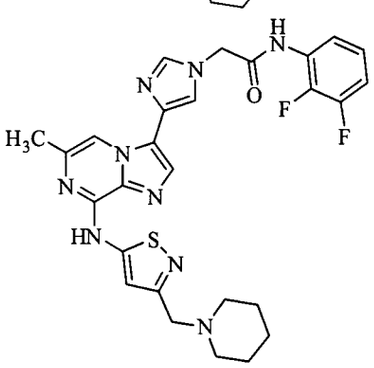


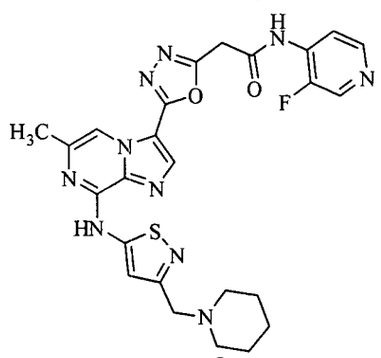


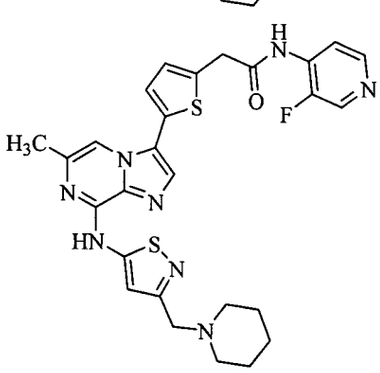


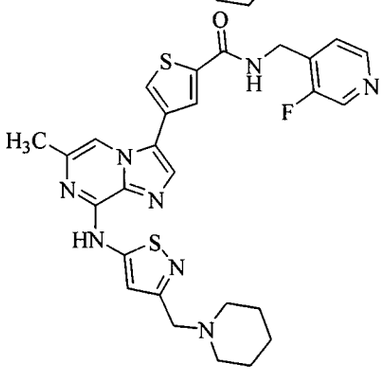


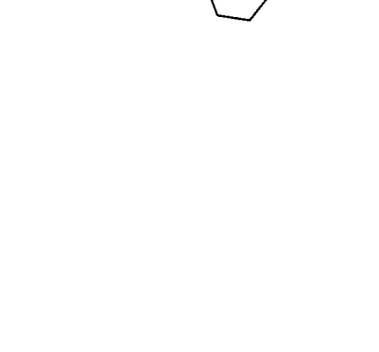




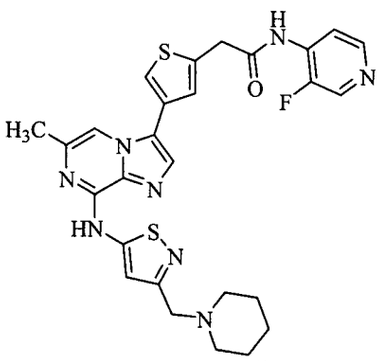


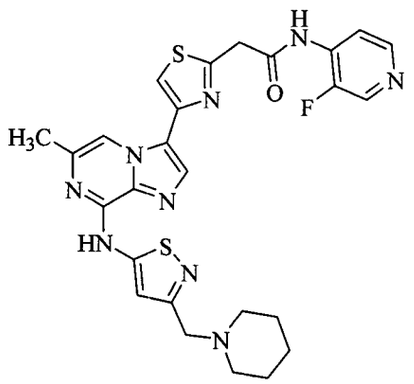


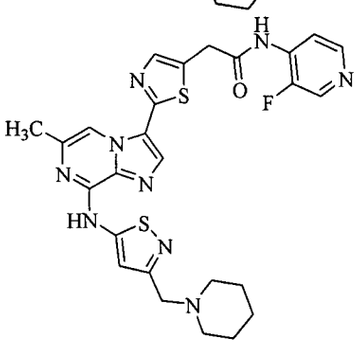


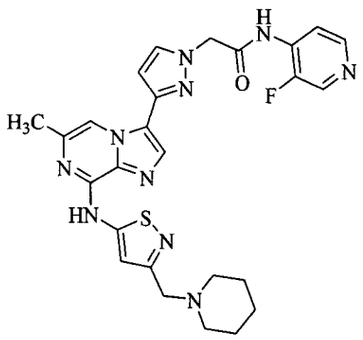


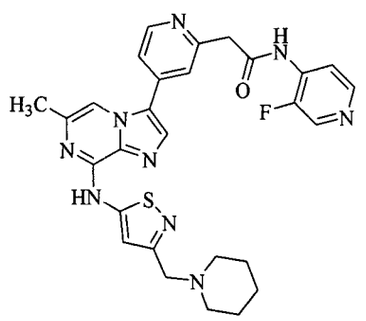
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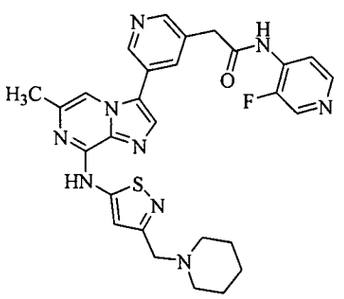


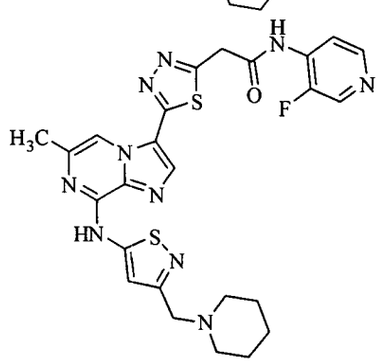


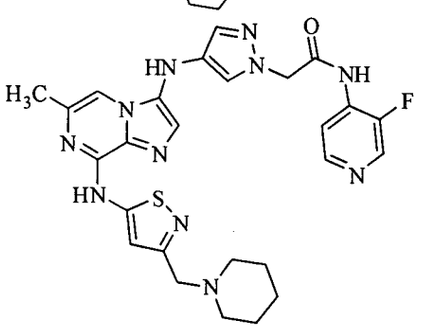


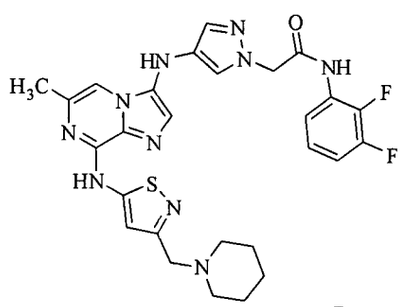


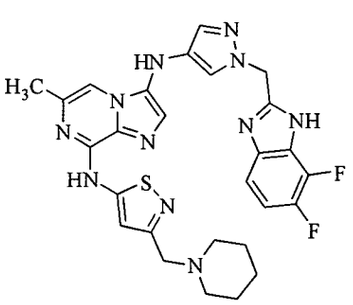


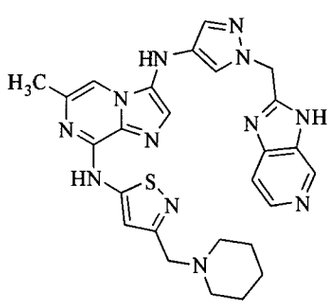


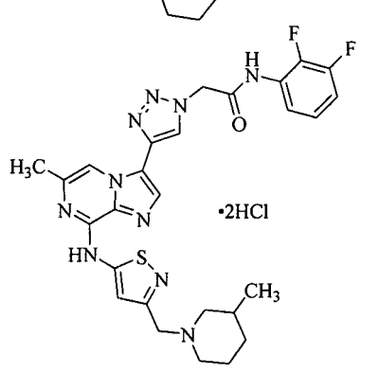




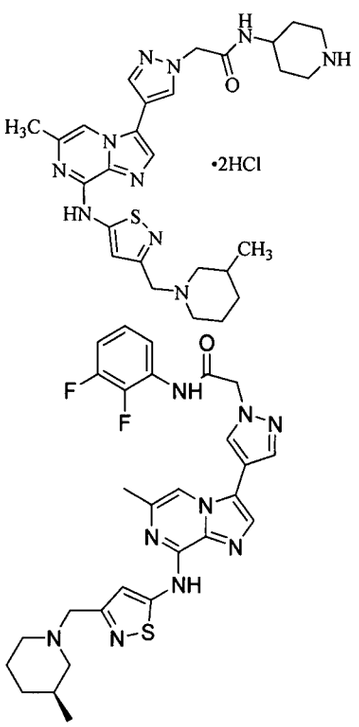


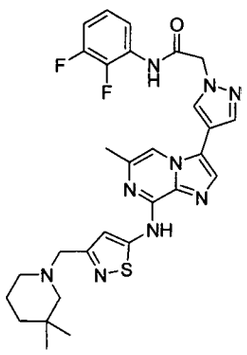


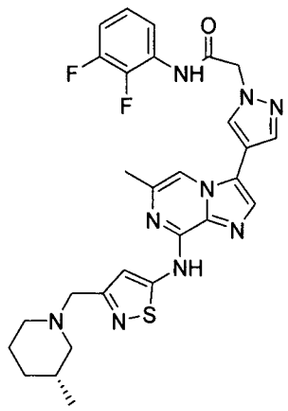




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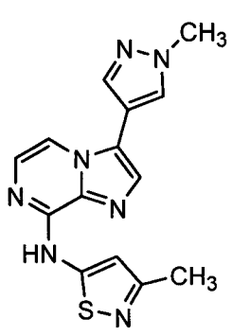
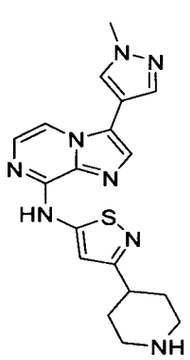
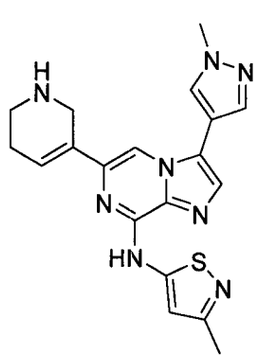




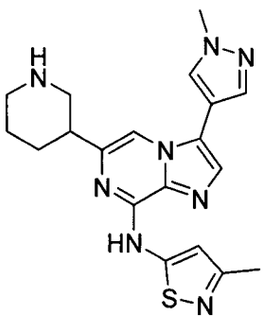
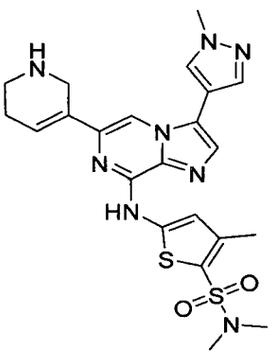
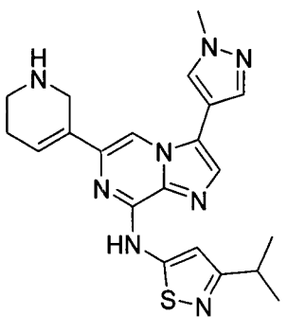
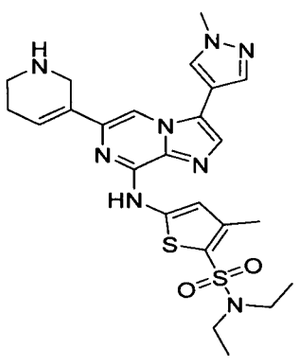
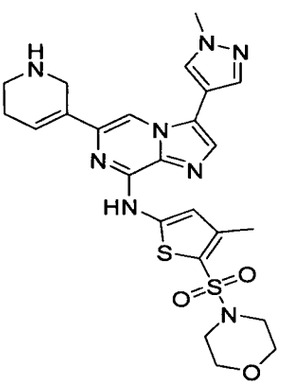
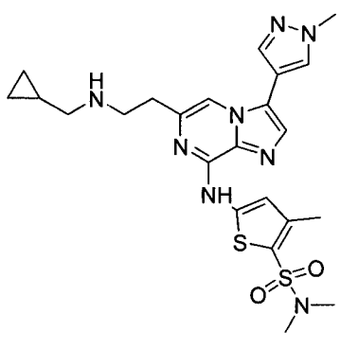
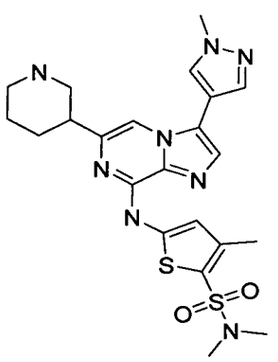
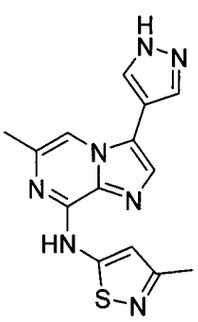
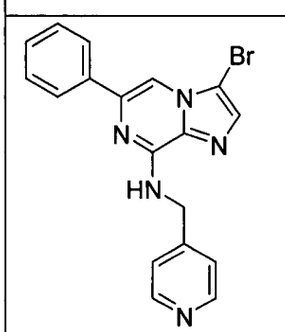
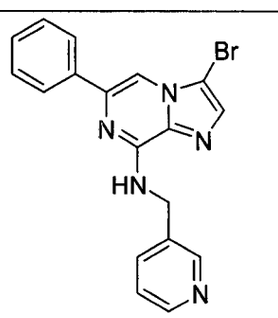
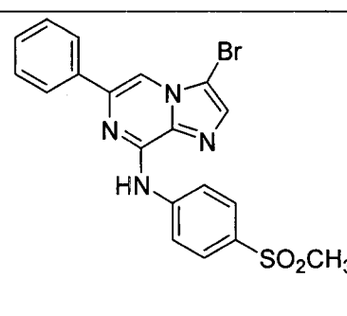


o una de sus sales, solvatos, ésteres o profármacos farmacéuticamente aceptables.

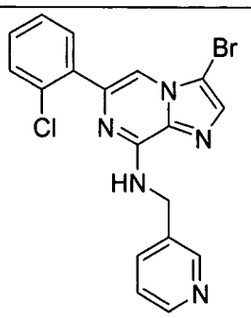
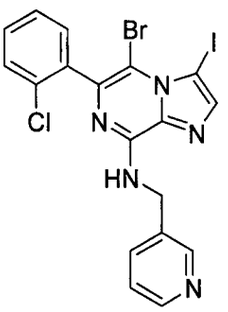
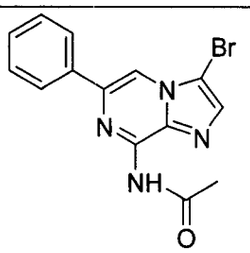
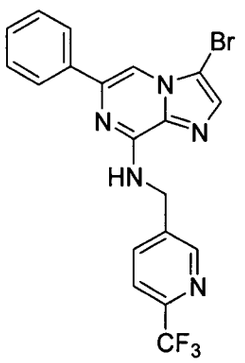
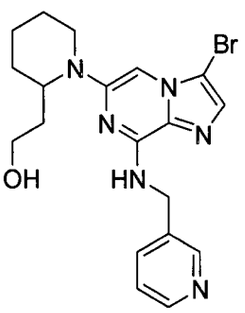
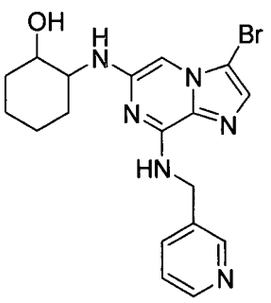
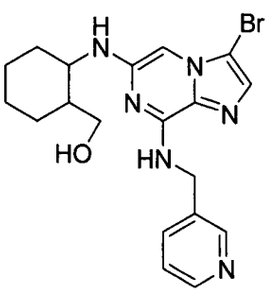
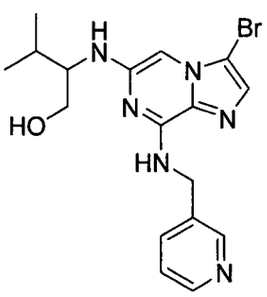
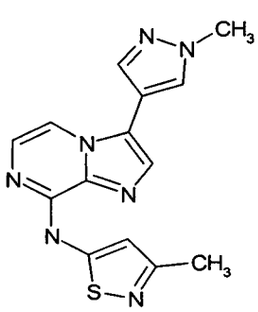
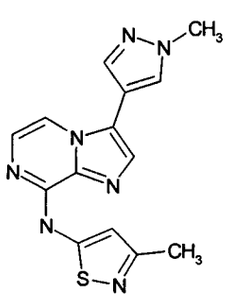
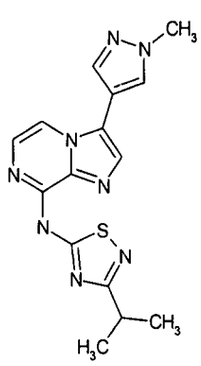
15. El método de acuerdo con la reivindicación 2, en donde dichos inhibidores de aurora quinasa representados por las fórmulas E–K están seleccionados del grupo que consiste en:

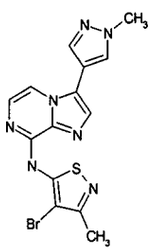
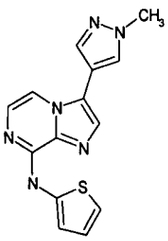
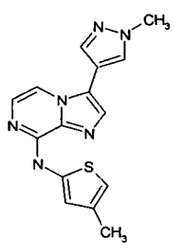
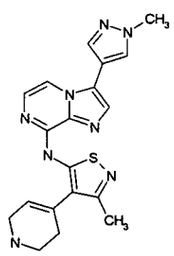
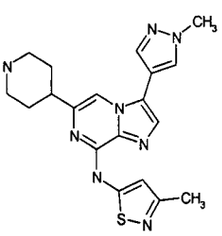
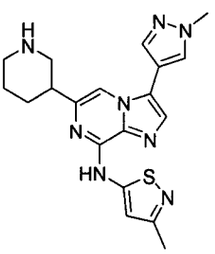
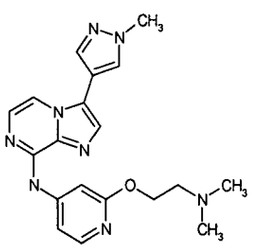
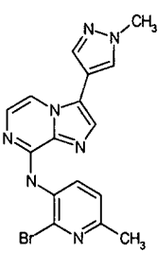
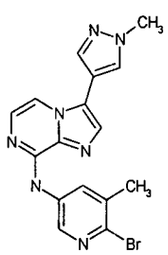
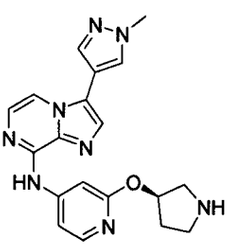
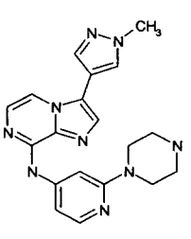
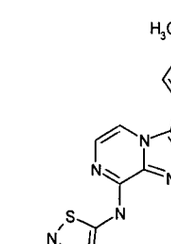
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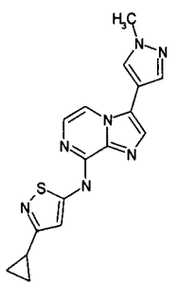
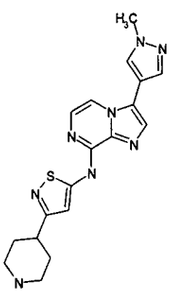
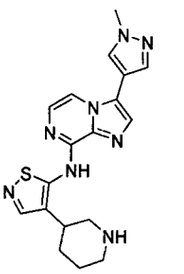
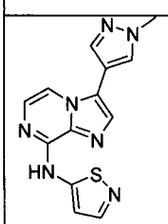
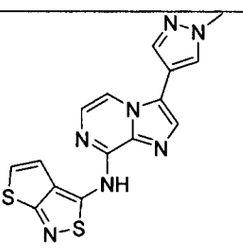
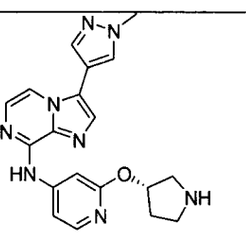
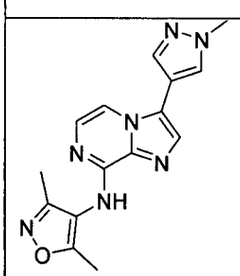
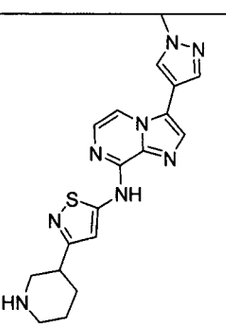
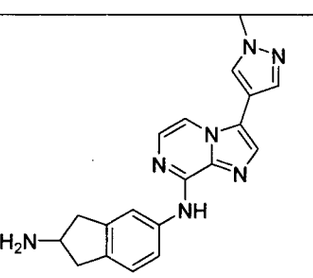
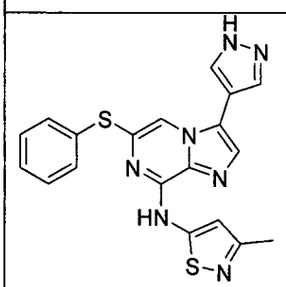
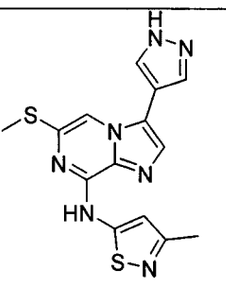
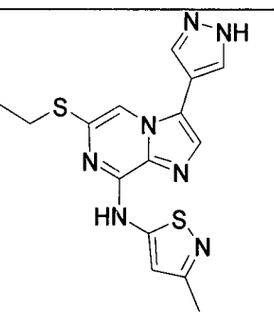
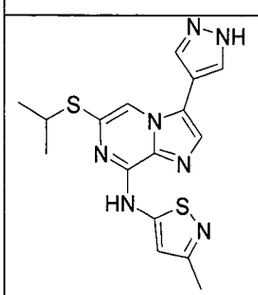
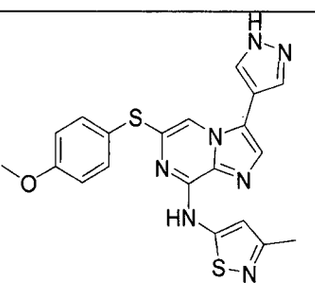
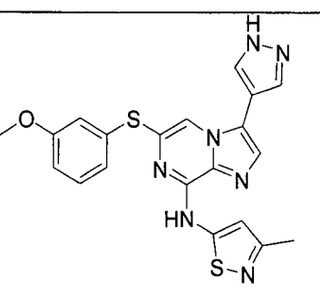
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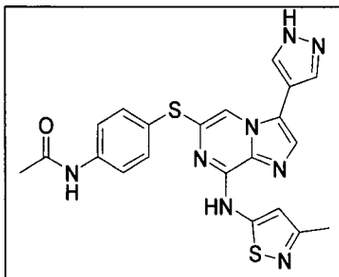
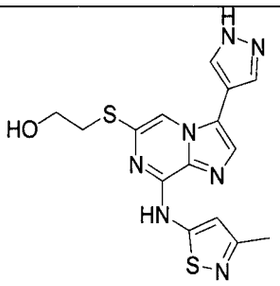
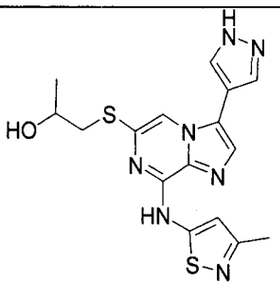
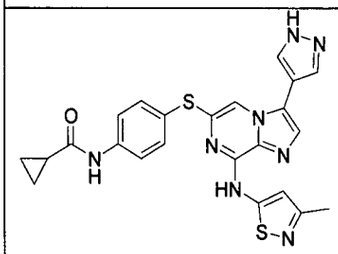
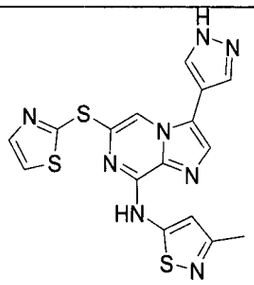
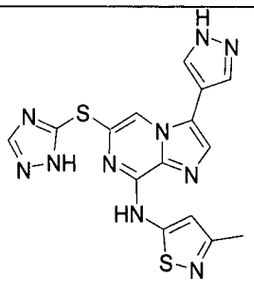
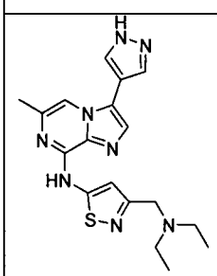
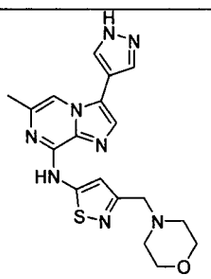
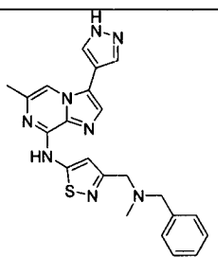
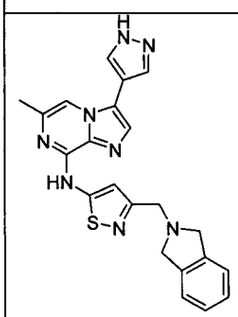
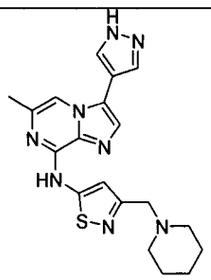
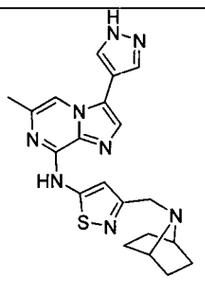
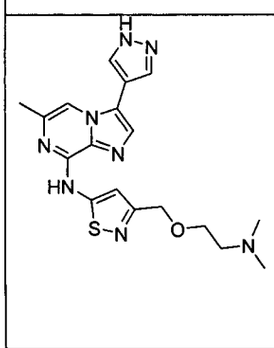
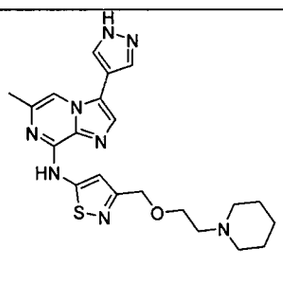
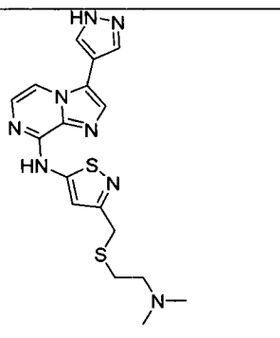
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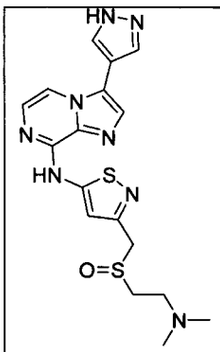
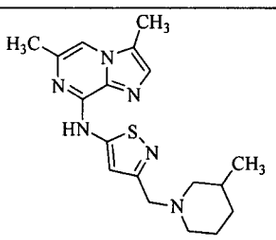
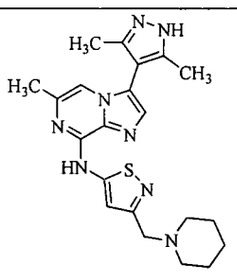
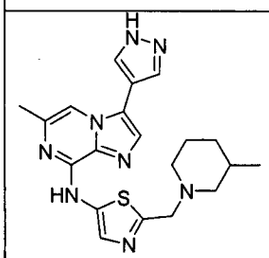
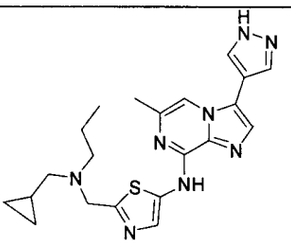
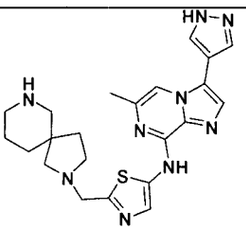
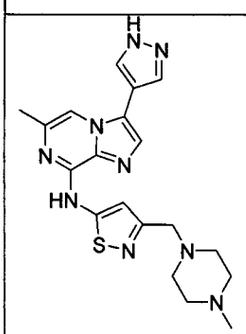
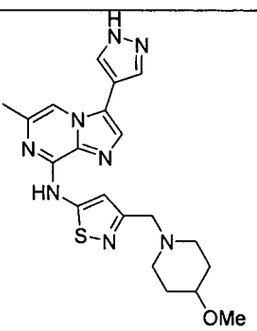
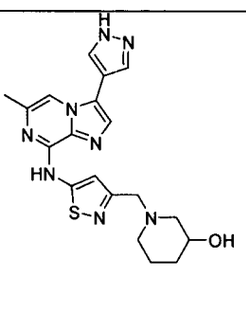
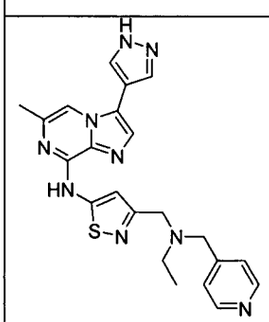
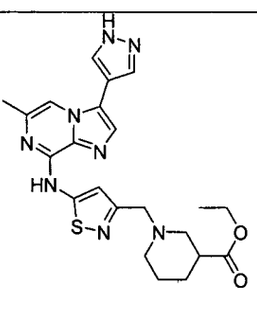
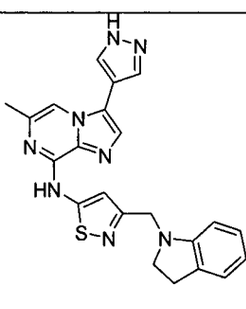
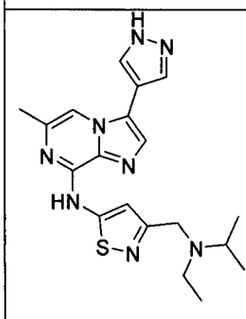
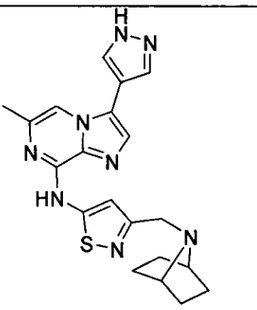
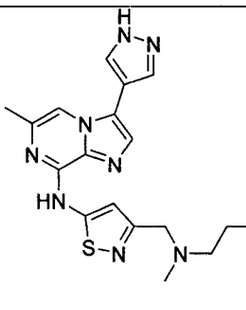
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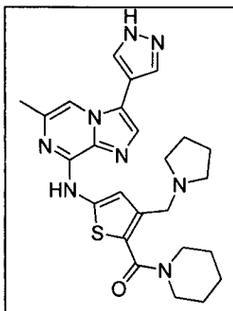
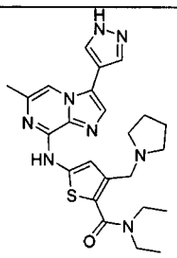
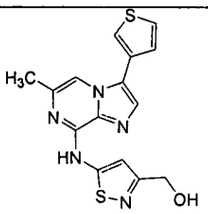
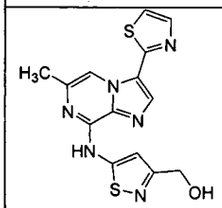
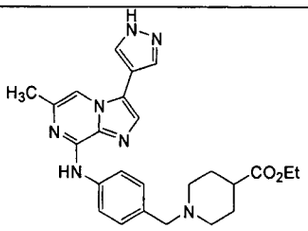
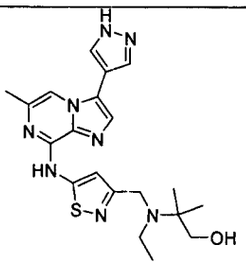
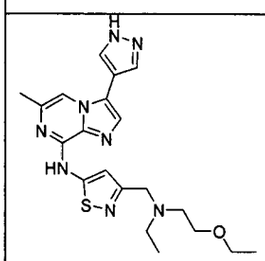
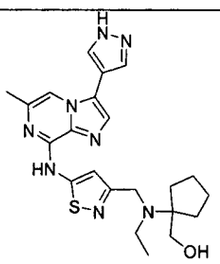
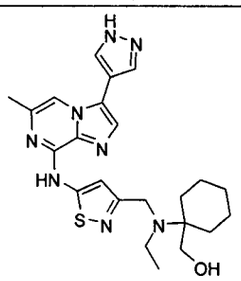
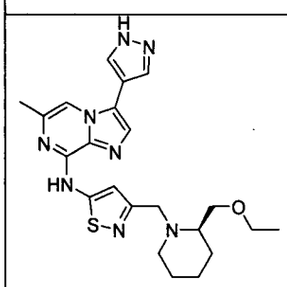
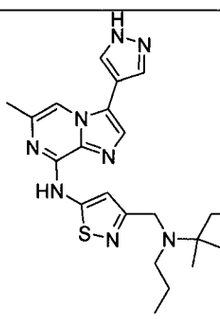
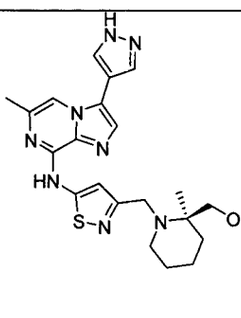
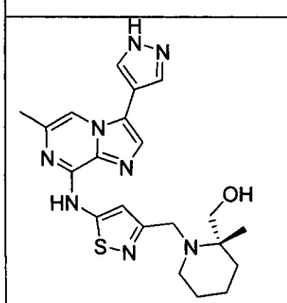
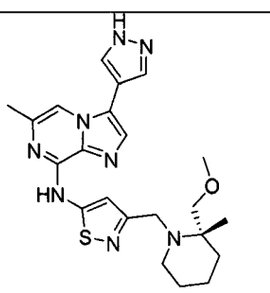
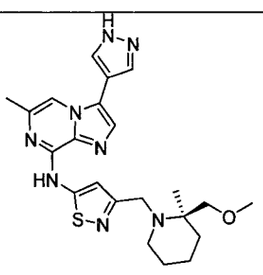
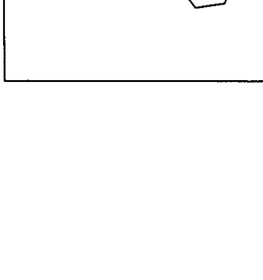
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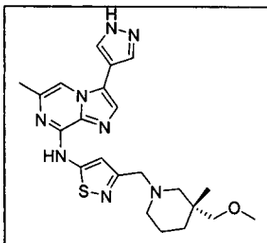
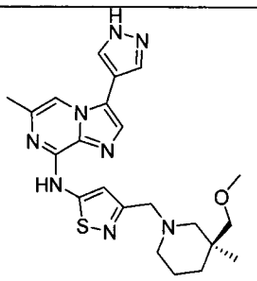
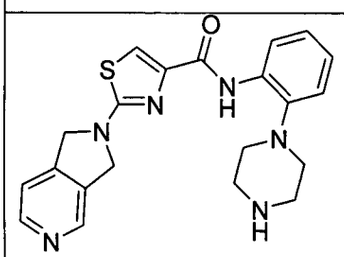
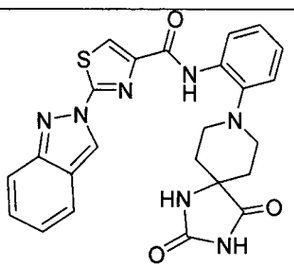
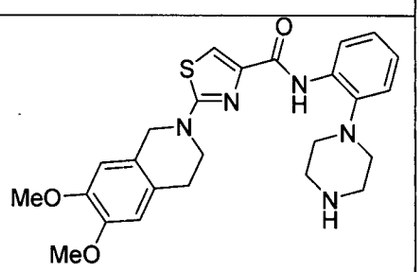
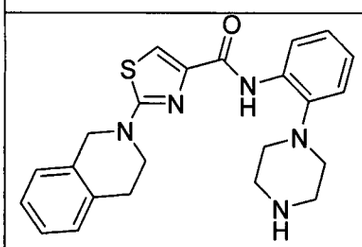
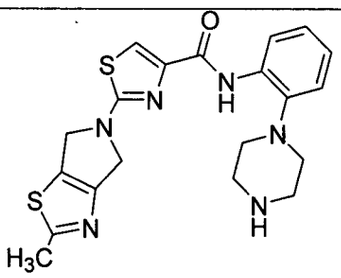
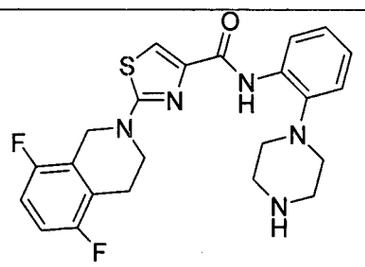
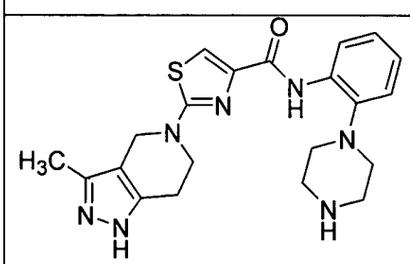
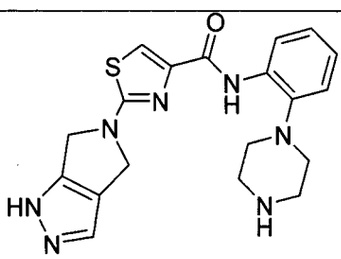
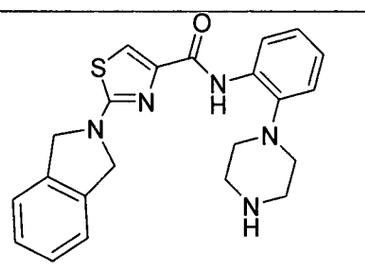
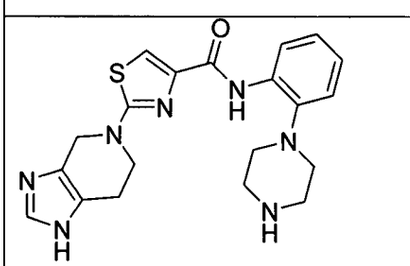
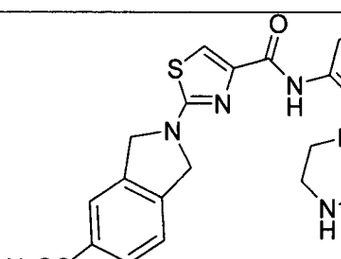
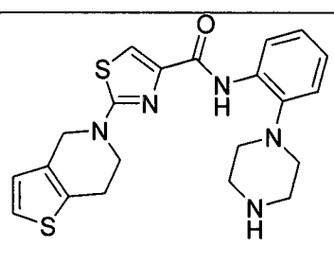
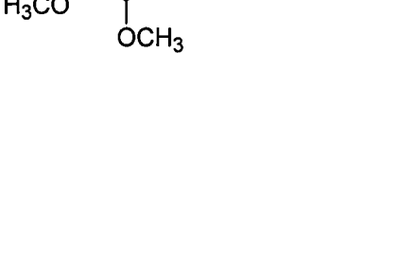
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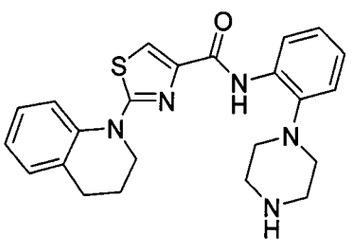
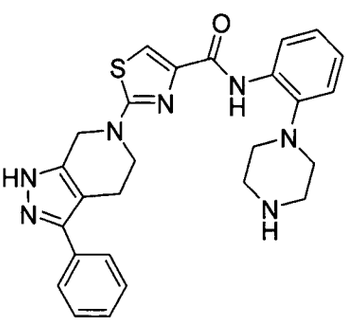
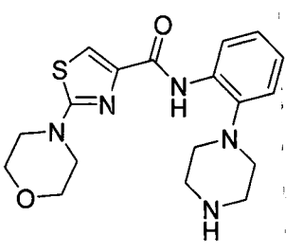
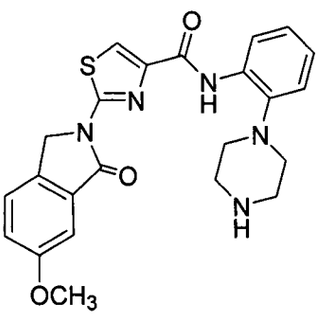
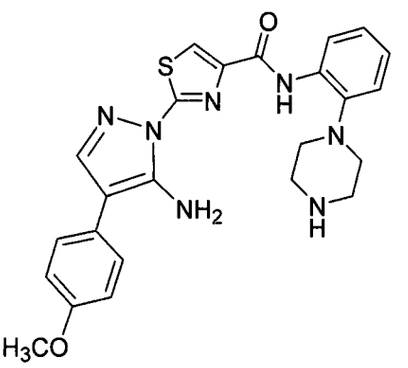
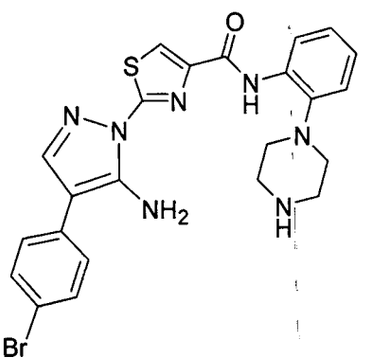
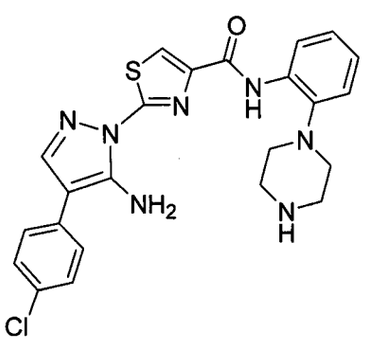
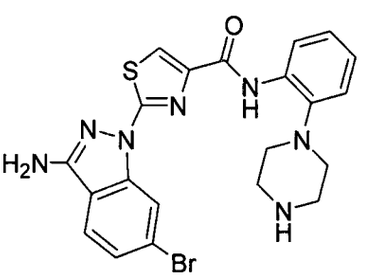
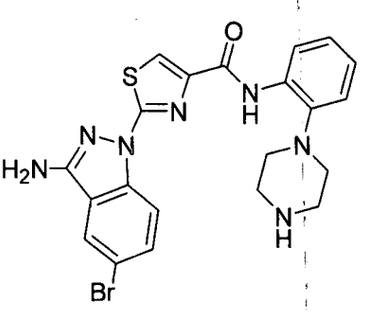
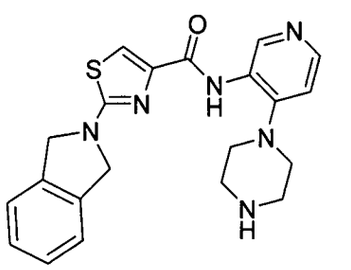
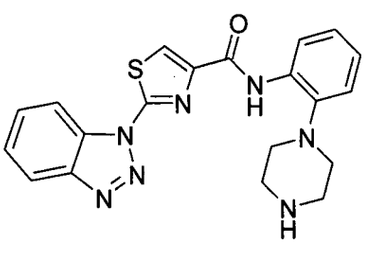
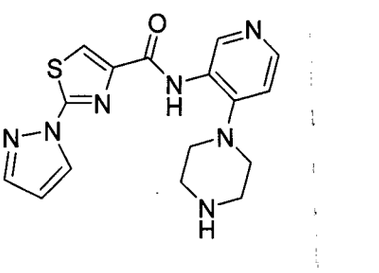
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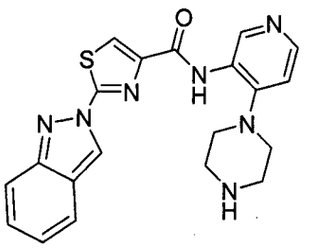
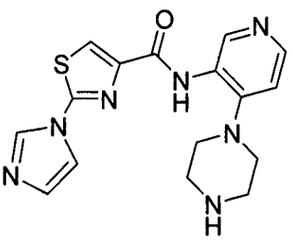
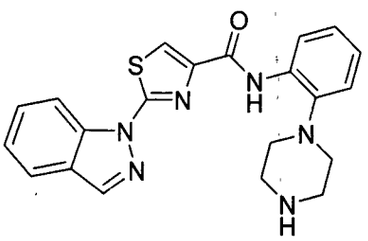
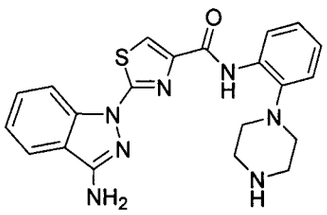
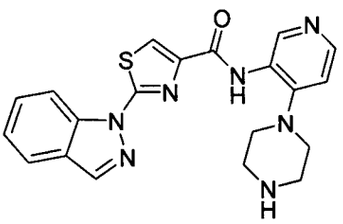
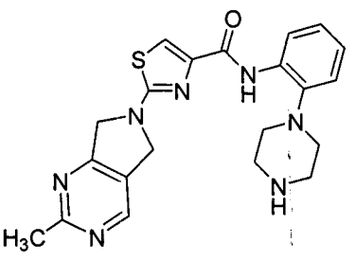
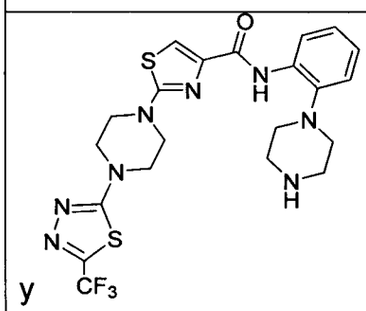
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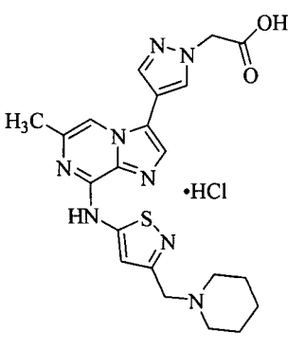
		
		
		
		
		
		

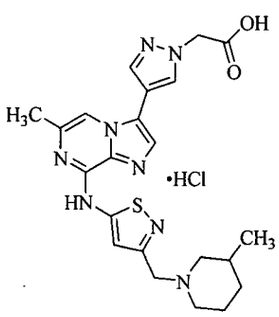
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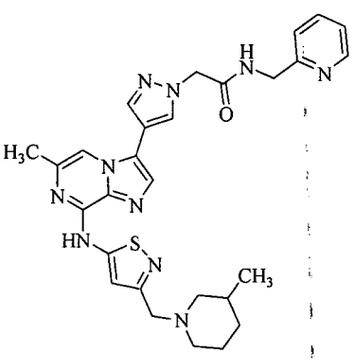
		
		
		
		

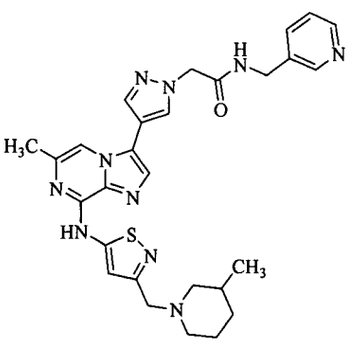
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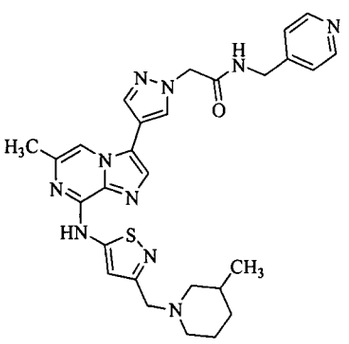
		
		
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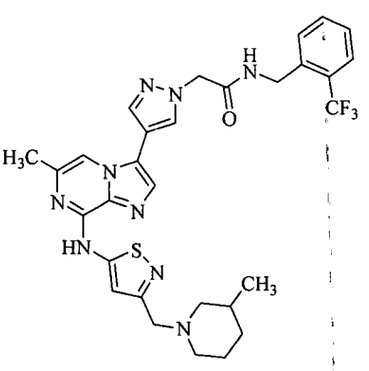




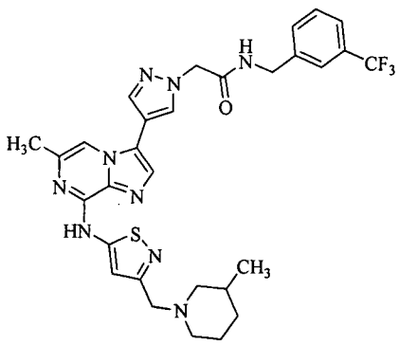


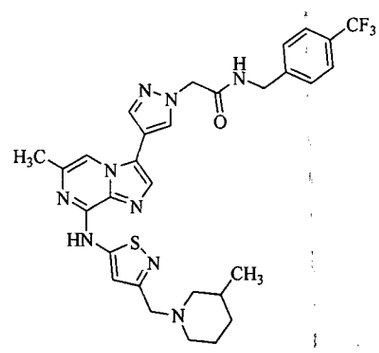


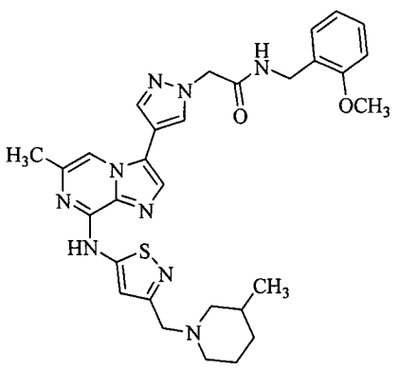


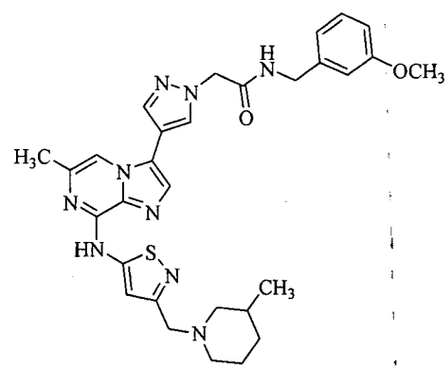


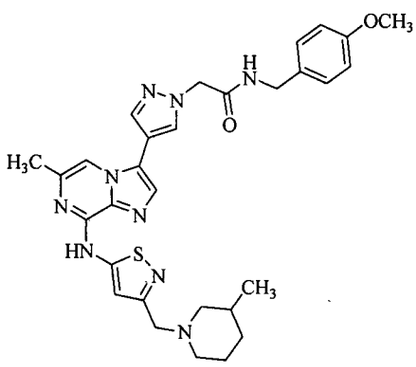
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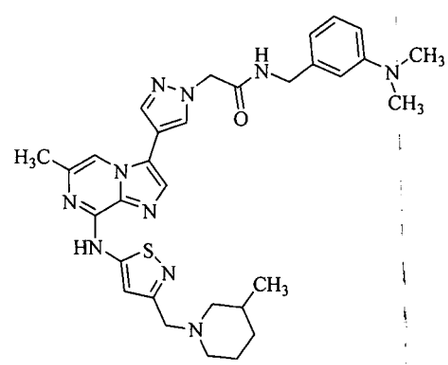


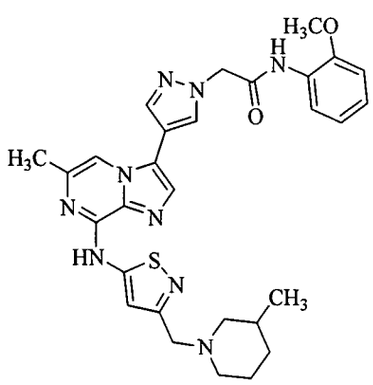


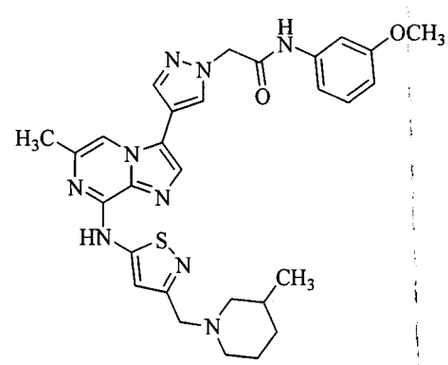


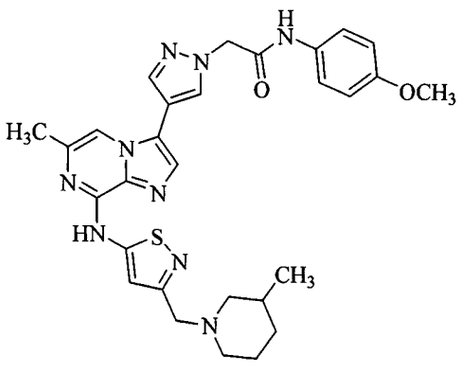


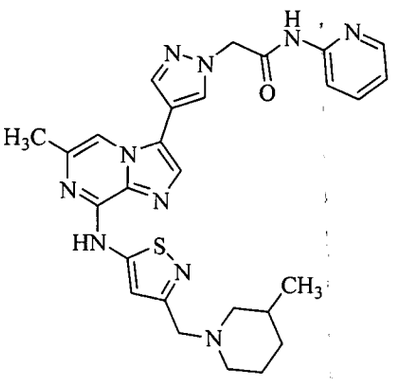


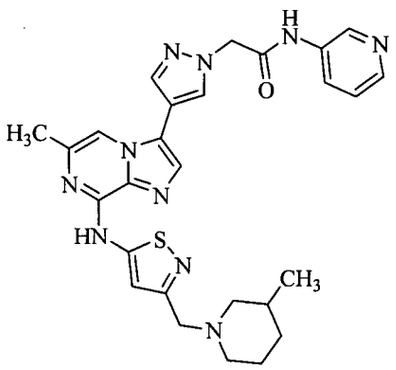


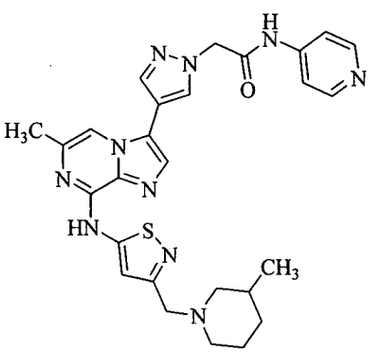


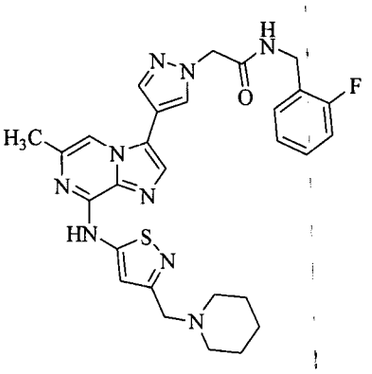


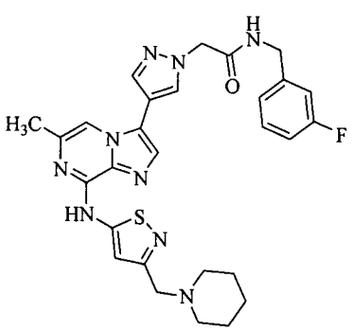


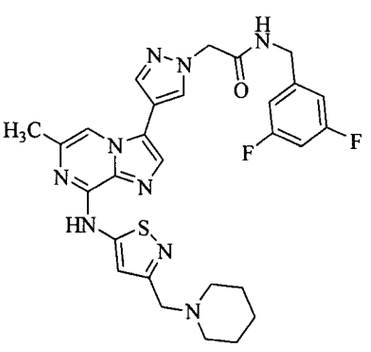


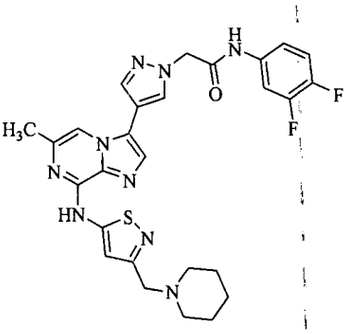


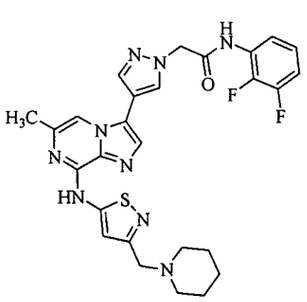


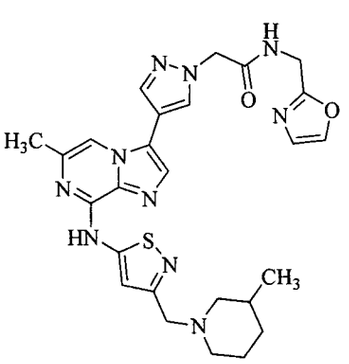


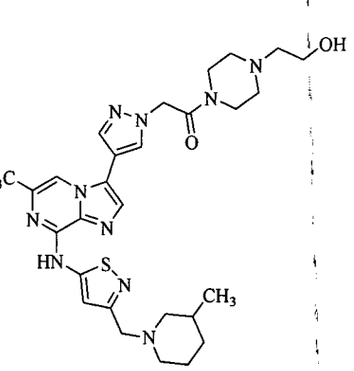




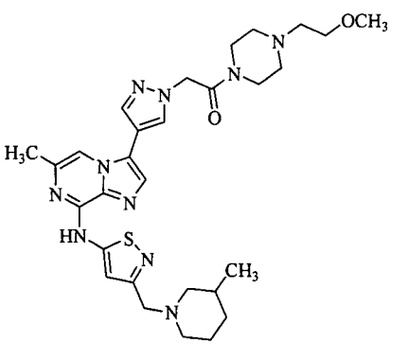


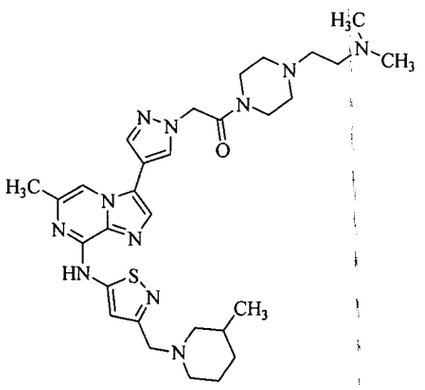


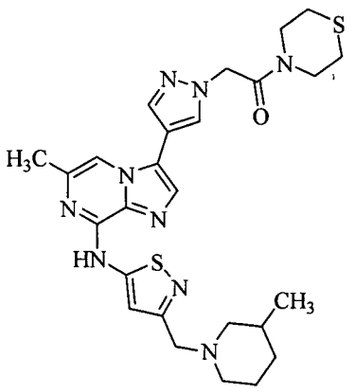


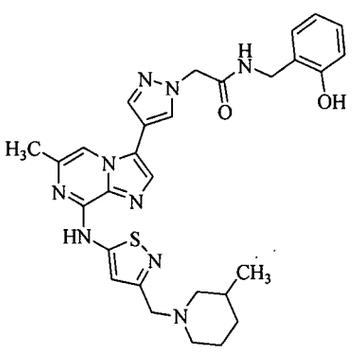


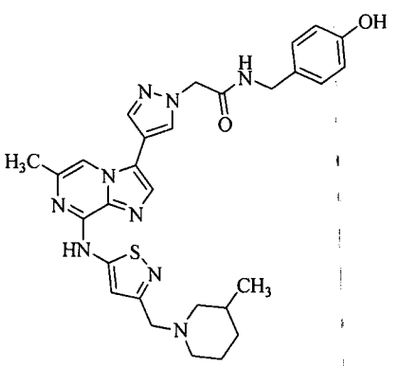
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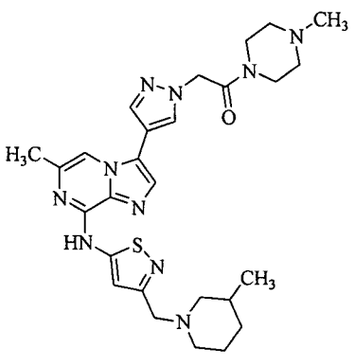


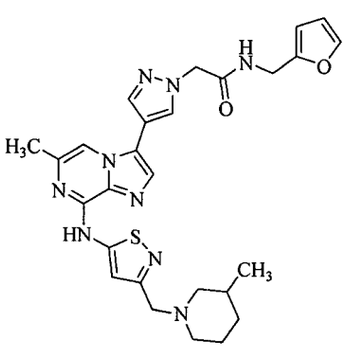


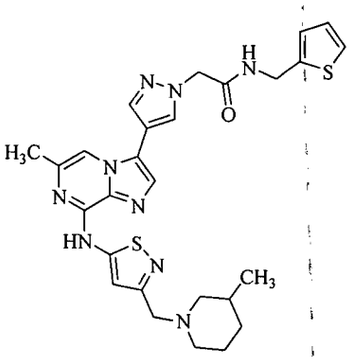


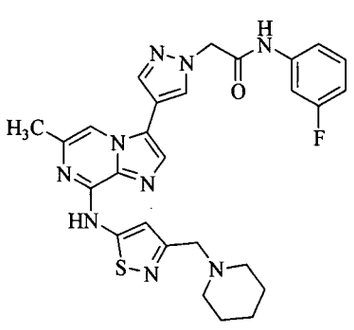


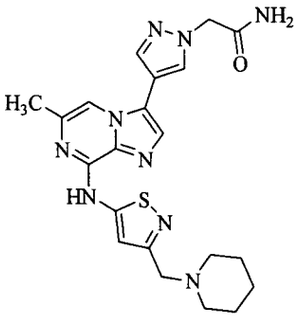


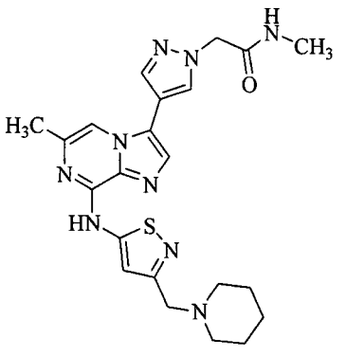


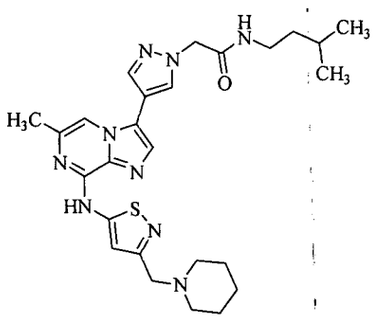


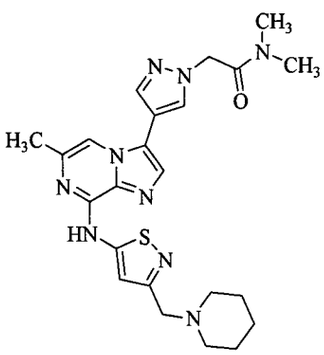


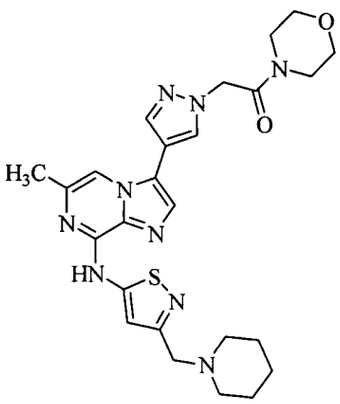


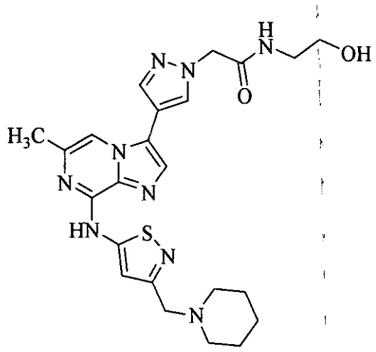


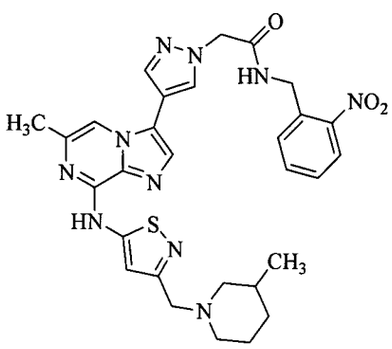


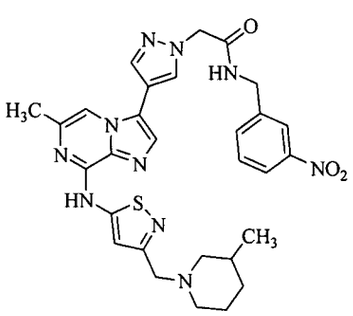


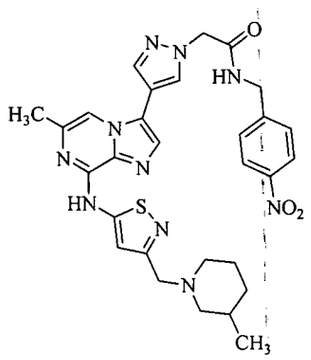


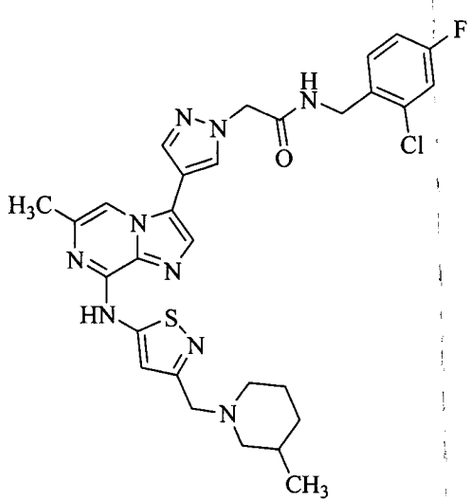


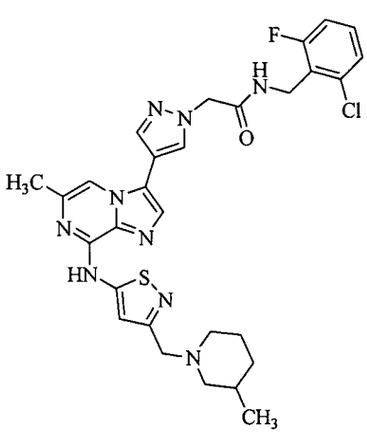


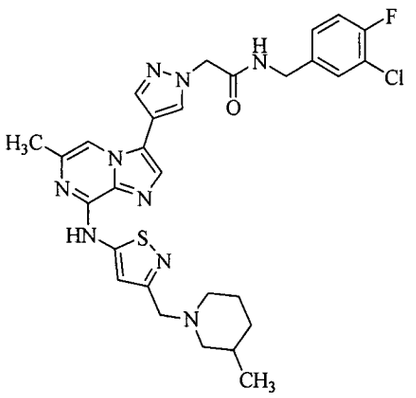


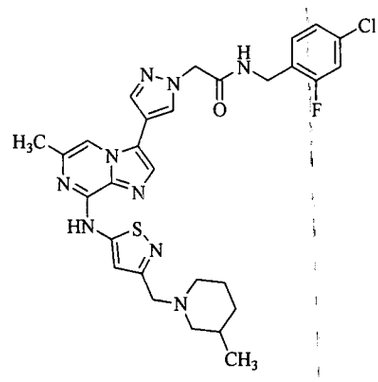


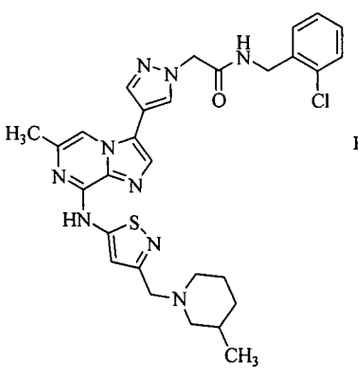


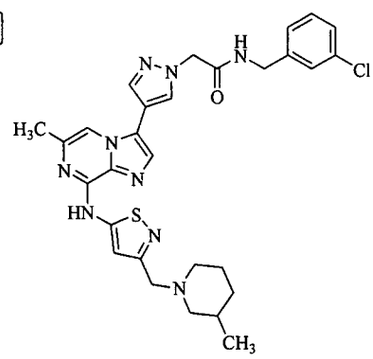


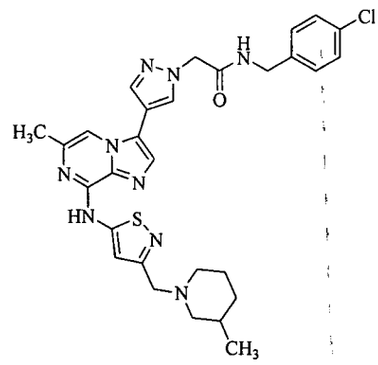


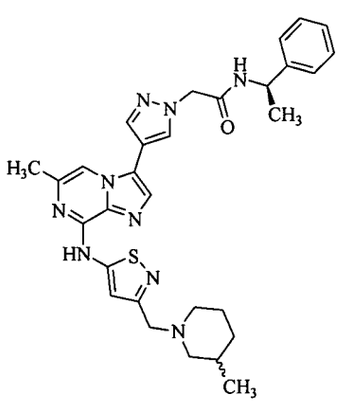


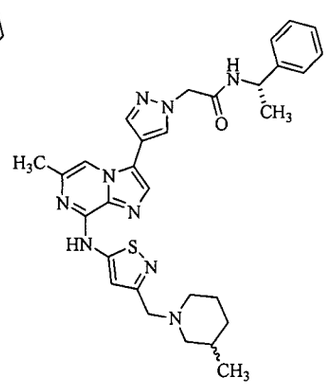


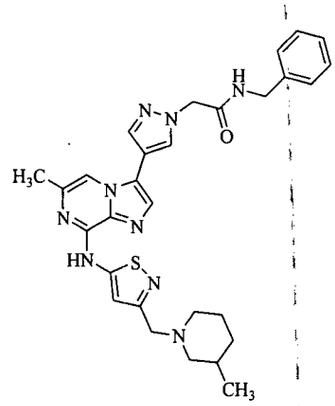


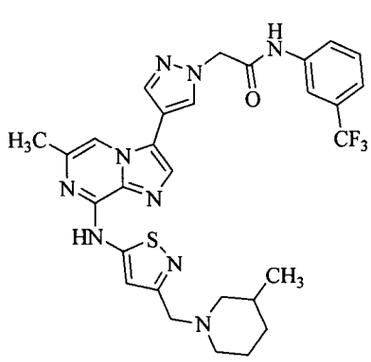


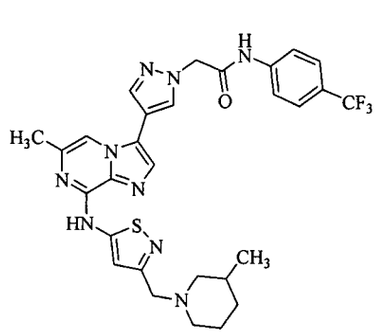


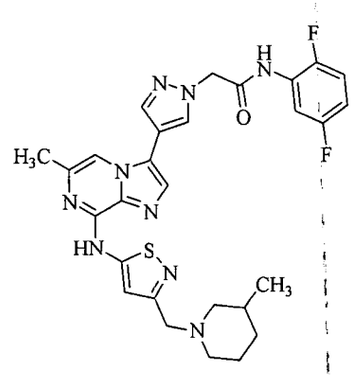


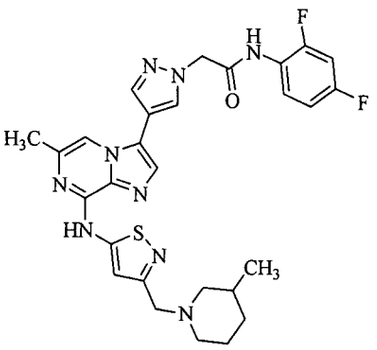


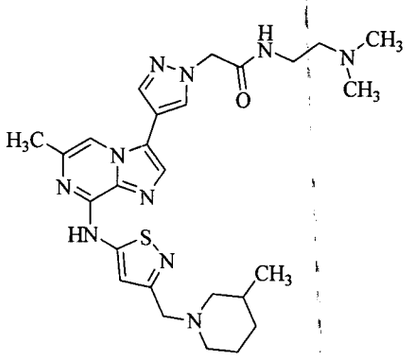


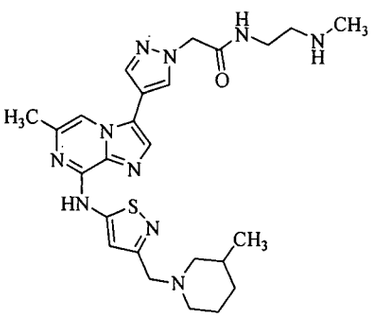


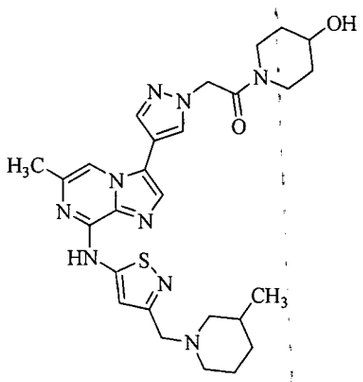


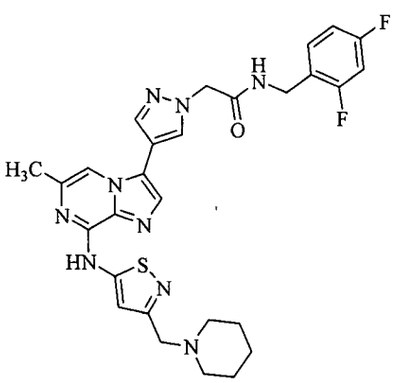


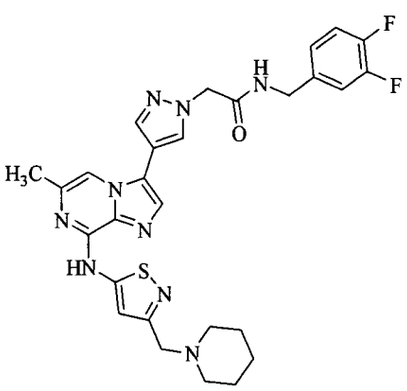


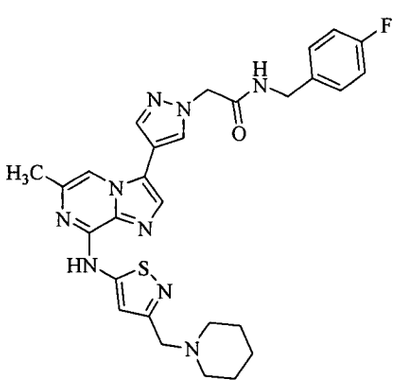


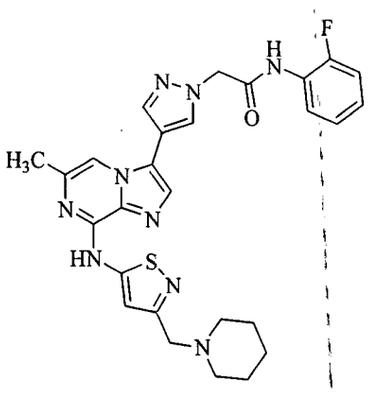


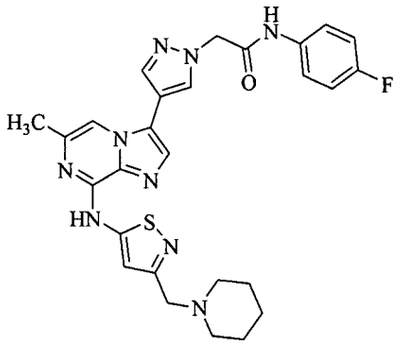


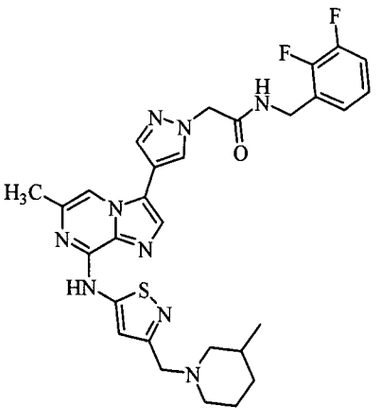


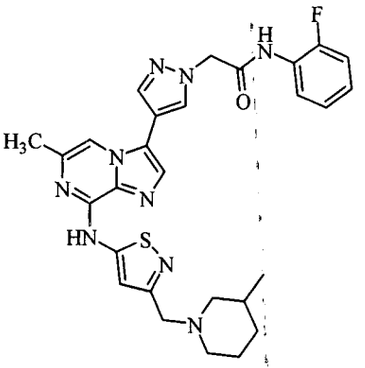


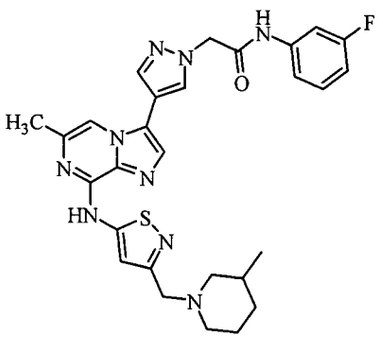


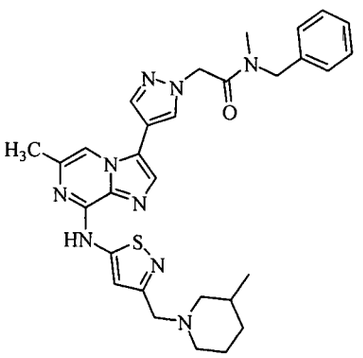


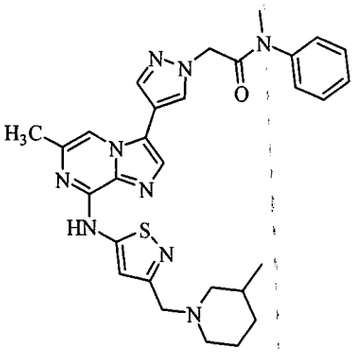


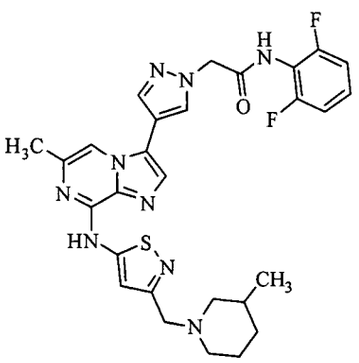


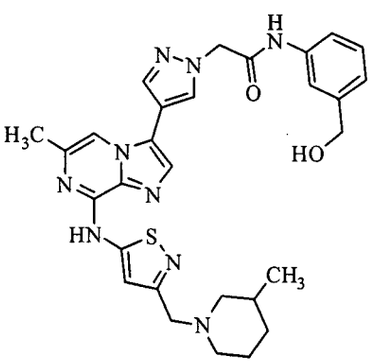


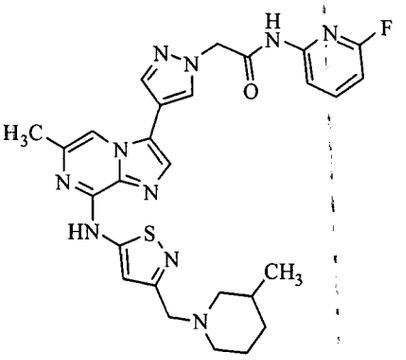


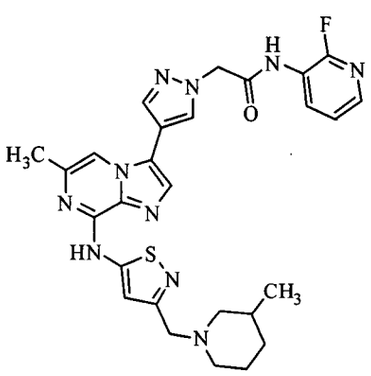


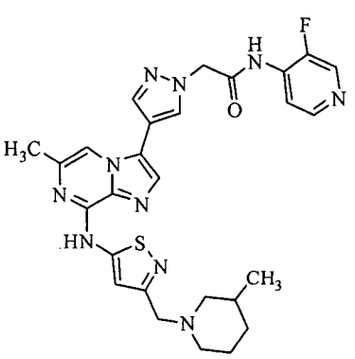


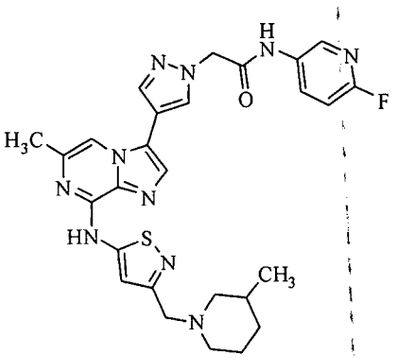


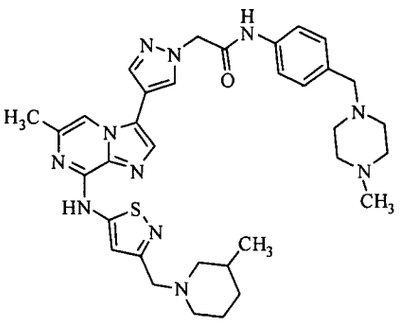


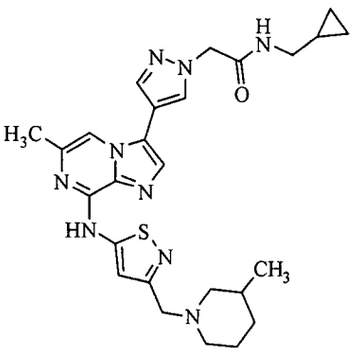


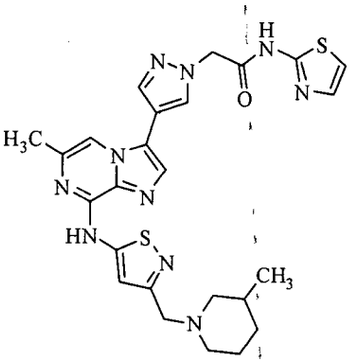


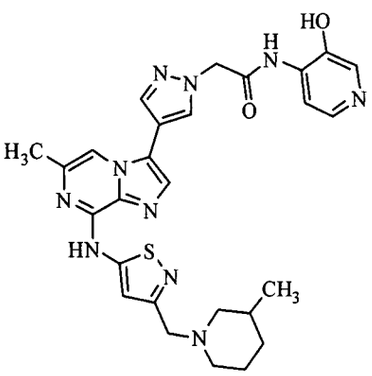


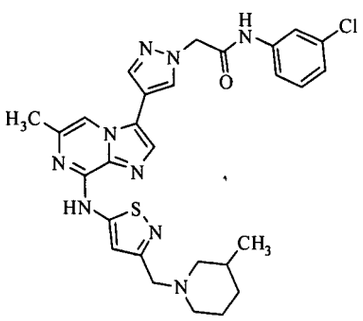


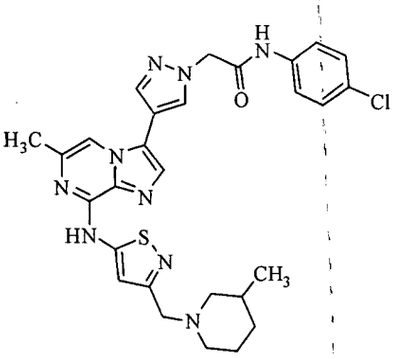


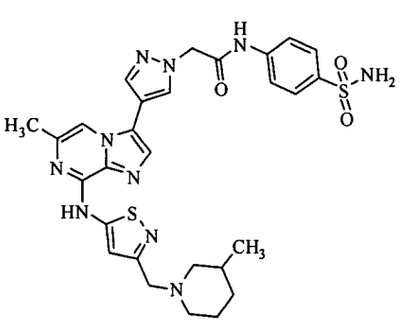


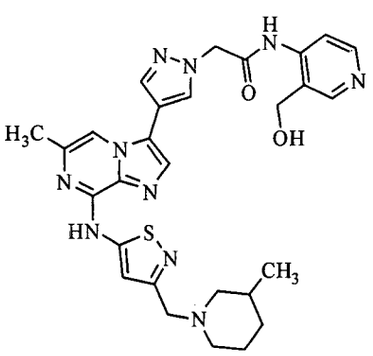


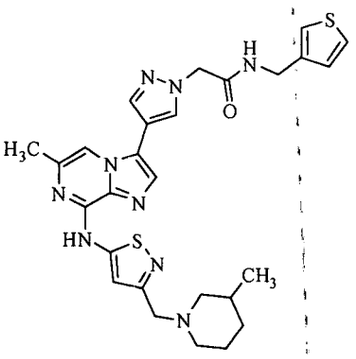


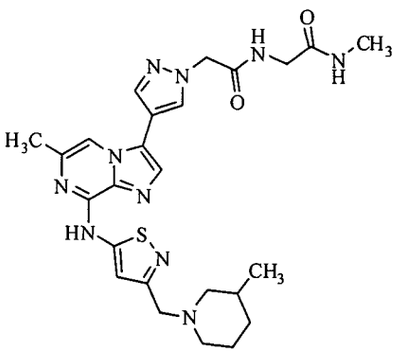


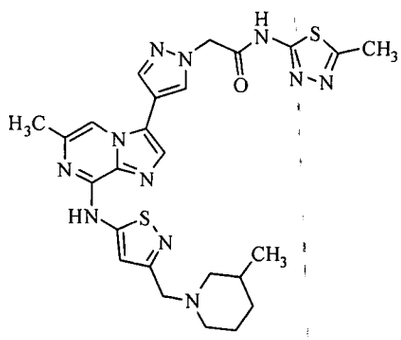


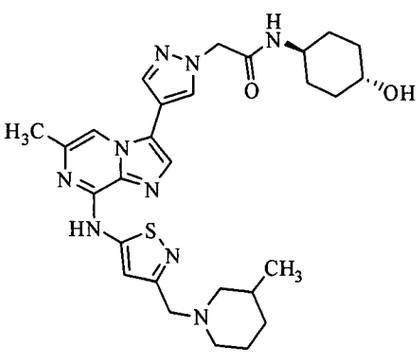


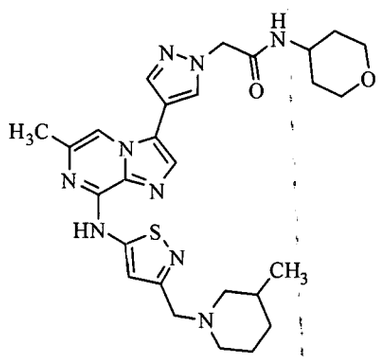


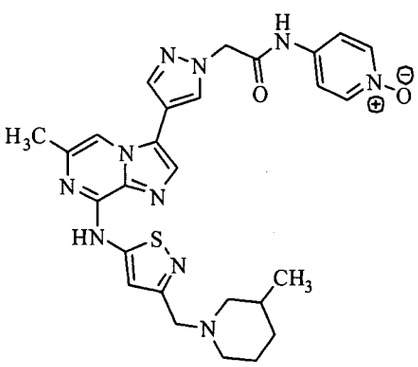


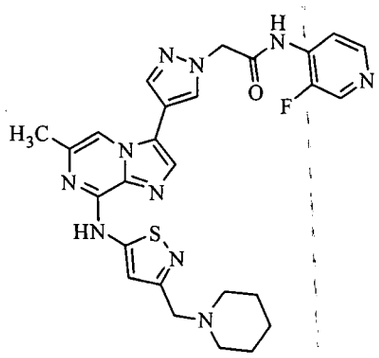


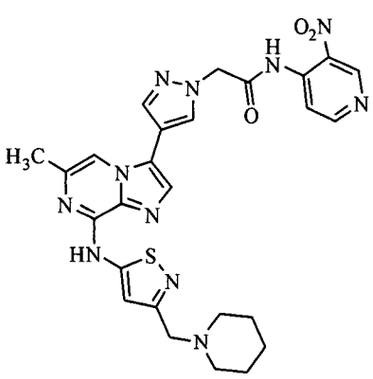


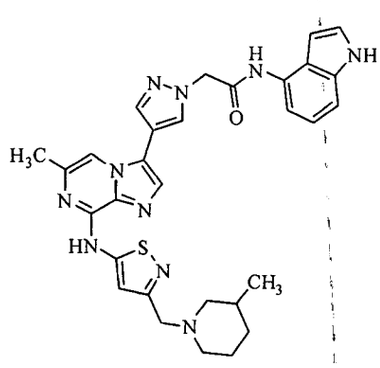




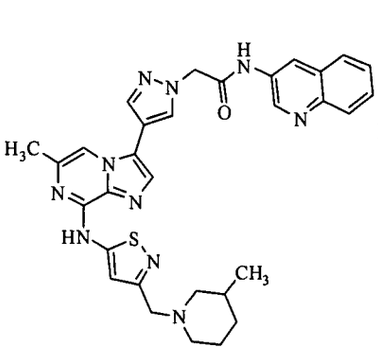


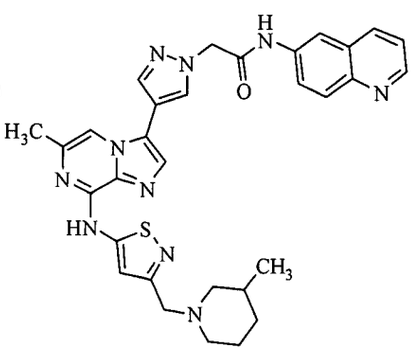


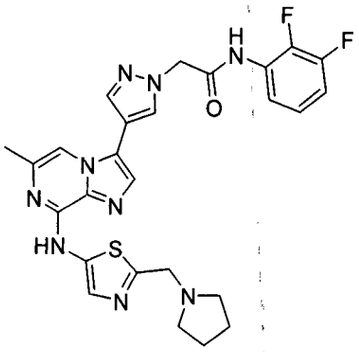


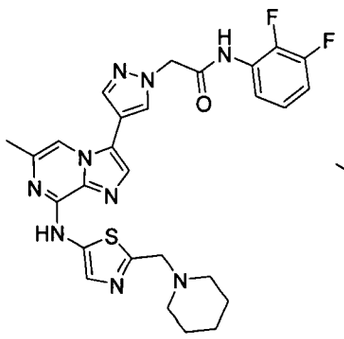


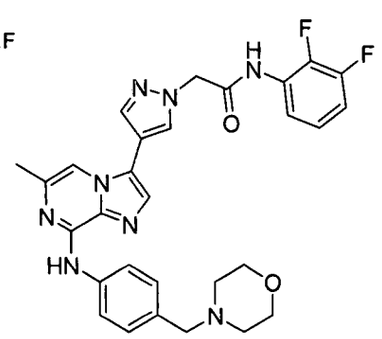
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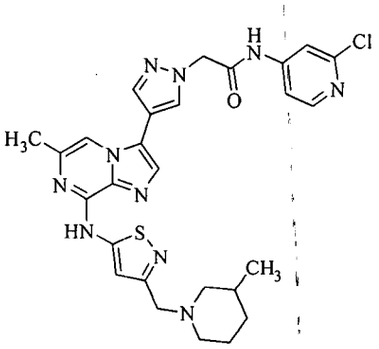


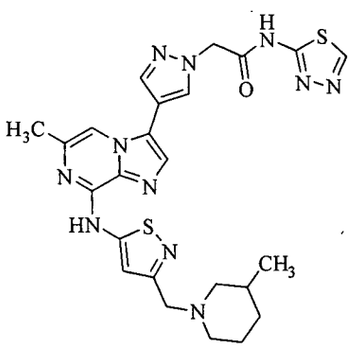


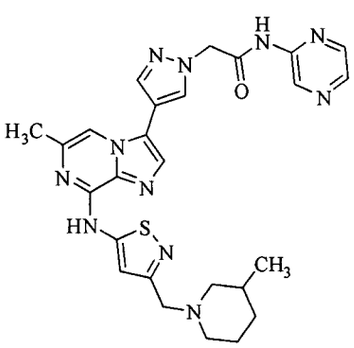


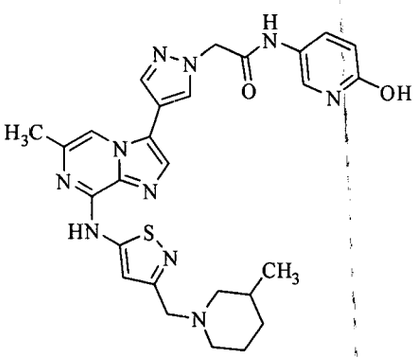


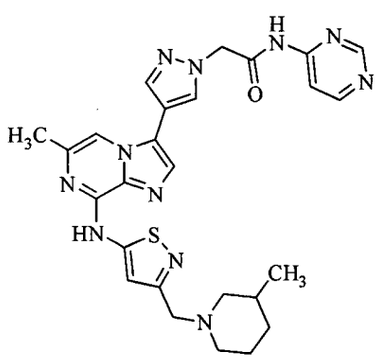


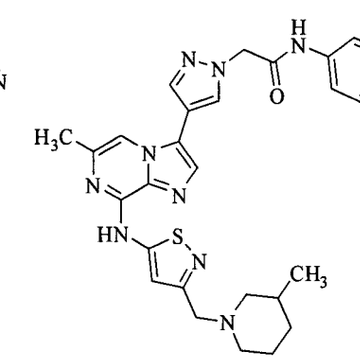


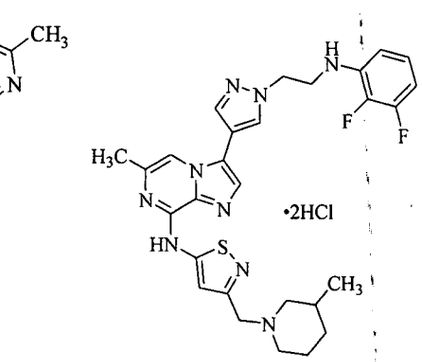




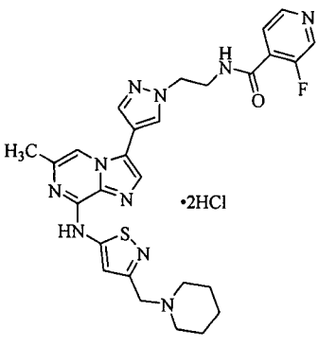


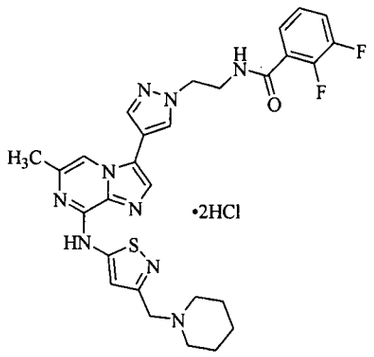


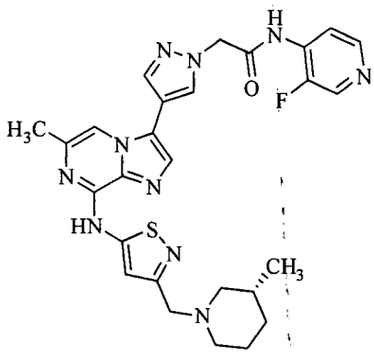


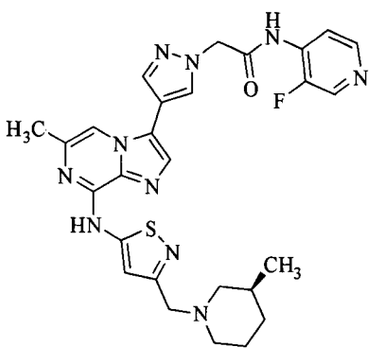


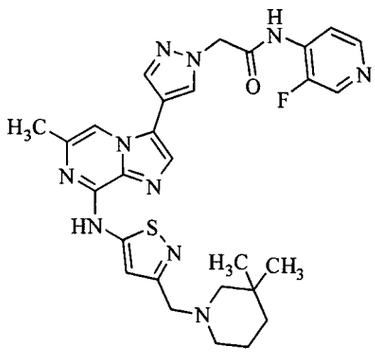


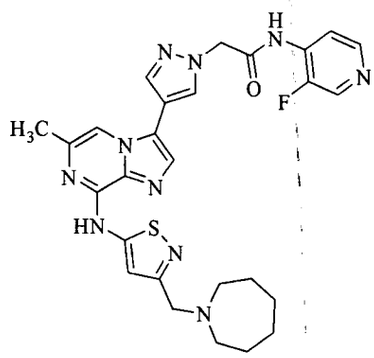

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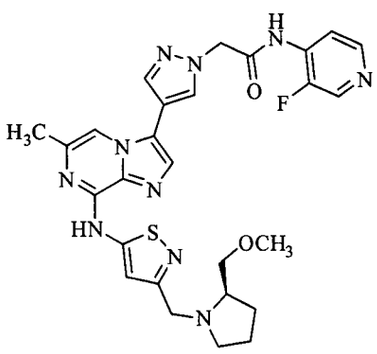

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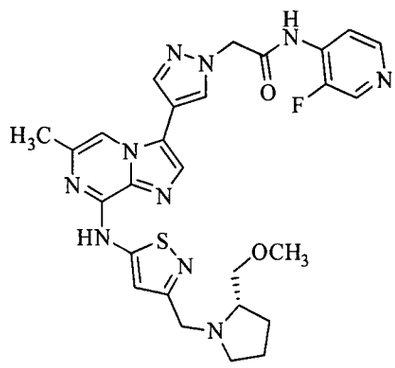


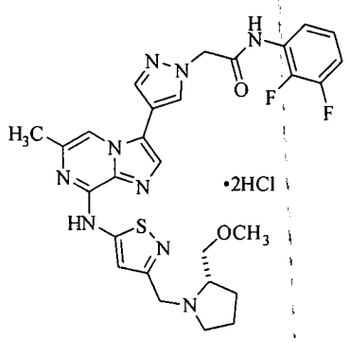


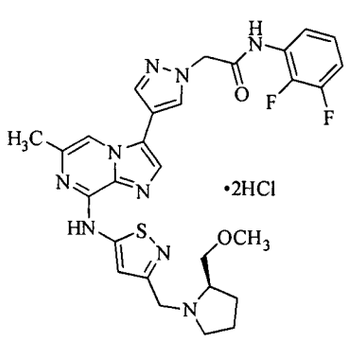


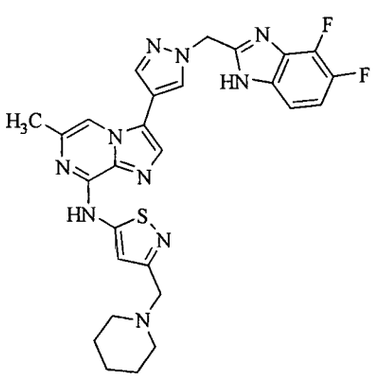


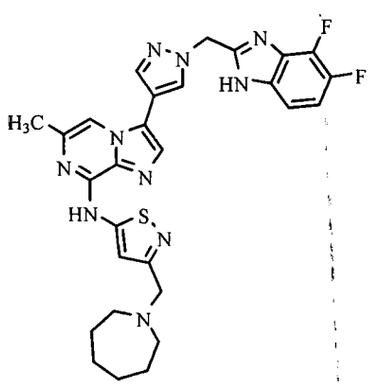


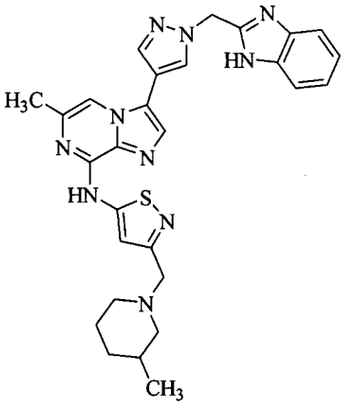


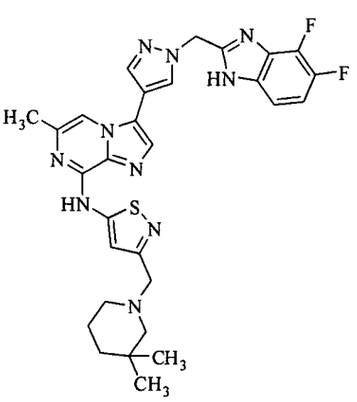

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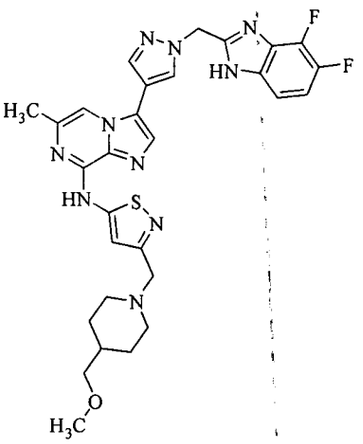

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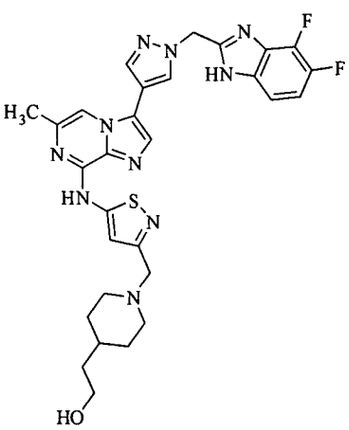


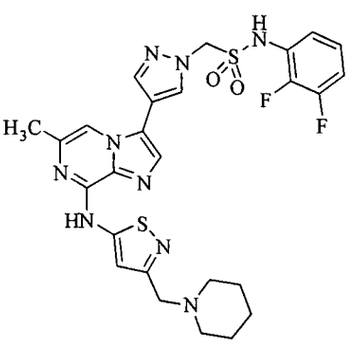


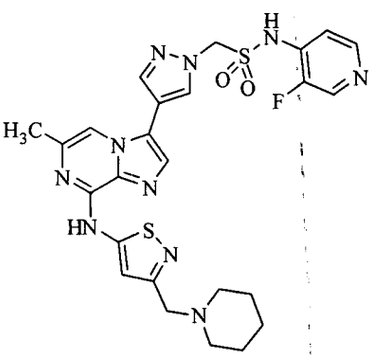


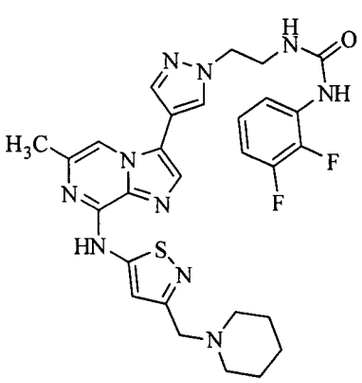


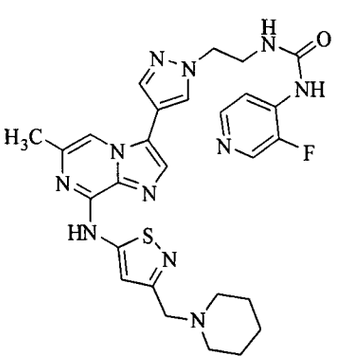


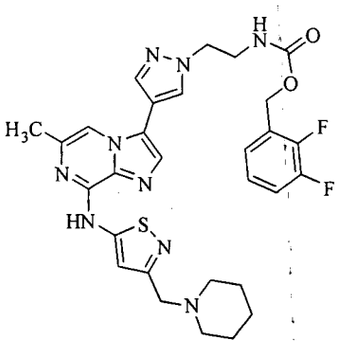


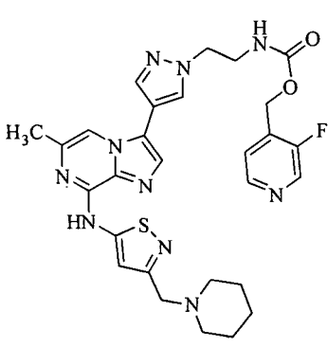


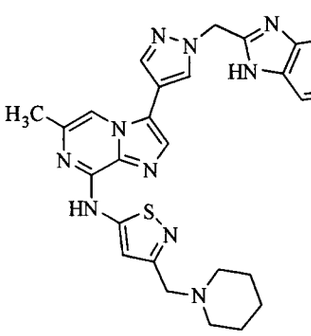


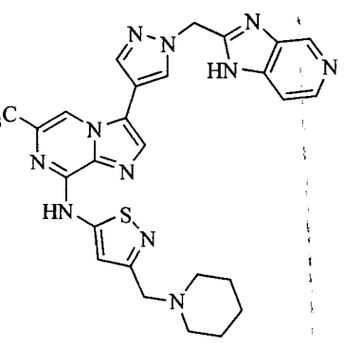




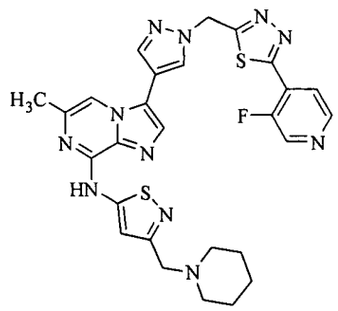


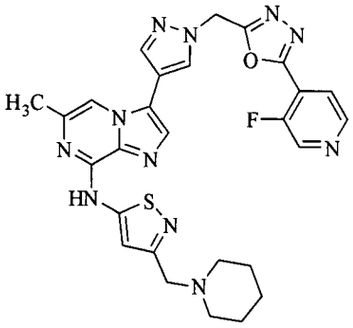


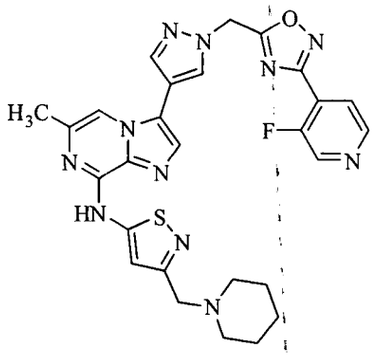


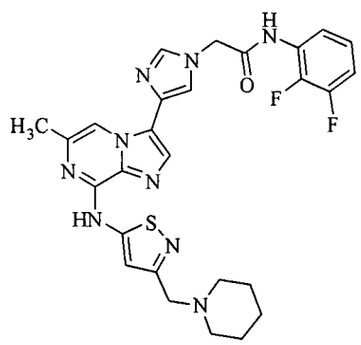


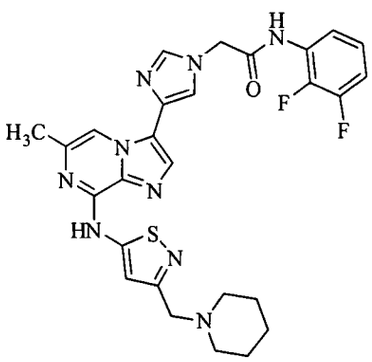
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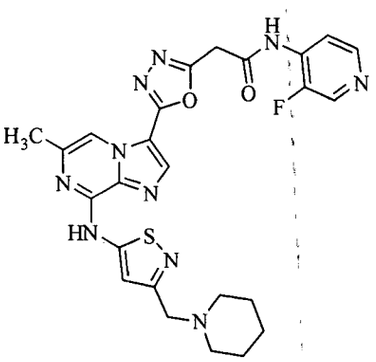


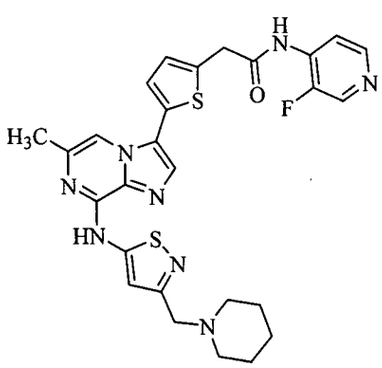


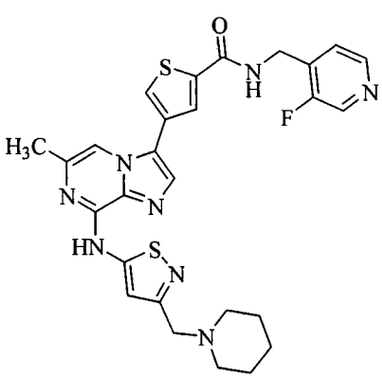


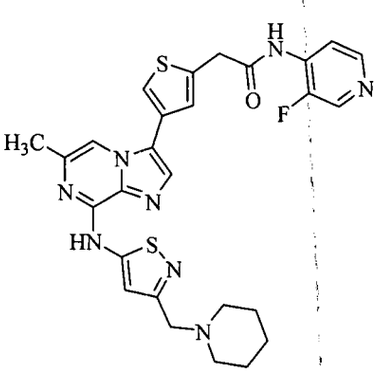


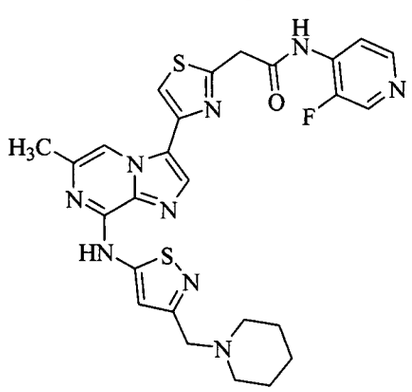


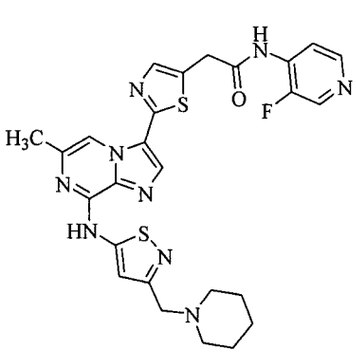


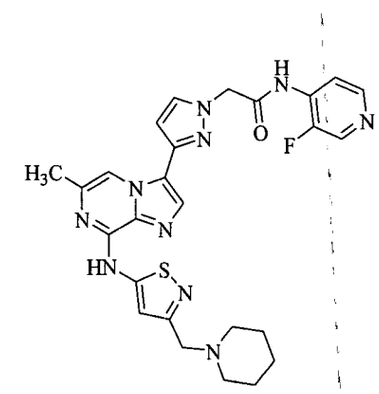




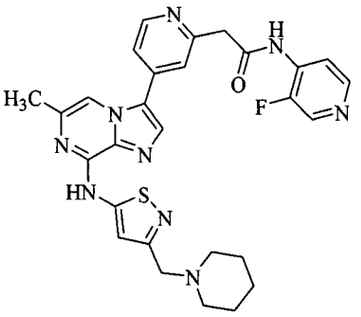


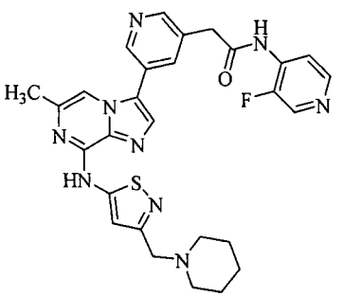


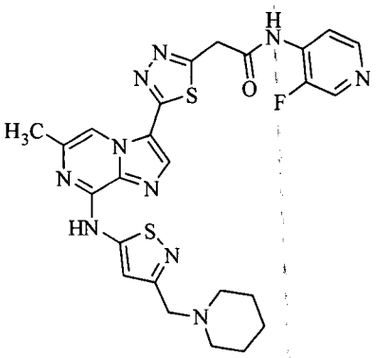


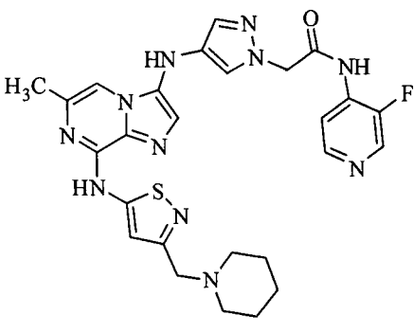


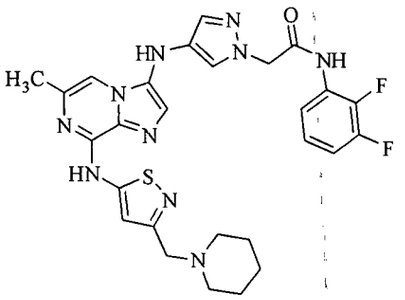
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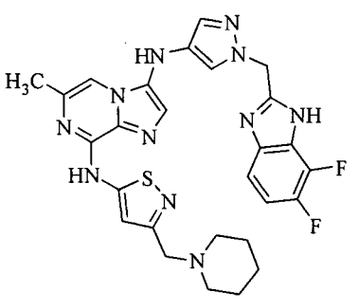


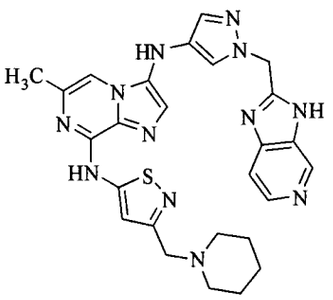


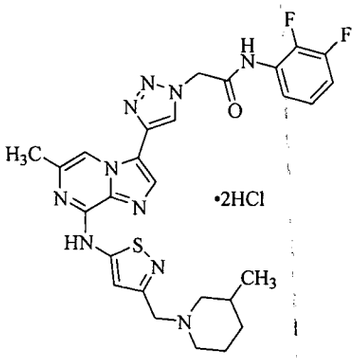




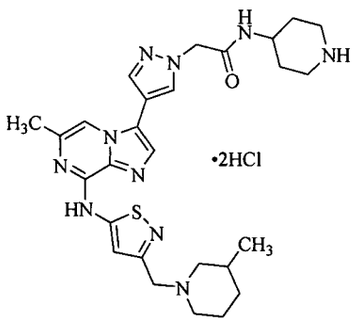


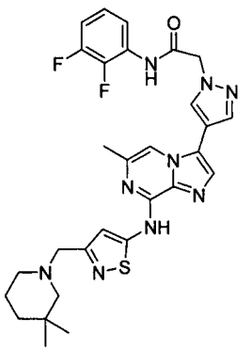


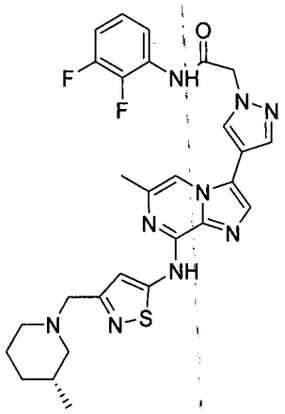


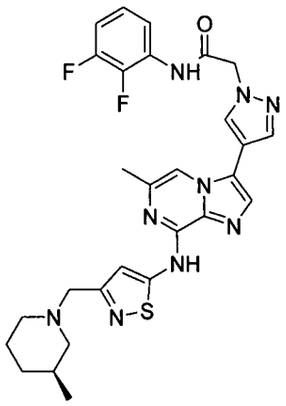


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o una de sus sales, solvatos, ésteres o profármacos farmacéuticamente aceptables.

16. La composición farmacéutica de acuerdo con la reivindicación 1, que también comprende un agente de liberación en el tiempo, en donde dicho inhibidor de aurora quinasa se libera después de la liberación de dicho agente antimitótico.

17. La composición farmacéutica de acuerdo con la reivindicación 14, que también comprende un agente de liberación en el tiempo, en donde dicho inhibidor de aurora quinasa se libera después de la liberación de dicho agente antimitótico.

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18. Un método de tratamiento o mejora del cáncer que comprende la administración de la composición farmacéutica de acuerdo con la reivindicación 1.

19. Un método de tratamiento o mejora del cáncer que comprende la administración de la composición farmacéutica de acuerdo con la reivindicación 17.

p. de: SCHERING CORPORATION

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RESUMEN

La presente invención se refiere a un método de tratamiento de cáncer por pretratamiento con agentes antimitóticos seguido de al menos un inhibidor de aurora quinasa. Se proveen extensas ilustraciones para los agentes antimitóticos e inhibidores de aurora quinasa que son de utilidad en el tratamiento de la invención.

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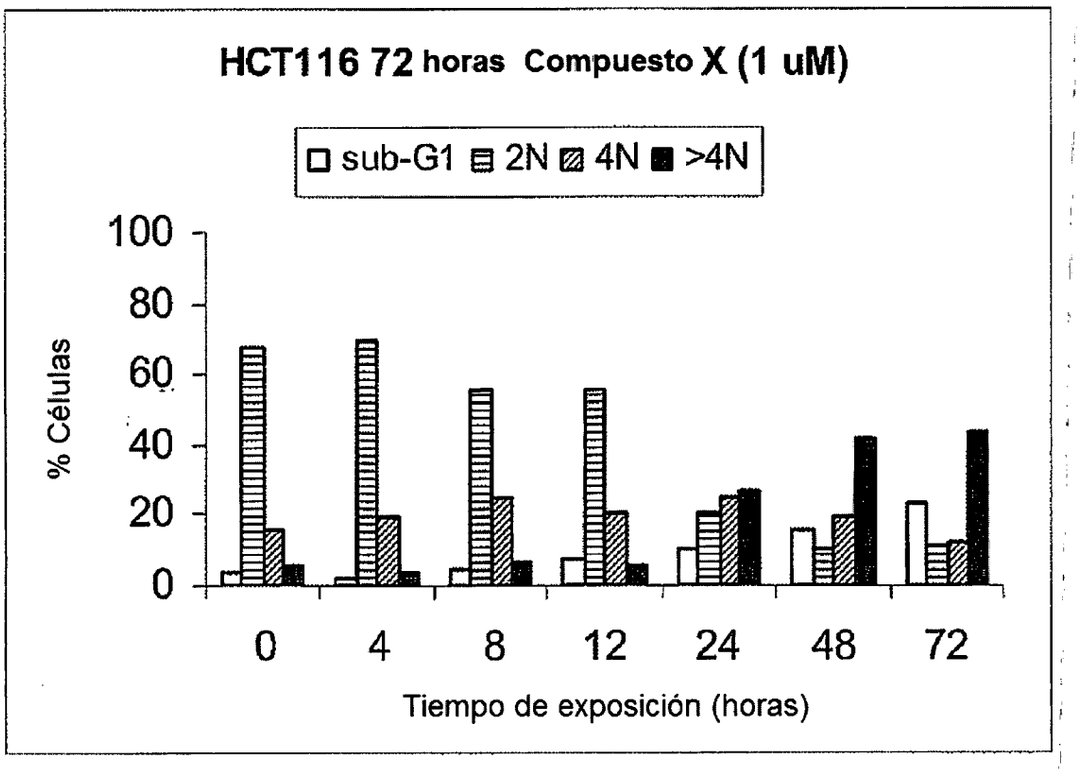

HCT116 72 horas Compuesto X (1 uM)
sub-G1
2N
4N
>4N
100
80
60
40
20
0
% Células
0
4
8
12
24
48
72
Tiempo de exposición (horas)

FIG. 1

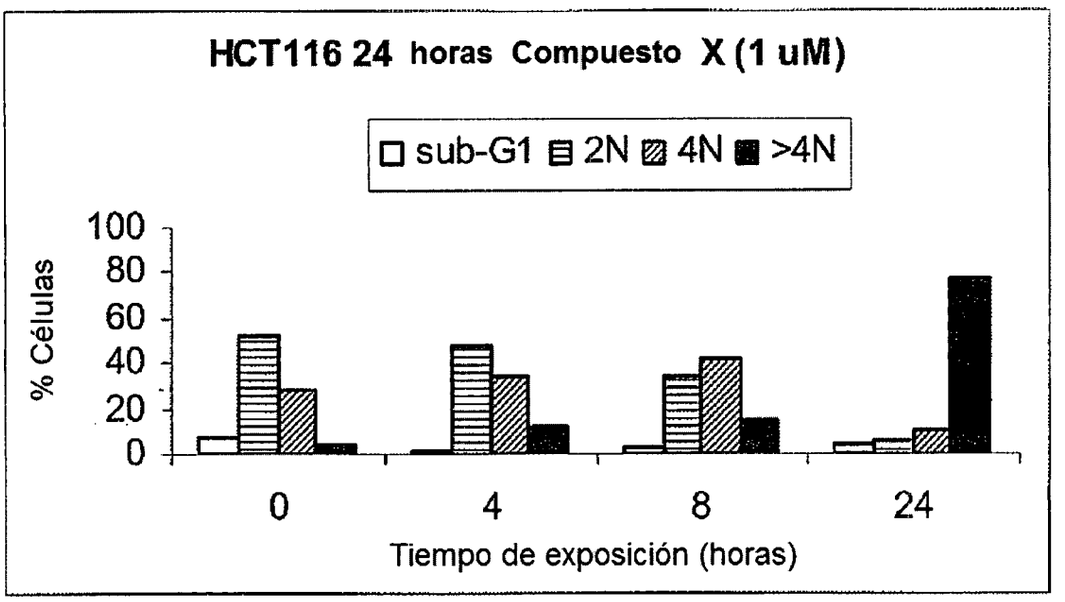

HCT116 24 horas Compuesto X (1 uM)
sub-G1
2N
4N
>4N
% Células
100
80
60
40
20
0
0
4
8
24
Tiempo de exposición (horas)

FIG. 2

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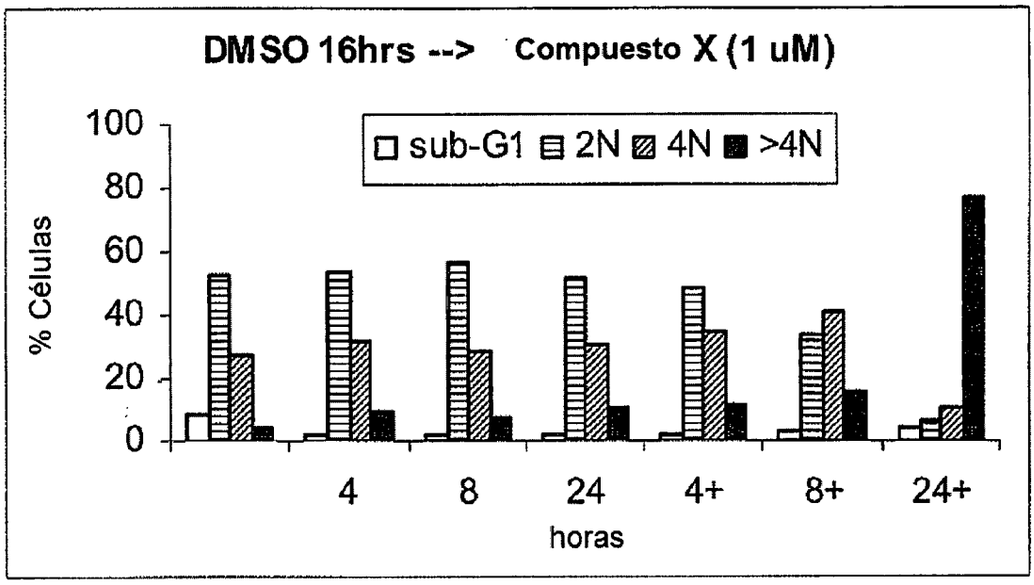


FIG. 3

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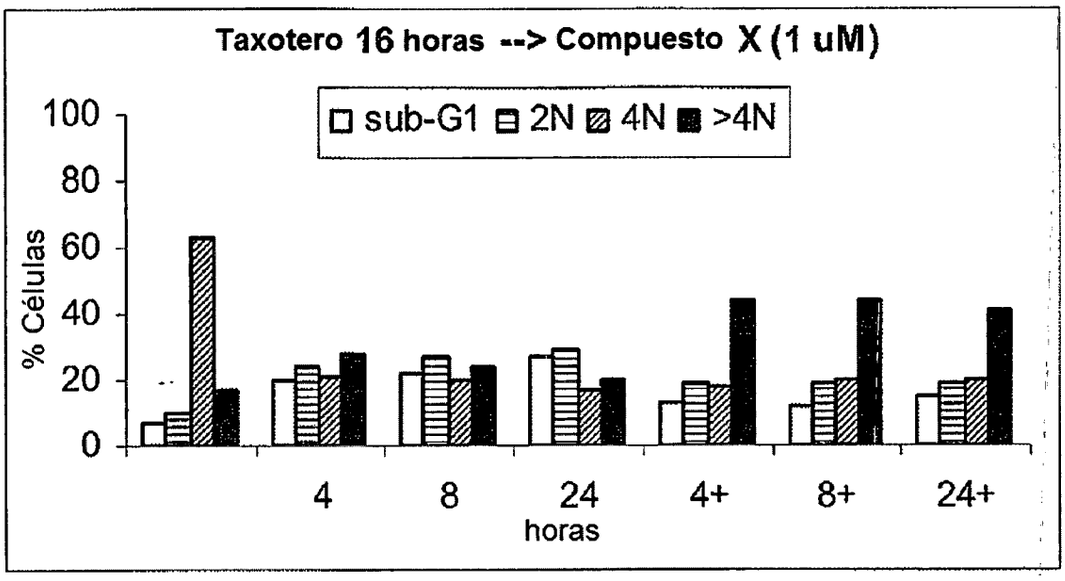


FIG. 4

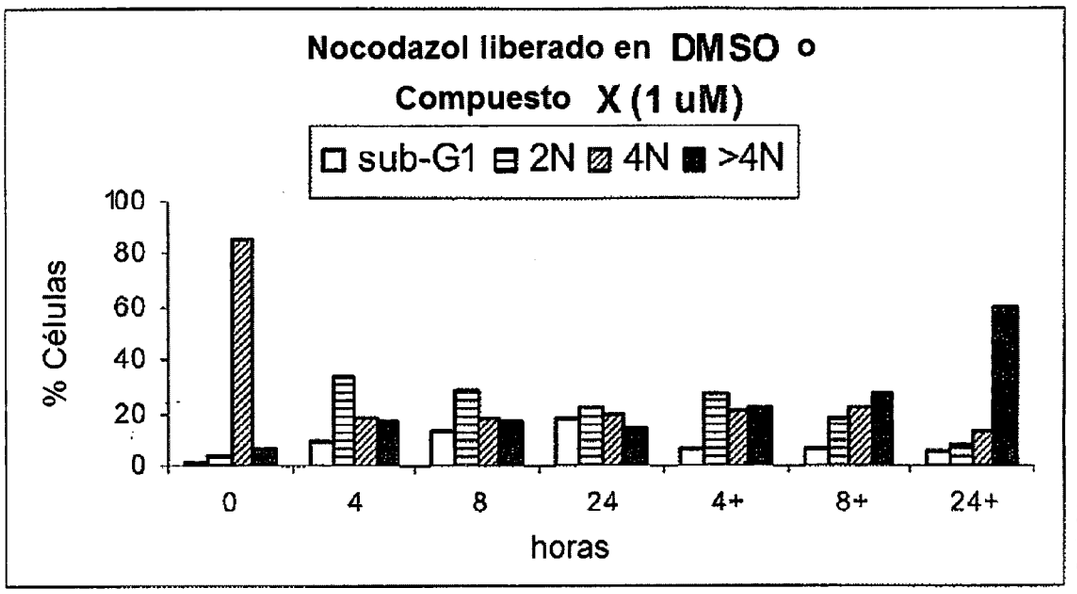

Nocodazol liberado en DMSO o
Compuesto X (1 uM)
sub-G1 2N 4N >4N
% Células
100
80
60
40
20
0
0
4
8
24
4+
8+
24+
horas

FIG. 5

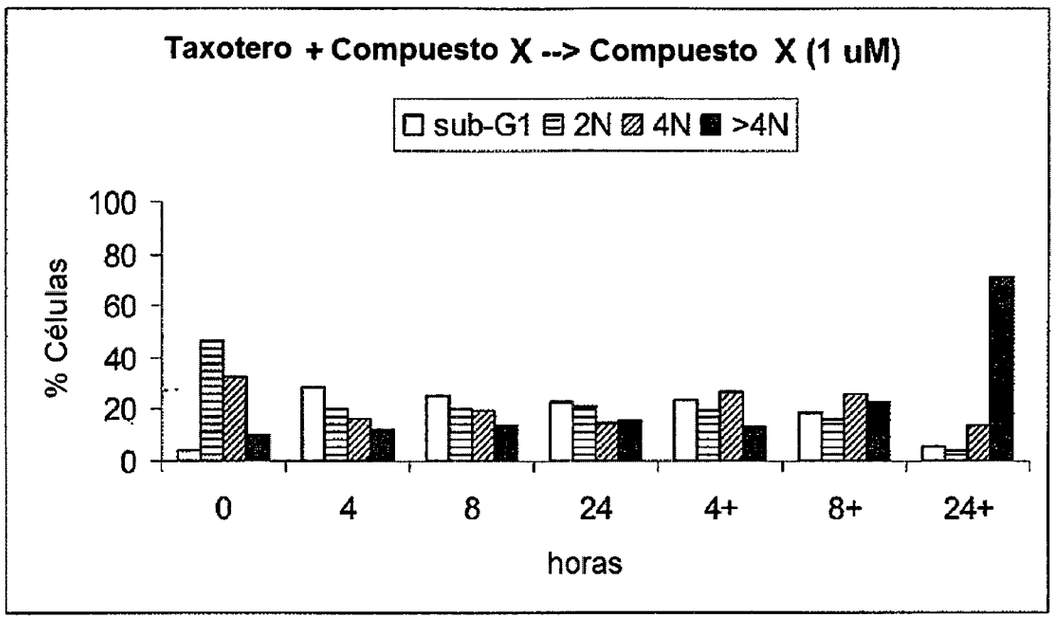

Taxotero + Compuesto X --> Compuesto X (1 uM)
sub-G1 2N 4N >4N
% Células
100
80
60
40
20
0
0
4
8
24
4+
8+
24+
horas

FIG. 6

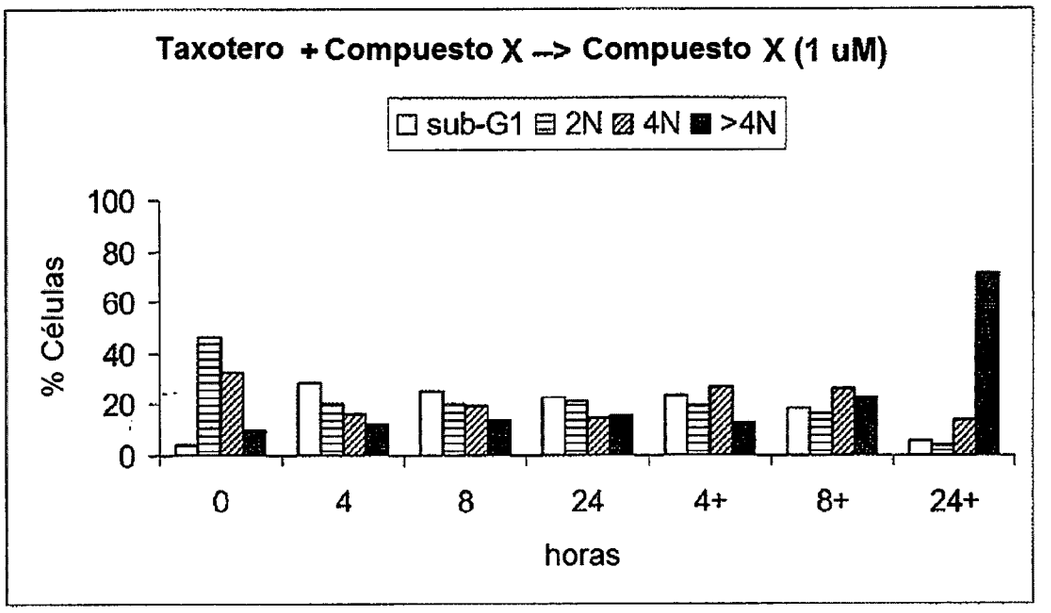

Taxotero + Compuesto X --> Compuesto X (1 uM)
sub-G1
2N
4N
>4N
% Células
100
80
60
40
20
0
0
4
8
24
4+
8+
24+
horas

FIG. 7

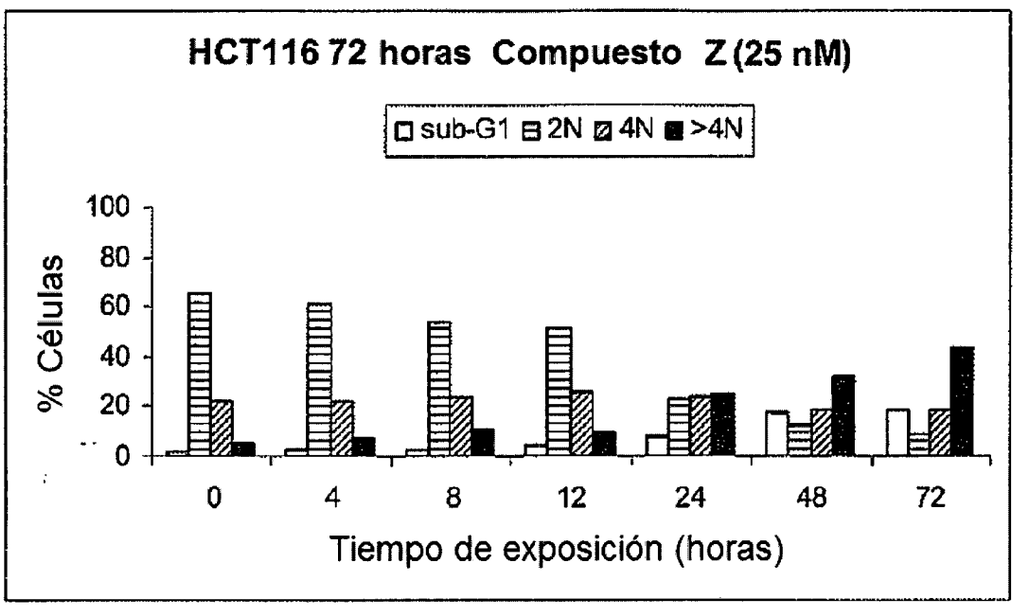

HCT116 72 horas Compuesto Z (25 nM)
sub-G1
2N
4N
>4N
% Células
100
80
60
40
20
0
0
4
8
12
24
48
72
Tiempo de exposición (horas)

FIG. 8

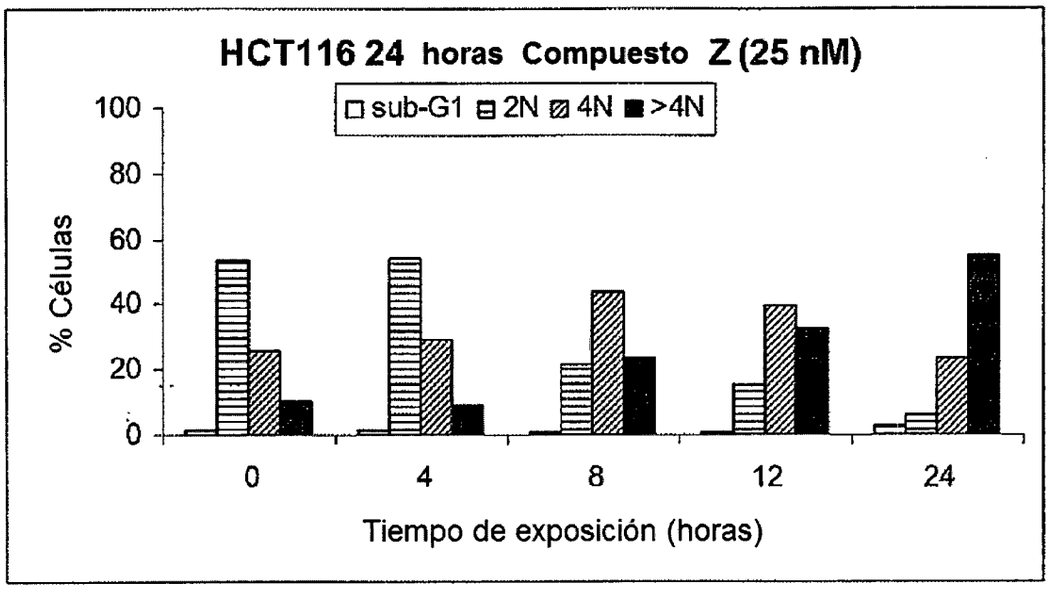

HCT116 24 horas Compuesto Z (25 nM)
sub-G1
2N
4N
>4N
100
80
60
40
20
0
% Células
0
4
8
12
24
Tiempo de exposición (horas)

FIG. 9

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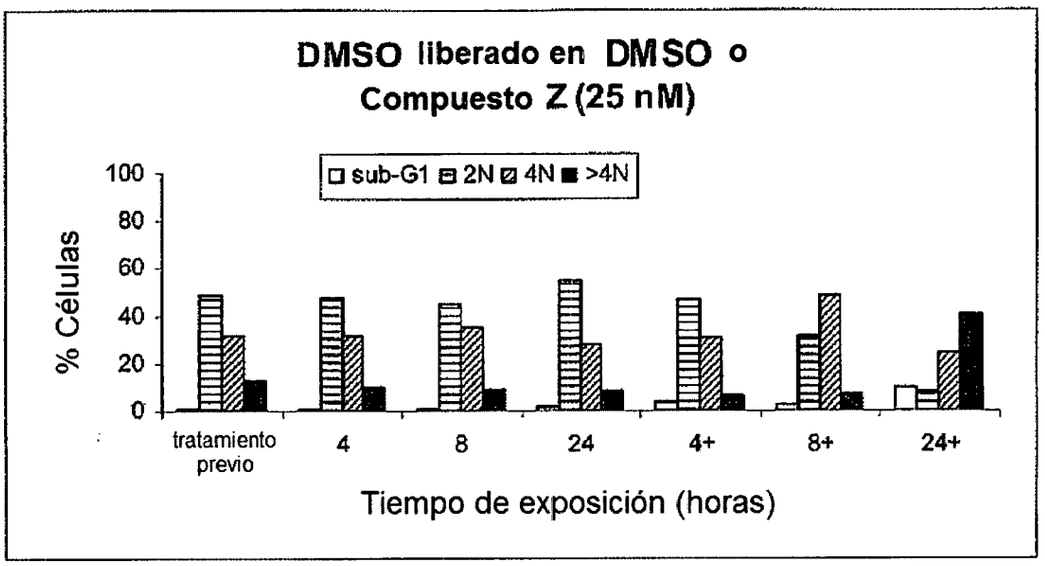


FIG. 10

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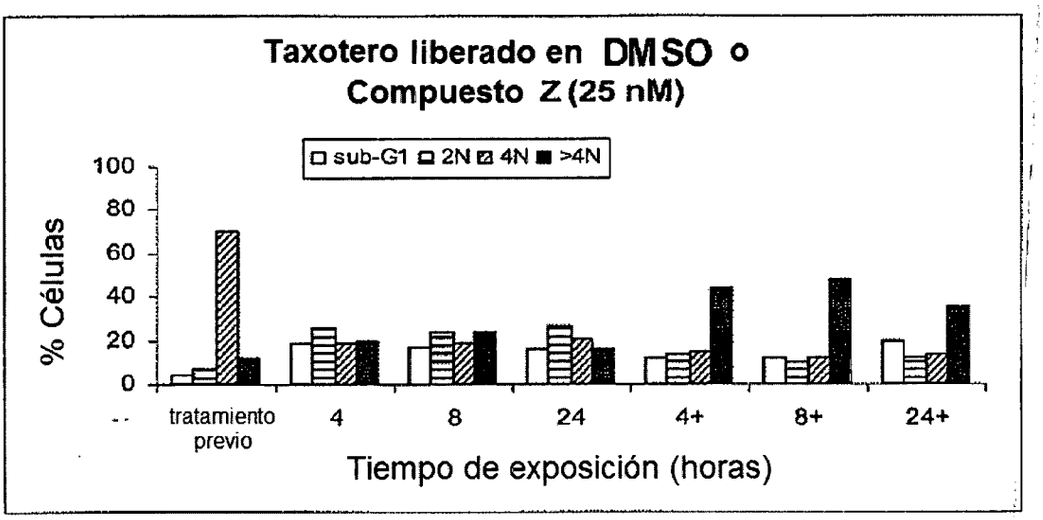


FIG. 11

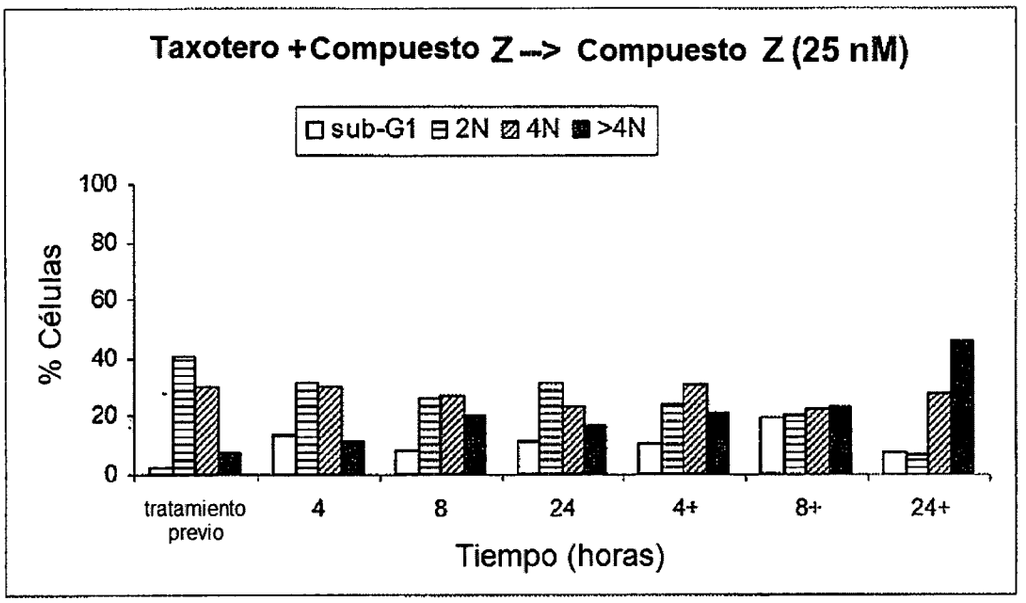

Taxotero +Compuesto Z --> Compuesto Z (25 nM)
sub-G1
2N
4N
>4N
% Células
100
80
60
40
20
0
tratamiento previo
4
8
24
4+
8+
24+
Tiempo (horas)

FIG. 12

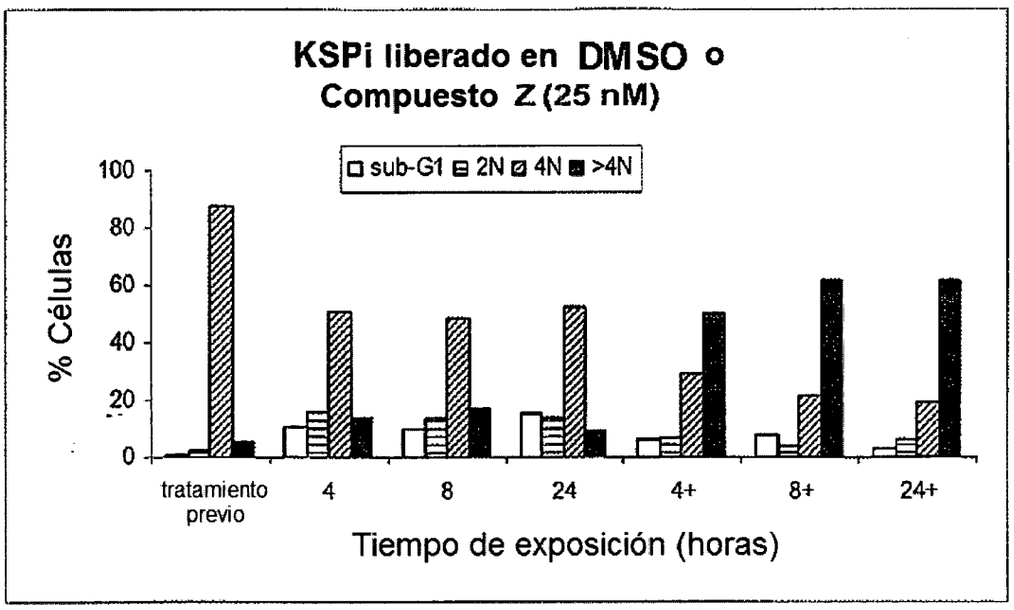

KSPi liberado en DMSO o
Compuesto Z (25 nM)
sub-G1 2N 4N >4N
% Células
100
80
60
40
20
0
tratamiento previo
4
8
24
4+
8+
24+
Tiempo de exposición (horas)

FIG. 13

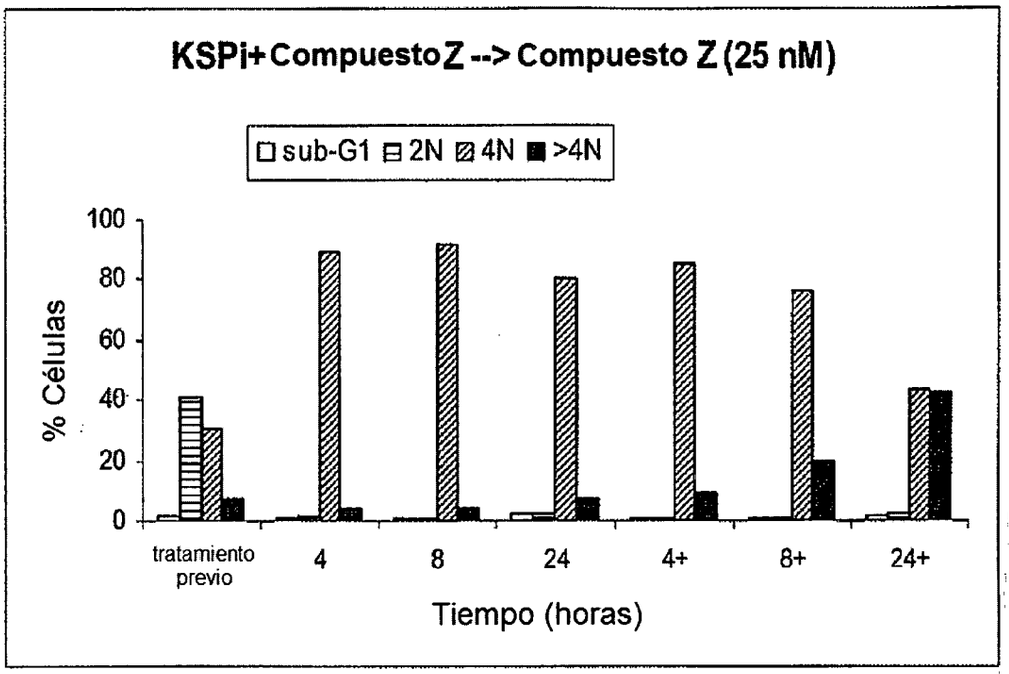

KSPi+CompuestoZ --> Compuesto Z (25 nM)
sub-G1
2N
4N
>4N
% Células
100
80
60
40
20
0
tratamiento previo
4
8
24
4+
8+
24+
Tiempo (horas)

FIG. 14

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

Declaration 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*

[Continued on next page]

(54) Title: ANTI-MITOTIC AGENT AND AURORA KINASE INHIBITOR COMBINATION AS ANTI-CANCER TREATMENT

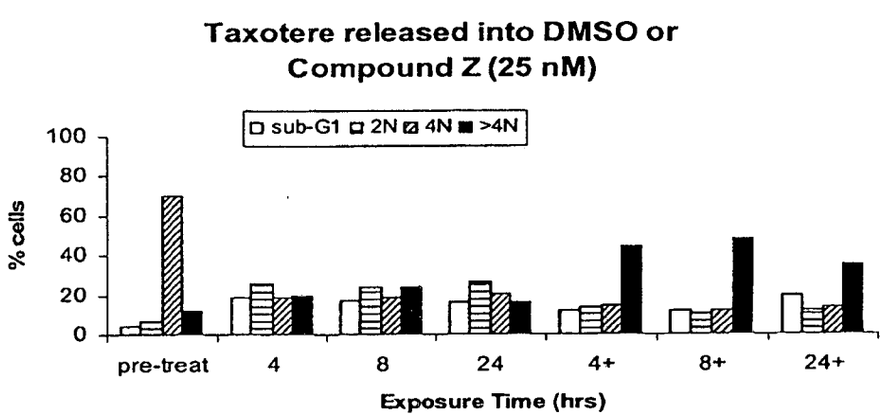


FIG. 11

(57) Abstract: The present invention relates to a method of treating cancer by pretreatment with anti-mitotic agents followed by at least one aurora kinase inhibitor. Extensive illustrations are provided for the antimitotic agents and aurora kinase inhibitors that are useful in the inventive treatment.

WO 2009/017701 A3

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

(88) Date of publication of the international search report:
7 May 2009

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/009108

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K45/06 A61P35/00 A61K31/337 A61K31/4365 A61K31/506
A61K31/517 A61K31/519

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)
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, WPI Data, EMBASE, BIOSIS, 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.
Y	WO 2006/098962 A (SCHERING CORP [US]; TAGAT JAYARAMAN R [US]; GUZI TIMOTHY J [US]; LABRO) 21 September 2006 (2006-09-21) abstract; claims 1-70	1-19
Y	US 2006/258699 A1 (DOLL RONALD J [US] ET AL) 16 November 2006 (2006-11-16) abstract; claims 1-21	1-19

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 March 2009	13/03/2009

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	Madalinska, K

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/009108

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	BLAGDEN, S. ET AL.: "Phase I study of ispinesib (SB-715992) in combination with docetaxel in patients with advanced solid tumors" 17TH AACR-NCI-EORTC INTERNATIONAL CONFERENCE ON MOLECULAR TARGETS AND THERAPEUTICS (NOVEMBER 14-18, PHILADELPHIA), [Online] 14 November 2005 (2005-11-14), pages 218-ABS C80, XP002517230 Retrieved from the Internet: URL:http://www.aacr.org/Uploads/DocumentRepository/pdf_files/2005MTCT/MT05_abstracts_C.pdf> [retrieved on 2008-02-27] abstract	1-19
Y	WO 2005/002571 A (UNIV CAMBRIDGE TECH [GB]; ANAND SHUBHA [GB]; VENKITARAMAN ASHOK [GB]) 13 January 2005 (2005-01-13) abstract; claims 1-51	1-19
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X	WO 2007/058873 A (SCHERING CORP [US]; GUZI TIMOTHY J [US]; PARUCH KAMIL [US]; DWYER MICH) 24 May 2007 (2007-05-24) abstract; claims 1-3,9-12 page 34, lines 1-20 page 36, lines 8-15	1-19
Y		1-19

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/009108

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/026877 A (SCHERING CORP [US]) 1 April 2004 (2004-04-01) abstract; claims 1-30	1-19
Y		1-19
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P,X	HOOVER R R ET AL: "The aurora kinase inhibitor MK-0457 (VX-680) demonstrates anticancer activity alone or in combination with docetaxel (Dtx)" EUROPEAN JOURNAL OF CANCER. SUPPLEMENTS., vol. 5, no. 4, September 2007 (2007-09), pages 66-67-POSTER 336, XP022332835 & 14TH EUROPEAN CANCER CONFERENCE (ECCO 14); BARCELONA, SPAIN; SEPTEMBER 23 -27, 2007 ISSN: 1359-6349 abstract	1-19

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2008/009108

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		US 2007117804 A1	24-05-2007

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 10-009533- -00000-0000

Fecha: 2010-01-29 17:33:14 Dep: 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 1281

Industria y Comercio
SUPERINTENDENCIA

LISTA DE CHEQUEO
ADMISIÓN A TRÁMITE – NUEVAS CREACIONES

PATENTE DE INVENCIÓN ☐ MODELO DE UTILIDAD ☐ Art 33 Decisión 486/00

- ☐ Indicación que se solicita una patente.
- ☐ Datos de identificación del solicitante o de la persona que p[illegible] 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 ☐

1203

Industria y Comercio
SUPERINTENDENCIA

Bogotá,
2020

Doctor(a)
OLARTE GARCIA CARLOS REYNALDO
Apoderado(a) y/o Representante de
SCHERING CORPORATION

REFERENCIA	Radicación No.	10 9533
	Solicitud internacional	PCT/US2008/009108
	Fecha inicio fase nacional	28/02/2010
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	

No 017671

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. El solicitante debe presentar un nuevo titulo que permita identificar la materia de la cual trata la solicitud, ya que el titulo relacionado no se encuentra con la precisión necesaria para identificar claramente el objeto de la solicitud de patente. (Regla 4.3 PCT, Art 26-27 D-486, Circular única 5.2.9)

2. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante, conforme a lo establecido por el artículo 26 literal k) de la Decisión 486 de la Comisión de la Comunidad Andina. Cuando se trate de documentos otorgados en el extranjero, estos deberán legalizarse de conformidad con lo dispuesto por los artículos 259 y 260 del Código de Procedimiento Civil. Cuando se trate de las declaraciones a que hace referencia la Regla 4.17 ii) del Tratado de Cooperación en Materia de Patentes PCT., el alcance de las tales declaraciones se determinará según indiquen claramente una cesión de derechos del inventor al solicitante o su causante, de conformidad con lo dispuesto en el numeral 5.2.15 del Capítulo Quinto, Título X de la Circular Única de Superintendencia de Industria y Comercio.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

Continua en la página siguiente...

BICENTENARIO 1810 2010

Industria y Comercio
SUPERINTENDENCIA

Radicación No.:10 9533

ALIX CARMENZA CESPEDES DE VERGEL
Directora de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista de fecha 09 ABR. 2010
adpa11

1285

Industria y Comercio
SUPERINTENDENCIA

Bogotá,
2020

Doctor(a)
OLARTE GARCIA CARLOS REYNALDO
Apoderado(a) y/o Representante de
SCHERING CORPORATION

REFERENCIA	Radicación No.	10 9533
	Solicitud internacional	PCT/US2008/009108
	Fecha inicio fase nacional	28/02/2010
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	04768

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 09 ABR. 2010
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